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Abstract

The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation

Jonathan Shepherd,* Keith Cooper, Petra Harris, Joanna Picot and Micah Rose

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Background: Juvenile idiopathic arthritis (JIA) is characterised by joint pain, swelling and a limitation of movement caused by inflammation. Subsequent joint damage can lead to disability and growth restriction. Treatment commonly includes disease-modifying antirheumatic drugs (DMARDs), such as methotrexate. Clinical practice now favours newer drugs termed biologic DMARDs where indicated.

Objective: To assess the clinical effectiveness and cost-effectiveness of four biologic DMARDs [etanercept (Enbrel®, Pfizer), abatacept (Orencia®, Bristol-Myers Squibb), adalimumab (Humira®, AbbVie) and tocilizumab (RoActemra®, Roche) – with or without methotrexate where indicated] for the treatment of JIA (systemic or oligoarticular JIA are excluded).

Data sources: Electronic bibliographic databases including MEDLINE, EMBASE, The Cochrane Library and the Database of Abstracts of Reviews of Effects were searched for published studies from inception to May 2015 for English-language articles. Bibliographies of related papers, systematic reviews and company submissions were screened and experts were contacted to identify additional evidence.

Review methods: Systematic reviews of clinical effectiveness, health-related quality of life and cost-effectiveness were undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. A cost–utility decision-analytic model was developed to compare the estimated cost-effectiveness of biologic DMARDs versus methotrexate. The base-case time horizon was 30 years and the model took a NHS perspective, with costs and benefits discounted at 3.5%.

Results: Four placebo-controlled randomised controlled trials (RCTs) met the inclusion criteria for the clinical effectiveness review (one RCT evaluating each biologic DMARD). Only one RCT included UK participants. Participants had to achieve an American College of Rheumatology Pediatric (ACR Pedi)-30 response to open-label lead-in treatment in order to be randomised. An exploratory adjusted indirect comparison suggests that the four biologic DMARDs are similar, with fewer disease flares and greater proportions of ACR Pedi-50 and -70 responses among participants randomised to continued biologic DMARDs. However, confidence intervals were wide, the number of trials was low and there was clinical heterogeneity between trials. Open-label extensions of the trials showed that, generally, ACR responses remained constant or even increased after the double-blind phase. The proportions of adverse events and serious adverse events were generally similar between the treatment and placebo groups. Four economic evaluations of biologic DMARDs for patients with JIA were identified but all had limitations. Two quality-of-life studies were included, one of which informed the cost–utility model. The incremental

cost-effectiveness ratios (ICERs) for adalimumab, etanercept and tocilizumab versus methotrexate were £38,127, £32,526 and £38,656 per quality-adjusted life year (QALY), respectively. The ICER for abatacept versus methotrexate as a second-line biologic was £39,536 per QALY.

Limitations: The model does not incorporate the natural history of JIA in terms of long-term disease progression, as the current evidence is limited. There are no head-to-head trials of biologic DMARDs, and clinical evidence for specific JIA subtypes is limited.

Conclusions: Biologic DMARDs are superior to placebo (with methotrexate where permitted) in children with (predominantly) polyarticular course JIA who have had an insufficient response to previous treatment. Randomised comparisons of biologic DMARDs with long-term efficacy and safety follow-up are needed to establish comparative effectiveness. RCTs for JIA subtypes for which evidence is lacking are also required.

Study registration: This study is registered as PROSPERO CRD42015016459.

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ABC	Arthritis and Biologicals in Children
ACR	American College of Rheumatology
ACR Pedi-20,-30,-50,-70,-90,-100	American College of Rheumatology Pediatric response level 20, 30, 50, 70, 90, 100
AE	adverse event
AiC	academic in confidence
AWAKEN	Abatacept Withdrawal study to Assess efficacy and safety in Key Endpoints
BMS	Bristol-Myers Squibb
BSPAR	British Society for Paediatric and Adolescent Rheumatology
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CI	confidence interval
CiC	commercial in confidence
CRP	C-reactive protein
CS	company submission
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EO	extended oligoarthritis
EQ-5D™	European Quality of Life-5 Dimensions
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
HRQoL	health-related quality of life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
IL-6	interleukin-6
ILAR	International League of Associations for Rheumatology
IQR	interquartile range
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
LOM	limitation of motion
MII	medically important infection
MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PA	psoriatic arthritis
PAS	patient access scheme
PGA	physician global assessment of disease activity
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RF–ve	rheumatoid factor negative
RF+ve	rheumatoid factor positive
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SDS	standard deviation score

SF-6D	Short Form questionnaire-6 Dimensions	TA	technology appraisal
SHTAC	Southampton Health Technology Assessments Centre	TNF	tumour necrosis factor
SPC	summary of product characteristics	VAS	visual analogue scale

Note

This monograph is based on the Technology Assessment Report produced for the National Institute for Health and Care Excellence (NICE). The full report contained a considerable number of data that were deemed academic-in-confidence and commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of academic-in-confidence and commercial-in-confidence data removed and replaced by the statement 'academic-in-confidence information (or data) removed' or 'commercial-in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

The term juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis of unknown cause that start before 16 years of age and persist for > 6 weeks. Treatment includes disease-modifying antirheumatic drugs (DMARDs), of which methotrexate is most commonly used in the UK. Current preferred treatment includes newer drugs termed biologic DMARDs. We identified the most up-to-date clinical effectiveness and cost-effectiveness evidence for four biologic DMARDs, namely abatacept (Orencia®, Bristol-Myers Squibb), adalimumab (Humira®, AbbVie), etanercept (Enbrel®, Pfizer) and tocilizumab (RoActemra®, Roche). The evidence was assessed systematically to evaluate whether or not treatment with a biologic DMARD (with or without methotrexate) benefits patients with JIA, taking into account treatment costs and health.

One study comparing the biologic DMARD with a (non-active) placebo treatment was identified for each drug. With the exception of the etanercept study, the majority of patients also received methotrexate. Patients who received biologic DMARD treatment experienced significantly fewer disease flare ups than those patients given placebo. Biologic DMARD treatment also led to a greater level of response (e.g. better overall well-being). No studies directly compared the drugs with each other. A statistical method used to compare them indirectly suggested that the four biologic DMARDs are similarly effective, but these results must be treated with caution. The proportions of adverse events were generally similar between the biologic DMARD and placebo groups.

Costs and health benefits appear to be generally similar for the four biologic DMARDs. Biologic DMARDs may therefore be an effective therapy, but uncertainties remain owing to the lack of evidence from direct comparisons between biologic DMARDs.

Scientific summary

Background

The term juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis of unknown cause with onset prior to 16 years of age and with symptoms that persist for > 6 weeks. Suggested incidence (1.6 to 23 per 100,000) and prevalence rates (3.8 to 400 per 100,000) vary widely. The disease is characterised by joint pain, swelling and a limitation of movement which is caused by an inflammation of the synovial membrane of the affected joints. Left untreated, this inflammation causes a progressive erosive arthritis, which may potentially lead to disability and growth restriction. However, disease severity and long-term outcomes are variable both between different JIA subtypes and between different individuals with the same JIA subtype. At onset, the particular subtype of JIA will be diagnosed according to the presenting features as oligoarthritis, polyarthritis, enthesitis-related JIA (ERA), psoriatic arthritis (PA), systemic-onset JIA or undifferentiated arthritis. Polyarticular-course JIA applies to patients who at a particular point in time 6 months or more after the onset of disease (JIA of any onset type) have five or more active joints. Polyarticular-course JIA can typically include rheumatoid factor-positive (RF+) and rheumatoid factor-negative (RF–) polyarthritis, extended oligoarthritis (EO), ERA, PA and systemic JIA (providing that there have been no active systemic symptoms during the previous 6 months).

The treatment of JIA includes non-steroidal anti-inflammatory drugs, intra-articular corticosteroids and disease-modifying antirheumatic drugs (DMARDs), of which methotrexate is the most common conventional (non-biologic) DMARD used in the UK. Clinical practice now favours earlier treatment with biologic DMARDs, where indicated.

Objectives

The aim of this multiple technology appraisal is to assess the clinical effectiveness and cost-effectiveness of the biologic DMARDs etanercept (Enbrel®, Pfizer), abatacept [Orencia®, Bristol-Myers Squibb (BMS)], adalimumab (Humira®, AbbVie) and tocilizumab (RoActemra®, Roche), in combination with methotrexate, where permitted, in the treatment of JIA. It updates and extends a previous National Institute for Health and Care Excellence (NICE) technology appraisal (TA) of etanercept conducted in 2002 (NICE TA35). The licensed indication for etanercept has broadened since 2002 and three newer biologic DMARDs have been licensed. This appraisal includes all subtypes of JIA, with the exception of systemic JIA with active systemic features or persistent oligoarticular JIA.

Methods

Clinical effectiveness systematic review

Electronic bibliographic resources including MEDLINE, EMBASE, The Cochrane Library and the Database of Abstracts of Reviews of Effects were searched for published studies from inception to May 2015 for English-language articles. Bibliographies of included articles and systematic reviews were also searched for additional studies, as were company submissions (CSs) to NICE. An expert advisory group was contacted to identify additional published and unpublished evidence.

Titles and abstracts were independently screened for eligibility by two reviewers using inclusion criteria that were defined a priori. Inclusion criteria were applied to full texts by one reviewer and checked by a second reviewer. Inclusion criteria were as follows:

- Population: patients with JIA including polyarthritis (both RF+ve and RF–ve, and EO, both onset and course), ERA and PA.
- Intervention: the biologic DMARDs abatacept, adalimumab, etanercept and tocilizumab (in combination with methotrexate where permitted), evaluated within their licensed indication. Studies of biologic DMARDs without concomitant methotrexate were permitted if patients were intolerant to it or if treatment with methotrexate was inappropriate.
- Comparators: DMARDs such as methotrexate (best supportive care if DMARDs are not tolerated), as well as abatacept, adalimumab, etanercept and tocilizumab compared with each other.
- Outcomes: disease activity, disease flares, physical function, joint damage, pain, corticosteroid reducing regimens, extra-articular manifestations (such as uveitis), body weight and height, mortality, adverse effects of treatment and health-related quality of life (HRQoL).
- Design: randomised controlled trials (RCTs). Non-randomised studies could be considered where RCT data were not available.

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved by discussion at each stage or in consultation with a third reviewer where necessary.

Data were synthesised through narrative reviews with tabulation of the results of included studies. An adjusted pairwise indirect comparison of the four biologic DMARDs was presented.

Economic evaluation

A systematic review of cost-effectiveness studies and a systematic review of HRQoL studies was conducted to identify relevant evidence to inform the economic evaluation. Studies were included in the systematic review of cost-effectiveness if they were full economic evaluations (cost-effectiveness, cost–utility, cost–benefit or cost–consequence analyses).

A cost–utility decision-analytic model was developed to compare the cost-effectiveness estimates of biologic DMARDs versus methotrexate. The model used a Markov approach to estimate the costs and health benefits for patients with JIA. The model consisted of three health states: on treatment (with biologic DMARD), off treatment and death, with a further health state of 'clinical remission off treatment' also included in a scenario analysis. The model cycles were 3 months in length to be consistent with timing between outpatient appointments in clinical practice. Patients discontinued treatment owing to adverse events (AEs), inefficacy of the treatment or remission. The model also included the cost and disutility of disease flares. The perspective of the analysis was that of the NHS and Personal Social Services. The model used a time horizon of 30 years and discount rates of 3.5% for costs and health benefits. The outcome of the economic evaluation is reported as cost per quality-adjusted life-year (QALY) gained.

Results

Clinical effectiveness

From 2554 references screened on title and abstract, 56 full texts were retrieved. One further conference abstract was identified from a pharmaceutical CS to NICE. From these, nine full papers and 12 conference abstracts met the inclusion criteria. The included papers and abstracts collectively described four multicentre RCTs, with one RCT each evaluating abatacept, adalimumab, etanercept and tocilizumab. Only the tocilizumab study included UK participants. All four studies were described as being withdrawal trials starting with an open-label lead-in phase (12–16 weeks) in which participants had to achieve an American College of Rheumatology (ACR) Pediatric (Pedi)-30 response level to be eligible for entry to the randomised

double-blind withdrawal phase of the study (16–32 weeks), followed by an open-label extension (OLE). All studies used a placebo as the comparator. With the exception of the etanercept trial, the majority of patients in the trials received methotrexate in addition to the biologic DMARD or placebo. The distribution of patients across the subtypes of JIA was reported for only two of the trials, with polyarthritis being the predominant subtype. The other two trials appeared to include patients with polyarticular-course JIA. Overall, the quality of the RCTs was reasonable, with a low risk of bias for most domains, but some aspects were rated as unclear, primarily owing to insufficient reporting.

Significantly fewer patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had arthritis flares than those receiving placebo in all four trials. Time to disease flare for participants receiving biologic DMARDs was statistically significantly longer (reported for adalimumab and etanercept). A greater proportion of those treated with biologic DMARDs achieved ACR Pedi responses of ≥ 30 and had inactive disease (reported for abatacept and tocilizumab only). Generally, the individual ACR Pedi core variables (reported for abatacept, etanercept and tocilizumab) were improved by biologic DMARDs when compared with placebo, as were joint-related outcomes (reported for etanercept only) and pain in two out of three studies (etanercept and tocilizumab, not abatacept). Not all studies reported a statistical comparison for each of these outcomes. Three studies (adalimumab, etanercept and tocilizumab) reported mortality, with no treatment-related deaths. Differences in HRQoL between trial arms reported in one study (abatacept) were not statistically significant. The proportions of AEs and serious adverse events (SAEs) were generally similar between the treatment groups. One study (tocilizumab) reported subgroup data, albeit without statistical comparisons between treatment groups. None of the studies reported data for outcomes such as corticosteroid dose reduction, extra-articular manifestations (such as uveitis), height or weight for the randomised withdrawal phase of the trials.

An adjusted indirect comparison suggests that the four biologic DMARDs appear to be similar in terms of disease flare and ACR Pedi-50 and -70 responses, with wide confidence intervals and clinical heterogeneity between the trials.

There were differences across the trials in the eligibility criteria for the OLE phase, and in how the results were reported. In some studies, it was not possible to differentiate between participants treated continuously with a biologic DMARD (i.e. from open-label lead-in and randomised withdrawal phase) and those who received placebo before being offered a biologic DMARD at entry to the OLE. Generally, patients' ACR responses remained constant over time or even increased after the double-blind phase. Limited data for adalimumab and tocilizumab reported in abstracts at week 104 appear to support the positive effect of these drugs on growth, but the use of different outcome measures prevents a comparison between the drugs.

In addition to the four RCTs, seven relevant ongoing trials were identified and summarised in this report (three investigating adalimumab and four investigating etanercept).

There is limited evidence for the clinical effectiveness of biologic DMARDs in specific JIA disease subtypes. An observational study (CLIPPER) assessing the safety and efficacy of etanercept in children and adolescents with EO JIA, ERA and PA found variations in response to treatment between JIA disease subtypes (commercial-in-confidence information has been removed). By week 96, similar ACR Pedi-90 (62–72%) and ACR Pedi-100 (51–60%) responses were achieved by participants with different JIA subtypes, and proportions of patients with inactive disease varied between 29% (ERA and PA) and 37% (EO).

Evidence from observational studies suggests that biologic DMARDs can improve uveitis symptoms, such as intraocular inflammation, in children with JIA. Adalimumab appears to be more effective than etanercept in improving uveitis.

Four pharmaceutical companies made submissions in support of their drugs to NICE. Only one of these (Pfizer, etanercept) provided a systematic review of clinical effectiveness. This was judged to be of a good standard. None of the submissions included any relevant RCTs that were additional to those identified in this assessment report.

Cost-effectiveness

The systematic review of published economic evaluations identified 388 potentially relevant publications. Of these, four studies (described in five publications) met the inclusion criteria. The studies were conducted in the UK, the Netherlands, Canada and the Russian Federation. There were two cost–utility studies, one cost-effectiveness study and one cost–consequence study. The studies were assessed for quality and generalisability to the UK but all contained limitations in the methodological quality or generalisability to the UK NHS. The study conducted in the UK was the assessment report for the previous NICE appraisal for etanercept in children with JIA (NICE TA35). The systematic review of HRQoL identified two studies reporting health-state utility values for patients with JIA.

In terms of the CSs to NICE, Roche (the manufacturer of tocilizumab) constructed a Markov state-transition model that compared tocilizumab with adalimumab in children with JIA. The base-case results conclude that tocilizumab is of similar effectiveness and is less expensive than adalimumab. Two companies, BMS (the manufacturer of abatacept) and Pfizer (the manufacturer of etanercept) assumed that the biologic DMARDs were equivalent in clinical effectiveness. They submitted cost analyses to compare the biologic DMARDs. BMS concluded that abatacept was the least costly treatment option and that tocilizumab was slightly cheaper than adalimumab. Pfizer concluded that for most ages, etanercept is the biological treatment with the lowest acquisition cost compared with tocilizumab and adalimumab. AbbVie (the manufacturer of adalimumab) did not submit an economic analysis and cited a number of methodological limitations to producing an economic model. Two companies, Roche (tocilizumab) and BMS (abatacept) submitted a confidential patient access scheme discount.

The independent model developed for this assessment report modelled one line of biological treatment for the comparison of adalimumab, etanercept and tocilizumab versus methotrexate. From this model, the incremental cost-effectiveness ratios (ICERs) for adalimumab, etanercept and tocilizumab versus methotrexate are estimated at £38,127, £32,526 and £38,656 per QALY gained, respectively, using the list price drug acquisition costs. Abatacept is licensed for second-line biological therapy after discontinuation of an antitumour necrosis factor. Abatacept was compared with methotrexate as a second-line biological treatment, following etanercept as the first-line biologic. In this analysis, abatacept had an ICER of £39,536 per QALY gained.

The model results are most sensitive to changes in the HRQoL utility values. The changes to the clinical effectiveness parameters, such as treatment discontinuation and disease flare had minimal effect on the model results. The differences in cost-effectiveness of the biologic DMARDs are primarily the effect of the differences in the drug acquisition cost.

Discussion

Biologic DMARDs (plus methotrexate where indicated) are superior to placebo (plus methotrexate where indicated) across a number of outcome measures in children with JIA who have had an insufficient response to previous treatment. Owing to the withdrawal trial design, results of the double-blind phase are applicable only to patients who have already achieved an initial (low) degree of benefit from a biologic DMARD. Long-term treatment effectiveness in terms of ACR Pedi response appears to be sustained for all four included RCTs and the occurrence of AEs is generally similar between biologic DMARD and placebo-treated patients. SAEs seem to be uncommon and the long-term safety profile of the biologic DMARDs is relatively favourable. An incremental analysis and the costs and health benefits of the four biologic DMARDs was not presented, as the DMARDs were similar in effects and costs.

There was insufficient evidence for all input parameters to permit a cost-effectiveness subgroup analysis for each of the respective types of JIA within the scope of the appraisal. The modelled patient population is people with JIA, although it is primarily relevant to those with polyarticular-course JIA.

The strengths of this assessment include the use of standard methods for evidence synthesis and economic modelling, and the transparent reporting of the scope and methods a priori in a published protocol. Limitations include the lack of head-to-head trial comparisons of biologic DMARDs, necessitating an indirect comparison, and the lack of available data to inform the economic evaluation, particularly HRQoL utility estimates (which were the most influential parameters of cost-effectiveness), long-term discontinuation rates and the long-term impact of treatment on disease progression. Assumptions have been made where possible based on best available evidence and expert opinion.

Conclusions

Implications for service provision

Given that biologic DMARDs are currently used in the treatment of JIA, any recommendation supporting their use is unlikely to have significant implications for service provision (e.g. in terms of changes to infrastructure, staff training).

Suggested research priorities

Randomised head-to-head comparisons of biologic DMARDs are necessary to establish comparative effectiveness. Trials should be sufficiently powered, with long-term follow-up of safety and efficacy, and should include an economic evaluation to assess cost-effectiveness.

Study registration

This study is registered as PROSPERO CRD42015016459.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Background

Description of the underlying health problem

Juvenile idiopathic arthritis (JIA) is an umbrella term that encompasses all forms of arthritis with onset before the age of 16 years and symptoms that persist for > 6 weeks for which the cause is unknown.[1,2] The role of infections (either bacterial or viral) in the development of JIA has been investigated but no unequivocal evidence to either support or rule out an association has been clearly demonstrated.[3] The term JIA has been in use since 1995 and was proposed by the International League of Associations for Rheumatology (ILAR) committee to replace the older terms 'juvenile rheumatoid arthritis' and 'juvenile chronic arthritis', which were the commonly used in the USA and in Europe, respectively.[4] JIA is characterised by joint pain, swelling and a limitation of movement which is caused by the inflammation of the synovial membrane of the affected joints. If untreated, this inflammation causes progressive erosive arthritis, which can lead to disability and growth retardation.[5] JIA is classified according to the Revised ILAR criteria[6] into seven subtypes: systemic arthritis, oligoarthritis (subcategories persistent and extended), polyarthritis rheumatoid factor negative (RF–ve), polyarthritis rheumatoid factor positive (RF+ve), psoriatic arthritis (PA), enthesitis-related arthritis (ERA) and undifferentiated arthritis (*Table 1*); some forms of the disease are more likely to be associated with extra-articular features such as uveitis (inflammation of the middle layer of the eye).

At onset, the particular subtype of JIA will be diagnosed according to the presenting features corresponding to one of the seven ILAR categories. As JIA progresses, more joints may become affected. For some, where JIA was classified at onset as oligoarthritis, problems with five or more joints develop after 6 months and the JIA type is then described as extended oligoarthritis (EO). Similarly, the term polyarthritis applies to patients who at a particular point in time 6 months or more after the onset of disease (JIA of any onset type) have five or more active joints. In this case they are said to have polyarticular-course JIA. The concept of polyarticular-course JIA has been used for clinical trials and can typically include RF+ve and RF–ve polyarthritis, EO, ERA, PA and undifferentiated arthritis. Systemic JIA may also be included in the definition of polyarticular-course JIA providing that there have been no active systemic symptoms during the previous 6 months.[14]

Severity of disease and long-term outcome are variable both between different JIA subtypes and between different individuals with the same JIA subtype (*Box 1*). Analyses of historical cohorts of JIA patients (comprising a mix of JIA subtypes) have shown that > 50% of patients continued to have active disease for as long as 17 years after disease onset and such patients would require treatment into adulthood.[15,16] However, it should be noted that in historical studies the patients, particularly at disease onset, were unlikely to have been treated with methotrexate or biologic disease-modifying antirheumatic drugs (DMARDs), which were not available. Even when biologic DMARDs became available, they may not have been widely used. Consequently, for all types of JIA, outcomes in general are likely to have improved owing to more widespread use of the newer treatment strategies, particularly early in the disease course. Nevertheless, one-third or more of children will still require treatment for JIA in adult life. JIA that persists into adulthood is distinct from adulthood rheumatoid arthritis and should not be considered similar.

A recent systematic review of the prevalence and incidence of JIA in Europe[17] found that rates varied greatly among published studies. Incidence rates ranged from 1.6 to 23 per 100,000 (33 studies) and prevalence rates from 3.8 to 400 per 100,000 (29 studies). The estimated annual incidence of JIA in England in the period 1989–91 was 11 per 100,000.[18] Prevalence in the UK has not been estimated since 1959 when a figure of 65 per 100,000 was reported.[18] The Children's Chronic Arthritis Association website states that annual incidence is approximately 1 per 10,000 (i.e. 10 per 100,000) and prevalence is about 1 per 1000 (i.e. 1000 per 1,000,000).[19]

TABLE 1 Juvenile idiopathic arthritis classification according to the revised ILAR criteria

JIA classification[6] and features[7–12]	Included in NICE appraisal scope?
Oligoarthritis	
• The most common type of JIA accounting for > 50% of JIA cases in the UK[13] • Usually starts before 6 years of age and is more common in girls than boys • Affects four or fewer joints in the first 6 months, most commonly one or both knees and/or ankles, which are swollen and may be painful • Regular checks for chronic anterior uveitis (painless eye inflammation) required	
The ILAR classification recognises two subcategories:	
• Persistent oligoarthritis: affecting four or fewer joints throughout the disease course, accounts for about 48% of JIA cases in the UK[13]	No
• EO: affecting a total of more than four joints after the first 6 months of disease, accounts for about 6% of JIA cases in the UK[13]	Yes
Polyarthritis	
Polyarthritis (RF+ve): accounts for about 4% of cases in the UK[13]	Yes (all forms of polyarthritis)
Polyarthritis (RF–ve): accounts for about 21% of cases in the UK[13] • Polyarthritis is the second most common type of JIA, affecting about one in four children with arthritis • Usually starts either before 7 years of age or later in childhood • Causes painful swelling of five or more joints in multiple sites. The same joints on both sides of the body will often be affected • RF–ve is the most common form. The RF+ve subtype is more often seen in teenage girls • Associated with chronic uveitis (painless eye inflammation)	
ERA	
• Accounts for about 6% of JIA cases in the UK[13] • Affects the entheses (sites at which tendons attach to bones) often of lower limb and pelvic joints as well as the joints themselves (spine or peripheral joints) • Can affect girls and boys, although teenage-onset disease mainly affects boys • Associated with acute uveitis (red, painful eye)	Yes
PA	
• Accounts for about 7% of JIA cases in the UK[13] • Joint pain associated with the skin condition psoriasis (although the typical rash of psoriasis may not occur until many years after the onset of arthritis) or with a family history of psoriasis. Typically affects finger and toe joints • Usually starts around 6 years of age and is about twice as common in girls as in boys • Chronic anterior uveitis is fairly common	Yes
Systemic arthritis	
• Accounts for about 6% of JIA cases in the UK[13] • Usually starts before 5 years of age and affects boys and girls approximately equally • General illness with fever, tiredness, rash, loss of appetite and weight loss as well as joint pain. May also have enlarged glands, spleen and liver and, more rarely, pericarditis (inflammation of the sac surrounding the heart)	Not active systemic onset JIA alone. Those who go on to have a form of JIA that is included (e.g. polyarthritis) do match the remit
Undifferentiated arthritis	
• JIA that does not fit into any of the above categories or that has features of more than one type. Accounts for about 4% of JIA in the UK[13]	Yes

EO, extended oligoarthritis; NICE, National Institute for Health and Care Excellence.

BOX 1 Long-term outcomes for different subtypes of JIA

Long-term outcome[7–12]

Persistent oligoarthritis

- Often mild and may resolve with little or no lasting damage to joints; has the best outlook of all the types of JIA.
- Approximately half of children will have symptoms for at least 10 years, one-third or more of children will have arthritis continuing into adulthood.
- Chronic anterior uveitis may cause blindness or visual loss if not detected and treated early enough.

Extended oligoarthritis

- Causes damage to joints so early treatment to minimise this is needed.
- Can be destructive and disabling.
- Approximately half of children will have symptoms for at least 10 years, one-third or more of children will have arthritis continuing into adulthood.
- Chronic anterior uveitis may cause blindness or visual loss if not detected and treated early enough.

Polyarthritis

- Approximately half of children will have symptoms for at least 10 years and at least one-third of children will have arthritis continuing into adulthood (most likely to be of the RF+ve type, which is more severe and can require more aggressive treatment).
- Joints may become damaged if inflammation is not controlled, leading to the potential need for joint replacement or serious disability.

ERA

- May evolve to ankylosing spondylitis in the adult years (especially in those with teenage onset) and may require long-term disease-modifying or biologic agents.

PA

- Although there are few long-term data, disease course may be similar to chronic arthritis (either oligoarthritis or polyarthritis) and is likely to continue into adulthood.

Systemic-onset JIA

- One-third of children will have one or two episodes that settle with treatment, one-third will have relapses and need intermittent treatment and one-third will require ongoing treatment into adulthood and are at risk of joint damage.

Undifferentiated arthritis

- Although there are few long-term data, clinical advisors indicate that the long-term outcome is likely to depend on the predominant features of the arthritis and whether it is persistent oligoarthritis or polyarticular-course arthritis.

The sources of these data are not given; however, the same data are available in the Interim Clinical Commissioning Policy Statement for biological therapies for the treatment of JIA.[20] Based on the mid-2013 population estimates for those aged ≤ 17 years in England (approximately 11.5 million) and Wales (approximately 630,000),[21] these incidence and prevalence values equate to an estimated incidence of 1150 cases a year in England and 63 cases a year in Wales, with an estimated 11,500 and 630 children with JIA overall in England and Wales, respectively.

A 2012 conference presentation[13] presented data from a multicentre long-term prospective inception cohort study of children with newly diagnosed inflammatory arthritis (the Childhood Arthritis Prospective Study). This provides information on JIA subtypes classified using the ILAR criteria for 1014 newly diagnosed children [median disease duration 5.2 months; interquartile range (IQR) 2.5–10.9 months]. Among this cohort, EO and polyarticular-course JIA may be under-represented because median disease duration is < 6 months. Nevertheless, the proportions of each JIA subtype are similar to those reported by an older study[22] for a smaller group of children ($n = 521$), as shown in *Table 2*.

Table 2 also reports the distribution of JIA subtypes from a dataset (n=346 children and young people) drawn from the British Society for Paediatric and Adolescent Rheumatology (BSPAR) etanercept cohort and the Biologics for Children with Rheumatic Diseases cohort.[23] These data are for patients starting a first-line biologic DMARD from 1 January 2010 to 28 August 2014, and although a smaller cohort, is more up to date than the other two cohorts. There are some differences in the distribution of subtypes, with a lower proportion of patients with persistent oligoarthritis and a higher proportion with EO. This may be because the children and young people in this cohort had longer disease duration (mean disease duration 2 years) and therefore more may have progressed from persistent to extended oligoarthritis (i.e. a total of more than four joints affected after the first 6 months of disease). Persistent oligoarthritis may be under-represented as it is a milder form of JIA and generally may be adequately managed without biologic DMARDs.

In addition to the immediate impacts of the joint pain, swelling and limitation of movement that characterise JIA, there are longer-term problems and other issues that may arise over time. Progressive joint damage can lead to permanent disability and eventually to a need for joint replacement. A retrospective review of 154 adolescents (aged 16–21 years) found that 14% had undergone a joint operation, with 30 separate surgeries (e.g. synovectomies, reconstructive finger or toe joint operations and one hip

TABLE 2 Proportions of different subtypes of JIA

JIA classification[6]	Newly diagnosed children, % ($n = 1041$)[13]	From 17 centres within the UK, %	Children starting first-line antibiotics, %
Oligoarthritis			
Persistent oligoarthritis	48.2 (502/1041)	30.1 (157/521)	12 (40/346)
EO	5.5 (57/1041)	15.2 (79/521)	17 (59/346)
Polyarthritis			
RF+ve	3.6 (37/1041)	7.1 (37/521)	29 (102/346)
RF–ve	20.6 (214/1041)	19.6 (102/521)	8 (28/346)
ERA	5.6 (58/1041)	6.5 (34/521)	6 (20/346)
PA	7.0 (73/1041)	7.1 (37/521)	6 (20/346)
Systemic arthritis	6.0 (62/1041)	14.4 (75/521)	16 (54/346)
Undifferentiated arthritis	3.7 (38/1041)	NR	2 (8/346)
Not recorded	N/A	N/A	4 (15/346)

N/A, not applicable; NR, not reported.

replacement) having been undertaken.[24] Growth impairment affects about 10–20% of patients with JIA (mainly those with systemic or polyarticular JIA and who require high doses of glucocorticoids),[25] and decreased bone mass, which can lead to the development of osteoporosis, is also a recognised problem.[26]

Juvenile idiopathic arthritis is associated with a range of extra-articular manifestations, including uveitis, inflammatory bowel disease and psoriasis. Uveitis commonly occurs in children with oligoarthritis and is less common in other subtypes of JIA. It is characterised by inflammation of the middle layer of the eye, the uveal tract. In severe cases that do not respond to treatment, uveitis can be associated with complications such as cataract, glaucoma and macular oedema, and can lead to sight impairment and blindness. Inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis) is typically associated with ERA, whereas psoriasis is associated with PA.

The incidence of childhood uveitis in North America and Europe is estimated at 4.3–6 per 100,000 children and the prevalence at 30 per 100,000 children.[27] Between 20% and 25% of uveitis cases in children are associated with JIA. The prevalence of uveitis in JIA is between 8% and 30%, but in children with oligoarticular onset JIA it may be between 45% and 57%.[28] Uveitis in patients with JIA commonly occurs with the early onset of arthritis (mean age at onset 3–5 years). Presentation in younger children may be delayed owing to their inability to articulate symptoms. Screening for uveitis has therefore been implemented for children with JIA in England.[28] Complications are present in between 30% and 50% of children with JIA with uveitis at diagnosis. A total of 50–70% of children with severe uveitis will develop visual impairment.[29]

A recent systematic review of qualitative studies that explored the experiences of children living with JIA highlighted the profound effect that JIA has on children's lives. In particular, pain was a constant reminder of their disease and limited children's abilities to participate in normal life, including social events and schooling. Their physical limitations meant that they had to look for alternative activities and potential career options which they would be able to pursue. Many children and adolescents felt misunderstood and some kept their illness a secret from their peers and others.[30]

Measures of response to treatment and definition of remission

The aim of JIA treatment is to achieve clinical remission (complete absence of active disease). Aggressive early treatment aims to control inflammation and thus symptoms (e.g. joint pain); to decrease the number of actively affected joints in order to prevent joint damage, loss of function and disability; and to maintain or improve quality of life (QoL). Response to treatment is assessed in clinical trials by a validated core set of variables that were adopted by the American College of Rheumatology (ACR) in 1997. This definition of response is now known as the ACR Pediatric (ACR Pedi) definition of improvement.[31] The lowest level of improvement is known as ACR 30 (or ACR Pedi-30). The ACR Pedi-30 core variables are:

1. physician global assessment of disease activity (PGA) using a visual analogue scale (VAS) range from best score of 0 mm to worst score of 100 mm (although in some studies this was reported as 0–10 cm)
2. patient or parent global assessment of overall well-being using a VAS (range 0–100 mm, where 0 is the best score)
3. functional ability as measured by the patient or parent using the Childhood Health Assessment Questionnaire (CHAQ) (range 0–3, where 0 is the best score)
4. number of joints with active arthritis
5. number of joints with a limited range of motion
6. laboratory marker of inflammation [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level].

A response at the ACR Pedi-30 level is defined as an improvement in three of any six of the core variables by at least 30%, and a worsening of no more than one of the remaining variables by > 30%. In addition to the ACR Pedi-30, higher levels of response can also be defined: the ACR Pedi-50, -70, -90 and -100 levels of response require at least 50%, 70%, 90% or 100% improvement, respectively, in at least three of any six of the core set variables, with no more than one of the remaining variables worsening by > 30%.[14,32] It should be noted that according to expert advice, ACR Pedi-30 is no longer accepted as a response but is considered a non-response or inadequate response, with response levels of at least ACR Pedi-50 or -70 sought from a drug intervention.

More recently, in 2009, the Juvenile Arthritis Disease Activity Score (JADAS) was proposed and validated.[33] The JADAS is a composite score that can be quickly calculated because it is the arithmetic sum of the scores from the following four individual component measures:

1. PGA, measured on a 10-cm VAS (range 0 = no activity and 10 = maximum activity)
2. parent/patient global assessment of well-being, measured on a 10-cm VAS (range 0 = very well and 10 = very poor)
3. count of joints with active disease
4. ESR.

The component measures are also measures used in the ACR Pedi definition of improvement.[31]

The count of joints with active disease in the JADAS is primarily based on a 27-reduced joint count (JADAS-27, total score range 0–57), although scores based on a full 71-joint count (JADAS-71, total score range 0–101) and a 10-joint count (JADAS-10, total score range 0–40) have also been validated.[33] Further studies have shown that a 3-item JADAS that does not use ESR data is also a robust measure,[34,35] which is of particular benefit for children who do not need to provide a blood sample for routine medication monitoring. As the JADAS has become more widely used, further proposals have been made that would define low, medium and high disease activity[35,36] and define improvement.[37] With these definitions in place, the future management goal would be to achieve minimal disease activity for all children with JIA.[38]

Preliminary criteria to define clinical remission in oligoarticular (persistent and extended), RF+ve and RF–ve polyarticular and systemic JIA have also been developed.[39] Two levels of clinical remission have been proposed, namely clinical remission on medication and clinical medication off medication. The criteria for both types of clinical remission are based on achieving inactive disease, which is defined as:

- no joints with active arthritis
- no fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA
- no active uveitis
- normal ESR or CRP (or both normal if both tested)
- a PGA that indicates no disease activity.

Clinical remission on medication is then proposed to have been achieved if all the criteria for inactive disease have been met for a minimum of 6 continuous months while the patient is on medication. Clinical remission off medication is proposed to have been achieved if all the criteria for inactive disease have been met for a minimum of 12 continuous months while the patient is off all antiarthritis and antiuveitis medications.

Since the original publication of the preliminary criteria to define clinical remission,[39] validation of the criteria for defining clinical inactive disease in oligoarticular (persistent and extended), polyarticular (RF+ve and RF–ve) and systemic JIA has been undertaken. This has led to three changes: the addition of a definition for no active uveitis (as defined by the Standardization of Uveitis Nomenclature Working Group); clarification that the ESR or CRP level should be within the normal limits in the laboratory where tested or, if elevated, not attributable to JIA; and one additional criterion (duration of morning stiffness of 15 minutes or less).[40]

In addition to definitions of response to treatment and clinical remission, some publications also report on the outcome of disease flare (periods in which symptoms worsen). A preliminary definition based on the ACR Pedi-30 core response variables was obtained from a single small study ($n = 51$).[41] This preliminary definition was worsening in any two of six core response variables by 40% or more without concomitant improvement of more than one of the remaining core response variables by 30% or more. However, other studies have used different flare definitions (e.g. a worsening of $\geq 30\%$ in three of six ACR Pedi-30 variables).[42]

Current service provision

There is currently no National Institute for Health and Care Excellence (NICE) clinical guideline on the treatment of JIA; however, there are two pieces of NICE guidance:

1. *Guidance on the Use of Etanercept for the Treatment of Juvenile Idiopathic Arthritis* [NICE Technology Appraisal (TA)35][43] (this assessment report will inform an update of this guidance)
2. *Tocilizumab for the Treatment of Systemic Juvenile Idiopathic Arthritis* (NICE TA238)[44] (active systemic JIA is not included within this assessment report).

There are currently two interim commissioning statements: *Biologic Therapies for the Treatment of Juvenile Idiopathic Arthritis*[20] and the draft NHS Clinical Commissioning Policy for severe refractory uveitis in paediatric patients.[29] The first interim clinical commissioning policy statement was published (January 2015) by NHS England Clinical Reference Group for Paediatric Medicine[20] in the absence of NICE guidance for other biologic DMARDs and to cover more recent changes to the licensed indications to etanercept and is being consulted on. The purpose of the interim policy statement is to provide guidance for the use of biologic DMARDs in patients with JIA until the planned NICE guidance is published. The statement has a broader remit than the planned NICE guidance [Arthritis (juvenile idiopathic) – abatacept, adalimumab, etanercept and tocilizumab (including review of TA35)] as it includes all biologic DMARDs and all types of JIA (i.e. including persistent oligoarticular JIA and systemic JIA, which are not included in the NICE scope for the planned guidance). A summary of the key features of the drug treatment pathway is provided in *Table 3*.

TABLE 3 Overview of the drug treatment pathway for JIA

When/why and who	What	Notes
At diagnosis to induce disease remission, all patients	Corticosteroids: EITHER intra-articular to all affected joints OR systemic, preferably intravenous [owing to the side effects (e.g. effect on growth or increased risk of osteoporosis) of oral corticosteroids]	In patients with mild disease limited to fewer than five joints, intra-articular steroids may induce remission of > 6 months, particularly if the long-acting corticosteroid triamcinolone hexacetonide is used Patients with more severe disease may need intravenous steroids to induce remission, although intra-articular steroids are used in some patients as an alternative
To maintain remission, patients with arthritis affecting more than five joints or arthritis severely affecting crucial joints (e.g. spine, ankles, hips, wrists)	MTX	This accounts for around half of all children who develop JIA Effective in reducing the amount and severity or arthritis but only induces complete remission in 30–50% of patients
When JIA remains active despite optimal MTX dosing OR when patient is intolerant of MTX	Biologic DMARD (many given in coadministration with MTX to optimise their effect)	Estimated that one-third of all children who start treatment with MTX need to progress to a biologic DMARD

MTX, methotrexate.

Clinical advice to the authors of this assessment report (hereafter referred to as the assessment group) suggested that the interim statement largely reflects current practice. However, it was acknowledged that there would still be some variability across the country owing to differences in interpretation and limitation on access and prescribing.

According to the second interim clinical commissioning policy statement (the draft NHS Clinical Commissioning Policy for severe refractory uveitis in paediatric patients[29]), patients with JIA-associated uveitis may be managed initially with topical corticosteroids or systemic corticosteroids if required. In more severe cases, a DMARD can be used, with methotrexate being a standard treatment. If the disease is not controlled with DMARDs, the next line of treatment is use of a tumour necrosis factor (TNF) inhibitor (TNF-α is shown to be implicated in the pathogenesis of uveitis). TNF inhibitors include etanercept (Enbrel®, Pfizer), adalimumab (Humira®, AbbVie), infliximab (REMICADE®, Centocor Ortho Biotech Inc.), golimumab (SIMPONI®, Centocor Ortho Biotech Inc.) and certolizumab (Cimzia®, UCB Pharma S.A.), although the last two of these may not be easily available in the UK, and only etanercept and adalimumab are licensed for the treatment of JIA in children in Europe. For severe refractory uveitis in paediatric patients, the draft NHS Clinical Commissioning Policy states that etanercept is not suitable for use in JIA patients with uveitis or uveitis not associated with JIA.[29] Adalimumab is recommended where methotrexate does not control symptoms, with infliximab used in patients in whom adalimumab is not tolerated or not effective.[29]

Description of the technology under assessment

Four biologic DMARDs are within the scope of the NICE appraisal and are therefore included in this assessment report: abatacept [Orencia®, Bristol-Myers Squibb (BMS)], adalimumab, etanercept and tocilizumab (RoActemra®, Roche). The licensed indication differs across these interventions (e.g. in terms of the age range of children and young people eligible for treatment, the previous treatment that they should have received and the subtype of JIA) as summarised in *Table 4*. The *Interim Clinical Commissioning Policy Statement: Biologic Therapies for the Treatment of JIA*[20] provides a pragmatic estimate of 950 children with JIA in England who are currently receiving a biologic DMARD. This estimate is based on current data from the biologics databases in the UK which indicate that in England alone 890 children are receiving a biologic DMARD for JIA (most of which are NICE-approved biologic DMARDs). Clinical advice to the assessment group suggested that this figure may be an underestimate. An alternative estimate of 1500 was suggested by one clinician.

As noted earlier in *Current service provision,* the interim clinical commissioning policy indicates that the initial biologic DMARDs to be considered for use would be a TNF inhibitor, which for the purposes of this assessment would be either adalimumab or etanercept (however, etanercept is not suitable for use in JIA patients with uveitis). If a treatment switch was required, the second-line biologic DMARD would initially be the alternative TNF inhibitor (i.e. a switch from adalimumab to etanercept or vice versa). If a further switch was necessary, the third-line biologic would be either abatacept or tocilizumab, and the final switch possible would be to change abatacept to tocilizumab or vice versa. However, in terms of the marketing authorisations, the licence for abatacept indicates that there should have been a prior insufficient response to at least one TNF inhibitor. There is no such indication in the licence for tocilizumab.

The summary of product characteristics (SPC) for each biologic DMARD should be consulted for the specific contraindications, special warnings and precautions for use; however, there are some aspects that are common to all biologic DMARDs, which are summarised here.[45–48] These drugs block aspects of normal immune system signalling and, consequently, it is recommended that all patients receiving a biologic DMARD carry an alert card to indicate that they are at increased risk of developing a serious infection. Patients are at risk not only of typical bacterial and viral infections but also of opportunistic infections

TABLE 4 Summary of licensed indications of the biologic DMARDs under consideration in this assessment

Drug (chief mode of action)	Polyarthritis (polyarticular)[a]			ERA	PA	Systemic onset
	RF+ve	RF–ve	EO			
Abatacept (prevents T-cell activation)	Yes	Yes	Yes	–[b]	–	–
	With MTX. Patients ≥ 6 years of age with insufficient response to DMARDs including at least one TNF inhibitor					
Adalimumab (TNF inhibitor)	Yes	Yes	Yes	Yes	–	–
	With MTX unless not tolerated/not appropriate Patients ≥ 2 years of age, with inadequate response to 1 or more DMARDs			Patients ≥ 6 years of age with inadequate response, to or intolerant of, conventional therapy		
Etanercept (TNF inhibitor)	Yes	Yes	Yes	Yes	Yes	–
	Children and adolescents from 2 years of age with inadequate response to, or intolerant of, MTX			Adolescents from 12 years of age with inadequate response, or intolerant of, conventional therapy	Adolescents from 12 years of age with inadequate response, or intolerant of, MTX	
Tocilizumab (IL-6 inhibitor)	Yes	Yes	Yes	–	–	Yes
	With MTX unless not appropriate. Patients ≥ 2 years of age who have responded inadequately to previous treatment with MTX					With MTX unless not appropriate. Patients ≥ 2 years of age with inadequate response to NSAIDs and systemic corticosteroids

IL-6, interleukin 6; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs.

a Patients with active systemic onset JIA alone will not be addressed in this multiple technology appraisal. Patients with systemic onset JIA and a form of JIA that is included in the multiple technology appraisal (such as polyarthritis) will be addressed in this multiple technology appraisal. Where systemic onset arthritis, ERA and PA go on to have a polyarticular course, they could be interpreted as falling within the marketing authorisations for all four of the drugs.

b Dashes indicate that the drug is not licensed for this disease subtype.

including invasive fungal infections. Existing latent infections (e.g. latent hepatitis B, latent tuberculosis) could potentially reactivate. Consequently, if patients have an existing infection, treatment with a biologic DMARD is not recommended until the infection is treated. Patients should be screened for latent infections, and childhood vaccinations should be brought up to date prior to beginning therapy with a biologic DMARD.

The SPCs for each of the four biologic DMARDs included in the review do not explicitly specify license upper age limits for treatment. Clinical advisors have indicated that if adolescents are responding to treatment then this should be continued into adulthood as required. Furthermore, some JIA patients may need to restart a biologic DMARD in adulthood and some JIA patients may require a biologic DMARD for the first time in adulthood.

Abatacept

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular JIA in paediatric patients aged ≥ 6 years, who have had an insufficient response to other DMARDs including at least one TNF inhibitor.[45]

Abatacept is a fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese hamster ovary cells. It inhibits T-cell activation by specifically binding to cluster differentiation (CD)80 and CD86, thereby selectively inhibiting a costimulatory pathway that is required for full activation of T lymphocytes.[45,49] Through this mechanism, abatacept modulates the downstream T lymphocyte-dependent antibody responses and inflammation that cause the symptoms of JIA.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA at the appropriate dosage as indicated in *Table 5*. Abatacept is not recommended in combination with TNF inhibitors.[45]

Adalimumab

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular JIA in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Adalimumab can be given as monotherapy in the case of intolerance to methotrexate, or when continued methotrexate treatment is inappropriate. Adalimumab is also indicated for the treatment of active ERA in patients aged ≥ 6 years, who have had an inadequate response to, or who are intolerant of, conventional therapy.[46]

Adalimumab is a fully human monoclonal antibody drug initially tested as a treatment for rheumatoid arthritis (hence the trade name Humira – HUman Monoclonal antibody In Rheumatoid Arthritis). It binds specifically to the inflammatory cytokine TNF, thereby neutralising its biological function[46] and modifying the inflammatory disease process. The European Medicines Agency (EMA) therapeutic indication for adalimumab was extended to the treatment of JIA in July 2008.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA at the appropriate dosage as indicated in *Table 6*.[46] The concomitant administration of adalimumab with other biologic DMARDs [e.g. anakinra (Kineret®, Swedish Orphan Biovitrum) and abatacept] or other TNF antagonists is not recommended.[46]

TABLE 5 Dosing regimen for abatacept

Mode of administration and cost	Dose (children aged 6–17 years)		Notes
Intravenous infusion given over a period of 30 minutes Cost: powder for reconstitution, net price for a 250-mg vial = £302.40	Body weight < 75 kg	10 mg/kg, repeated at 2 weeks and 4 weeks after initial infusion, then every 4 weeks	Review treatment if no response within 6 months
	Body weight 75–100 kg	750 mg, repeated at 2 weeks and 4 weeks after initial infusion, then every 4 weeks	Dosing for patients weighing ≥ 75 kg follows the adult dosing regimen
	Body weight > 100 kg	1 g, repeated at 2 weeks and 4 weeks after initial infusion, then every 4 weeks	

TABLE 6 Dosing regimen for adalimumab

Mode of administration and cost	Dosage		Notes
Polyarticular JIA			
Subcutaneous injection given EOW (volume for injection is selected from a chart based on patient height and weight) Cost: net price for a 40-mg prefilled pen or prefilled syringe = £352.14; 40-mg/0.8-ml vial = £352.14	Patients aged 2 to < 4 years	24 mg/m^2 BSA up to a maximum single dose of 20 mg	A clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period Contraindicated in patients with moderate to severe heart failure (New York Heart Association class III/IV)
	Patients aged 4–12 years	24 mg/m^2 BSA up to a maximum single dose of 40 mg adalimumab	
	Patients aged ≥ 13 years	40 mg administered EOW regardless of body surface area	
ERA			
	Patients ≥ 6 years of age	24 mg/m^2 BSA up to a maximum single dose of 40 mg	No indication for stopping treatment is provided

BSA, body surface area; EOW, every other week.

Etanercept

Etanercept (Enbrel®, Pfizer) is a fully humanised soluble TNF receptor fusion protein produced by recombinant DNA technology in Chinese hamster ovary cells. It is a dimer with two copies of the extracellular domain of the TNF receptor (p75) linked with the Fc component of human immunoglobulin 1, binding to TNF-α.[50] The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell-surface TNF receptor, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g. cytokines, adhesion molecules or proteinases) that are induced or regulated by TNF.[47] The EMA therapeutic indication for etanercept in the treatment of JIA was extended in July 2012 to include:

- treatment of polyarthritis (RF+ve or RF–ve) and EO in children and adolescents aged ≥ 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate
- treatment of PA in adolescents aged ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate
- treatment of ERA in adolescents aged ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

The age for treating polyarticular disease has been reduced from 4 to 2 years of age and the upper age limit of 17 years has been removed.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA at the appropriate dosage as indicated in *Table 7*. The combined use of etanercept and anakinra or etanercept and abatacept is not recommended.

TABLE 7 Dosing regimen for etanercept

Mode of administration and cost	Dose for JIA	Notes
Subcutaneous injection Cost: net price of a 10-mg vial (with solvent) = £35.75 25-mg vial (with solvent) = £89.38 25-mg prefilled syringe = £89.38 50-mg prefilled pen or prefilled syringe = £178.75	0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly with an interval of 3–4 days between doses OR 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly	Consider discontinuation in patients who show no response after 4 months

Tocilizumab

Tocilizumab (RoActemra®, Roche) in combination with methotrexate is indicated for the treatment of juvenile idiopathic polyarthritis (RF+ve or RF–ve and EO) in patients ≥ 2 years of age who have responded inadequately to previous therapy with methotrexate. When the patient is intolerant to methotrexate or where continued treatment with methotrexate is inappropriate, tocilizumab can be given as monotherapy.[48] Tocilizumab is also indicated for the treatment of active systemic JIA but this indication is not included within the current NICE appraisal.

Tocilizumab is a humanised, monoclonal, antihuman interleukin-6 (IL-6) receptor (IL-6R) antibody that binds to membrane and soluble IL-6R, inhibiting IL-6-mediated signalling – a key cytokine in rheumatoid arthritis pathogenesis.[51] IL-6 is involved in causing inflammation and is found at high levels in patients with rheumatoid arthritis, systemic JIA and polyarticular JIA. By preventing IL-6 from attaching to its receptors, tocilizumab reduces the inflammation and other symptoms of these diseases.[48] The EMA was granted a licence for tocilizumab in the treatment of JIA in May 2011.

Treatment should be initiated by health-care professionals experienced in the diagnosis and treatment of JIA at the appropriate dosage as indicated in *Table 8*.

TABLE 8 Dosing regimen for tocilizumab

Mode of administration and cost	Dose for polyarticular JIA in patients over 2 years of age		Notes
Intravenous infusion over 1 hour Cost: net price for 4 ml (80-mg vial) = £102.40 10-ml (200-mg) vial = £256.00; 20-ml (400-mg vial) = £512.00	Body weight < 30 kg Body weight ≥ 30 kg	10 mg/kg once every 4 weeks 8 mg/kg once every 4 weeks	Dose interruptions (including discontinuation) are recommended for liver enzyme abnormalities, low absolute neutrophil count and low platelet count according to the tables provided in the SPC Clinical improvement is expected within 12 weeks of initiation of treatment. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this time frame

Chapter 2 Definition of the decision problem

Decision problem

In line with the scope of the NICE appraisal, the clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for the treatment of JIA will be assessed.

The comparators for this assessment are: DMARDs (such as methotrexate), if DMARDs can be tolerated; best supportive care, if DMARDs are not tolerated; biologic DMARDs (etanercept, abatacept, adalimumab and tocilizumab) compared with each other within their licensed indications where appropriate.

The relevant population are children and young people with JIA diagnosed at onset either as polyarthritis (RF+ve and RF–ve) or EO, and those with other forms of polyarticular-course arthritis (e.g. ERA, PA or undifferentiated arthritis). Children/young people with JIA and uveitis are also relevant. The age of the children/young people may vary by intervention owing to differences in the licensed indications.

As specified in the NICE scope, the following clinical effectiveness outcome measures are relevant to the decision problem: disease activity, disease flares, physical function, joint damage, pain, reduced use of corticosteroids; occurrence of extra-articular manifestations (such as uveitis), changes in body weight and height, mortality, adverse effects of treatment and health-related quality of life (HRQoL).

Overall aims and objectives of the assessment

The aim of this multiple technology appraisal (MTA) is to assess the clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating JIA.

The objectives are:

- to undertake systematic reviews of the clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for the treatment of JIA, and of the HRQoL of people with JIA
- to critique the company submissions (CSs) to NICE from AbbVie (adalimumab), BMS (abatacept), Pfizer (etanercept) and Roche (tocilizumab), and to identify the strengths and weaknesses of the respective submissions
- to conduct an economic evaluation to establish the cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for the treatment of JIA.

Patients with systemic onset JIA exhibiting typical systemic features, such as spiking fever and rash, are excluded from this MTA but if those features are no longer present (no active systemic symptoms during the previous 6 months) and the patients have gone on to have polyarticular-course JIA, they will be included. Similarly, patients with undifferentiated arthritis, ERA and PA that has a polyarticular course will also be included.

Chapter 3 Methods

Note

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

The a-priori methods for systematically reviewing the evidence of clinical effectiveness and cost-effectiveness are described in a research protocol published on the NICE website and registered with the PROSPERO international prospective register of systematic reviews database (registration number CRD42015016459). The protocol was sent to our expert advisory group (see *Acknowledgements*) for comment. Minor amendments were made as appropriate. None of the comments that were received identified specific problems with the methods of the review.

Identification of studies

Sensitive search strategies were developed and refined by an experienced information specialist. Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness and HRQoL.

The following databases were searched for published studies and ongoing research from inception to May 2015: The Cochrane Library, including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Centre for Reviews and Dissemination (University of York) Database of Abstracts of Reviews of Effects, the NHS Economic Evaluation Database and the Health Technology Assessment (HTA) database; MEDLINE (Ovid); EMBASE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded and Conference Proceedings Citation Index – Science (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); Zetoc (Mimas); National Institute for Health Research (NIHR)-Clinical Research Network Portfolio; Clinical Trials.gov; International Standard Randomised Clinical Trial Number; UK Clinical Trials Gateway; and World Health Organization International Clinical Trials Research Platform. In addition, PsycINFO (EBSCO*host*) was searched for HRQoL studies. Searches were not limited to particular trial designs and, although searches were not restricted by language, only full texts of English-language articles were retrieved during the study selection process. Cost-effectiveness and HRQoL searches were conducted from database inception to May 2015. References were downloaded into Reference Manager (Professional Edition Version 12, Thomson Reuters, New York, NY, USA) and deduplicated where necessary.

Bibliographies of included articles and systematic reviews were also searched. The CSs to NICE were searched for any additional studies that met the inclusion criteria (see *Chapter 4, Review of clinical effectiveness in company submissions to the National Institute for Health and Care Excellence* and *Chapter 5, Review of cost-effectiveness in company submissions to the National Institute for Health and Care Excellence*). Members of our advisory group were asked to identify additional published and unpublished evidence. Further details, including search dates for each database and an example search strategy, can be found in *Appendix 1*.

Inclusion and exclusion criteria

The following inclusion/exclusion criteria were applied to the clinical effectiveness review:

- Interventions: etanercept, abatacept (with or without methotrexate), adalimumab (with or without methotrexate) and tocilizumab (with or without methotrexate). Each drug was evaluated within its licensed indication. Studies of treatment without methotrexate were permitted if patients were intolerant to methotrexate or for patients for whom treatment with methotrexate is inappropriate.
- Comparators: DMARDs (such as methotrexate, which is the most common conventional treatment in the UK) if DMARDs can be tolerated and best supportive care if DMARDs are not tolerated. Etanercept, abatacept, adalimumab and tocilizumab compared with each other.
- Population: patients with JIA including:
    - polyarthritis (RF+ve, RF–ve and EO, both onset and course)
    - ERA
    - PA.

Studies of patients with systemic JIA were not included, as this was the subject of a separate NICE appraisal (NICE TA 238).[44]

- Outcomes: studies reporting one or more of the following outcomes were included:
    - disease activity
    - disease flares
    - physical function
    - joint damage
    - pain
    - corticosteroid reducing regimens
    - extra-articular manifestations (such as uveitis)
    - body weight and height
    - mortality
    - adverse effects of treatment
    - HRQoL.

- Study design: randomised controlled trials (RCTs). Non-randomised studies could be considered where RCT data were not available. Any relevant systematic reviews identified in the systematic review of clinical effectiveness were used as a source of references. Studies published as abstracts or conference presentations were only included if published from 2012 onwards and sufficient details were presented (or available elsewhere, e.g. in a full paper reporting on the same RCT) to allow an appraisal of the methodology and the assessment of results to be undertaken.

The inclusion/exclusion criteria for the cost-effectiveness and HRQoL studies are presented in *Chapter 5, Systematic review of cost-effectiveness evidence* and *Systematic review of health-related quality-of-life studies*, respectively.

Data extraction strategy

Reference screening

All studies were selected for inclusion through a two-stage process. Titles and abstracts were screened independently by two reviewers for potential eligibility, using a standardised and piloted eligibility selection worksheet (see *Appendix 2*) containing the inclusion/exclusion criteria detailed above.

Full-paper screening

Full texts for potentially relevant studies were obtained and screened using a standardised and piloted eligibility section worksheet (see *Appendix 3*) by one reviewer and checked by a second reviewer, and a final decision regarding inclusion was agreed. At each stage, any disagreements were resolved by discussion or with the involvement of a third reviewer when necessary.

Critical appraisal strategy

Clinical effectiveness studies were appraised using the Cochrane Risk of Bias criteria (e.g. selection bias, detection bias, performance bias, attrition bias and selective reporting bias).[52] Aspects of study quality, including statistical procedures, outcome measurement and generalisability, were also assessed.

A critical appraisal of the included clinical effectiveness and cost-effectiveness studies (*Chapter 5, Systematic review of cost-effectiveness evidence*) was conducted by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus or in consultation with a third reviewer where necessary.

Method of data synthesis

Details of the trial outcomes in the clinical effectiveness review were synthesised through narrative review with tabulation of the results of included studies. Quantitative pooling of outcomes across clinical effectiveness studies in a meta-analysis was not possible as the identified evidence included only one trial per biologic DMARD, all of which used placebo as the comparator. It was not considered appropriate to meta-analyse the four biologic DMARDs together owing to clinical heterogeneity.

An adjusted indirect comparison of the four biologic DMARDs was performed using the method described by Bucher and colleagues.[53] An indirect comparison refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions. A distinction is often made between adjusted and naive (unadjusted) indirect comparisons. In the adjusted indirect comparison, the comparison of the interventions of interest is adjusted by preserving the strength of randomisation. Unadjusted indirect comparisons are considered to be observational evidence and are, therefore, not recommended.[54,55]

Chapter 4 Clinical effectiveness

Results

Quantity and quality of available research

Titles and, where available, abstracts of a total of 2651 references identified by searches (after deduplication) were screened and full copies of 60 references were retrieved. Of these, 29 articles were excluded after inspection of the full text as shown in *Figure 1* and these are listed in *Appendix 4*. The most common reason for exclusion of a reference was an irrelevant study design (e.g. systematic reviews, which were used as a source of references, commentaries). One full text[56] was of unclear relevance to the review because the type of JIA was not stated and it was not clear whether or not participants met the licensed indication for etanercept therapy in respect of having an inadequate response or intolerance to methotrexate. One full paper and eight conference abstracts relating to four ongoing studies that seemed to be relevant were tagged for inclusion in *Ongoing trials* (note that a further three ongoing studies were identified from a separate search specifically undertaken for ongoing studies, which is not represented in *Figure 1*; therefore, a total of seven ongoing studies are summarised in *Ongoing trials*).

Nine full texts and 12 conference abstracts described four RCTs (each of which was described by at least one full paper) that met the inclusion criteria of the review (see *Figure 1*). As the full texts provided the most complete data, these were the primary source of information for this review.

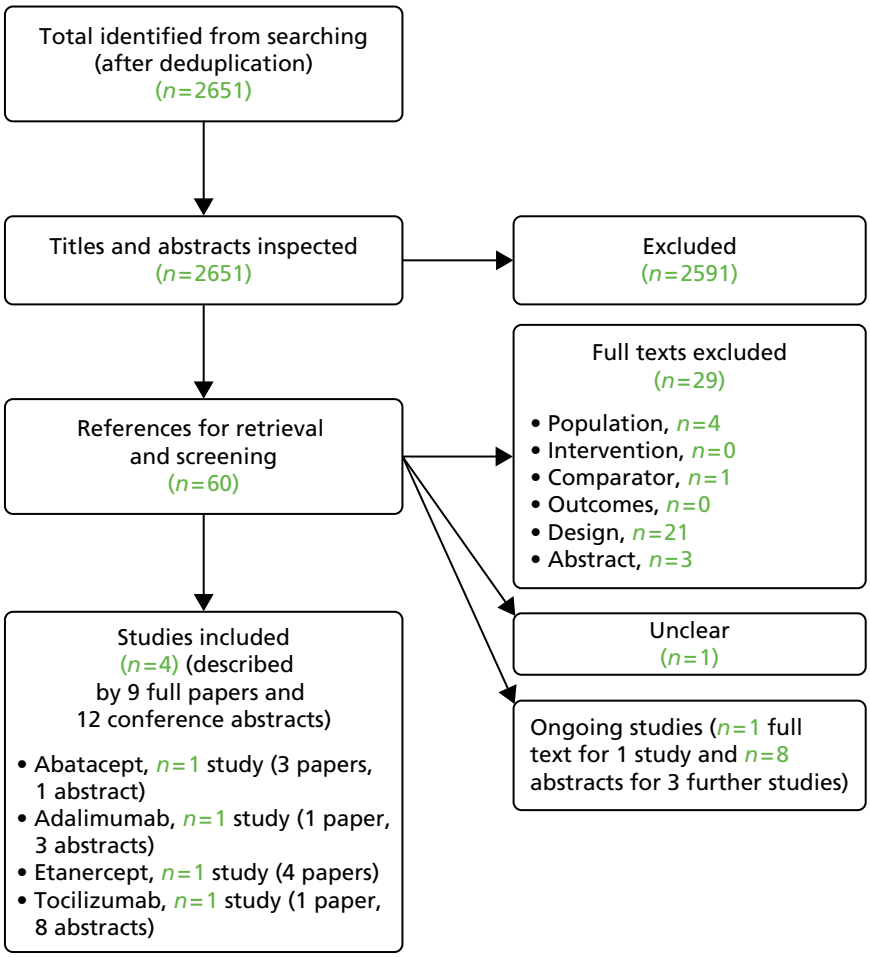

FIGURE 1 Flow chart for the identification of studies.

One of the RCTs evaluated abatacept[57–60] [the AWAKEN (Abatacept Withdrawal study to Assess efficacy and safety in Key Endpoints) trial], one RCT, by Lovell and colleagues, evaluated adalimumab,[61–64] one RCT evaluated etanercept (Lovell *et al.*[42,65–67]) and one RCT evaluated tocilizumab[68–76] (the CHERISH trial). For the sake of brevity, generally only the key reference for each RCT is cited in the main text of this report. All four RCTs used placebo as the comparator; however, with the exception of the etanercept trial, the majority of the patients in the trials received methotrexate in addition to the biologic DMARD or placebo. The key characteristics of the trials are presented in *Table 9*, with the primary and secondary outcomes measured in trials summarised in *Table 10*. All studies were multicentre RCTs, with the number of centres ranging from 9 in the etanercept study[42] to 58 in the tocilizumab study.[68] Locations of the studies included the USA (all four studies), Canada (one study[42]), Europe (three studies,[57,61,68] with only the tocilizumab study[68] including UK centres), Latin America (two studies[57,68]), Australia (one study[68]) and the Russian Federation (one study[68]). In each study, participants were initially treated in an open-label phase with the

TABLE 9 Summary characteristics of included studies

Characteristic	Abatacept	Adalimumab	Etanercept	Tocilizumab
Study details	AWAKEN, Ruperto *et al.* (2008),[57] Ruperto *et al.* (2010),[58] Ruperto *et al.* (2010),[59] Lovell *et al.* (2012)[60] Multicentre withdrawal RCT at 45 centres in Europe (not UK), Latin America and the USA	Lovell *et al.* (2008),[61] Lovell *et al.* (2012),[62] Ruperto *et al.* (2013),[63] Ruperto *et al.* (2014)[64] Multicentre withdrawal RCT at 31 centres in Europe (not UK) and the USA	Lovell *et al.* (2000),[42] Lovell *et al.* (2003),[65] Lovell *et al.* (2006),[66] Lovell *et al.* (2008)[67] Multicentre withdrawal RCT at nine centres in Canada and the USA	CHERISH, Brunner *et al.* (2015),[68] Brunner *et al.* (2014),[69] Baildam *et al.* (2014),[70] Brunner *et al.* (2013),[71] De Benedetti *et al.* (2013),[72] Baildam *et al.* (2013),[73] De Benedetti *et al.* (2013),[74] Brunner *et al.* (2012),[75] Bharucha *et al.* (2014)[76] Multicentre withdrawal RCT at 58 centres in Australia, Europe (including the UK), Latin America, Russia and the USA
Study phases[a]	16-week open-label lead-in **24-week randomised double-blind withdrawal** OLE	16-week randomised open-label **32-week randomised double-blind withdrawal** OLE	12-week open-label **16-week randomised double-blind withdrawal** OLE	16-week open-label lead-in **24-week randomised double-blind withdrawal** OLE
Intervention[b]	Abatacept: $n = 60$ Abatacept 10 mg/kg at about 28-day intervals for 24 weeks or until disease flare	Adalimumab: $n = 38$ Adalimumab 24 mg/m^2 of BSA (to maximum of 40 mg) EOW for 32 weeks	Etanercept: $n = 25$ Etanercept 0.4 mg/kg twice weekly until disease flare or for 16 weeks	Tocilizumab: $n = 82$ 10 mg/kg < 30 kg body weight, $n = 16$ 8 mg/kg < 30 kg body weight, $n = 11$ 8 mg/kg ≥ 30 kg body weight, $n = 55$
Comparator[b]	Placebo: $n = 62$	Placebo: $n = 37$ Placebo ≥ 10 mg/m^2 BSA/week	Placebo: $n = 26$	Placebo: $n = 84$ 10 mg/kg < 30 kg body weight, $n = 15$ 8 mg/kg < 30 kg body weight, $n = 13$ 8 mg/kg ≥ 30 kg body weight, $n = 56$

TABLE 9 Summary characteristics of included studies (*continued*)

Characteristic	Abatacept	Adalimumab	Etanercept	Tocilizumab
Key inclusion criteria	Age 6–17 years Active[c] JIA (extended oligoarticular, polyarticular, RF+ve or RF–ve, systemic without systemic manifestations) Inadequate response or intolerance to ≥ 1 DMARD including biologic agents ACR Pedi-30 for entry to randomised double-blind phase	Age 4–17 years Active[c] polyarticular-course JIA (any onset type) Inadequate response to NSAIDs ACR Pedi-30 at week 16 for entry to double-blind withdrawal phase	Age 4–17 years Active[c] JIA Inadequate response to NSAIDs and methotrexate at doses of ≤ 10 mg/m^2 BSA/week	Age 2–17 years Active[c] polyarticular-course or extended oligoarticular JIA (RF+ve or RF–ve) for ≥ 6 months Inadequate responses to or intolerant of methotrexate. Either never treated with biologics or use discontinued for a specified minimum period

BSA, body surface area; EOW, every other week; NSAIDs, non-steroidal anti-inflammatory drugs; OLE, open-label extension.
a The key phase of interest for efficacy outcomes is in bold text with lengths of phases reported in weeks for all studies for ease of comparison.
b During randomised double-blind withdrawal phase.
c Inclusion criteria for active disease were very similar for the adalimumab, etanercept and tocilizumab studies (key aspects were at least five swollen joints and at least three joints with a limitation of motion). The abatacept study required at least five active joints (with swelling or limitation of motion accompanied by pain or tenderness) and active disease (at least two active joints and two joints with a limitation of motion).

TABLE 10 Summary of outcomes measured

Parameter	Abatacept	Adalimumab	Etanercept	Tocilizumab
Primary outcome	Time to disease flare	Proportion of participants not receiving methotrexate with disease flares (weeks 16–48)	Number of patients with disease flare	Proportion of patients in whom a JIA flare occurred during part 2 (up to and including week 40) compared with week 16
Secondary outcomes	Proportion of patients at end of 6-month double-blind phase who had disease flare	AEs	Not specifically stated (ACR core variables, mortality and AEs among others reported)	JIA–ACR Pedi-30, -50, -70, -90 responses (week 40)
	Changes from baseline in ACR core variables			Change from baseline in ACR core response variables (week 40)
	Pain			Clinically inactive disease (week 40)
	Assessment of safety and tolerability			
	HRQoL			

AE, adverse event.

biologic DMARD under investigation and had to achieve at least an ACR Pedi-30 response to the biologic DMARD to be eligible for entry to the randomised double-blind withdrawal phase, with the number of participants randomised ranging from 51 in the etanercept study to 166 in the tocilizumab study. As each study investigated a different biologic DMARD, study-specific details are provided below by study drug.

Abatacept

The abatacept RCT[57] was funded by BMS and consisted of three phases: a 4-month open-label lead-in phase (days 1–113); a 6-month double-blind randomised withdrawal phase (days 114–283); and an open-label extension (OLE) phase [up to day 1681 (5.5 years) for efficacy and up to 7 years for safety]. Enrolled participants all received abatacept intravenously (10 mg/kg to a maximum of 1000 mg) and were permitted to continue to take stable methotrexate during the 4-month lead-in phase. Those achieving an ACR Pedi-30 response were then eligible to be randomised in a 1 : 1 ratio to continued abatacept ($n = 60$) or placebo ($n = 62$). In the 6-month randomised withdrawal phase, abatacept was given at randomisation and at about 28-day intervals (see *Table 9*).

Patients were eligible for the trial if they were aged 6–17 years and had EO, polyarticular (RF+ve or RF–ve) or systemic JIA without systemic manifestations.

Participants were required to have at least five active joints (defined as swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness), active disease (defined as at least two active joints and two joints with a limited range of motion) and an inadequate response to, or intolerance of, at least one DMARD, which could include biologic agents (e.g. etanercept, infliximab and adalimumab). Exclusion criteria included active uveitis, any major concurrent medical conditions and pregnancy or lactation.

The primary outcome measure was time to disease flare during the double-blind period. Disease flare was defined in three ways depending on the measure used: worsening of $\geq 30\%$ in at least three of the six ACR core-response variables for JIA, and at least 30% improvement in no more than one variable during the double-blind period; a worsening of ≥ 20 mm on the 100-mm VAS if a global assessment by either a physician or a parent was used; worsening in two or more joints if the number of active joints or joints with limited range of motion was used. Clinical assessments preceded drug administration at each visit. Secondary outcomes included the proportion of patients at the end of the 6-month double-blind phase who had disease flare, changes from baseline in each of the six ACR core variables, pain, assessment of safety and tolerability and HRQoL.

Adalimumab

The Lovell and colleagues RCT[61] was funded by a research grant from Abbott Laboratories and consisted of three phases: a 16-week randomised open-label phase, a 32-week randomised double-blind withdrawal phase and an OLE phase. Enrolled participants all received adalimumab subcutaneously (24 mg/m^2 of body surface area, to a maximum of 40 mg) every other week and methotrexate (at least 10 mg/m^2 of body surface area per week) during the 4-month lead-in phase. Those achieving an ACR Pedi-30 response were then eligible to be randomised in a 1 : 1 ratio to continued adalimumab plus methotrexate ($n = 38$) or placebo plus methotrexate ($n = 37$) (see *Table 9*). The trial included two further study arms (adalimumab only and placebo only), but because the majority of participants in these arms had never received methotrexate, they did not meet the licensed indication and are not included in this report.

Patients were eligible for the trial if they were aged 4–17 years and had polyarticular-course JIA of any onset type. If systemic onset, then patients had to be free of any systemic JIA manifestations for at least 3 months prior to study qualification.[77] Participants were required to have active disease (defined as five or more swollen joints and three or more joints with a limited range of motion), to have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs), and to have neither previously been treated with methotrexate nor, if previously treated with methotrexate, have had adverse events (AEs) or an inadequate response. Exclusion criteria included clinically significant deviations in haematological, hepatic or renal indicators;

ongoing infection or a recent major infection that had required hospitalisation or intravenous antibiotics; and recent receipt of live or attenuated vaccines. Patients who had previously been treated with other biologic agents at any time or who had received recent treatment with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs (other than methotrexate) or corticosteroids administered by intra-articular, intramuscular or intravenous routes were also excluded from participation.

The primary outcome for the study (percentage of participants not receiving methotrexate who had a disease flare during the double-blind period) related to the two study arms that, as noted above, do not meet the licensed indication and are therefore not included in this report. Disease flare was reported for the two study arms relevant to this assessment and it was defined in different ways depending on the measure used: worsening of $\geq 30\%$ in at least three of the six core criteria for JIA and at least 30% improvement in no more than one of the criteria during the double-blind period; an increase of $> 30\%$ on the 0–100mm VAS if a global assessment was used; an increase in the number of active joints to at least two when the patient had none or only one if the number of active joints was used, with the same approach used for defining flare using joints with loss of motion. Outcomes were assessed every 12 weeks. The occurrence of AEs was a secondary outcome.

Etanercept

The Lovell and colleagues RCT[42,65–67] was funded by the Immunex Corporation and consisted of three phases: an open-label lead-in phase of up to 3 months; a 4-month double-blind randomised withdrawal phase; and an OLE phase. All enrolled participants received etanercept subcutaneously (0.4 mg/kg twice weekly) during the 4-month lead-in phase. Those who improved and achieved an ACR Pedi-30 response were then eligible to be randomised to continue to receive etanercept ($n = 25$) or placebo ($n = 26$) during the withdrawal phase (see *Table 9*).

Patients were eligible for the trial if they were aged 4–17 years and had active polyarticular JIA despite treatment with NSAIDs and methotrexate doses of at least 10 mg/m^2 of body surface area per week. Active disease was defined as at least five swollen joints and at least three joints with limited motion with pain, tenderness or both. Exclusion criteria included any major concurrent medical conditions and pregnancy or lactation.

The primary outcome measure was the number of patients with disease flare during the double-blind withdrawal period. Disease flare was defined depending on the measure used: worsening of $\geq 30\%$ in at least three of the six ACR core-response variables for JIA, at least 30% improvement in no more than one variable and a minimum of two active joints; a change of at least two units on a scale from 0 to 10 if a global assessment was used. Clinical assessments during the withdrawal phase took place on day 1, day 15 and at the end of each month. Secondary outcomes were not specifically listed.

Tocilizumab

The tocilizumab RCT[68] consisted of three phases: a 16-week open-label lead-in phase; a double-blind randomised withdrawal phase (weeks 16–40); and an OLE phase (64 weeks). Some funding for manuscript preparation was provided by F. Hoffmann-La Roche Ltd.

Enrolled participants were permitted to receive methotrexate and all received tocilizumab intravenously (three groups). Those with a body weight of < 30 kg were randomised to either 10 mg/kg or 8 mg/kg every 4 weeks. Those with a body weight of 30 kg or more received 8 mg/kg every 4 weeks during the 16-week lead-in phase. Those achieving an ACR Pedi-30 response were then eligible to be randomised in a 1 : 1 ratio to continue tocilizumab ($n = 82$) or placebo ($n = 84$), given every 4 weeks until week 40 unless they experienced disease flare (see *Table 9*).

Patients were eligible for the trial if they were aged 2–17 years and had polyarticular-course or EO JIA that was either RF+ve or RF–ve for 6 months or more. Systemic JIA or any other categories of JIA were excluded from the trial.[78] Participants were required to have at least five active joints with a limited range

of motion in at least three active joints and have an inadequate response, or intolerance, to methotrexate. If participants were taking methotrexate (10–20 mg/m^2) or low-dose oral glucocorticoids ($\leq$ 0.2 mg/kg/day, daily maximum 10 mg), the dose had to have been stable for 8 weeks or more (for methotrexate) or 4 weeks or more (for oral glucocorticoids). Patients had to be treatment-naive for biologics or had to have discontinued use for a specified minimum period. No other exclusion criteria were specified.

The primary outcome measure was the proportion of participants with disease flare during the double-blind period (up to and including week 40 compared with week 16). Disease flare was defined as worsening of $\geq$ 30% in at least three of the six ACR core-response variables for JIA and at least 30% improvement in no more than one variable during the double-blind period. Outcomes were assessed every 4 weeks. Secondary outcomes included the ACR Pedi-30, -50, -70, -90 responses, the change from baseline in JIA core response variables and clinically inactive disease (PGA indicating no disease activity plus the absence of all the following: joints with active arthritis, uveitis and ESR of > 20 mm/hour).

Overview of the participants in the withdrawal phases of the included studies

For three of the four trials (abatacept,[57] adalimumab[61] and etanercept[42]) baseline characteristics are provided for the participants who had achieved an ACR Pedi-30 response and who were randomised to the double-blind withdrawal phase of each trial. The tocilizumab trial publication,[68] however, presented participant baseline characteristics for participants as randomised to the initial open-label lead-in phase, where three groups of participants all received the study drug (if body weight was < 30 kg then participants were randomised to either 10 mg/kg or 8 mg/kg every 4 weeks; if body weight was $\geq$ 30 kg then participants received 8 mg/kg every 4 weeks). Selected baseline characteristics are presented in *Table 11*, with the full set of characteristics available in the data extraction forms (see *Appendix 5*). The mean age of trial participants reflected the differing entry criteria for the trials. Participants in the abatacept trial[57] (participants aged 6–17 years were eligible) had the highest mean age (12–13 years), whereas those in the adalimumab[61] and etanercept trials[42] (eligible ages were 4–17 years) had a slightly lower mean age (approximately 9–12 years) which was similar to those enrolled in the open-label phase of the tocilizumab study[68] (eligible ages 2–17 years; mean age approximately 11 years). The majority of participants in all four studies were female (ranging from 67% in the etanercept study[42] to 80% in the adalimumab study[61]) and of white ethnicity (73% in the etanercept study[42] to 96% in the adalimumab study[61]). The proportion of patients across the subtypes of JIA were reported for only two of the trials (abatacept[57] and etanercept[42]). In these two trials polyarthritis was the predominant subtype. In the abatacept trial just under 20% of patients had systemic JIA (without systemic manifestations),[57] whereas in the etanercept trial around one-third had systemic JIA (with apparent systemic manifestations: spiking fever and rheumatoid rash).[42] The proportion of participants who were RF+ve ranged from 22% in the adalimumab study[61] to 29% in the tocilizumab study,[68] and the duration of JIA from just under 4 years in the abatacept study[57] to approximately 6 years in the etanercept study.[42]

The treatment groups in the abatacept study[57] appear similar on most variables, although the placebo group had a smaller proportion of RF+ve patients than the abatacept group (19% vs. 32%). The adalimumab study report[61] indicated that there were no significant differences in baseline characteristics between the placebo and adalimumab groups. Groups were described as well balanced in the etanercept study[42] with the exceptions of age group (4–8 years: 52% etanercept vs. 19% placebo; $p < 0.02$), ethnicity (white ethnicity: 56% etanercept vs. 88% placebo; $p < 0.02$) and corticosteroid use (corticosteroid use at wash out: etanercept 24% vs. 50% placebo; $p = 0.05$). The tocilizumab study did not report baseline characteristics for those participants who entered the double-blind wash-out phase of this study.

TABLE 11 Selected baseline characteristics of trial participants

	Abatacept[57]		Adalimumab[61]		Etanercept[42]		Tocilizumab[68]		
Baseline characteristics	**Abatacept ($n = 60$)**	**Placebo ($n = 62$)**	**Adalimumab ($n = 38$)**	**Placebo ($n = 37$)**	**Etanercept ($n = 25$)**	**Placebo ($n = 26$)**	**TCZ 8 mg/kg < 30 kg ($n = 34$)[a]**	**TCZ 10 mg/kg < 30 kg ($n = 35$)[a]**	**TCZ 10 mg/kg ≥ 30 kg ($n = 119$)[a]**
Age (years), mean (SD)	12.6 (3)	12.0 (3)	11.7 (3.3)	10.8 (3.4)	8.9	12.2	*7.6 (2.71)*	*6.9 (3.02)*	*13.1 (2.78)*
Sex female, *n* (%)	43 (72)	45 (73)	30 (79)	30 (81)	19 (76)	15 (58)	*24 (71)*	*30 (86)*	*90 (76)*
Ethnicity, *n* (%)									
White	46 (77)	49 (79)	36 (95)	36 (97)	14 (56)	23 (88)	NR		
Black	5 (8)	4 (7)	0	0	3 (12)	1 (4)			
Hispanic	NR	NR	NR	NR	6 (24)	2 (8)			
Other	9 (15)	9 (15)	2 (5)	1 (3)	2 (8)	0			
Type of JIA, *n* (%)									
Pauciarticular[b]					2 (8)	1 (4)	Eligible patients had RF+ve or RF–ve polyarticular-course JIA or EO JIA but no further detail is provided		
Persistent oligoarthritis	0	2 (3)	Described as 'polyarticular course' but with no further detail (this older nomenclature could have included patients who would now be defined as having ERA or PA)						
EO	9 (15)	7 (11)							
Polyarthritis (RF+ve)	14 (23)	12 (19)			14 (56)	17 (65)			
Polyarthritis (RF–ve)	26 (43)	28 (45)							
Systemic	11 (18)[c]	12 (19)[c]			9 (36)	8 (31)			
RF+ve, *n* (%)	19 (32)	12 (19)	10/37 (27)[d]	6/36 (17)[d]	4 (16)	8 (31)	*2 (6)*	*4 (11)*	*48 (40)*
Duration of JIA (years), mean (SD)	3.8 (3.7)	3.9 (3.5)	4.3 (4.1)	4.0 (3.5)	5.3	6.4	*3.5 (2.57)*	*3.4 (2.39)*	*4.7 (4.16)*

NR, not reported; SD, standard deviation; TCZ, tocilizumab.

a Baseline data in italics for the tocilizumab study were presented only for all patients randomised to the initial open lead-in phase of the study. Of these participants, 15/188 (7.9%) did not achieve an ACR Pedi-30 response and were not randomised to the double-blind withdrawal phase of the study.

b Pauciarticular-course arthritis would now be called oligoarticular arthritis. It is not clear from the paper whether these participants had persistent oligoarthritis or EO.

c Systemic without systemic manifestations.

d Calculated by reviewer.

Assessment of the risk of bias of included studies

The Cochrane risk of bias criteria[52] focus on various aspects of study design, conduct and reporting which may help to gauge the internal validity (whether or not the study answered the research question in a manner that was free from bias) of the individual studies. The risk of bias in the included trials is summarised in *Table 12* and further details are presented in the data extraction tables (see *Appendix 5*).

Only the abatacept trial[57] reported sufficient details of the methods for generating the random sequence (computer generated) and allocation concealment (interactive voice-randomisation system) to establish that there was a low risk of selection bias in this trial. In the three other trials (adalimumab,[61] etanercept[42] and tocilizumab[68]) the risk of selection bias associated with randomisation and allocation were unclear because either no details were reported or there was insufficient information to make a judgement. The randomised withdrawal phases of all four trials were described as double-blind with three of the trials providing some information to support this statement (e.g. placebo identical in appearance,[57] indication of who was unaware of treatment assignment[42,61]). The risk of performance bias and detection bias was judged to be low for all four trials. Attrition bias (systematic differences in withdrawals between trial arms) was judged to be low for all outcomes in three trials[42,61,68] (either because attrition was similar between groups or because incomplete data were addressed). In the abatacept trial,[57] however, a larger proportion of patients dropped out of the placebo group in the double-blind phase (placebo 50%, abatacept 18%), with the main reason being a lack of efficacy.

Although this was addressed for some outcomes (e.g. analysis of ACR variables), it was not addressed for HRQoL, where the analysis was based on available data at each time point, hence the risk of attrition bias is high for this outcome. Selective reporting bias was judged to be low for all the trials, as all outcomes were reported on. The only other uncertainty surrounding study biases was the risk of bias attributable to intercentre variability, which was not discussed in the adalimumab,[61] etanercept[42] and tocilizumab[68] trials. In contrast, the abatacept study[57] reported that training was in place for joint assessors from each centre who had specific and standardised joint assessment training.

TABLE 12 Summary of risk-of-bias assessment

Criteria	Abatacept	Adalimumab[61]	Etanercept[42]	Tocilizumab[68]
Selection bias				
Random sequence generation	Yes	Unclear	Unclear	Unclear
Allocation concealment	Yes	Unclear	Unclear	Unclear
Performance bias				
Blinding of participants and personnel	Yes	Yes	Yes	Yes
Detection bias				
Blinding of outcome assessment	Yes	Yes	Yes	Yes
Attrition bias *Incomplete outcome data addressed*				
Non-HRQoL outcomes	Yes	Yes	Yes	Yes
HRQoL outcome	No	N/A	N/A	N/A
Reporting bias				
Selective reporting	Yes	Yes	Yes	Yes
Other bias				
Other sources	Unclear	Unclear	Unclear	Unclear

N/A, not applicable; no, high risk of bias; unclear, uncertain risk of bias; yes, low risk of bias.

Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus placebo (with methotrexate where permitted)

Disease flare

The primary outcome for all four trials was disease flare, although there were some differences in the ways in which this outcome was reported. Data on disease flare from the trials contribute to the economic model in this assessment report (see *Chapter 5, Data sources*). The definitions for disease flare were broadly consistent between the studies (a worsening of at least 30% in three or more of the six core criteria for JIA and an improvement of ≥ 30% in no more than one of the criteria), with some studies also including flare definitions based on global assessments and the number of active joints. In all four studies, there were statistically significantly fewer arthritis flares in patients being treated with biologic DMARDs than in those patients receiving placebo, and in the three studies that reported time to disease flare this was statistically significantly longer in patients being treated with biologic DMARDs than in those receiving placebo (*Table 13*).

In the abatacept study,[57] by the end of the RCT period, disease flare had occurred in 20% of patients receiving the study drug compared with 53% of patients receiving placebo ($p = 0.0003$). Median time to disease flare was 6 months for the placebo group and this was statistically significantly greater than in the

TABLE 13 Disease flare during the randomised withdrawal phase

Study (length: open-label, RCT[a]), outcome	Intervention	Comparator	Statistical significance
Abatacept[57] (4-month open-label, 6-month RCT)	***ABA (n = 60)***	***PBO (n = 62)***	**p-*value***
Time to flare (months), median	Not reached	6	0.0002
Disease flares, *n* (%)	12 (20)	33 (53)	0.0003
Disease flares, hazard ratio	0.31 (95% CI 0.16 to 0.59)		NR
Adalimumab[61] (4-month open-label, 8-month RCT)	***ADA (n = 38)***	***PBO (n = 37)***	**p-*value***
Disease flares, *n/N* (%)	14/38 (37)	24/37 (65)	0.02
Time to onset of disease flare (weeks)	> 32	≈ 20	0.03
Etanercept[42] (3-month open-label, 8-month RCT)	***ETA (n = 25)***	***PBO (n = 26)***	**p-*value***
Disease flare, *n* (%)	7 (28)	21 (81)	0.0031[b]
Corticosteroid use at baseline[c]			0.05
Yes	3/6 (50)	12/13 (92)	
No	4/19 (21)	9/13 (69)	
Time to flare (days), median	> 116	28	< 0.001
Tocilizumab[68] (4-month open-label, 6-month RCTs)	***TCZ (n = 82)***	***PBO (n = 81)[d]***	***Difference[e] TCZ vs. PBO (95% CI);* p-*value***
Proportion with JIA flare, *n* (%)	21 (25.6)	39 (48.1)	–0.21 (–0.35 to –0.08); 0.0024

ABA, abatacept; ADA, adalimumab; CI, confidence interval; ETA, etanercept; NR, not reported; PBO, placebo; TCZ, tocilizumab.
a For ease of comparison, lengths of open-label and RCT phases are presented as time in months (where originally presented in weeks, the value has been divided by 4; where originally presented in days, the value has been divided by 28).
b $p < 0.001$ after adjustment for baseline characteristics in logistic regression model.
c Authors state that with the exception of corticosteroid use at baseline ($p = 0.05$), none of the baseline characteristics was a significant predictor of flare rates ($p > 0.15$).
d Of the 84 participants who achieved at least ACR Pedi-30 and were then randomised to placebo, three discontinued (one owing to an insufficient therapeutic response and two owing to AEs). These three did not receive any study drug in the randomised part of the study and so were excluded from the analyses.
e Adjusted for baseline stratification factors (background use of methotrexate and oral glucocorticoids).

abatacept group ($p = 0.0002$), but the authors state that insufficient events occurred in the abatacept group for this to be assessed. The risk of disease flare in patients randomised to continued abatacept during the RCT phase was just under one-third of that for those receiving placebo [hazard ratio 0.31, 95% confidence interval (CI) 0.16 to 0.95; no *p*-value reported].

Disease flare occurred in 37% of patients receiving adalimumab[61] compared with 65% of those receiving placebo ($p = 0.02$) and the time to onset of disease flare was longer in the adalimumab group.

In the etanercept study, disease flare occurred in 28% of patients receiving etanercept[42] compared with 81% receiving placebo ($p = 0.003$). The authors of the etanercept study state that after adjustment for the effects of baseline characteristics, the rates of flare remained significantly lower in the etanercept group ($p < 0.001$), with only corticosteroid use at baseline being a significant predictor of flare rates ($p = 0.05$). The median time to disease flare with etanercept was > 116 days compared with 28 days for the placebo group, with 13/25 patients still receiving etanercept at the end of the study (day 116) ($p < 0.001$).

In those participants receiving tocilizumab, disease flare occurred in 26% of patients compared with 48% receiving placebo (adjusted difference in flare rate −0.21, 95% CI −0.35 to −0.08; $p = 0.0024$), with authors stating that flares in the placebo group were evident as early as 28 days after randomisation.

American College of Rheumatology Pediatric responses

ACR Pedi-30, -50 and -70 responses were reported by all four studies, with all but the etanercept study[42] also reporting ACR Pedi-90 responses. The abatacept and tocilizumab studies[57,68] additionally report inactive disease, which was defined similarly in the two studies (no joints with active arthritis, normal ESR of ≤ 20 mm per hour, PGA < 10 on a 100-mm VAS,[57] or PGA also < 10 on a 100-mm VAS), indicating no disease activity with the tocilizumab study,[68] also including an absence of uveitis (patients with uveitis were excluded from the abatacept study). In all groups that continued to receive biologic DMARDs during the randomised withdrawal phase of the study, the proportion of participants with ACR Pedi responses of 30 or more were greater than in the placebo group and when a *p*-value was reported the differences were statistically significant in all but two instances (*Table 14*).

Although more patients receiving abatacept (82%) achieved an ACR Pedi-30 response than those patients receiving placebo (69%), the difference was not statistically significant ($p = 0.1712$).[57] However, a statistically significantly greater proportion of patients in the abatacept treatment group achieved an ACR Pedi-50, -70 or -90 response than those receiving placebo ($p = 0.0071$, $p = 0.0185$ and $p = 0.0062$, respectively). In addition, statistically significantly more patients treated with abatacept (30%) than those receiving placebo (11%; $p = 0.0195$) were classified as having inactive disease.

A statistically significantly higher percentage of patients being treated with adalimumab achieved ACR Pedi-30, -50 and -70 responses compared with those receiving placebo ($p = 0.03$, $p = 0.03$ and $p = 0.002$, respectively).[61] The percentage of patients with ACR Pedi-90 response rates was also greater for adalimumab-treated patients than for patients receiving placebo (42 vs. 27 placebo); however, this difference was not statistically significant ($p = 0.17$).

In the etanercept study, ACR Pedi-30, -50 and -70 responses were achieved by a greater proportion of patients being treated with etanercept during the randomised withdrawal phase than those receiving placebo. However, a statistical comparison showing that this difference was statistically significant was reported only for ACR Pedi-30 ($p < 0.01$).

A statistically significantly higher proportion of tocilizumab-treated patients achieved ACR Pedi-30, -50 and -70 responses than those receiving placebo during the randomised withdrawal phase of the study ($p = 0.0084$, $p = 0.0050$ and $p = 0.0032$, respectively). Although the ACR Pedi-90 response was also higher in the tocilizumab group, no *p*-value was provided. The proportion of patients with inactive disease was 36.6% for the tocilizumab group compared with 17.3% for the placebo group (no *p*-value provided).

TABLE 14 American College of Rheumatology Pediatric responses relative to baseline

Study (length: OL, RCT), outcome	Intervention	Comparator	Statistical significance
Abatacept[57] (4-month OL, 6-month RCT)			
ACR Pedi, n *(%)*[a]	*ABA* (n = *60)*	*PBO* (n = *62)*	p-*value*
30	49 (82)	43 (69)	0.1712
50	46 (77)	32 (52)	0.0071
70	32 (53)	19 (31)	0.0185
90	24 (40)	10 (16)	0.0062
Inactive disease[b]	18 (30)	7 (11)	0.0195
Adalimumab[61] (4-month OL, 8-month RCT)			
ACR Pedi, %	*ADA* (n = *38)*	*PBO* (n = *37)*	p-*value*
30	63	38	0.03
50	63	38	0.03
70	63	27	0.002
90	42	27	0.17
Etanercept[42] (3-month OL, 4-month RCT)			
ACR Pedi, n *(%)*[c]	*ETA* (n = *25)*	*PBO* (n = *26)*	p-*value*
30	20 (80)	9 (35)	$p < 0.01$
50	18 (72)	6 (23)	NR
70	11 (44)	5 (19)	NR
Tocilizumab[68] (4-month OL, 6-month RCT)			
ACR Pedi, n *(%)*	*TCZ* (n = *82)*	*PBO* (n = *81)*	*Difference*[d] *TCZ vs. PBO (95% CI);* p-*value*
30	61 (74.4)	44 (54.3)	0.09 (0.05 to 0.33); 0.0084
50	60 (73.2)	42 (51.9)	0.20 (0.06 to 0.34); 0.0050
70	53 (64.6)	34 (42.0)	0.22 (0.07 to 0.37); 0.0032
90	37 (45.1)	19 (23.5)	0.21 (0.07 to 0.35); NR
Inactive disease	30 (36.6)	14 (17.3)	0.18 (0.05 to 0.32); NR

ABA, abatacept; ADA, adalimumab; ETA, etanercept; NR, not reported; OL, open label; PBO, placebo; TCZ, tocilizumab.
a Assessed after the 6-month RCT phase or at the time of flare for patients who did not complete this period.
b Defined as number of joints with active arthritis, a PGA of ≤ 10 on a 100-mm VAS and a normal ESR rate.
c If a patient had a flare they were classified as having no response (ACR Pedi < 30) from that point on, regardless of their ACR Pedi response at that time. Missing values were also imputed as non-responses.
d Adjusted for baseline stratification factors (background use of methotrexate and oral glucocorticoids).

American College of Rheumatology Pediatric core variables

The adalimumab study[61] did not report outcomes for the ACR Pedi core variables. The three remaining studies, however, reported data as mean (abatacept[57]), median (etanercept[42]) or an adjusted mean for change from baseline (tocilizumab[68]). In addition, the etanercept study reports additional joint and pain outcomes, whereas the abatacept and tocilizumab studies also report additional pain outcomes (see *Joint-related outcomes* and *Pain*).

Generally, the core-response variable outcomes were in favour of treatment with the biologic DMARDs compared with placebo. However, as can be seen in *Table 15*, there were some exceptions. For abatacept,[57] differences in the adjusted mean percentage change (adjustment based on an analysis of covariance model with treatment as factor and baseline value as covariate) over the double-blind period (from day 113 to day 282) for the parent's global assessment and ESR rates between the treatment groups were not significantly different ($p = 0.6992$ and $p = 0.9562$, respectively). The mean scores for the CHAQ disability index at the end of the double-blind withdrawal trial period (day 282) were the same for both

TABLE 15 American College of Rheumatology Pediatric response core variables

Study (length: OL, RCT), outcome	Intervention	Comparator	Statistical significance
Abatacept[57] (4-month OL, 6-month RCT) *Core-response variables, mean (SD)[b]*	***ABA (n = 60)***	***PBO (n = 62)***	**p-*value*[a]**
PGA (VAS: 100 mm)	14.7 (18.9)	23.2 (21.8)	0.0004
Parent's global assessment (VAS: 100 mm)	17.9 (22.2)	23.9 (21.6)	0.6992
Physical function (CHAQ disability index: 0–3, best–worst)	0.8 (0.9)	0.8 (0.7)	0.0388
Number of active joints (number assessed not stated)	4.4 (7.0)	6.0 (5.8)	0.0245
Number of joints with LOM (number assessed not stated)	8.8 (12.8)	8.6 (12.0)	0.0128
ESR (mm/hour)[c]	25.1 (26.4)	30.7 (30.1)	0.9562
Etanercept[42] (3-month OL, 4-month RCT) *JIA core set criteria, median[b]*	***ETA (n = 25)***	***PBO (n = 26)***	**p-*value***
PGA of disease severity (0–10, best–worst)	2	5	NR
Patient/parent global assessment of overall well-being (0–10, best–worst)	3	5	NR
CHAQ scores (0–3, best–worst)	0.8	1.2	NR
Total number of active joints (out of 73 joints)	7.0	13.0	NR
Number of joints with LOM and with pain, tenderness, or both (out of 71 joints; 0–10, best–worst)	1.0	4.5	NR
ESR (normal ranges 1–30 mm/hour for females, 1–13 mm/hour for males)[c]	18	30	NR
Tocilizumab[68] (4-month OL, 6-month RCT) *JIA: core response variables, change from baseline – adjusted mean[b]*	***TCZ (n = 82)***	***PBO (n = 81)***	***Difference[d] TCZ vs. PBO (95% CI);* p-*value***
PGA of disease severity (0–100, 0 = inactive disease)	–45.2	–35.2	–9.9 (–16.5 to –3.4); 0.0031
Patient global assessment of well-being (0–100, 0 = very poor)	–32.1	–24.7	–7.4 (–14.8 to 0.0); NR
CHAQ: disability index score (0–3, 0 = no disability)	–0.8	–0.6	–0.2 (–0.4 to 0.0); NR
Number of active joints (range 0–71)	–14.3	–11.4	–2.9 (–5.7 to –0.1); 0.0435
Number of joints with LOM (range 0–67)	–9.5	–7.7	–1.8 (–4.1 to 0.5); 0.1229
ESR (mm/hour)	–26.3	–12.0	–14.3 (–19.6 to –9.0); NR

ABA, abatacept; ESR, Erythrocyte sedimentation rate; ETA, etanercept; LOM, limitation of motion; PBO, placebo; NR, not reported; OL, open label; SD, standard deviation; TCZ, tocilizumab.

a Abatacept study: *p*-values are based on the difference in the adjusted mean percentage change from day 113 to day 282 (start and end of the double-blind period).

b Missing values were imputed with last-observation carried forward.

c CRP values were also reported by these studies: mean (SD) ABA 0.16 (0.25) vs. PBO 0.29 (0.54); $p = 0.0255$.[57] Median ETA: 0.4 vs. PBO 3.0 (normal range 0–0.79 mg per decilitre).[42]

d Adjusted for baseline stratification factors (background use of methotrexate and oral glucocorticoids).

groups (0.8). However, when the difference in the adjusted mean percentage change values for the CHAQ disability index from the start to the end of the double-blind period (day 113 to day 282) are compared, a statistically significant *p*-value is reported in favour of the abatacept group ($p = 0.0388$).

For etanercept,[42] all core variable outcomes appear to be in favour of the etanercept group compared with placebo; however, no statistical comparisons between treatment groups were reported. For the tocilizumab study,[68] differences in adjusted mean changes from baseline between treatment groups for PGA of disease and number of active joints are reported to be statistically significant in favour of tocilizumab (*p*-values of 0.0031 and 0.0435, respectively); no *p*-values for the remaining outcomes were reported.

Joint-related outcomes

None of the trials reported any radiographic outcomes. However, in addition to the ACR Pedi core variable outcomes that capture the numbers of active joints and joints with limited range of motion, the etanercept study[42] presented data for some additional joint-related outcomes (see *Table 16*).

No statistical comparisons for these outcomes were reported between the etanercept and the placebo group; however, the median number of swollen joints (4.0 vs. 11.0 placebo), number of joints with limitation of motion (LOM) (9 vs. 22 placebo), articular severity score (38 vs. 66 placebo) and duration of stiffness (5 vs. 38 placebo) all favoured the etanercept treatment group (*Table 16*).

Pain

The adalimumab study[61] did not report a pain outcome. All the other studies (abatacept,[57] etanercept[42] and tocilizumab[68]) report pain assessed on a VAS, and the data are reported differently (mean, median and mean change from baseline, respectively) (*Table 17*). The difference between the abatacept[57] (mean pain 15 mm) and the placebo (mean pain 21 mm) treatment groups was not statistically significant ($p = 0.105$) and reported mean pain scores were lower for patients being treated with abatacept. The etanercept study[42] did not report a statistical comparison between treatment groups; however, median pain scores for patients being treated with etanercept (VAS 1.5 cm) were less than half of those for patients receiving placebo (VAS 3.5 cm). The tocilizumab study[68] reported the adjusted mean change from baseline, which, compared with the placebo group, was statistically in favour of the tocilizumab treatment group ($p = 0.0076$).

Corticosteroid-reducing regimens

None of the included RCTs reported the effectiveness of biologic DMARDs on reducing the need for corticosteroids.

Extra-articular manifestations (such as uveitis)

None of the included RCTs reported outcomes for extra-articular manifestations. Of note, one of the trials (abatacept) excluded patients with active uveitis.[57]

TABLE 16 Joint-related outcomes (other than ACR Pedi)

Study (length: OL, RCT), outcome	Intervention	Comparator	Statistical significance
Etanercept[42] (3-month OL, 4-month RCT)	***ETA (n = 25)***	***PBO (n = 26)***	**p-*value***
Number of swollen joints (out of 66), median	4.0	11.0	NR
Number of joints with LOM (out of 71), median[a]	9	22	NR
Articular severity score (0–962, best–worst), median	38	66	NR
Duration of morning stiffness (minutes), median	5	38	NR

ETA, etanercept; LOM, limitation of motion; NR, not reported; OL, open label; PBO, placebo.
a Although 'number of joints with LOM' are part of the ACR Pedi core variables, authors reported results under 'other' rather than under the core variables in the publication.

TABLE 17 Pain

Study (length: OL, RCT), outcome	Intervention	Comparator	Statistical significance
Abatacept[57] (4-month OL, 6-month RCT)	***ABA (n = 60)***	***PBO (n = 62)***	**p-*value***
Pain (parent global assessment of pain, CHAQ VAS: 100 mm), mean	15[a]	21[a]	0.105
Etanercept[42] (3-month OL, 4-month RCT)	***ETA (n = 25)***	***PBO (n = 26)***	**p-*value***
Pain (VAS: 0–10 cm, best–worst), median	1.5	3.5	NR
Tocilizumab[68] (24 weeks)	***TCZ (n = 82)***	***PBO (n = 81)***	***Difference[b] TCZ vs. PBO (95% CI);* p-*value***
Pain (VAS: no details reported), adjusted mean change from baseline	–32.4	–22.3	–10.2 (–17.6 to –2.7); 0.0076

ABA, abatacept; ETA, etanercept; NR, not reported; OL, open label; PBO, placebo; TCZ, tocilizumab.
a Read off from graph by reviewer. Analysis based on available data, but the number of patients at this time point contributing data to this outcome is unclear; 49/60 in the abatacept group and 31/62 in the placebo group completed the 6-month double-blind period.
b Adjusted for baseline stratification factors (background use of methotrexate and oral glucocorticoids).

Height and body weight

None of the studies reported differences in height or body weight between the treatment groups for the double-blind, randomised controlled withdrawal phase of the trial.

Mortality

No deaths occurred in the adalimumab,[61] etanercept[42] and tocilizumab[68] studies; this outcome was not reported in the abatacept study.[57]

Quality of life: Child Health Questionnaire

The outcome measures for QoL in the abatacept study were summary physical scores, summary psychosocial scores (both measured on a 100-mm VAS) and 15 Child Health Questionnaire (CHQ) health concepts.[58] Differences between the abatacept and placebo treatment groups were not statistically significant for either the reported summary scores ($p = 0.666$ and $p = 0.056$, respectively), although there appears to be a positive trend for the latter (*Table 18*). Abatacept-treated patients ($n = 52$) had improved scores for 14 of the 15 subscales, and placebo-treated patients ($n = 34$) for 6 of the 15 CHQ subscales ($p > 0.05$ for abatacept versus placebo for all subscales; details not data extracted).

Adverse events

A summary of AEs reported during the double-blind withdrawal trial phases is provided here with complete details for the AEs reported by each of the studies available in the data extraction forms (see *Appendix 5*). AEs reported during trial OLEs are presented below (see *Adverse events open-label extension*).

TABLE 18 Child Health Questionnaire

Study (length: OL, RCT), outcome	Intervention	Comparator	Statistical significance
Abatacept[57] (4-month OL, 6-month RCT)	***ABA (n = 52)[a]***	***PBO (n = 34)[a]***	**p-*value***
CHQ: physical summary score	43.6	41[b]	0.666
CHQ: psychosocial summary score	51.7	47[b]	0.056

ABA, abatacept; OL, open label; PBO, placebo.
a Original group sizes were ABA $n = 60$ and placebo $n = 62$, but not all participants contributed data to these analyses.
b Estimated from graph by reviewer. Number of patients in the trial arms not clear.

Abatacept[57]

During the 6-month double-blind withdrawal period, there were no statistically significant differences in AEs between the abatacept and placebo treatment groups. The total number of AEs (occurring in ≥ 5% of patients in the open-label and double-blind phase) was 62% for the abatacept and 55% for the placebo group, with two serious adverse events (SAEs) occurring in the placebo group but none in the abatacept group (*Table 19*). The most common class of AEs in both treatment groups were infections and infestations (44–45%).

TABLE 19 Adverse events

Study, outcome	Intervention	Comparator	Statistical significance
Abatacept*[57] *(during 6-month double-blind period)	***ABA* (n = *60*)**	***PBO* (n = *62*)**	**p-*value***
Total SAEs, *n* (%)	0	2 (3)	0.50
Total AEs, *n* (%)[a]	37 (62)	34 (55)	0.47
Adalimumab*[61] *(during 8-month double-blind period)	***ADA* (n = *38; 18.3 patient-years*)**	***PBO* (n = *37; 15 patient-years*)**	
Any AE, number of events (number of events per patient-year)	234 (12.8)	155 (10.3)	
SAEs, possibly related to study drug, *n* of events (*n* of events per patient-year)[b]	0	1 (0.1)	
AEs leading to the discontinuation of the drug, *n*	0	0	
Etanercept*[42] *(time period unclear unless stated below)	***ETA* (n = *25*)**	***PBO* (n = *26*)**	
Hospitalisation for SAEs, *n*	2	0	
Injection-site reactions during the 4-month double-blind period, *n*	1	1	
Most common AEs: injection-site reaction, number of events (number of events per patient-year)	57 (3.8)	73 (4.0)	
Tocilizumab*[68] *(during 6-month double-blind period) *SAEs and AEs occurring in ≥ 5% of patients,* n *(%)*	***TCZ* (n = *82*)[c]**	***PBO* (n = *81*)[c]**	
Duration in study (years)	32.33	27.41	
Patients with ≥ 1 AE	58 (70.7)	60 (74.1)	
Total number of AEs[d]	147	141	
Rate of AEs per 100 patient-years	454.7	514.4	
SAEs			
Patients with ≥ 1 SAE	3 (3.7)	3 (3.7)	
Rate of SAEs per 100 patient-years	9.3	10.9	
Patients with ≥ 1 infectious SAE	1 (1.2)	0	
Rates of infectious SAEs per 100 patient-years	3.1	0	
AEs leading to study drug discontinuation	1 (1.2)[e]	1 (1.2)[f]	

ABA, abatacept; ADA, adalimumab; ETA, etanercept; PBO, placebo; TCZ, tocilizumab.
a AEs that occurred in ≥ 5% of patients in the open-label and double-blind phases.
b SAEs were death or any event that was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, congenital anomaly, or spontaneous or elective abortion, or required medical or surgical intervention to prevent another serious outcome.
c AE data on open-label TCZ escape therapy were excluded.
d Multiple occurrences of the same AE in one individual were counted.
e Increased blood bilirubin level, highest total bilirubin reading, 50 µmol/l (normal range, 3–24 µmol/l); two consecutive readings > 51 mmol/l mandated withdrawal per protocol. The event resolved without sequelae.
f Gastroenteritis occurred 46 days after the last of five doses of placebo.

AEs were also reported under the headings of gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders and respiratory, thoracic and mediastinal disorders (see *Appendix 5*).

Adalimumab[61]

There were 234 AEs in the adalimumab group (12.8 per patient-year) and 155 AEs in the placebo group (10.3 per patient-year) during the 8-month double-blind period. No statistical comparisons in AEs between treatment groups were reported. Only one SAE possibly related to the study drug was reported and this was gastroduodenitis, which occurred in one patient in the placebo group. The most common AEs were related to injection-site reactions [adalimumab: 73 events (4.0 events per patient-year); placebo: 57 events (3.8 events per patient-year)]. Other reported AEs were contusion, nasopharyngitis, upper respiratory tract infection, viral infection, vomiting and excoriation (see *Appendix 5*). No AEs led to the discontinuation of the treatment drug (see *Table 19*). Sixteen per cent of patients (27/171) had at least one positive test for antiadalimumab antibody during the open-label and double-blind phases [methotrexate: 5/85 (6%); no methotrexate: 22/86 (26%)], but this did not lead to a greater rate of discontinuation of the study drug, nor did it increase the incidence of SAEs. The study authors state that there was no occurrence of opportunistic infections, malignant conditions, demyelinating diseases or lupus-like reactions.

Etanercept[42]

Two patients who received etanercept needed hospitalisation for SAEs (one for depression and a personality disorder and the other for gastroenteritis-flu syndrome). It is not clear at what point in the trial these events occurred. One patient withdrew after the first dose of etanercept (presumably at the start of the open-label period) because of urticaria. There were only two reported injection-site reactions during the double-blind phase of the trial, one in each treatment group (see *Table 19*). All other AEs were reported to be of mild-to-moderate intensity, with no significant difference in the frequency of AEs between the treatment groups during the double-blind phase. There were no laboratory abnormalities requiring urgent treatment in the etanercept group. No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease. Two patients tested positive for non-neutralising antibody to etanercept.

Tocilizumab[68]

The safety population consisted of all patients who received more than one dose of study medication. During the double-blind period, the total number of patients with at least one AE was 58 in the tocilizumab group (454.7 AEs per 100 patient-years) and 60 in the placebo group (514.4 AEs per 100 patient-years). The most frequently reported AE in both treatment groups was nasopharyngitis (tocilizumab: 17%, placebo 11%). Other reported AEs were headache, upper respiratory infection, cough, pharyngitis, nausea, diarrhoea, rhinitis, vomiting, abdominal pain, oropharyngeal pain and rash (see *Appendix 5*). Two AEs led to drug discontinuation, one in each treatment group (tocilizumab: increased blood bilirubin level; placebo: gastroenteritis) and 3.7% of patients in each treatment group had more than one SAE. One patient in the tocilizumab group suffered with more than one infectious SAE. Rates of SAEs per 100 patient-years were similar between groups (tocilizumab: 9.3; placebo: 10.9), whereas the rate of infectious SAEs per 100 patient-years was 3.1 for the tocilizumab group. Other reported SAEs included pneumonia, upper limb fracture, uveitis, psychosomatic disease, enterocolitis and complicated migraine, with one case in each category and varying by treatment group (see *Appendix 5*).

Subgroup analyses

Only the tocilizumab study[68] reported subgroup analyses, which reported on ACR Pedi-70 and ACR Pedi-90 responses at week 40 in three subgroups: patients with background treatment of methotrexate; background treatment of glucocorticoid; and previous biologic agent use at baseline. It is unclear if these analyses were pre-planned or post hoc. The trial authors also stated that no differences were observed in response to tocilizumab between patients who were RF+ve and those who were not, but no data in support of this statement were presented. No statistical comparisons between treatment groups were reported and it is therefore unclear if differences between the subgroups were statistically significant.

Background methotrexate

Patients receiving background methotrexate in both the tocilizumab and the placebo groups had higher ACR Pedi-70 and -90 response rates at the end of the double-blind RCT withdrawal phase than those who were not in receipt of background methotrexate (*Table 20*). However, patients receiving tocilizumab with or without background methotrexate had better response rates than patients in the corresponding placebo groups.

Background glucocorticoid

At the end of the double-blind RCT phase (week 40) in the tocilizumab group, a slightly higher proportion of participants receiving background glucocorticoid achieved an ACR Pedi-70 and -90 response than those who were not in receipt of background glucocorticoid (see *Table 20*). However, among participants in the placebo group the opposite pattern was observed, with a lower proportion of those who were in receipt of background glucocorticoid achieving ACR Pedi-70 and -90 responses (see *Table 20*). Response rates for both ACR Pedi-70 and -90 were higher in subgroups of patients receiving tocilizumab than in subgroups of patients receiving placebo, regardless of whether or not patients received background glucocorticoid.

Previous biologic agent

Patients in either the tocilizumab or placebo groups who had received previous treatment with a biologic agent (primarily comprising antiTNF agents) had lower ACR Pedi-70 responses at the end of the double-blind RCT phase (week 40) than patients who had not previously been treated with a biologic agent (see *Table 20*). Patients receiving placebo who had not received previous treatment with a biologic agent had better ACR Pedi-70 and -90 response rates than patients on tocilizumab who had previous biologic agent experience (see *Table 20*).

Results: open-label extensions

All four studies included OLEs with some differences in which participants were eligible to enter and how data were presented. ACR Pedi results are presented in *Table 21* and with additional outcomes presented either in the study data extraction forms (see *Appendix 5*) or published papers [adalimumab: minimal disease activity; abatacept: ACR Pedi component items, analysis according to prior exposure to biologic agents, ACR Pedi data for those in the OLE who had not taken part in the double-blind phase and information on antiabatacept and anticytotoxic T-lymphocyte-associated antibody production; etanercept: ACR Pedi component items, minimal disease activity; tocilizumab: ACR Pedi component items, minimal disease activity].

TABLE 20 American College of Rheumatology Pediatric response by background medication use at baseline at the end of the double-blind RCT phase

Concomitant therapies and previous exposure to biologic agent	Response level	Tocilizumab[68] (4-month OL, 6-month RCT)[a]			
		TCZ (*n* = 82), *n/N* (%)		PBO (*n* = 81), *n/N* (%)	
		Yes	No	Yes	No
Background methotrexate	ACR Pedi-70	45/67 (67.2)	8/15 (53.3)	30/64 (46.9)	4/17 (23.5)
	ACR Pedi-90	32/67 (47.8)	5/15 (33.3)	18/64 (28.1)	1/17 (5.9)
Background glucocorticoid	ACR Pedi-70	23/33 (69.7)	30/49 (61.2)	4/38 (36.8)	20/43 (46.5)
	ACR Pedi-90	16/33 (48.5)	21/49 (42.9)	5/38 (13.2)	14/43 (32.6)
Previous biologic agent	ACR Pedi-70	13/27 (48.1)	40/55 (72.7)	2/23 (8.7)	32/58 (55.2)
	ACR Pedi-90	5/27 (18.5)	32/55 (58.2)	2/23 (8.7)	17/58 (29.3)

ITT, intention to treat; OL, open label; PBO, placebo; TCZ, tocilizumab.

a Proportion of patients in the intention-to-treat population with ACR Pedi-70 and ACR Pedi-90 response at the end of the double-blind phase (week 40) by background methotrexate, glucocorticoid and previous biologic agent use at baseline. Patients who withdrew or escaped to open-label TCZ or for whom the end point could not be determined were classified as non-responders.

TABLE 21 American College of Rheumatology Pediatric outcomes from trial OLE periods

Study (follow-up), outcome	Intervention	Comparator (during RCT phase)
Abatacept[59] (OLE day 589)		
ACR Pedi, n/N *(%)*	*ABA* (n = *51)*	*PBO* (n = *47)*
30	46/51 (90)	41/47 (87)
50	45/51 (88)	39/47 (83)
70	38/51 (75)	35/47 (75)
90	29/51 (57)	19/47 (40)
100	20/51 (39)	9/47 (19)
Inactive disease	22/51 (43)	11/47 (23)
Adalimumab[61] (OLE week 104)		
ACR Pedi, %	*ADA* (n = *128[a])*	*PBO group from RCT phase not separately reported*
30	89	
50	86	
70	77	
90	59	
100	40	
Etanercept[67] (OLE up to 8 years)		
ACR Pedi response, 8 years (LOCF[b]), n/N *(%)*	*ETA* (n = *58[c])*	*PBO group from RCT phase not separately reported*
30	40/48 (83)	
50	36/47 (77)	
70	28/46 (61)	
90	19/46 (41)	
100	8/45 (18)	
Tocilizumab[69,71,74] (104 weeks)		
ACR Pedi, proportion of patients with improvement relative to baseline, n *(%)[69]*	*TCZ* (n = *82)*	*PBO* (n = *73[d])*
70[e]	71/82 (86.6)	NR
90[e]	58/82 (70.7)	NR
Proportion with inactive disease[f]	52/82 (63.4)	NR

ABA, abatacept; ADA, adalimumab; ETA, etanercept; LOCF, last observation carried forward; NR, not reported; PBO, placebo; TCZ, tocilizumab.

a Only 71/128 (58%) of this group received methotrexate during the open-label and double-blind phases of the study and met the licensed indication for adalimumab.

b A LOCF analysis was necessary because data were not available for all participants who entered the eighth year of follow-up ($n = 26$) and because the remaining 32/58 (55%) of participants had discontinued the OLE already.

c Total number of participants who entered the OLE. As this is greater than the total number of participants who took part in the double-blind phase of the study ($n = 51$), it is presumed that some of these participants entered the OLE directly from the initial open-label treatment phase of the study.

d *n* calculated by reviewer (155 completed 104 weeks; 82 TCZ group completed 104 weeks).

e Two abstracts[69,74] contain a table with a footnote to indicate patients who withdrew were excluded; however, in the third abstract[71] the table footnote states that patients who withdrew owing to non-safety reasons are non-responders, whereas patients who withdrew owing to safety are included using LOCF.

f No active joints, no active uveitis, ESR < 20 mm/hour and PGA VAS ≤ 10.

Abatacept[59]

The abatacept study reported ACR Pedi data separately for those who had been treated with abatacept continuously (lead-in, double-blind and OLE phases) and those whose abatacept had been interrupted by placebo during the double-blind-RCT phase. The OLE included 85% of the abatacept group and 76% of the placebo group from the double-blind phase. For those receiving continuous abatacept therapy, treatment length ranged from 31 to 52 months (participants who had entered the study earliest had been treated longest). Those who received placebo during the double-blind phase usually received abatacept for a shorter period (length not stated), but the ACR Pedi scores achieved were similar for ACR Pedi-30, -50 and -70 to those whose abatacept treatment had been continuous (see *Table 21*). The proportions of participants who had received placebo during the double-blind phase achieving ACR Pedi-90 and ACR Pedi-100 and having inactive disease are lower than those whose abatacept treatment had been continuous.

Adalimumab[61]

Results were reported for those who entered the OLE phase as a single group of participants ($n = 128$). This group included 35 of 38 (92%) participants who received adalimumab and methotrexate, and 36 of 37 (97%) participants who received placebo and methotrexate in the double-blind phase of the study. However, also within this group of 128 are 57 (45%) participants from two further study arms (adalimumab only and placebo only) who are not included in this report because the majority of participants in these arms had never received methotrexate and therefore do not meet the licensed indication. Through the first 104 weeks of the OLE phase there was no diminution of the ACR Pedi responses, such that after 104 weeks of open-label treatment in the extension phase, 40% of participants had an ACR Pedi-100 response (see *Table 21*).

Etanercept[42]

All 69 participants who began the open-label lead-in phase of the study (51 of whom took part in the double-blind randomised withdrawal phase) were eligible to enter the OLE phase but only 58 did so. Of the 58 who took part in the OLE, 26 entered the eight year of follow-up; therefore a last observation carried forward analysis was used to calculate the ACR Pedi responses reported in *Table 21*. These responses appear to have remained constant over the OLE. Although last observation carried forward analyses are commonly used in drug trials, this method can be prone to bias when used in progressive diseases such as JIA, and results should be interpreted with caution.

Tocilizumab[68]

Results from the OLE of the tocilizumab study[68] are reported in conference abstracts.[69,71,74] Only participants who achieved at least ACR Pedi-30 during the open-label phase and who then continued into the double-blind RCT phase of the trial were eligible to enter the OLE, either after a JIA flare or when they completed the double-blind RCT phase. One-hundred and sixty (96%) of the 166 participants eligible to enter the OLE did so and 155 (97%) completed 104 weeks of follow-up (16-week open-label plus 24 weeks double-blind RCT plus 64 weeks OLE). ACR Pedi-70, ACR Pedi-90 and proportion with inactive disease are presented (see *Table 21*) only for the 82 participants who received continuous tocilizumab throughout the study and the proportion achieving each of these measures increased since the end of the double-blind phase (see *Table 21*).

Growth

Adalimumab[61]

Two abstracts[62,63] report limited data for growth from a post hoc analysis of JIA patients who had taken part in any arm of the double-blind phase of the RCT and entered the OLE (this includes $n = 58$ who were not receiving methotrexate and who were therefore not receiving adalimumab treatment according to the licensed indication). All patients who received more than one dose of adalimumab +/– methotrexate were included in the analysis ($n = 133$). Patients were assigned by baseline weight into two groups: $\leq$ 33rd percentile (41%, $n = 55$) and > 33rd percentile (59%, $n = 59$) based on the US Centres for Disease Control and Prevention growth charts. Missing data were analysed using last observation carried forward. Those in

the ≤ 33rd percentile baseline weight group had a higher mean percentile change from baseline in height at week 104 than those in the > 33rd percentile group (values for mean height percentile change from baseline estimated from graph by reviewer 5.5 and 3.3, respectively).[62] Similar patterns were stated to have been observed for weight and body mass index. At week 104 there were no statistically significant differences between the methotrexate and the non-methotrexate groups in mean changes from baseline in height, weight or body mass index ($p > 0.26$). Long-term adalimumab treatment appears to show improvement in growth for JIA patients who were in the ≤ 33rd percentile weight group at baseline receiving adalimumab with or without the addition of methotrexate. However, caution in the interpretation of the results is recommended owing to the limitations in the data presented and the absence of an appropriate control group.

Tocilizumab[76]

The Roche CS included data for growth and glucocorticoid treatment at week 104 based on a conference abstract[76] from the CHERISH trial.[68] Most growth data came from a subset of patients ($n = 123$) with the highest growth potential, represented by patients with Tanner stage < 4 at baseline. The Tanner stages are based on a scale of physical development in children, adolescents and adults (boys: development of external genitalia; girls: breast development; boys and girls: pubic hair), with stage 5 being the final adult/mature stage. Growth measures included height standard deviation scores (SDSs) and height velocity. The mean height SDS of patients with polyarticular JIA and Tanner stage < 4 was below normal at baseline {–0.68 [standard deviation (SD) 1.23]} and rose to –0.19 (SD 1.14) at week 104 ($n = 103$) with the difference being statistically significant ($p < 0.001$ vs. baseline). Of these patients, 71.8% had an increased height SDS. The CS states (CS page 16)[78] that there was no observed difference in patients who received placebo during the randomised phase of the trial (based on 154 patients of the growth population with height SDS data at both time points); however, fewer than half of the patients received placebo through the entire 24 weeks of the randomised phased of the trial, as most escaped to tocilizumab before week 40. For the entire growth population ($n = 187$; i.e. not restricted to those with Tanner stage < 4), the reported mean change in height SDS from baseline to week 104 was 0.25 (SD 0.54) (no *p*-value for comparison with baseline reported). The mean daily oral glucocorticoid dose decreased from baseline [0.05 mg/kg (SD 0.08 mg/kg)] to week 104 [($n = 103$) (0.02 mg/kg (SD 0.05 mg/kg)]. A multiple linear regression analysis for the same 103 patients indicated that height velocity at week 52 was related to baseline age ($p < 0.001$) and oral glucocorticoid use at the end of week 52 ($p = 0.0002$). No data for week 104 were reported. Caution in the interpretation of the growth results is recommended owing to the limitations in the data presented and the absence of an appropriate control group.

Adverse events

This is a summary of OLE AEs presented in the published papers.

Abatacept: OLE to day 589 and year 7

In the abatacept study,[57] common AEs (occurring in 10% or more of the total group, no data extracted) and common SAEs (occurring in 1% or more of the total group) were reported separately for those who had been in the abatacept group and those who had been in the placebo group during the double-blind period of the trial, and those who had not entered the double-blind phase because they did not achieve an ACR Pedi-30 response during initial open-label treatment. SAEs by day 589 (approximately 20–21 months) occurred in 23/153 patients (*Table 22*); the most common SAEs were arthritis flares ($n = 6$), arthralgia ($n = 2$), foot deformity ($n = 2$), pyrexia ($n = 2$) and vomiting ($n = 2$). The proportions of SAEs at day 589 were similar in the three groups. At 7-year follow-up (reported in an abstract[60]), 30/153 (19.6%) patients had SAEs. Most were unrelated and were primarily musculoskeletal or infectious events. The incidence rate (per 100 patient-years) of SAEs in the OLE at 7 years (5.6/100 patient-years) did not increase versus the 6-month double-blind rate (6.8/100 patient-years).

TABLE 22 Open-label extension AEs for abatacept

Abatacept[57] (OLE: day 589,[59] 7 years[60])			
SAEs	DB ABA ($n = 58$), n (%)[a]	DB PBO ($n = 59$), n (%)[a]	Patients with less than an ACR Pedi-30 response initially ($n = 36$), n (%)
Total SAEs, *n/N* (%)	8/58 (14)	8/59 (14)	7/36 (19)
Most common SAEs			
Arthritis flares[b]	3 (5.2)		3 (8.3)
Arthralgia[b]	1 (1.7)	1 (1.7)	1 (2.8)
Foot deformity[b]	1 (1.7)	1 (1.7)	
Pyrexia	1 (1.7)	1 (1.7)	
Vomiting		1 (1.7)	
SAEs year 7, *n/N* (%)	30/153 (19.6)		

ABA, abatacept; DB, double blind; PBO, placebo.
a Patients who had been in the randomised double-blind phase.
b All related to underlying disease.

Adalimumab: open-label extension ongoing

The OLE was ongoing at the time the key trial publication was published, and the time period for which events were reported is not clear.[61] SAEs possibly related to study drug occurred in seven patients during the OLE (a table in the published paper[61] suggests none was receiving methotrexate, in which case they were not receiving adalimumab treatment according to the licensed indication). Three patients discontinued treatment owing to AEs during the OLE.

Etanercept: year 8

In the etanercept study[42] OLE, the safety analyses captured SAEs, medically important infections (MIIs) and mortality, as well as some 'events of interest' (including opportunistic infections, tuberculosis, lupus, demyelinating disorders, malignancies and lymphomas). Non-SAEs were not recorded.[67] There were a total of 39 SAEs based on 318 patient-years of etanercept exposure ($n = 69$), with 26 patients entering their eighth year of etanercept treatment, equating to 0.12 events per patient-year (*Table 23*). There were nine MIIs resulting in the need for intravenous antibiotic therapy or hospitalisation, equating to 0.03 events per patient-years, with only one reported MII since 4-year follow-up (pyelonephritis).

TABLE 23 Open-label extension AEs for etanercept

Etanercept[42] (OLE: up to 8 years[67])				
	SAE[a]		MII[b]	
Year of etanercept treatment from RCT (excluding gaps between RCT and OLE)	Number of events	Number of events/ patient-year	Number of events	Number of events/ patient-year
1 ($n = 69$; 57 patient-years of drug exposure)	5	0.09	2	0.04
9 ($n = 14$; 4 patient-years of drug exposure)	0	0	0	0
Total for all years ($n = 69$; 318 patient-years of drug exposure)	39	0.12	9	0.03

a SAEs occurring during the study or within 30 days of the last dose of etanercept. Defined as events that were fatal or life-threatening, required hospitalisation or prolonged an existing hospitalisation, resulted in a persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect.
b Defined as MIIs resulting in the need for intravenous antibiotic therapy or hospitalisation.

The most common new SAEs reported beyond 4 years of drug exposure were flares or worsening of disease, occurring in 6/9 patients (67%).

Tocilizumab: 104 weeks

Long-term AEs rates based on a safety population of 188 patients (307 patient-years) were 406.5 per 100 patient-years over 104 weeks (approximately 2 years) in patients receiving tocilizumab, based on an abstract only.[69] The equivalent SAEs rate was 11.1 per 100 patient-years (*Table 24*). Infections categorised into the most common AEs and SAEs were 151.4 and 5.2 per 100 patient-years, respectively. The study also reports AE safety population data for elevations of alanine aminotransferase and aspartate aminotransferase, grade 2/3/4 thrombocytopenia, grade-3 lowest neutrophil count and low-density lipoprotein cholesterol (see data extractions in *Appendix 5*).

Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus each other (with methotrexate where permitted)

Background

None of the RCTs included in the systematic review of clinical effectiveness directly compared any of the biologic DMARDs with each other. It was therefore necessary to undertake an indirect comparison of the drugs to inform the assessment of comparative clinical effectiveness. One published indirect comparison was identified through literature searching, by Otten and colleagues.[79] This was a systematic review of RCTs that constructed two separate evidence networks: polyarticular-course JIA and systemic JIA. For each network, a series of pairwise indirect comparisons was conducted, with placebo as a common comparator, using the method described by Bucher and colleagues.[53]

Three RCTs were included in Otten and colleagues'[79] polyarticular-course JIA network,[42,57,61] all of which have been included in this assessment report. However, this network did not include tocilizumab, as at that time no RCT evidence for that drug in polyarticular-course JIA was published. The network therefore included only comparisons of three of the four biologic DMARDs of relevance to the scope of this assessment (abatacept, adalimumab and etanercept). We have conducted a similar adjusted indirect comparison to Otten and colleagues[79] including the recently published tocilizumab RCT by Brunner and colleagues (the CHERISH trial).[68] *Figure 2* illustrates the design of the analysis, representing what is termed a star network.[80]

Otten and colleagues[79] indirectly compared the drugs in relative risk (RR) of disease flare. We have similarly included disease flare as an outcome and, in addition, have chosen ACR Pedi-50 and -70 responses as an outcome. ACR Pedi-50 and -70 were chosen as opposed to ACR Pedi-30, as it was considered that a higher level would be a more clinically relevant level of treatment response. Furthermore, owing to the design of the RCTs, all patients who were randomised had achieved an ACR Pedi-30 response at the end of the open-label lead-in phase.

TABLE 24 Open-label extension AEs for tocilizumab

Tocilizumab[68] (OLE: 104 weeks[69])	
AEs and SAEs	**Safety population = 188 patients with 307 patient-years of tocilizumab exposure**
AEs, rates/100 patient-years	406.5
SAEs, rates/100 patient-years	11.1
Most common AE: infections	151.4
Infections: SAE	5.2

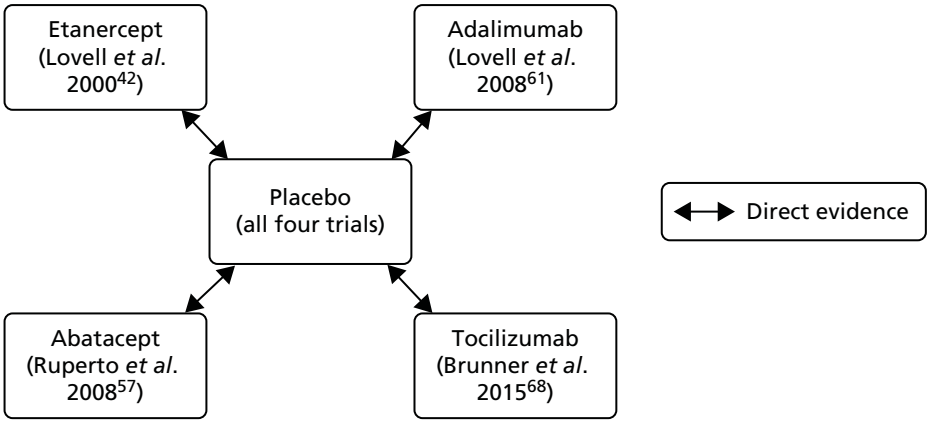

FIGURE 2 Indirect comparison of biologic DMARDs.

The adjusted indirect comparison should be considered to be exploratory rather than definitive owing to limitations in the evidence base and heterogeneity between the included trials.

- There is only one trial available for each drug. Although the trials were considered to be of generally good methodological quality and low risk of bias, evidence networks are considered weaker if informed by small numbers of studies and small numbers of participants.[81] The number of patients in the trials was also relatively low (ranging from 51 to 163).
- There is some variation in the proportion of subtypes of JIA in the included trials. Although the network is considered to be most applicable to polyarticular-course JIA, in one trial (etanercept[42]) around one-third of patients were classified as having systemic JIA with apparent systemic manifestations (which is outside the scope of the current appraisal). There was insufficient evidence from RCTs to construct a network for PA, or ERA because outcome data for these subtypes of JIA were not reported separately in trials, even though some cases with these subtypes may have been included.
- The duration of JIA ranged from just under 4 years[57] to approximately 6 years across the trials.[42] A study by the BSPAR etanercept cohort found that shorter disease duration was an independent predictor of achieving an excellent response to treatment (ACR Pedi-90) at one year.[82] Disease duration has also been found to be a predictor of response to etanercept[83] and to methotrexate[84] among patients from the German Biologika in der Kinderrheumatologie (BIKER) registry. Differences between the trials in disease duration may therefore potentially confound results.
- Three of the four trials permitted patients to take methotrexate in addition to the biologic DMARD (in proportions of patients varying from 74% to 100%), whereas the fourth trial (etanercept)[83] did not permit use of methotrexate.
- Previous therapy with biologic DMARDs had been received by approximately one-third of participants who entered the initial open-label run-in of two trials (abatacept[57] and tocilizumab[68]). Prior therapy with another biologic DMARD was an exclusion criterion for the adalimumab trial[61] and was not mentioned for the earliest trial (etanercept[42]), presumably because no other biological therapies were available at the time. Currently, it is unclear whether or not prior biologic DMARD treatment influences the effectiveness of subsequent biologic treatment.
- The mean age of patients across the trials varied from around 7.5 years to 13 years. Part of this variation may reflect the age ranges specified in the inclusion criteria of the trials and potentially the mix of JIA subtypes in the trials, which have a different mean age at onset. Age could be an effect modifier given the progressive nature of JIA.
- The duration of the double-blind randomised treatment phase of the trials varied from 4 months[42] to 8 months.[61] Treatment duration may affect outcomes that are time dependent, such as disease flare.

Results

Figure 3 illustrates the results of the four included RCTs comparing the biologic DMARDs with placebo (with background methotrexate where permitted) on the outcome of disease flare (the adalimumab trial[61] stratified results according to whether or not patients received methotrexate background therapy, and we have included data only for patients who did receive methotrexate, in accordance with the licensed indication – this applies to disease flare and to ACR Pedi-50/-70). Treatment with each of the four DMARDs resulted in a statistically significant reduction in the RR of a disease flare, ranging from 0.38 to 0.57. (We have not presented a pooled RR given differences between the DMARDs and also heterogeneity between the trials.)

Table 25 reports adjusted pairwise indirect comparisons for the four biologic DMARDs for the outcome of disease flare. The point estimate for risk of flare was lower for etanercept than the other three comparators. Abatacept had a lower risk of flare than adalimumab and tocilizumab. Tocilizumab had a lower risk of flare than adalimumab only. Adalimumab was associated with a higher risk of disease flare than the other three comparators. The ranking of treatments in terms of risk of flare was therefore etanercept, abatacept, tocilizumab and adalimumab. However, none of the comparisons demonstrated a statistically significant difference between the treatments being compared, with CIs crossing 1 in every case. The results of our analysis match those of Otten and colleagues,[79] with the exception of the comparison with tocilizumab, which was not included in their polyarticular-course JIA trial network (as discussed above).

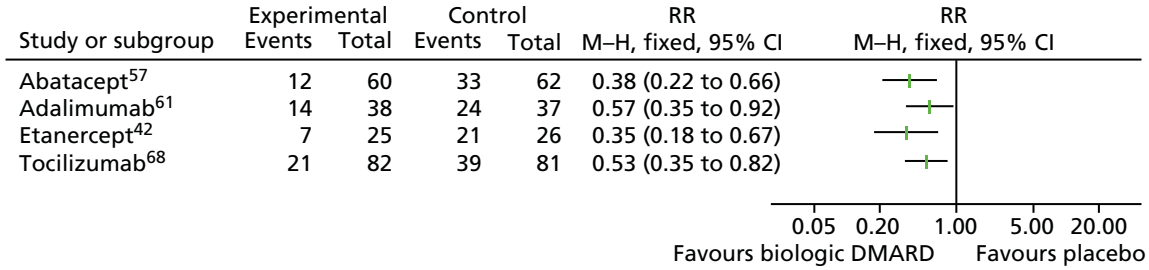

FIGURE 3 Summary forest plot of biologic DMARDs vs. placebo: disease flare. M–H, Mantel–Haenszel.

TABLE 25 Indirect comparisons of biologic DMARDs: disease flare

Comparison	RR (95% CI)
Etanercept vs. adalimumab	0.61 (0.27 to 1.38)
Etanercept vs. abatacept	0.92 (0.39 to 2.18)
Etanercept vs. tocilizumab	0.65 (0.30 to 1.43)
Adalimumab vs. abatacept	1.51 (0.72 to 3.15)
Adalimumab vs. tocilizumab	1.07 (0.56 to 2.04)
Abatacept vs. tocilizumab	0.71 (0.35 to 1.43)

Figure 4 illustrates the results of the four included RCTs comparing the biologic DMARDs with placebo (with background methotrexate where permitted) on the outcome of ACR Pedi-50 response. Treatment with each of the four DMARDs led to a statistically significant greater proportion of participants with ACR Pedi-50 response, with the RR ranging from 1.41 to 3.12.

Table 26 reports adjusted pairwise indirect comparisons for the four biologic DMARDs for the ACR Pedi-50 response outcome. Etanercept had a higher RR for treatment response than the other three comparators. Adalimumab had a higher RR for treatment response than abatacept and tocilizumab. Adalimumab had a higher RR for treatment response than tocilizumab. The ranking of treatments in terms of treatment response was therefore etanercept, adalimumab, abatacept and tocilizumab. With the exception of etanercept compared with tocilizumab, none of the comparisons indicated a statistically significant difference between the treatments being compared, with CIs crossing 1.

Figure 5 illustrates the results of the four included RCTs comparing the biologic DMARDs with placebo (with background methotrexate where permitted) on the ACR Pedi-70 response outcome. Treatment with each of the four DMARDs led to a statistically significant greater proportion of participants with ACR Pedi-70 response, with the RR ranging from 1.54 to 2.34.

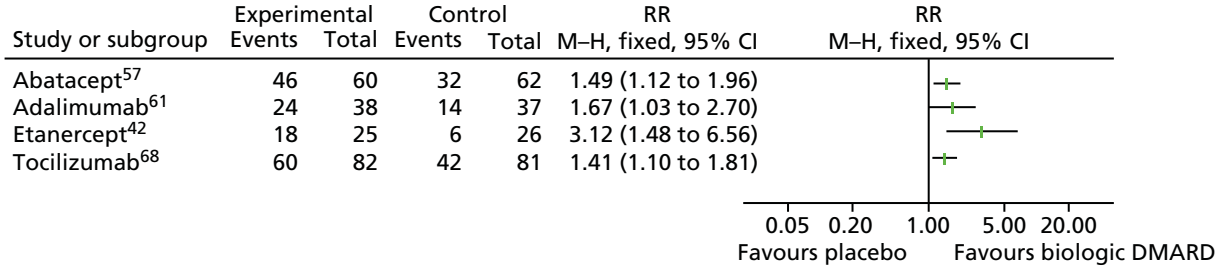

FIGURE 4 Summary forest plot of biologic DMARDs vs. placebo: ACR Pedi-50 response. M–H, Mantel–Haenszel.

TABLE 26 Indirect comparisons of biologic DMARDs: ACR Pedi-50 response

Comparison	RR (95% CI)
Etanercept vs. adalimumab	1.87 (0.77 to 4.53)
Etanercept vs. abatacept	2.10 (0.95 to 4.64)
Etanercept vs. tocilizumab	2.21 (1.01 to 4.84)
Adalimumab vs. abatacept	1.12 (0.65 to 1.96)
Adalimumab vs. tocilizumab	1.18 (0.69 to 2.02)
Abatacept vs. tocilizumab	1.05 (0.72 to 1.53)

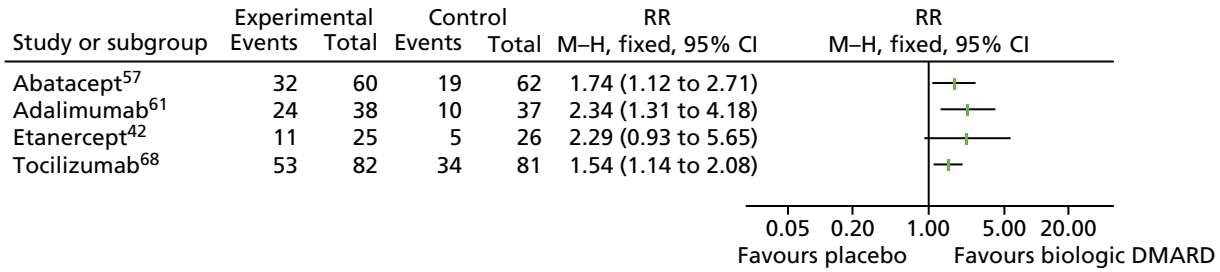

FIGURE 5 Summary forest plot of biologic DMARDs vs. placebo: ACR Pedi-70 response. M–H, Mantel–Haenszel.

Table 27 reports adjusted pairwise indirect comparisons for the four biologic DMARDs for the outcome of ACR Pedi-70 response. Etanercept had a higher RR for treatment response than abatacept and tocilizumab but a slightly lower RR for treatment response than adalimumab. Adalimumab had a higher RR for treatment response than abatacept and tocilizumab. Abatacept had a higher RR for treatment response than tocilizumab. The ranking of treatments in terms of treatment response for ACR Pedi-70 (adalimumab, etanercept, abatacept and tocilizumab) was therefore different from the ACR Pedi-50. None of the comparisons indicated a statistically significant difference between the treatments being compared, with CIs crossing 1.

The results of this exploratory analysis based on the limited evidence available currently (only one trial for each of the four biologic DMARDs) supports etanercept being more effective than the other three biologic DMARDs in terms of preventing disease flares and achieving a response to treatment based on a composite index (ACR Pedi-50), whereas the ACR Pedi-70 exploratory analysis shows adalimumab with a slight advantage over etanercept (although see comment below about CIs). Abatacept appeared to be superior to tocilizumab for all outcome measures. Adalimumab appeared to be less effective than abatacept and tocilizumab in terms of preventing disease flare but more effective in terms of ACR Pedi-50 and -70 responses. Therefore, there was no consistent ranking of treatment comparisons across these outcome measures. The indirect comparisons were generally not statistically significant and CIs were wide, so caution is advised in the interpretation of these results. Furthermore, the etanercept trial[42] appears to have some differences from the other trials which may confound the results, namely the absence of methotrexate background therapy and the longer duration of JIA disease. There was also a noticeably higher rate of flares in the placebo arm of that trial than in the other three trials (81% compared with 48–65%) which may account for the bigger treatment effect seen. Taking the above limitations into account, an overall interpretation of the results of the indirect comparison is that, owing to the absence of statistically significant differences between the biologic DMARDs, they currently appear to be similar in treatment effectiveness. This accords with the conclusion reached by Otten and colleagues[79] who suggested that the short-term efficacy of the biologic DMARDs in polyarticular-course JIA seem similar. Furthermore, the clinical advisors to the assessment group felt that these data generally reflect clinical experience in that when used for the same indication in the same population, effectiveness was likely to be similar. However, there was also a recognition that for individual patients, and potentially for particular subgroups of JIA patients, differential effects of each biologic DMARD might be apparent but these differential effects have not yet been captured by current trial data.

TABLE 27 Indirect comparisons of biologic DMARDs: ACR Pedi-70 response

Comparison	RR (95% CI)
Etanercept vs. adalimumab	0.98 (0.33 to 2.87)
Etanercept vs. abatacept	1.31 (0.48 to 3.60)
Etanercept vs. tocilizumab	1.49 (0.57 to 3.85)
Adalimumab vs. abatacept	1.34 (0.65 to 2.79)
Adalimumab vs. tocilizumab	1.52 (0.79 to 2.92)
Abatacept vs. tocilizumab	1.13 (0.66 to 1.93)

Summary of the systematic review of clinical effectiveness

- Four multicentre RCTs, one each evaluating abatacept, adalimumab, etanercept and tocilizumab, met the inclusion criteria of this review. Only the tocilizumab RCT included UK patients. Seven additional RCTs (three for adalimumab and four for etanercept) are described as ongoing (details summarised in *Ongoing trials*, below).
- Each RCT had three phases, an open-label lead-in period, a randomised withdrawal period and an OLE. The lengths of the lead-in and randomised phases varied between studies (open-label lead-in: 12–16 weeks; randomised double-blind withdrawal phase 16–32 weeks). In each study patients had to achieve an ACR Pedi-XX response during the initial open-label phase in order to be eligible for entry to the randomised double-blind withdrawal phase. Therefore, results are applicable only to patients who have already achieved an initial (low) degree of benefit from a biologic DMARD.
- The quality of the included RCTs was reasonable overall, with a low risk of bias judged for most items, although some aspects were rated as unclear, mainly owing to a lack of reporting.
- Disease flare: this was the primary outcome in all four RCTs, with definitions broadly consistent between the studies. Patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had statistically significantly fewer arthritis flares than those receiving placebo in all four studies, whereas time to disease flare reported in three studies (abatacept, adalimumab and etanercept) was statistically significantly longer in those treated with biologic DMARDs.
- ACR Pedi: a greater proportion of patients receiving biologic DMARDs during the randomised withdrawal phase of the studies achieved ACR Pedi responses of ≥ 30 than placebo-treated patients, with differences statistically significant in all but two instances where *p*-values were reported. The proportion of biologic DMARD-treated patients with inactive disease was more than twice that of placebo-treated patients in the two studies (abatacept and tocilizumab) reporting this outcome.
- ACR Pedi core variables: in the three studies reporting this outcome (abatacept, etanercept and tocilizumab) results were generally in favour of treatment with biologic DMARDs when compared with placebo.
- Joint-related outcomes: one study (etanercept) reported additional joint outcomes without statistical comparisons. All outcomes favoured etanercept over placebo.
- Pain: three studies reported pain (abatacept, etanercept and tocilizumab). A statistically significant difference in the mean change from baseline favoured the tocilizumab group. Although pain scores were lower for those receiving biologic DMARDs in the remaining two studies, differences between treatment groups were not statistically significant in the abatacept study and no statistical comparison reported in the etanercept study.
- Mortality: no treatment-related deaths were reported in the three studies reporting this outcome (adalimumab, etanercept and tocilizumab).
- Outcomes not reported by the included RCTs for the randomised withdrawal phase of the trials were corticosteroid-reducing regimens, extra-articular manifestations (such as uveitis), height and weight.
- HRQoL: reported by the abatacept study only, with differences between treatment groups for the physical and psychosocial summary scores not statistically significant. Those treated with abatacept had improved scores for 14 of the 15 CHQ subscales compared with 6 out of 15 for placebo-treated patients.
- AEs: during the randomised withdrawal phase of the trials, the proportions of AEs and SAEs were generally fairly similar between the biologic DMARDs and the placebo groups.
- Subgroup analyses: the tocilizumab study reported data for subgroups but no statistical comparisons between treatment groups were reported.
- OLE: all four studies included an OLE phase. There were differences in eligibility criteria between studies and in how data were presented. Only results for ACR Pedi, AEs and growth are included in this report.

- OLE ACR Pedi:
  - Abatacept: the proportion of patients achieving ACR Pedi-30, -50 and -70 scores were similar for those with continuous abatacept therapy and those who received placebo during the double-blind phase, but were greater at achieving ACR Pedi-100 and inactive disease in abatacept-treated patients (ACR Pedi-100 abatacept 39%, placebo 19%; inactive disease abatacept 43%, placebo 23%).
  - Adalimumab: there was no diminution of ACR Pedi responses, and 40% of patients had an ACR Pedi-100 response after open-label treatment in the extension phase, but results included patients not meeting the licensed indication.
  - Etanercept: 26/58 (45%) patients who took part in the OLE entered the eighth year of follow-up. ACR Pedi responses appear to have remained constant over the OLE.
  - Tocilizumab: limited results were based on conference abstracts for 82 patients who received continuous tocilizumab throughout the study. The proportion of patients achieving ACR Pedi-70 and -90 increased since the end of the double-blind phase, with 63% having inactive disease.
- OLE AEs:
  - Abatacept: at 7-year follow-up, 19.6% of patients had SAEs, with similar incidence rates between the OLE phase (5.6 per 100 patient-years) and the 6-month double-blind phase (6.8 per 100 patient-years).
  - Adalimumab: SAEs possibly related to study drug occurred in seven patients during the OLE, but would appear to be in patients not in line with licensed indication (OLE phase ongoing, time period unclear). Three patients discontinued treatment owing to AEs.
  - Etanercept: there were a total of 39 SAEs based on 318 patient-years of etanercept exposure, with 26/69 patients entering their eighth year of etanercept treatment (0.12 events per patient-year). Nine MIIs resulted in the need for intravenous antibiotic therapy or hospitalisation (0.03 events per patient-year).
  - Tocilizumab: AEs rates were 406.5 per 100 patient-years and the SAEs rate 11.1 per 100 patient-years over around 2 years, with the most common AEs and SAEs related to infections (151.4 and 5.2 per 100 patient-years, respectively).
- Growth: limited data reported in abstracts at week 104 for adalimumab and tocilizumab appear to support the positive effect of these drugs on growth, but the use of different outcome measures prevents a comparison between the drugs.
- An exploratory adjusted indirect comparison found that there was a lack of statistically significant differences between the four biologic DMARDs in terms of disease flare and ACR Pedi-50/-70 response, with wide CIs and clinical heterogeneity between the trials.

Review of clinical effectiveness in company submissions to the National Institute for Health and Care Excellence

Four companies made submissions in support of their drugs to NICE: BMS for abatacept, AbbVie for adalimumab, Pfizer Ltd for etanercept and Roche for tocilizumab. A review of the information presented about the economic evaluation of biologic DMARDs for treatment of JIA in the CSs can be found in *Chapter 5, Review of cost-effectiveness in company submissions to National Institute for Health and Care Excellence*.

Review of Bristol-Myers Squibb company evidence submission for abatacept

The company did not report a systematic review of clinical effectiveness of abatacept.[85] There is no indication that any databases were searched and no search strategies were supplied. Furthermore, there is no search or report for any ongoing studies. The majority of the clinical effectiveness information in the CS

comes from published papers with a few details that are commercial-in-confidence (CiC) which come from the clinical study reports.

The CS includes one phase-III double-blind randomised withdrawal study, the AWAKEN trial. Although not clearly summarised, the CS draws on two published papers,[57,58] one conference presentation[86] and the trial clinical study reports. The published papers[57,58] met the inclusion criteria of this assessment report. One published paper[59] relating to the AWAKEN trial that was identified in this assessment report was not cited by the CS but the data in this appear to have been superseded by the more recent conference presentation.[86] However, the more recent efficacy data are not presented according to the randomised groups in the double-blind period, whereas the safety summary data are.[86] Furthermore, there is limited detail regarding the length of follow-up, which is stated to be ≥ 56 months and up to 7 years of total follow-up. No critical appraisal is reported for any of the studies cited in the CS.

A summary of the AWAKEN trial is provided in the CS which is broadly similar to the information presented in the published papers.[57,58,86] Information from the OLE phase drawn from the conference presentation[86] is more recent than the data from the published paper,[59] which is included in the assessment report. Furthermore, an analysis was conducted (using Fisher's exact test) to compare SAEs during the double-blind phases of trials of abatacept, adalimumab etanercept and tocilizumab (CS section 3.4.6). The CS highlights the lack of statistical power attributable to the low numbers of patients and event rates, which should be taken into account in the interpretation of their finding that the incidence of SAEs was likely to be similar between the biologic DMARDs.

The CS focuses on abatacept, with very little information provided regarding the other biologic DMARDs included in this MTA. However, information is presented in the CS on indirect pairwise comparisons for the four biologic DMARDs for the outcome of disease flare. The comparisons for abatacept, adalimumab and etanercept are taken from a published paper by Otten and colleagues[79] and this is supplemented by new indirect pairwise comparisons with tocilizumab, taking data from a RCT[68] that has been published since the Otten and colleagues study (the CHERISH trial.[68]) The results of the indirect comparisons reported in the CS (tables 4 and 5) match those reported in the indirect comparisons conducted for this assessment report [see *Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus each other (with methotrexate where permitted)*].

In summary, the CS has not conducted a systematic review of clinical effectiveness but has summarised data from the AWAKEN trial,[57] presented indirect pairwise comparisons of the four biologic DMARDs included in this appraisal and conducted an analysis to compare SAEs during the double-blind phases of trials of the four biologic DMARDs. No additional RCTs were included in the CS that would have met the inclusion criteria of this assessment report.

Review of AbbVie company evidence submission for adalimumab

AbbVie submitted a report to NICE on adalimumab as a treatment for JIA.[77] The clinical effectiveness evidence has been briefly appraised.

The company did not conduct a formal systematic review of the clinical effectiveness evidence, but provided what they describe as 'an iterative literature review' (CS page 15). The company asserts that all RCTs of adalimumab in the treatment of JIA have been identified (CS page 15). It would appear that RCTs were identified chronologically from an adalimumab trial programme, and there is no mention that any databases were searched and no search strategies were provided. There is no search for or report of any ongoing studies, but the CS does contain information about a trial in progress, the SYCAMORE RCT.[87] This trial is evaluating the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of JIA-associated uveitis (further information on this trial is given *Ongoing trials* of this assessment report). Data from abstracts/conference proceedings are also presented in the CS.

The submission contains narrative summaries for the pivotal RCT by Lovell and colleagues,[61] which formed the basis of the original marketing authorisation in 2008; an ongoing RCT of adalimumab treatment in patients with ERA by Burgos-Vargas and colleagues[88–93] (see *Ongoing trials* of this assessment report for details of this study); two open-label single-arm studies[94,95] and supporting data from an ongoing registry (STRIVE) funded by AbbVie. The multinational STRIVE registry is assessing the long-term safety and effectiveness of adalimumab in patients with moderate to severe polyarticular JIA. Some data from this registry are given in the CS, for efficacy outcomes up to 1 year, and safety outcomes for longer (mean duration of drug exposure was 643 days for methotrexate patients and 653 days for adalimumab and methotrexate patients). The registry does not appear to include patients from the UK. Other evidence such as case series, open-label trials, a systematic review[96] and data from an Italian registry were included to provide evidence for the effectiveness of adalimumab in JIA-associated uveitis (see *JIA-associated uveitis* of this assessment report for details of these).

Based on the Lovell and colleagues RCT,[61] the key outcomes of disease flares and ACR Pedi responses are the same in the CS and the assessment report.

The CS notes several methodological concerns that prevented the presentation of a network meta-analysis comparing the four biologic DMARDs. An indirect comparison was therefore not presented.

In summary, the CS has not conducted a systematic review of clinical effectiveness but has summarised data separately for RCTs and other non-randomised studies, as well as data from a registry. No indirect comparison of the biologic DMARDs was conducted by the company. No additional RCTs were included in the CS that met the inclusion criteria for systematic review in this assessment report; however, some of the non-randomised study evidence in the CS is presented in this assessment report for patient subgroups where randomised evidence is lacking (i.e. ERA and JIA-associated uveitis) (see *Additional supporting evidence*).

Review of Pfizer Ltd company evidence submission for etanercept

The company report a systematic review of clinical effectiveness of etanercept (in addition they report a systematic review of observational evidence on etanercept-associated innovation, caregiver burden and treatment adherence, plus a systematic review of HRQoL associated with etanercept).[97] Details of the literature search strategy are provided and the search appears to be comprehensive, up to date and reproducible. A search for ongoing studies was also conducted. A systematic process was followed to screen studies for inclusion, with titles, abstracts and full texts screened independently by two reviewers. The inclusion criteria are in keeping with the scope of the appraisal, with the exception that only studies of etanercept were included, not the other biologic DMARDs. A broad range of study designs were eligible, with the exception of case reports. The majority of the data are in the public domain, although some information is either academic-in-confidence (AiC) or CiC.

The review included 11 publications relating to five primary interventional studies and three extension studies (see CS table 7, CS page 44). It also included 41 observational studies (including registry studies) plus 2 unpublished studies (see CS table 18, CS page 81). Of the five included primary interventional studies, only one meets the inclusion criteria for the systematic review in this current report – Lovell and colleagues.[42] Of the remaining four studies, three were not relevant, as they were single-arm studies, and a fourth was a RCT reported in a conference abstract[98] with only limited detail available. However, one of the single-arm studies – the CLIPPER study[99] – is noteworthy as it focuses specifically on the JIA subtypes that were absent from the pivotal Lovell and colleagues trial,[42] namely EO JIA, ERA and PA. Details are presented in *Additional supporting evidence*.

Of the three extension studies, only one was relevant to the inclusion criteria of this assessment report, namely the long-term follow-up publications[65–67] of the Lovell and colleagues RCT,[42] all of which have been included in the data extraction for this study (see *Appendix 5*). The other two extension studies included a Japanese open-label single-arm multicentre study followed by a double-blind, randomised dose-down

extension study (two doses of etanercept – no comparator), and an open-label multicentre Phase-IIIb long-term safety and efficacy study of the CLIPPER study (reported in *Additional supporting evidence*).[99]

A critical appraisal of the interventional studies is provided in CS section 4.7. The company's appraisal of the Lovell and colleagues RCT[42] is provided in CS table 13 (CS page 62). Our critical appraisal differs slightly from the company's (see *Quantity and quality of research available*). Specifically, we did not consider that adequate details had been provided of the study's randomisation method or concealment of allocation. We also note that there was a large imbalance in drop-outs between the randomised groups (see *Table 12* and *Appendix 5*).

A narrative synthesis of the interventional and observational studies is provided in the CS, with detailed tabulation of study characteristics and results. A meta-analysis was not considered feasible or appropriate by the company, and an indirect comparison was not conducted as it was not considered feasible to conduct one owing to differences in respective marketing authorisations across biologic treatments, paucity of data and heterogeneity.

Of note, some of the observational studies of etanercept included in the CS reported (limited) data for outcomes relevant to the scope of the appraisal that were not included in the RCT by Lovell and colleagues,[42] namely corticosteroid reduction, growth and disease activity according to the JADAS (see CS section 4.12.5).

In summary, the systematic review of clinical effectiveness reported in the CS appears to be of a good standard and no additional RCTs were included in the CS that met the inclusion criteria for the systematic review in this assessment report.

Review of Roche company evidence submission for tocilizumab

The company did not conduct a formal systematic review of the clinical effectiveness evidence, but provided 'most relevant literature' on the use of tocilizumab in patients with polyarticular JIA and EO (CS page 7). There is no evidence that searches were conducted and no search strategies were reported. The CS does state that a systematic literature review was completed for the indirect comparison presented in the submission but provides no further detail. The CS did not report searching conference proceedings or details of any ongoing trials, but data from abstracts/conference proceedings are included in the submission. CiC data are limited to the economic model.

The submission contains narrative summaries of two studies. One of the studies is a RCT comparing tocilizumab with placebo (CHERISH)[68] linked to six additional conference publications/abstracts.[69,71–73,76,100] The CHERISH RCT[68] met the inclusion criteria of this assessment report and was reported above in *Results*. Of the six conference publications/abstracts linked to the CHERISH RCT, only two were related to the randomised phase of the trial[72,73] and the remaining four were related to the OLE phase. One of these four conference abstracts was not identified by searches for this assessment report, but if it had been, it would not have met the inclusion criteria as none of the outcomes reported was relevant.[100]

The other study was a single-arm open-label study of efficacy, pharmacokinetics and safety of adalimumab in Japanese patients with polyarticular JIA.[95]

The CS presents all the evidence separately for each study in the form of a narrative summary. Individual tables of baseline patient characteristics, as well as details of methods and design are reported for both the CHERISH trial[68] and the open-label Japanese study.[95] No quality assessment of the studies is presented. The CS reports growth data from the OLE phase of the CHERISH trial at week 104, which have been included in this assessment report. The assessment report contains additional data for ACR Pedi-90 responses relative to baseline at week 40 and inactive disease from the CHERISH trial, both of which are not reported in the CS.

The CS includes a hierarchical Bayesian indirect treatment comparison of adalimumab and tocilizumab, conducted in WinBUGS version 1.4 software (Medical Research Council Biostatistics Unit, Cambridge, UK) and using methods described by Dias and colleagues.[101] Limited detail is provided on the specific methods used to conduct the indirect comparison (e.g. which adalimumab trial was used to compare against tocilizumab; this is likely to be Lovell and colleagues[61] but is not explicitly stated). An indirect comparison with abatacept was not considered possible owing to the difference in trial design, the fact that it is not approved (appraised) by NICE, and also because of slight differences in licences (i.e. lower age for which treatment is indicated). We note the heterogeneity between the RCTs that increases uncertainties in any indirect comparison, although the fact that abatacept has not been appraised by NICE is not an adequate justification for not performing the comparison. The CS provides an additional analysis which assumes a class effect across antiTNF drugs (based on the indirect comparison with adalimumab which showed 'overlapping ACR response rates'), permitting a comparison between tocilizumab with etanercept (CS section 5.17). The exploratory pairwise indirect comparisons of all four biologic DMARDS presented in this assessment report showed no statistically significant differences between the drugs [see *Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus each other (with methotrexate where permitted)*].

Most of the AE and safety data are presented for the CHERISH RCT.[68] The AE data reported at week 40 (end of the randomised phase of the RCT) in the CS do not include any data for the placebo group, which is presented in this assessment report.

In summary, the CS has not conducted a systematic review of clinical effectiveness but has summarised data from the CHERISH trial and an open-label Japanese study, presented an indirect pairwise comparisons of two of the biologic DMARDs included in this appraisal (tocilizumab and adalimumab), as well as exploratory analysis comparing tocilizumab with etanercept. No additional RCTs were included in the CS that met the inclusion criteria of the assessment report.

Ongoing trials

As stated above (*Quantity and quality of research available*), citations relating to four ongoing RCTs were identified from the electronic bibliographic database literature search (see *Figure 1*) and a separate search specifically for ongoing studies identified a further three ongoing RCTs. Three trials are investigating adalimumab and four etanercept. Each trial is described, in turn, below, with preliminary results presented where possible. It should be noted that online clinical trial registers generally provide less information (and no outcome data) in comparison with published conference abstracts.

Adalimumab ongoing trial 1

This is a Phase-III, multicentre, randomised, double-blind study (NCT01166282) described by six conference abstracts (Burgos-Vargas and colleagues[88–93]) in children aged ≥ 6 to < 18 years with ERA based on ILAR criteria, with active disease not responsive to ≥ 1 NSAID and ≥ 1 DMARD. No full paper appears to have been published so far, and the six abstracts provide limited information, hence preventing a full assessment of the methodology and trial quality and risk of bias. In addition, baseline characteristics were reported only for the overall trial population and not separately for each randomised group. The estimated study completion date was December 2015; however, the study was published in full after the submission date of this report in July 2015.[102]

Forty-six patients were randomised in a 2 : 1 ratio (adalimumab $n = 31$; placebo $n = 15$) to receive blinded adalimumab (24 mg/m^2 body surface area up to 40 mg every other week) or placebo for 12 weeks followed by open-label adalimumab every other week for up to 144 weeks. It is unclear whether or not patients also received methotrexate. A table in one of the abstracts[93] shows that 11/15 placebo patients and 21/31 adalimumab patients received DMARDs at baseline.

The primary endpoint of this study was per cent change from baseline in the number of active joints with arthritis (active joint count) at week 12 and secondary variables assessed included enthesitis count, tender and swollen joint counts, and ACR Pedi-30/-50/-70 responses. Active disease was defined as ≥ 3 active joints (swelling or loss of motion and pain/tenderness) and enthesitis in ≥ 1 location (past or present). Safety was assessed in terms of AEs, laboratory values and vital sign measurements. Some interim data were reported for 52 weeks including discontinuation of concomitant medication (at the discretion of the treating physician).

Authors state that no children discontinued the double-blind period, while at the same time reporting that seven children 'escaped early' to open-label adalimumab.

Results

At baseline, children had a mean age of 12.9 years, with 2.6 mean years of ERA symptoms, and a mean enthesitis count and active joint count of 8.1 and 7.8, respectively (*Table 28*). It is unclear if baseline characteristics between the treatment groups were balanced.

Only the primary outcome per cent change from baseline in the number of active joints with arthritis showed a statistically significantly greater improvement ($p = 0.039$) in the adalimumab treatment group (–62.6) than in the placebo group (–11.6) (*Table 29*). Secondary outcomes were reported to be mostly numerically greater in the adalimumab group, but none of the improvements was statistically significant.

TABLE 28 Baseline characteristics

Parameter, mean (SD)[a]	All children
Age, years	12.9 (2.9)
ERA symptoms, years	2.6 (2.3)
AJC	7.8 (6.6)
EC	8.1 (8.4)

AJC, active joint count; EC, enthesitis count.
a Not specially stated, but presumed to be standard deviation.

TABLE 29 Results week 12

Primary outcome[a]	ADA ($n = 31$)	PBO ($n = 15$)	*p*-value
AJC, % change from baseline at week 12	–62.6 (SD 59.5) (median % change –88.9%)	–11.6 (SD 100.5) (median % change –50.0%)	0.039
Secondary outcomes, change from baseline, mean (SD)[b]			
Number of enthesitis sites (0–35)	–4.4 (6.2)	–2.7 (5.0)	NS
Tender joint count (0–72)	–7.9 (8.3)	–4.5 (9.0)	NS
Swollen joint count (0–8)	–3.5 (5.6)	–2.4 (4.7)	NS
ACR Pedi response,* n *(%)[c]			
ACR Pedi-30 responder	21 (67.7)	10 (66.7)	NS
ACR Pedi-50 responder	20 (64.5)	7 (46.7)	NS
ACR Pedi-70 responder	16 (51.6)	4 (26.7)	NS

ADA, adalimumab; AJC, active joint count; PBO, placebo; NS, not significant.
a Presumed mean and SD, but not specifically stated.
b Last observation carried forward.
c Analysed with non-responder imputation.

Adverse events

Only one patient (in the adalimumab group) experienced a SAE (abdominal pain and headache). Around two-thirds of the children in the adalimumab treatment group and just over half in the placebo group experienced an AE, whereas nearly one-third of children in the adalimumab treatment group but only one-fifth in the placebo group experienced infectious AEs (*Table 30*).

Open-label week-52 results

The authors state that treatment response was maintained with continued adalimumab therapy up to 52 weeks [% change from baseline at week 52 in active joint court: –88.7 (SD 26.1)]. In those receiving at least one dose of adalimumab through to week 52, > 91% of children experienced an AE and > 76% experienced infectious AEs (*Table 31*). SAEs were reported in approximately 11% of children, with no reported deaths, tuberculosis or malignancies. Eight (19%) of the 43 participants who remained in the study at week 52 had completely discontinued concomitant ERA medication.

Adalimumab ongoing trial 2

The second adalimumab RCT (SYCAMORE, ISRCTN10065623)[87] is funded by the NIHR HTA programme and Arthritis Research UK. The study is assessing adalimumab combined with methotrexate compared with placebo combined with methotrexate for JIA-associated uveitis in participants aged between 2 and 18 years. All participants will receive 18 months of treatment with a 3-year follow-up. The study will also include an assessment of cost-effectiveness. Originally expected to report findings in 2020, it has recently been announced that the trial has closed for recruitment early following interim analysis showing a favourable effect for adalimumab. Analysis of the primary outcome is under way and key findings will therefore be available earlier than expected. Collection and analysis of health economic data will continue as planned.

TABLE 30 Adverse events week 12

AEs	ADA (*n* = 31), %	PBO (*n* = 15), %
Any AE	67.7	53.3
SAE	3.21 (1 patient)	0
Infectious AE	29.0	20.0

ADA, adalimumab; PBO, placebo.

TABLE 31 Adverse events in children receiving > 1 dose of adalimumab to week 52

AEs	ADA, %[a]
Any AEs	91.3
SAEs	10.9
Infectious AEs	76.1

ADA, adalimumab.
a Number of patients receiving ADA treatment during open label not reported.

Adalimumab ongoing trial 3

This third adalimumab RCT [Effect of Adalimumab for the Treatment of Uveitis in Juvenile Idiopathic Arthritis (ADJUVITE); NCT01385826] is also currently in progress and is not expected to report findings until June 2016. The study is set in France (seven hospital ophthalmology departments) and assesses the efficacy of 2-month adalimumab treatment versus placebo treatment on reduction of ocular inflammation quantified by laser flare photometry in patients aged ≥ 4 years, with JIA-associated uveitis that is resistant to steroid therapy. The investigators plan to include 40 patients, follow-up appears to be 12 months and the final data collection date for the primary outcome measure is November 2015. The primary endpoint of this study is improvement of uveitis.

Etanercept ongoing trial 1

This is a RCT evaluating the efficacy of etanercept in 124 Chinese JIA patients (no clinical trial registration number has been found for this study).[98] No full paper appears to have been published so far and only one conference abstract was identified, which includes very limited information. The abstract states that a 'randomised principle was applied' to divide the JIA patients into a control and a treatment group. Although no baseline characteristics were reported, the authors of the abstract state that there were no significant differences of clinical classification and basic treatment between the groups.

Sixty-two patients in the treatment group (oligoarticular JIA $n = 17$, polyarticular JIA $n = 15$ and systemic JIA $n = 30$) received 0.8 mg/kg per week of subcutaneous etanercept for 6 months. No details for the control group are reported.

American College of Rheumatology Pedi-30, -50 and -70 responses were used to assess the clinical efficacy (primary outcome not stated) and adverse reactions were recorded.

Results

The authors state that the remission rates 'of different cases' (this is presumed to mean different types of JIA) in the treatment group differed at each time point (3- and 6-month time points are mentioned), with no obvious difference in ACR Pedi-30, -50 and -70 remissions for patients with oligoarticular and polyarticular JIA. Eighty per cent of these patients had ACR Pedi-50 remission after 6 months of treatment and > 50% had ACR Pedi-70 remission. The remission rate of systemic JIA cases was lower than the two other types (data not extracted). Although the differences between the randomised groups are said to be significant, no data were reported.

Adverse events

There were no reported AEs for patients with oligoarticular or polyarticular JIA. Details of AEs for the systemic JIA subgroup are reported (not extracted).

Etanercept ongoing trial 2

The second placebo-controlled etanercept RCT [Remission Induction by Etanercept in Enthesitis related Arthritis JIA-Patients (REMINDER) Study, EudraCT Number: 2010–020423–51] was identified from the search of ongoing clinical trials registers. The trial is set in Germany and has a start date of February 2016. This study has a withdrawal RCT design, with a 12-week open-label treatment phase prior to the controlled randomised double-blind phase The study will assess the safety and effectiveness of etanercept in patients diagnosed with ERA-JIA age ≥ 6 years and < 18 years having met all criteria for eligibility for treatment with etanercept according to SPC and local guidelines, with expectation of the requirement of a minimum of five affected joints. The online record does not provide the treatment time for the double-blind phase or report any follow-up period. The primary endpoint of the study will be inactive disease of ERA-JIA.

Etanercept ongoing trial 3

The third multicentre etanercept RCT was identified from a conference abstract[103] which does not provide a clinical trial registration number. This trial appears to be set in Germany, has enrolled patients with ERA and has a withdrawal design, with a 24-week open-label etanercept treatment phase prior to the 24-week placebo-controlled double-blind withdrawal phase. Patients had to achieve at least an ACR Pedi-30 response in order to be randomised to the double-blind phase (terminated in case of a disease flare or at week 48, whichever occurs earlier). No details of the study's inclusion or exclusion criteria are reported in the abstract.

Results

Forty-one patients entered the open-label phase, of whom two patients discontinued prematurely (one owing to intolerance and one owing to protocol deviation). Thirty-eight patients (93%) achieved at least an ACR Pedi-30 response and were randomised to the double-blind phase. As can be seen in *Table 32*, during the double-blind phase the majority of flares occurred in the placebo group, with 10 (56%) placebo-treated patients compared with 18 (90%) etanercept-treated patients reaching week 48 without a flare [odds ratio 7.2 placebo vs. etanercept (1.3 to 40.7; although not stated, this is presumed to be a 95% CI); $p = 0.016$].

The authors state that in patients continuously treated with etanercept at week 48 ($n = 20$), JADAS 10 decreased to a mean of 3.4 (17.4 to 1.9 at week 24), with 12 (60%) patients reaching JADAS-minimal disease activity and 11 (55%) JADAS remission. The equivalent data for the placebo group are not reported.

Adverse events

There were 166 AEs in 39 patients and three SAEs. All were said to be considered unrelated and resolved without sequelae. It is unclear if these data are for the combined open-label and double-blind phases, but considering the number of patients reported ($n = 39$) this may indeed be the case.

Etanercept ongoing trial 4

The fourth multicentre etanercept RCT (set in the Netherlands) assessed when and in whom to stop etanercept after successful treatment of JIA (NCT01287715) and was identified from the search of ongoing clinical trials registers. Estimated enrolment was 50, the study completed in September 2013 and final data collection for the primary outcome measure is reported as September 2012 in the online record. No publication of data has been identified. Patients aged 4–17 years and in remission were selected from the National Arthritis and Biologicals in Children (ABC) register, an observational study including all Dutch JIA patients on etanercept therapy. The inclusion criteria states no or low dose of methotrexate and it is therefore unclear if patients were intolerant or had a previous inadequate response to methotrexate. All JIA subtypes were included in the study. Patients were randomised to a stop arm (discontinuation of etanercept – half of the dose for 3 months and discontinuation thereafter) or a control arm (etanercept continued for another 9 months and, if still meeting the eligibility criteria, discontinued thereafter). The primary outcome of the study was flare rate.

TABLE 32 Flares: 24-week double-blind phase

Time	ETA ($n = 20$)	PBO ($n = 18$)
Week 28	2	2
Week 32	0	4
Week 48	0	2

ETA, etanercept; PBO, placebo.

Additional supporting non-randomised evidence

This section includes additional non-randomised study evidence relating to aspects of JIA where adequate RCT data in the systematic review of clinical effectiveness were lacking. This evidence has been identified from the systematic review search itself, and from relevant studies included in the CSs to NICE (see *Review of clinical effectiveness in company submissions to the National Institute for Health and Care Excellence*). Evidence relating to two aspects is presented: JIA ERA and PA subtypes, and JIA-associated uveitis.

Enthesitis-related arthritis and psoriatic arthritis

The most informative study available for these subtypes is the CLIPPER study.[99]

This is a single-arm, Phase-IIIb open-label, multicentre interventional study funded by Wyeth (subsequently acquired by Pfizer Inc.). The study was designed to assess the safety and efficacy of etanercept in children and adolescents with three JIA subtypes classified using the ILAR criteria: EO, ERA and PA. There are two parts to the study. Part 1 (which has been published[99]) has investigated the efficacy and safety of etanercept in the three JIA subtypes over an initial 12-week period with a primary endpoint of the percentage of patients achieving ACR Pedi-30 criteria at week 12. Part 2 of the study is a 96-week OLE, assessing the long-term safety and efficacy of etanercept in JIA subtypes, which is currently published in poster format only.[104] This study formed part of the evidence base supporting the licence extension for etanercept across the JIA subtypes in 2012. The assessment group has extracted 12-week data from the published paper[99] on ACR Pedi response rates and inactive disease, change in CHAQ score, PGA of pain, number of active joints, number of joints with LOM and JIA category-specific assessments (data at week 12 compared with historical placebo data, historical active control data and data from a meta-analysis have not been data extracted). Data from the conference poster[104] on ACR Pedi response rates and inactive disease have also been extracted and this summary is supplemented with some data presented in the Pfizer CS.

The study included 127 patients with the JIA subtypes of ERA ($n = 38$, age 12–17 years), EO ($n = 60$, age 2–17 years) and PA ($n = 29$, age 12–17 years) who received 0.8 mg/kg of etanercept once weekly (maximum dose 50 mg/week). Key inclusion criteria were ≥ 2 active joints (swollen or LOM accompanied by either pain or tenderness); history of intolerance or unsatisfactory response to at least a 3-month course of ≥ 1 DMARD or, for ERA only, unsatisfactory response to at least a 1-month course of ≥ 1 NSAID (i.e. for ERA, prior methotrexate treatment was not required). A stable dose of concomitant medication (only one DMARD, one oral corticosteroid and one NSAID) was permitted. The inclusion criteria extended below the threshold number of active joints for the classification of polyarticular disease. Key exclusion criteria included other rheumatic diseases, active uveitis within 6 months of baseline and any prior receipt of biologic DMARDs. A total of five patients failed to complete part 1 of the study (completed part 1: EO 97%, ERA 95% and PA 97%) and 13 patients part 2 (completed part 2: EO 90%, ERA 79% and PA 86%).

Key baseline characteristics can be seen in *Table 33* (additional baseline characteristics are available in the published paper[99]).

TABLE 33 Key baseline characteristics

Parameter [mean (SD) unless stated otherwise]	All patients ($n = 127$)	EO ($n = 60$)	ERA ($n = 38$)	PA ($n = 29$)
Age, years	11.7 (4.5)	8.6 (4.6)	14.5 (1.6)	14.5 (2.0)
Female, %	56.7	68.3	21.1	79.3
JIA duration	26.8 (26.4)	31.6 (31.7)	23.0 (19.8)	21.8 (20.2)
Age at onset, months	9.5 (4.8)	6.1 (4.5)	12.5 (2.1)	12.6 (2.7)
Concomitant medication use, *n* (%)				
Any DMARD	109 (85.8)	54 (90.0)	32 (84.2)	23 (79.3)
Oral corticosteroid	16 (12.6)	7 (11.7)	8 (21.1)	1 (3.5)
Oral NSAID	74 (58.3)	32 (53.3)	26 (68.4)	16 (55.2)
Number of active joints	6.7 (4.6)	7.6 (5.1)	5.2 (3.6)	7.0 (4.3)
Number of joints with LOM	5.7 (4.2)	6.3 (4.4)	4.8 (4.0)	5.6 (4.1)
Number of painful joints	6.4 (5.2)	5.5 (4.1)	6.7 (4.9)	7.8 (7.0)
Number of swollen joints	5.5 (4.2)	6.5 (4.8)	3.8 (2.8)	5.6 (3.7)
CHAQ score[a]	0.8 (0.6)	0.9 (0.7)	0.7 (0.5)	0.7 (0.6)
Parent global assessment pain (VAS)	5.1 (2.5)	4.8 (2.6)	5.8 (25)	4.6 (2.3)
JIA category-specific characteristics				
Tender entheseal score			5.9 (9.4)	
Overall back pain VAS, mm			25.9 (28.0)	
Nocturnal back pain VAS, mm			16.4 (27.8)	
Modified Schober's test, cm			15.0 (1.9)	
Psoriasis BSA, %				10.4 (13.4)
Parent global assessment of psoriasis				1.8 (1.4)

BSA, body surface area.
a CHAQ: 0–3 scale, no disability-severe disability; VAS: parent global assessment pain 0–10, overall and nocturnal back pain 0–100.

Patients with EO and PA had a higher number of active joints and number of joints with LOM [EO: mean 7.6 (SD 5.1) and 6.3 (SD 4.4), respectively; PA: mean 7.0 (SD 4.3) and 5.6 (SD 4.1), respectively] at baseline than ERA patients [mean 5.2 (SD 3.6) and 4.8 (SD 4.0), respectively]. The number of painful joints was highest in PA patients [mean 7.8 (SD 7.0)] compared with the other two subgroups, and the number of swollen joints was the lowest in ERA patients [mean 3.8 (SD 2.8)] (*Table 34*). Mean CHAQ subgroup scores ranged between 0.7 and 0.9, and the parent global assessment of pain VAS ranged between 4.6 and 5.8. Also reported are JIA category-specific assessments [ERA: tender entheseal score, back pain (VAS) and modified Schober's test; PA: body surface area and PGA of psoriasis] at baseline. Limitations of the study noted by the authors were the difference in concomitant medication use at baseline which may have affected efficacy responses and the lower age limit of 12 years set for inclusion of EO patients (the licensed indication is from 2 years of age).

TABLE 34 American College of Rheumatology Pediatric response and inactive disease results at week 12 and week 96 (CiC information has been removed)

	All patients ($n = 127$)		EO ($n = 60$)		ERA ($n = 38$)		PA ($n = 29$)	
Parameter	***n***	**% (95% CI)**	***n***	**% (95% CI)**	***n***	**% (95% CI)**	***n***	**% (95% CI)**
Week 12								
ACR Pedi-30	CiC information has been removed	88.6 (81.6 to 93.6)	CiC information has been removed	89.7 (78.8 to 96.1)	CiC information has been removed	83.3 (67.2 to 93.6)	CiC information has been removed	93.1 (77.2 to 99.2)
ACR Pedi-50		81.1 (73.1 to 87.7)		CiC information has been removed		CiC information has been removed		CiC information has been removed
ACR Pedi-70		61.5 (52.2 to 70.1)						
ACR Pedi-90		29.8 (21.8 to 38.7)						
Inactive disease	12.1 (6.9 to 19.2)		11.9 (4.9 to 22.9)		16.7 (6.4 to 32.8)		6.9 (0.8 to 22.8)	
Week 96[a]	***All patients* (n = *108*), % (95% CI)**		***EO***[b] **(n = *53*), %**		***ERA***[b] **(n = *30*), %**		***PA***[b] **(n = *25*), %**	
ACR Pedi-30	99.1 (94.9 to 100)		99		100		98	
ACR Pedi-50	98.1 (93.5 to 99.8)		99		97		98	
ACR Pedi-70	92[b]		94		87		98	
ACR Pedi-90	65.4 (55.6 to 74.4) ($n = 107$)		62		67		72 ($n = 24$)	
ACR Pedi-100	54[b] ($n = 107$)		54		51		60 ($n = 24$)	
Inactive disease	34 (25.0 to 43.8) ($n = 106$)		37		29 ($n = 28$)		29	

a Efficacy analyses were based on observed data.
b Data estimated by reviewer from poster graphs using Engauge digitizer (version 4.1, © Mark Mitchell) software[104] CiC data are unpublished, taken from the CS.

Results

At week 12, the overall ACR Pedi-30 response rate for patients was almost 89%, with response for the separate JIA disease type subgroups varying from around 83% to 93% (see *Table 34*). The overall ACR Pedi-90 response rate for patients was just under 30%, and 12% of patients had inactive disease. JIA disease subgroups varied in ACR Pedi-90 response rates between (CiC information has been removed). At week 12, 12%, 17% and 7% of EO, ERA and PA patients, respectively, had inactive disease, as can be seen in *Table 34*.

By week 96, around 99% of all patients achieved a ACR Pedi-30 response and > 65% an ACR Pedi-90 response. Thirty-four per cent of all patients had inactive disease. Overall, patients in the ERA subgroup appeared to have received the greatest benefit from etanercept therapy at 12 weeks, but by 96 weeks the subgroups achieved similar levels of ACR Pedi-90 (62% to 72%) and ACR Pedi-100 (51% to 60%) responses. Inactive disease at 96 weeks varied between 29% (ERA and PA) and 37% (EO). (CiC information has been removed.)

At week 12 mean change from baseline for CHAQ scores were similar for the subgroups (improvement of 51% to 58%), but there were differences in the parent global assessment of pain VAS. The lowest mean change in pain VAS occurred in patients with ERA and PA (decreases of 45% and 47%, respectively) compared with patients with EO (59% decrease). The mean decreases from baseline for the number of active joints ranged between 70% and 78% and between 64% and 72% for the number of joints with LOM (*Table 35*). It is unclear why details about changes from baseline for the number of painful and the number of swollen joints are not reported.

TABLE 35 Mean change from baseline week effectiveness measures at week 12 (observed cases)

Parameter	Overall ($n = 123$), mean (95% CI) [% change]	EO ($n = 58$), mean (95% CI) [% change]	ERA ($n = 36$), mean (95% CI) [% change]	PA ($n = 29$), mean (95% CI) [% change]
CHAQ	−0.5 (−0.6 to −0.4) [−53.6]	−0.5 (−0.7 to −0.4) [−52.2]	−0.5 (−0.7 to −0.3) [−57.8]	−0.4 (−0.6 to −0.2) [−51.3]
Parent global assessment of child's pain VAS	−3.0 (−3.5 to −2.6) [−51.9]	−3.2 (−3.8 to −2.5) [−58.9]	−3.2 (−4.2 to −2.2) [−44.9]	−2.6 (−3.4 to −1.8) [−46.6]
Number of active joints	−5.1 (−5.8 to −4.3) [−73.0]	−5.5 (−6.7 to −4.2) [−69.8]	−4.3 (−5.4 to −3.1) [−77.7]	−5.2 (−6.8 to −3.6) [−73.8]
Number of joints with LOM	−4.1 (−4.8 to −3.4) [−66.9]	−4.5 (−5.6 to −3.3) [−64.1]	−3.4 (−4.1 to −2.6) [−67.4]	−4.3 (−5.7 to −2.9) [−71.7]
JIA category-specific assessments				
Tender entheseal score			−4.4 (−6.3 to −2.4) [−57.8]	
Overall back pain VAS, mm			−12.5 (−21.3 to −3.7) [−21.2]	
Nocturnal back pain VAS, mm			−8.9 (−16.7 to −1.2) [−6.8]	
Modified Schober's test, cm			0.35[a] (−0.02 to 0.72) [9.7] ($n = 35$)	
Psoriasis BSA, %				−6.7 (−10.6 to −2.9) [−48.2]
PGA of psoriasis				−1.0 (−1.4 to −0.6) [−39.6] ($n = 28$)

BSA, body surface area.
a Change from baseline calculated after subtracting 10 from the baseline and week 12 scores.

The greatest improvements in JIA category-specific assessments was a 58% improvement from baseline in tender entheseal score at 12 weeks in patients with ERA, and for patients with PA a 48% improvement in body surface area of psoriasis and a 40% improvement in PGA of psoriasis (see *Table 35*).

Adverse events

The highest number of treatment-emergent AEs per patient-year of etanercept exposure occurred in the ERA subgroup (1.827; EO: 1.313; PA: 1.036), which also had the lowest number of treatment-emergent infections per patient-year of etanercept treatment (0.979; EO subgroup: 2.114; PA: 1.514). As *Table 36* illustrates, patients with ERA appear to experience more treatment-related injection-site reactions than patients with either EO or PAA.

Treatment-emergent AEs leading to patient withdrawal occurred only in the ERA subgroup (events 3, etanercept exposure 7.9), and there were two events of treatment emergent infections causing withdrawal (one each in the EO and PA groups). The rate of serious treatment-emergent AEs and serious treatment-emergent infections appears to be low in all three subgroups (see *Table 36*), as does the rate of treatment-emergent autoimmune disorder events. Of the two cases of uveitis (EO $n = 1$, PA $n = 1$), one was reported in a patient with EO after 7.8 months of etanercept plus methotrexate. This resolved and the patient completed the 96-week study. There were a total of three cases of Crohn's disease in patients with ERA, of which two cases were considered to be unrelated to etanercept therapy.

TABLE 36 Adverse events at week 96

All values are reported as number of events (events per patient-year of exposure to etanercept) unless otherwise stated	Overall ($n = 127$) EXP = 215.086	EO ($n = 60$) EXP = 103.603	ERA ($n = 38$) EXP = 61.298	PA ($n = 29$) EXP = 50.185
Treatment-emergent AEs[a]	300 (1.395)	136 (1.313)	112 (1.827)	52 (1.036)
Treatment-emergent infections	355 (1.651)	219 (2.114)	60 (0.979)	76 (1.514)
Treatment-emergent ISRs	63 (0.293)	22 (0.212)	29 (0.473)	12 (0.239)
Treatment-emergent AEs causing withdrawal, *n* (%)[a]	3 (2.4)	0	3 (7.9)	0
Treatment-emergent infections causing withdrawal, *n* (%)	2 (1.6)	1 (1.7)	0	1 (3.4)
Serious treatment-emergent AEs[a]	16 (0.074)	2 (0.019)	11 (0.179)	3 (0.060)
Serious treatment-emergent infections	10 (0.046)	4 (0.039)	3 (0.049)	3 (0.060)
Opportunistic infections[b]	1 (0.005)	0	1 (0.016)	0
Infections considered preventable by vaccination in patients not previously vaccinated	7 (0.033)	5 (0.048)	1 (0.016)	1 (0.020)
Infections considered preventable by vaccination in patients previously vaccinated	1 (0.005)	1 (0.010)[c]	0	0
Treatment-emergent autoimmune disorders[d]	4 (0.019)	1 (0.010)	2 (0.033)	1 (0.020)

EXP, etanercept exposure; ISR, injection-site reaction.
a Excluding infections and ISRs.
b One case of herpes zoster affecting two dermatomes was considered an opportunistic infection and one case of latent tuberculosis (purified protein derivative conversion) was not considered an opportunistic infection.
c One case of rubella.
d Two cases of uveitis (EO and PA subtypes), one case of iridocyclitis (a subtype of uveitis; ERA subtype) and one case of Crohn's disease (ERA subtype) were treatment emergent. One case of Crohn's disease (ERA subtype) was not considered treatment emergent based on missing last-dose data.

Juvenile idiopathic arthritis-associated uveitis

As stated earlier, the effects of biologic DMARD on extra-articular manifestations such as uveitis were not assessed by the included RCTs. However, evidence from non-randomised studies is available, as summarised by systematic reviews.

A recently published systematic review by Simonini and colleagues[96] assessed the effectiveness of antiTNF drugs for childhood uveitis. To be included, studies had to include patients with autoimmune uveitis refractory to topical and/or systemic steroids and at least one immunosuppressive therapy (e.g. methotrexate). The antiTNFα drugs of relevance to the review were etanercept, infliximab and adalimumab (infliximab is not within the scope of this NICE appraisal). The primary outcome was improvement in intraocular inflammation, with additional outcomes including tapering/stopping systemic steroid administration, improvement in visual acuity and treatment discontinuation among others. A number of bibliographic databases were searched from January 2000 to October 2012.

The review included 23 studies, mainly retrospective chart reviews with very small patient numbers. Of these 23 studies, only 7 were conducted exclusively in JIA uveitis patients (one RCT of etanercept; two retrospective studies of etanercept; two retrospective studies of infliximab; and two retrospective studies of adalimumab). Eleven studies comprised mixed study populations with uveitis associated with a range of conditions, including JIA. The remaining five studies included populations that did not include any children with JIA. It was not possible to analyse results separately by uveitis-associated condition. However, of the 229 children included across all the studies, 152 had chronic uveitis associated with JIA. The results can therefore be interpreted as being generally relevant to JIA uveitis.

A pooled analysis of the observational studies found that adalimumab and infliximab were more efficacious at improving intraocular inflammation than etanercept. The proportion of children with improved intraocular inflammation (responders) was 87% (95% CI 75% to 98%) for adalimumab, 72% (95% CI 64% to 79%) for infliximab, and 33% (95% CI 19% to 47%) for etanercept. There was no statistically significant difference in the proportion of responders between adalimumab and infliximab ($p = 0.08$), but there was a significant difference for both compared with etanercept ($p = 0.001$ for both comparisons).

Simonini and colleagues[96] did not pool the results of the single RCT identified in the systematic review with the observational studies.[56] This was a small RCT ($n = 12$ children) of treatment with etanercept. The authors state that this study did not report substantial benefits for the biologic treatment. (Owing to limitations in reporting, this RCT was judged to be unclear for inclusion in our systematic review of clinical effectiveness, as it was not clear whether or not the etanercept was given within its licensed indication). Caution is advised in the interpretation of the findings of the Simonini and colleagues[96] systematic review given the weaknesses of the study designs included.

The assessment group are aware of only one other recent systematic review of biologic DMARD treatment of children with uveitis, by Cordero-Coma and colleagues.[105] The most recent search date for literature was October 2011. This review had a broader inclusion criteria than that of Simonini and colleagues[96] and a total of 61 studies was included. Again, much of the included evidence was from observational studies. A total of 14 studies assessed adalimumab, 11 assessed etanercept and 50 studies assessed infliximab [studies assessing certolizumab and golimumab were also included]. Of the 1093 patients included across the studies, 316 (30%) were classed as having JIA uveitis. The review does not provide any formal synthesis and quantification of the effectiveness of treatment, but provides a narrative conclusion for each biologic DMARD and a level of evidence. Adalimumab and infliximab were considered by the authors to be effective in autoimmune uveitis, both based on level-2b evidence (individual cohort study or low-quality RCT). Etanercept was judged ineffective, based on level-1b evidence (individual RCTs with narrow CIs).

The Abbvie CS to NICE[77] provides narrative summaries of five selected studies published since the Simonini and colleagues[96] systematic review. All of them were observational in design (three case series;[106–108] one Italian registry-based study;[109] one comparative cohort study[110]), and all assessed treatment with adalimumab (with one also assessing infliximab[110] in uveitis patient populations with varying proportions of JIA uveitis. We have not performed an independent critical appraisal of these studies in this assessment report. From the summaries given it appears that adalimumab is associated with improvements in intraocular inflammation and visual acuity, and a decrease in use of corticosteroids. AEs appeared to be minor. The other CSs to NICE did not present much detail of studies of treatment of JIA uveitis with other biologic DMARDs.

In summary, the evidence from observational studies suggests that biologic DMARDs can improve uveitis symptoms in children with JIA, such as intraocular inflammation. Adalimumab and infliximab appear to be more effective than etanercept in improving uveitis. The effects of the treatments in terms of arthritis outcomes in JIA uveitis patients have not been reported. As noted above (see *Ongoing trials*), the UK-based SYCAMORE RCT[87] has investigated adalimumab in the treatment of JIA uveitis patients, and the results of the trial (which will be available sooner than expected, although an exact date has not been specified) will provide more rigorous evidence for effectiveness than that currently available.

Chapter 5 Economic analysis

Introduction

The aim of the economic evaluation is to assess the cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for people with JIA compared with alternative treatments. The economic evaluation comprises:

- a systematic review of the cost-effectiveness of biologic DMARDs for people with JIA
- a systematic review of studies of the HRQoL of people with JIA
- a critical appraisal of the submissions from the relevant drug companies received as part of the NICE appraisal process
- a de novo economic model and cost-effectiveness evaluation developed by Southampton Health Technology Assessments Centre (SHTAC) to inform the NICE appraisal.

Systematic review of cost-effectiveness evidence

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations of the biologic DMARDs, within the NICE scope for this appraisal. Studies were included if they were full economic evaluations (cost-effectiveness, cost–utility, cost–consequence or cost–benefit analyses) conducted in children and young people with JIA that compared one or more biologics with a DMARD, such as methotrexate. Studies that were not reported in the English language or that did not provide sufficient information on the model structure, data and results were excluded. This systematic review aimed to summarise the currently available evidence and inform the construction of a de novo model.

Results of the systematic review

Searches for economic evaluations identified 387 potentially relevant references, and a further study was identified through ad hoc searching. The full texts for 17 papers were retrieved for further screening. A summary of the selection process and the reasons for exclusion are presented in *Figure 6* and a list of excluded studies can be found in *Appendix 6*. Although seven studies reported as abstracts appeared to meet the a priori inclusion criteria, they did not contain sufficient information on the methods used and the results to permit formal data extraction or critical appraisal.[111–117] Five studies were found not to be economic evaluations.[118–122] Four studies were included, described in a total of five publications.[123–127] The characteristics of the four included economic evaluations are shown in *Table 37*. Data extraction forms for the studies can be found in *Appendix 7*.

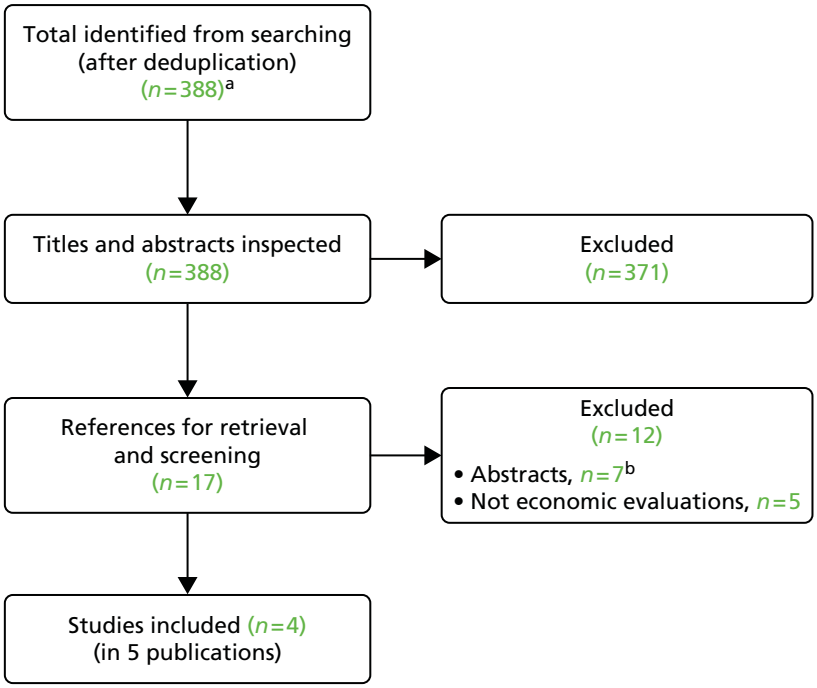

FIGURE 6 Flow chart of identification of studies for inclusion in the review of cost-effectiveness. a, including one study found through hand searching; b, the abstracts provided insufficient details of methods and results to allow inclusion in the systematic review.

TABLE 37 Characteristics of economic evaluations

Characteristic	Cummins *et al.* (2002)[123]	Prince *et al.* (2011)[124]	Simpson *et al.* (2012)[125]	Costa *et al.* (2010)[126] and Ungar *et al.* (2011)[127]
Country	UK	Netherlands	Russia	Canada
Funding source	UK HTA programme	Dutch Board of Health Insurance and Wyeth International	Not stated	Ontario Ministry of Health and Long-term Care Drug Innovation Fund
Analysis type	Cost–utility analysis	Cost–consequence analysis	Cost–utility analysis	Cost-effectiveness analysis
Perspective	Health-care system	Health-care system	Health-care system and societal	Societal
Study population	Children with polyarticular juvenile rheumatoid arthritis	Dutch JIA patients younger than 18 years eligible for treatment with etanercept; various types of JIA	Patients from adalimumab trial:[61] children aged 4–17 years with JIA	Patients with JIA with a prior inadequate response to, or intolerance of, DMARDs
Intervention(s)	Etanercept	Etanercept	Adalimumab	Etanercept, adalimumab, abatacept and infliximab vs. methotrexate
Intervention effect	Effect size measured in terms of CHAQ and mortality. Cost per HAQ point	Six response variables measured, including overall assessment of well-being, CHAQ score and number of active joints. HUI3 also measured	CHAQ scores and active joint counts	Proportion of patients who had a reduction in symptoms at 1 year according to the ACR Pedi-30 criteria

TABLE 37 Characteristics of economic evaluations (*continued*)

Characteristic	Cummins *et al.* (2002)[123]	Prince *et al.* (2011)[124]	Simpson *et al.* (2012)[125]	Costa *et al.* (2010)[126] and Ungar *et al.* (2011)[127]
Currency base	UK pounds (GBP, £)	Euros (EUR, €)	Russian roubles (RUB)	Canadian dollars (CAD, $)
Model type, health states	Not clear	None	Markov model	Decision-analysis model
Time horizon	Life course	27 months	7 years/lifetime	1 year
Base-case results	Incremental cost £28,022; incremental effectiveness in terms of QALY 1.7; ICER £16,082 Sensitivity analysis ICER varied from £3900 to £34,000	HUI3 score increases from 0.53 to 0.78 after 28 months; total direct medical costs were €12,478 per patient-year after start of etanercept compared with €3720 before start	For a lifetime horizon, the incremental cost–utility ratio for adalimumab vs. conventional non-biologic therapy was 1,571,500 RUB/QALY	Costs per ACR Pedi-30 responder were $26,061, $46,711, $16,204 and $31,209 for etanercept, adalimumab, abatacept and infliximab, respectively, compared with methotrexate

HAQ, Health Assessment Questionnaire; HUI3, Health Utilities Index-3; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Critical appraisal of the studies

The cost-effectiveness studies were assessed using a critical appraisal checklist (*Table 38*). The checklist assessed study quality and generalisability to the UK. The checklist was adapted by the review authors from checklists by Philips and colleagues,[128] Drummond and colleagues[129] and methodological requirements stated in the NICE reference case.[130]

The Cummins and colleagues study was conducted in the UK,[123] whereas the generalisability of the other studies to the NHS is unclear. The other studies were conducted in the Netherlands,[124] Russia[125] and Canada;[127] used appropriate modelling methodology; and included relevant costs.

In terms of the analytical and modelling methodology used, the studies were generally considered appropriate, except for the model reported in Cummins and colleagues,[123] which was based upon a number of questionable assumptions as a result of limitations in the data available at the time.

The data inputs for the model were clearly described and justified by two studies,[123,127] but the description of some of the data inputs are missing from Simpson and colleagues.[125] Prince and colleagues[124] conducted a cost–consequence analysis based on a prospective observational study that collected cost and utility data. The study did not measure quality-adjusted life-years (QALYs).

Two of the studies, Cummins and colleagues[123] and Simpson and colleagues,[125] used appropriate time horizons, measured the health outcomes in QALYs and discounted costs and outcomes. The model by Ungar and colleagues[127] did not use QALYs in the model and used a 1-year time horizon, eliminating the need for discounting.

All three modelling studies analysed results incrementally and assessed uncertainty through sensitivity analyses.[123,125,127]

In summary, the cost-effectiveness studies have certain limitations with regard to methodology, reporting of results or generalisability to the UK NHS (see *Table 38*).

TABLE 38 Critical appraisal checklist for economic evaluations

Item	Cummins *et al.* (2002)[123]	Prince *et al.* (2011)[124]	Simpson *et al.* (2012)[125]	Costa *et al.* (2010)[126] and Ungar *et al.* (2011)[127]
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Yes	Yes	Yes	Yes
2. Is the setting comparable to the UK?	Yes	Unclear	Unclear	No
3. Is the analytical and modelling methodology appropriate?	No	Yes[a]	Yes	Yes
4. Are all the relevant costs and consequences for each alternative identified?	No	Yes	Yes	Yes
5. Are the data inputs for the model described and justified?	Yes	N/A	No	Yes
6. Are health outcomes measured in QALYs?	Yes	No	Yes	No
7. Is the time horizon considered appropriate?	Yes	No	Yes	No
8. Are costs and outcomes discounted?	Yes	No	Yes	No
9. Is an incremental analysis performed?	Yes	Unclear[a]	Yes	Yes
10. Is uncertainty assessed?	Yes	No[a]	Yes	Yes

N/A, not applicable; QALY, quality-adjusted life-year.
a The methodology is appropriate for a cohort-based evaluation; however, a full incremental cost–utility analysis has not been performed.

Cummins and colleagues[123]

Approach

The Cummins and colleagues[123] study consisted of a HTA conducted as part of the NICE appraisal of etanercept for JIA (NICE TA35).[131] The HTA includes a systematic review of clinical effectiveness and a critical appraisal of a CS to NICE from Wyeth Laboratories (manufacturer of etanercept). The HTA does not provide an independent economic model owing to considerable uncertainties in the available evidence for JIA at that time. The CS contained a cost–utility analysis of etanercept in patients with JIA, compared with other treatment options. The cost–utility model was based upon a model developed for rheumatoid arthritis in adults. The model used the results from the etanercept RCT by Lovell and colleagues.[42] The model assumed a positive linear relationship between the Health Assessment Questionnaire (HAQ) score and costs, modelling responders, non-responders and deaths at each time point.

The model used European Quality of Life-5 Dimensions (EQ-5D™) values derived from mapping HAQ values in adult rheumatoid arthritis patients. Mortality was related to HAQ values, with a 38% increase in mortality per unit change in HAQ. The model assumed a RR of mortality in JIA.

Estimation of effectiveness

The HAQ progression rate was 0 for responders for 0–4 years, 0.034 for responders after 4 years and 0.0669 for non-responders. No definition was given for response.

Cummins and colleagues[123] reported the evidence limitations attributable to limited or non-existent long-term data on efficacy and lifelong impacts of the disease and treatment. The Juvenile Rheumatoid Arthritis-30 efficacy measure was assumed to be equivalent to ACR Pedi-20, HAQ and CHAQ were assumed equivalent, and utility and mortality were derived from an adult rheumatic arthritis trial. Owing to limited evidence on potential adverse effects, disease progression and long-term prognosis for treatment-resistant JIA, assumptions were made in the economic evaluation that are insufficiently supported. The authors of the review expressed concerns about the validity of the economic model and the assumptions made to extrapolate beyond the limited evidence base.

Estimation of quality-adjusted life-years

Utility values were derived from EQ-5D estimates for adults with rheumatoid arthritis, as there was limited evidence on HRQoL in JIA. The model assumed that the HAQ was equivalent to CHAQ and that adult values were therefore appropriate for children. The HAQ score for the placebo arm was 1.3 at baseline and 1.2 after 7 months, and the HAQ score for the etanercept arm was 1.6 at baseline and 0.8 at 7 months (lower scores indicate better health). In the base case, the model reported a 1.7 incremental QALY gain in favour of etanercept. However, this result was questioned by Cummins and colleagues[123] owing to the limitations in the evidence for HRQoL.

Estimation of costs

Resource use was considered similar to that for the adult rheumatoid arthritis population. Information regarding resource use was not available from the JIA etanercept trial.[42] Costs were discounted at 6% per annum and benefits at 1% per annum. The cost offset per HAQ point was £860.

Results

The incremental QALYs were 1.74 for the patients on etanercept compared with placebo. The incremental cost-effectiveness ratio (ICER) was £16,082 per QALY gained in the base-case analysis, and in the sensitivity analyses ICERs ranged between £3900 (cost-offsets assumption changed to exclude nursing home and home help costs but to include indirect costs) and £34,000 (Short Form questionnaire-36 items regression used). Probabilistic results were not reported.

Key issues

- There were concerns about the validity of the results owing to a lack of suitable evidence for model input parameters, particularly with regard to HRQoL.

Prince and colleagues[124]

Approach

Prince and colleagues[124] reported a cost–consequence analysis of etanercept therapy in patients with JIA in the Netherlands, who had an insufficient response to the maximum dose of methotrexate. Forty-nine JIA patients were evaluated at start of treatment and after 3, 15 and 27 months of therapy from the National ABC register. For all included patients, data were collected on the use of etanercept, disease activity and HRQoL. Most of the patients had polyarticular JIA (45%), followed by EO (22%) and systemic JIA (22%). The remainder had ERA (4%) or juvenile arthritis psoriatica (6%). The median age of patients at the start of etanercept treatment was 11.6 years and median disease duration was 3.6 years.

Estimation of effectiveness

The outcome measure used to assess disease activity consisted of six response variables: (1) overall assessment of disease activity by the physician by means of the VAS; (2) CHAQ by the patient or parent; (3) overall assessment of well-being by the patient or parent through the VAS; (4) number of active joints (joints with swelling and/or limited motion with pain or tenderness); (5) number of joints with limited motion; and (6) a laboratory marker of inflammation, ESR.

After 3 months' use of etanercept, the mean number of active joints decreased from 16.7 to 3.99 per person and the CHAQ score decreased from 1.70 to 1.00. These outcomes further improved at 27 months to 2.45 active joints per person and a CHAQ score of 0.50 (lower score indicates better outcome).

Estimation of quality-adjusted life-years

Health-related quality-of-life data were collected for patients in the study using the Health Utilities Index (HUI)-3. The questionnaire consists of eight health domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, each with five or six levels representing the range of functioning. HRQoL was collected by proxy by the parents of the study participants because children were considered unable to value health states. The HRQoL data are reported in more detail in the systematic review of HRQoL studies (see *Systematic review of health-related quality-of-life studies*).

Estimation of costs

Costs were collected for direct medical costs (i.e. medication, diagnostic and hospitalisation costs). The base year was 2008 for all costs, with costs retrieved from other years converted to 2008 euros using the general Dutch price index rate. Unit costs for medication were retrieved from the Pharmacotherapeutic Compass provided by the Dutch Board of Health Insurances, and treatment costs were calculated with the exact dose of medication and administration period as reported in the patients' files. Prices for all hospital-related costs were based on real prices from the co-ordinating centre (Erasmus MC Sophia Children's Hospital Rotterdam, the Netherlands). The etanercept unit cost was estimated at €10,478 per year.

Results

Mean total direct medical costs after the start of etanercept were, on average, €12,478 per patient-year compared with €3720 before the start of etanercept treatment. The utility for patients was 0.53 before start of etanercept treatment and increased to 0.78 over 27 months of etanercept treatment.

Key issues

- The study does not report cost-effectiveness.
- The study was based in the Netherlands, so unclear how generalisable results are to the NHS.

Simpson and colleagues[125]

Approach

Simpson and colleagues[125] reported results from a Markov model developed to assess the cost-effectiveness of adalimumab relative to methotrexate for the treatment of JIA. Cost-effectiveness analyses were performed from the perspective of the Russian health-care system (base model) and society as a whole (secondary model). The base-case model reported outcomes for a cohort of 100 children with a mean age of 11 years. Sensitivity analyses assessed the variation in the age of children at treatment initiation. The model has two parts. The first part followed children from 11 to 18 years of age with 4-month long cycles. This part of the model used data derived from the adalimumab RCT (Lovell and colleagues[61]). Additional analyses followed patients aged 7 years at treatment initiation for a period of 11 years. The second part of the model was derived from the literature on adult rheumatoid arthritis and modelled the remaining lifetime of the patients (age > 18 years). The adalimumab RCT[61] compared adalimumab plus methotrexate with placebo plus methotrexate for the treatment of JIA in children aged 4–17 years (further detail of this trial can be found in *Chapter 4*).

Disease activity was defined as mild, moderate or severe using the CHAQ scores and active joint counts from the adalimumab RCT.[61] Health states from the childhood model were used to capture the effects of joint damage and the need for hip replacement for the treatment of JIA in adulthood (> 18 years). The base model included five health states (remission no disease, remission disease, activity mild, activity moderate and activity severe). The remission disease group was introduced to capture the effect of joint damage and the need for joint replacement.

Estimation of effectiveness

Effectiveness estimates were based on observed changes from the adalimumab trial,[61] assessed using the CHAQ. These effects within the model were translated to HUI2 utility values, using a mapping algorithm developed by the authors.[132]

Estimation of quality-adjusted life-years

For the first part of the model (< 18 years), CHAQ items were transformed to HUI2 utility values, using the mapping algorithm. QALY estimates were based on these utility values. Utility values for the second part of the model were derived from the literature and were based on adult patients with rheumatoid arthritis. Mean predicted utility values varied from 0.56 to 0.98 (range 0.18 to 1.00).

Estimation of costs

Health-care costs were derived from a study by Yagudina and colleagues[133] reporting the cost of JIA during a 15-month period in Russia. The costs were for the year 2011. Given that this study reported the cost of 1-month inpatient and 14-month outpatient treatments, the cost attributable to each health state was adjusted using this as starting point. Base-case costs were discounted at a rate of 3%, whereas additional sensitivity analysis used a discounting rate of 5%.

Results

Relative to conventional non-biologic therapy, adalimumab was assessed to be cost-effective when used to treat JIA patients whose disease severity was comparable to that of participants in the adalimumab RCT.[61] Adalimumab plus methotrexate was reported to be more effective and more costly than methotrexate with an incremental cost per QALY ratio of approximately 1,437,480 roubles (£16,974 at current exchange rate) for the base case (7 years) and 119,496 roubles (£1411) adopting a lifetime horizon.

Key issues

- There was uncertainty relating to the predicted utility values used to estimate QALYs; a recent study indicated how using different algorithms to convert HAQ to utility values affects the cost-effectiveness and HTA results.[134]
- The lifelong model uses utility estimates derived from adult patients with rheumatoid arthritis. JIA that persists into adulthood has a different disease process to rheumatoid arthritis, and, therefore, assumptions of similarity between the two conditions are not valid.
- Cost estimates may not be applicable to the UK.
- Mortality rates are assumed to be equal to published rates for Russia; it is not clear if this refers to the general population or to JIA- and age-specific mortality rates.

Ungar and colleagues[127]

Approach

Ungar and colleagues[127] developed a decision-analysis model for etanercept, infliximab, adalimumab and abatacept for polyarticular-course JIA patients in Canada, who had had an inadequate response or intolerance to DMARDs. The model had a 1-year time horizon and consisted of two consecutive 6-month cycles, with no discounting. The model incorporated the probabilities that patients would, based on their response at 6 months, either continue with the same treatment or switch to an alternative treatment. Patients switched as a result of lack of response, intolerance to therapy or AEs. Where data on switching

biologic DMARDs were not available in paediatric studies, the RR of switching from biologic DMARDs owing to non-response or AEs was extrapolated from studies of rheumatoid arthritis in adults. Patients who switched from methotrexate were assumed to receive a biologic DMARD for the next 6 months, where the cost of the biologic was represented by the average cost of all the biologic DMARDs.

Estimation of effectiveness

The model compared each of the biologic DMARDs with methotrexate, but did not compare them with each other, given that head-to-head trials were not available and that the study populations differed by JIA onset type. The effectiveness measure was the proportion of patients who had a reduction in symptoms at 1 year in accordance with the ACR Pedi-30 criteria. To derive 6-month response rates for each biologic DMARD, data from the key RCTs (Lovell and colleagues[42,61] and Ruperto and colleagues[57,135]) were combined with data from registry and observational studies in a meta-analysis. For the base-case analysis, the proportion of patients achieving ACR Pedi-30 at 6 months varied between 79% and 82% for the biologic DMARDs, with the assumption that 30% of patients treated with methotrexate would achieve ACR Pedi-30. Probabilities for switching owing to non-response and AEs were estimated from the RCTs and observational studies.

Estimation of quality-adjusted life-years

Health-related quality of life was not included in the analysis.

Estimation of costs

The model included the costs of medication, monitoring costs and costs associated with treating serious infections. Costs were in Canadian dollars and the price year was 2008. In the base-case analysis a 40-kg patient was assumed, based upon the mean weight of patients in the two paediatric trials that reported weight. The direct medical costs included drug acquisition costs for biologic DMARDs and methotrexate, concomitant drug costs, drug administration materials, nursing time, dispensing fees, physician assessments and laboratory tests. Unit prices of health resources were obtained from public sources, including the Quebec and Ontario provincial drug plan formularies for medications, and the Ontario Ministry of Health and Long-Term Care fee schedules (laboratory tests and physician fees).

Results

The model reports results as additional cost per additional ACR Pedi-30 responder at 1 year of $26,061, $46,711, $16,204 and $31,209 for etanercept, adalimumab, abatacept and infliximab versus methotrexate, respectively. Probabilistic sensitivity analyses were conducted for each treatment versus methotrexate, and cost-effectiveness acceptability curves were calculated. If a decision-maker was willing to pay no more than $30,000 per additional responder, then the probability that etanercept would demonstrate a net economic benefit would be 95%. The willingness-to-pay points at which the biologic DMARDs had a 50% probability of cost-effectiveness were $45,000, $17,000 and $27,500 for adalimumab, abatacept and infliximab, respectively.

Key issues

- The time horizon was inadequate to model treatment of a long-term condition (only 1 year).
- This was not a cost–utility study as no HRQoL data were included.

Summary of published economic evaluations

- A systematic review of economic evaluations of biologic treatments included four studies, two of which were cost–utility analyses, one of which was a cost-effectiveness study and one of which was a cost–consequence study.
- The evaluations were published between 2002 and 2012 in the UK,[123] the Netherlands,[124] Russia[125] and Canada.[127]
- The studies varied in design and structure. The time horizons varied between 1 year[127] and lifetime.[123]

- The comparators differed between studies. One study compared etanercept with methotrexate,[123] one compared adalimumab with methotrexate,[125] one compared etanercept, adalimumab, abatacept and infliximab with methotrexate[127] and the remaining study compared a cohort before and after receiving etanercept.[124]
- There were limitations in the methodological quality in all the studies identified, including limited reporting of model parameters and assumptions. The UK study[123] is now considered out of date, and it is unclear how generalisable the results from the other studies are given the methodological limitations.

Systematic review of health-related quality-of-life studies

Methods for the systematic review

A systematic literature review was undertaken to assess the HRQoL of people with JIA treated with biologic DMARDs. The aim of the review was to provide data to populate the de novo economic model in this report with health-state utility values to calculate QALYs. The description of the search strategy is shown in *Appendix 1*. The inclusion criteria included primary studies that investigated HRQoL in people with JIA. To be eligible, the study should report health utility values using any generic preference-based HRQoL measure [e.g. EQ-5D, Short Form questionnaire-6 Dimensions (SF-6D)] or choice-based valuation methods (e.g. time trade-off, standard gamble). Studies that were not reported in English or did not provide sufficient information were excluded. The methodology used for searching and data extraction is outlined in *Chapter 3* of this assessment report.

Results of the systematic review

The database searches identified 2249 references, with one further study retrieved by hand searching, making the total number of references identified 2250. Full-text papers for 28 references were retrieved, meeting the a priori inclusion criteria. *Figure 7* presents a flow chart of the selection process and the excluded studies, with reasons for exclusion listed in *Appendix 8*. A total of 6 references were considered to have insufficient information on the study methods, population and results, 9 included an inappropriate population and 10 did not report a relevant outcome measure. Two studies, described in three

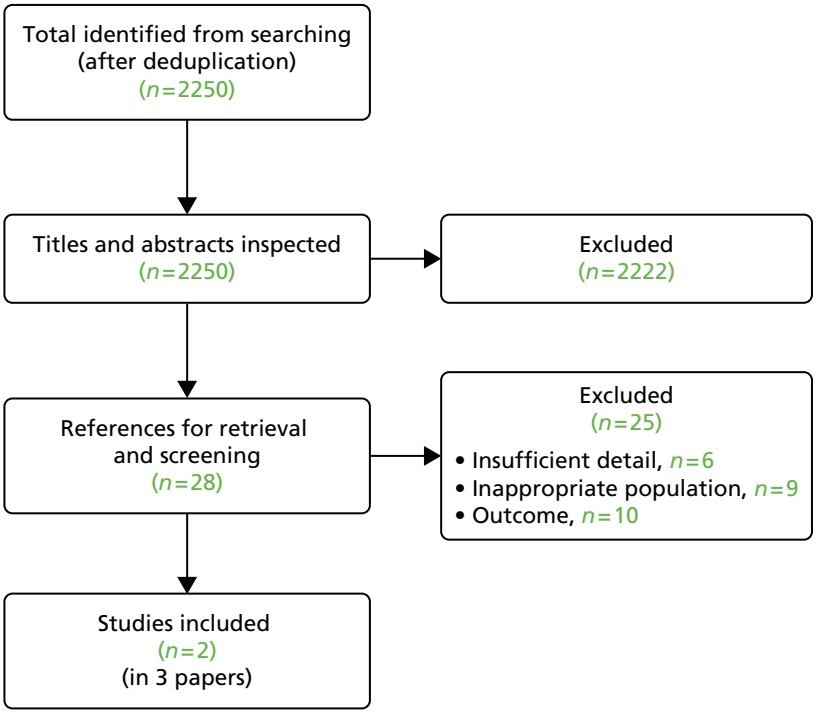

FIGURE 7 Flow chart of identification of studies for inclusion in the review of QoL studies.

publications, met the inclusion criteria and the characteristics of these studies are presented in *Table 39*. Data extraction forms for the included studies can be found in *Appendix 9*.

The two HRQoL studies are each now described in more detail.

Hendry and colleagues[136]

Hendry and colleagues[136] conducted an exploratory RCT to assess the effectiveness of a multidisciplinary foot care programme in children with JIA, and to investigate the methodological considerations of such a trial.

Children and adolescents with a definitive diagnosis of JIA and inflammatory joint disease affecting the foot/ankle were recruited at a single hospital (the Royal Hospital for Sick Children, Glasgow, UK). Participants were included if they satisfied at least one of the following criteria: (1) previously documented foot arthritis including small joints derived from medical case notes; (2) previously documented foot arthritis in one or more large joints derived from medical case notes; or (3) current widespread polyarthritis involving large and small foot joints derived from clinical examination by a consultant paediatric rheumatologist. Patients with an unconfirmed diagnosis of JIA, and/or only upper limb, jaw or neck involvement were excluded. Therefore, a subgroup of the JIA patient population of relevance to this assessment report (i.e. those whose disease had not affected the foot/ankle) was excluded from the study (*Table 40*).

Enrolled participants ($n = 44$) were randomly allocated to the intervention group receiving multidisciplinary foot care (individualised care packages including foot orthoses and targeted home exercise programmes) or to the control group treated with standard care (normal outpatient medical care from their consultant paediatric rheumatologists). Treatment groups were similar in terms of pharmacological treatment and

TABLE 39 Characteristics of included quality-of-life studies

Characteristic	Hendry *et al.* (2013)[136]	Prince *et al.* (2011);[124] Prince *et al.* (2010)[137]
Country	UK	Netherlands
Study type	RCT	Prospective observational study
Study population	Children/adolescents with JIA and inflammatory joint disease affecting the foot/ankle ($n = 44$)	Children and adolescents with refractory JIA from the National ABC register ($n = 49$)
Study population age (mean)	10 years old	11.6 years old
Intervention(s)	Multidisciplinary foot care intervention informed by musculoskeletal ultrasound	Etanercept therapy
Comparator population	Standard care	No treatment
QoL instrument used	EQ-5D	HUI3
Time period where HRQoL instruments administered	At baseline and 12 months	Baseline, 3 months, 15 months and 27 months
Methodology of collecting HRQoL data	EQ-5D was completed by patient (using EQ-5D-Y) and by proxy (using EQ-5D-3L)	The parents of the JIA patients completed the HUI3
Results	EQ-5D was 0.57 and 0.69 for the intervention group at baseline for the self-reported and proxy groups. Results were similar at 12 months and in the control group	Utility was 0.53 at baseline and increased to 0.78 after 27 months

EQ-5D-3L, European Quality of Life-5 Dimensions 3-level questionnaire; EQ-5D-Y, European Quality of Life-5 Dimensions (Youth).

TABLE 40 Characteristics of included HRQoL study by Hendry and colleagues[136]

Characteristics	Multidisciplinary foot care	Standard care
Participants, *n*	21	23
Age (years), mean (SD)	10.1 (4.22)	10.0 (3.39)
***Sex,* n**		
Male	7	6
Female	14	17
Disease subtypes,* n *(%)		
Persistent oligoarthritis	7 (33)	4 (17)
EO	4 (19)	5 (22)
Polyarthritis RF–ve	6 (29)	10 (43)
Polyarthritis RF+ve	0 (0)	2 (9)
PA	2 (10)	1 (4)
ERA	2 (10)	0 (0)
Undifferentiated	0 (0)	1 (4)
Pharmacological management,* n *(%)		
Analgesics	2 (9)	3 (13)
NSAIDs	2 (9)	3 (13)
Methotrexate	18 (86)	16 (70)
Etanercept	7 (33)	5 (22)
Methotrexate and etanercept	5 (24)	5 (22)
Sulphasalazine	1 (5)	0 (0)
Rituximab	0 (0)	1 (4)
EQ-5D utility index at baseline		
Self, mean (SD)	0.57 (0.31)	0.58 (0.35)
Self, median (IQR)	0.62 (0.52–0.76)	0.66 (0.52–0.75)
Proxy, mean (SD)	0.69 (0.29)	0.60 (0.33)
Proxy, median (IQR)	0.69 (0.58–1)	0.62 (0.55–0.82)
Change in EQ-5D utility index at 12 months, median (IQR)		
Self	0 (–0.1 to 0.01)	0 (–0.04 to 0.04)
Proxy	0 (0 to 0.11)	0 (0 to 0.1)

both had a proportion of patients receiving etanercept. There were small differences in proportions of JIA disease subtypes, but there were no statistically significant differences in baseline characteristics (see *Table 40*).

Patients' HRQoL was collected at baseline and 12 months using the EQ-5D (Youth) (patients) and EQ-5D 3-Levels (parents/guardians). There were no significant differences in HRQoL between treatment groups at 12 months, and both self- and proxy-reported outcomes were similar (see *Table 40*).

Prince and colleagues[124,137]

Prince and colleagues[124,137] evaluated changes in HRQoL in patients with refractory JIA who were being treated with etanercept, following an insufficient response to the maximum tolerated dose of methotrexate (This study was also discussed above; see *Systematic review of existing cost-effectiveness evidence*). Data were collected from Dutch patients registered at the National ABC) register, supplemented by prospectively collected additional data from patients who started etanercept treatment from 2003 until 2006. Three HRQoL questionnaires were used, one of which was the HUI3 preference-based HRQoL instrument. HRQoL questionnaires were completed at the start and after 3, 15 and 27 months of treatment.

Prince and colleagues[124,137] report the results in two publications, and the results differ slightly between the publications. In the publication including costs,[124] four fewer patients are included, as these patients did not continue treatment with etanercept for at least 27 months, whereas the publication reporting QoL only reports the results for all 53 patients. For the purposes of this assessment report, the smaller dataset is of more relevance,[124] but results from both datasets are shown in *Table 41*.

The results from the study indicated a statistically significant improvement in the HUI3 utility score from 0.53 at baseline to 0.78 at 27 months' follow-up. Mean utility values were 0.69 at 3 months and 0.74 at 15 months' follow-up. For the cohort with more patients, there was a mean utility improvement of 0.25 during the 27 months of treatment.[137] The baseline mean utility value was 0.51, and significant changes were observed in the domains of pain, ambulatory and dexterity.

TABLE 41 Characteristics of patients included in Prince and colleagues[124,137]

Characteristic	Prince *et al.* (2010)[137]	Prince *et al.* (2011)[124]
Participants, *n*	53	49
Age, median (IQR)	11.9 (8.1–14.9)	11.6 (7.9–14.6)
Sex, %		
Male	38	41
Female	62	59
Proportion of sample with systemic JIA, %	26 (14/53)	22 (11/49)
Proportion of sample receiving methotrexate, %	80	79
HUI utility value (SD) baseline	0.51 (0.04)	0.53 (0.04)
HUI utility value (SD) follow-up (27 months)	0.77 (0.08)	0.78 (0.07)

Summary and conclusions of the health-related quality-of-life review

The included studies assessed the HRQoL of children and adolescents with JIA, applying EQ-5D and HUI3 preference-based utility measures. Although both studies reported utility values, they are not directly comparable. The study by Hendry and colleagues[136] assessed the effectiveness of a foot care programme in a RCT, whereas Prince and colleagues[124,137] conducted an observational study reporting HRQoL and costs from patients in the Dutch ABC registry to assess the effect of treating patients with etanercept. The mean utility values reported for baseline by Hendry and colleagues[136] for the intervention and control group (0.57 and 0.58, respectively) are relatively similar to the baseline values reported by the Prince and colleagues study (0.51 and 0.53, respectively).[124,137] The HRQoL values may be higher for Hendry and colleagues[136] owing to 23% of patients receiving etanercept, whereas no patients received etanercept at baseline in the Prince and colleagues study.[124,137] The sample size of both cohorts is considered relatively small, but it is reasonable given the population group. The cohort used in the Prince and colleagues study[124,137] included patients with systemic JIA, who are outside the scope of the current review; however, the proportion of patients within the group with systemic JIA is relatively small (< 30%). Neither of the studies can be considered fully informative for the de novo economic evaluation in this assessment report. However, estimates provided by Prince and colleagues[124,137] are considered reasonably appropriate for use in the economic evaluation, despite not being considered directly generalisable to the UK population.

Review of cost-effectiveness in company submissions to the National Institute for Health and Care Excellence

All four pharmaceutical companies submitted evidence to be considered for the NICE appraisal. Two of these submissions [by BMS (abatacept) and Roche (tocilizumab)][78,85] consisted of a written report and an electronic economic model, and the other two submissions [by AbbVie (adalimumab) and Pfizer (etanercept)][77,97] comprised only a written report.

A structured data extraction form was used by the assessment group to assess the CSs (see *Appendix 10*). A description and critique of each of the submissions in turn is provided in the following subsections. Greater description is provided for the Roche and BMS submissions as these conducted economic models. (a description and critique of the companies' clinical effectiveness evidence is given in *Chapter 4, Review of clinical effectiveness in company submissions to the National Institute for Health and Care Excellence*).

Review of Bristol-Myers Squibb's submission to the National Institute for Health and Care Excellence (abatacept)

The company submitted a de novo economic model that included all comparators specified in the NICE scope except for methotrexate monotherapy (i.e. abatacept, etanercept, adalimumab and tocilizumab).[85] The company states that methotrexate monotherapy was not included owing to inconsistency with the clinical effectiveness data (i.e. all patients in the RCTs either did not have sufficient response with methotrexate or were refractory to methotrexate). The scope reflects the licensed indication of abatacept, namely polyarticular JIA patients aged ≥ 6 years who have received at least one TNFα inhibitor (etanercept or adalimumab). All included drugs were assumed to be administered with subcutaneous methotrexate.

Modelling approach

The model presented in the CS is a cohort-based cost-minimisation model, in which all drugs were assumed to have identical efficacy. The base-case model presents a cohort of 12-year-old polyarticular JIA patients and follows them until aged 18 years in 4-week cycles. The model is essentially a one-state model. Patients gain weight and height as they age, but their disease does not change; only the costs associated with treating the disease increase owing to weight- and body surface area-based dosing among the drugs. The drug acquisition cost values within the model were appropriately derived from Monthly Index of Medical Specialties data.[138]

Assumptions

The model contained a number of assumptions that appear reasonable: a 52-week year, a dosing regimen for methotrexate consistent between < 16-year-olds and > 16-year-olds, a constant weight after the age of 20 years, methotrexate dosing based on an algorithm for lowest cost when > 30 mg of methotrexate is necessary, a normal distribution for height and weight, a truncation of the model starting age in the probabilistic sensitivity analysis (PSA) to represent only between age 6 and 16 years as starting ages, assumptions for standard errors where they were unavailable and no vial sharing of drugs.

Critical appraisal of model

Although the comparators and population within the model were generally consistent with the NICE scope, the model does not adequately represent all the available evidence for the treatment pathway or natural history of the disease.

The model time horizon and structure are inadequate to capture long-term treatment effects or the treatment pathway of the disease, as many JIA patients continue to receive treatment into adulthood. The model does not allow for drug discontinuation or treatment switching, which is known to happen in clinical practice. The CS indicates that the model was validated by an internal reviewer but full details were not reported of this validation.

Estimation of effectiveness

The model did not include clinical effectiveness data to represent clinical outcomes or to represent events that incur costs such as disease flare, vision loss or joint surgery. The effectiveness of the biologic DMARDs was assumed to be equivalent as a justification for the use of cost-minimisation methods. The CS cites the systematic review and indirect comparison by Otten and colleagues[79] for evidence of equivalent effectiveness (as discussed in *Chapter 4*).

Estimation of quality-adjusted life-years

Health-related quality of life was not assessed in the model and the CS indicates that this was due to uncertainty in the QoL values for JIA in the literature.

Estimation of costs

Intervention dosages and prices were derived from Monthly Index of Medical Specialties data,[138] whereas costs for subcutaneous injection and infusion drug delivery methods were derived from a previously published HTA of biologic DMARDs in rheumatoid arthritis.[139] A confidential patient access scheme (PAS) was incorporated for abatacept. Sensitivity analyses were run for the price of tocilizumab using various assumed percentage price discounts, as a confidential PAS has been agreed for tocilizumab.

The costs were derived from appropriate sources and are clearly reported, but it is assumed that the drugs had identical AE costs, discontinuation rates and clinical effectiveness. The details for drug costs and dosages used in the BMS company model are shown in *Table 42*.

Results

The model was a cost minimisation and analysed only costs, assuming equivalent clinical effectiveness for all biologic DMARDs. The results of the base-case analysis are shown in *Table 43*. The model results presented by the manufacturer include a PAS discount of (CiC information has been removed) for abatacept.

In the base case, the company found that abatacept was the least costly biologic DMARD. The CS states that abatacept has similar efficacy and safety to the other biologic DMARDs. Deterministic sensitivity analyses and PSA were conducted for a variety of scenarios. The findings were found to be robust to a wide range of scenarios.

TABLE 42 Unit costs and dosages used in the BMS company model (list prices)

Drug	Cost, £	Dose, mg
Abatacept	302.40	250
Etanercept	35.75	10
	89.38	25
	178.75	50
Adalimumab	352.14	40
Tocilizumab	102.40	80
	256.00	200
	512.00	400
Methotrexate	14.85	7.5
	15.29	10
	16.50	12.5
	16.57	15
	17.50	17.5
	17.84	20
Administration method		
Infusion	154.00	
Subcutaneous injection	3.05	

TABLE 43 Results of the BMS model base case (CS table 13) (CiC information has been removed)[a]

Costs	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug costs	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Administration costs, £	11,797	871	871	11,646
Total costs	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Cost savings with abatacept		CiC information has been removed	CiC information has been removed	CiC information has been removed

a 12-year-olds, 6-year time horizon, from Excel 2010 (Microsoft Corporation, Redmond, WA, USA) model.

The company undertook a number of deterministic and scenario sensitivity analyses:

- A sensitivity analysis was undertaken wherein the infusion costs for tocilizumab were increased owing to the longer infusion time.
- The starting age of patients in the model was varied between 6 and 16 years. In the biologic DMARD trials the mean age was 11 years at baseline, but the drug licences were for much younger ages.
- The time horizon of the model was varied between 6 months and 20 years. Longer time horizons were meant to represent that one-third of children with JIA will have it into adulthood.
- PAS discount for tocilizumab was tested for a range of percentages of list price reductions and calculated to show the tocilizumab discount with identical drug costs to abatacept.
- Methotrexate was excluded from the etanercept arm.

There were no analyses that varied more than one parameter at a time. None of the one-way sensitivity analyses was accompanied by a probabilistic analysis that reassessed the probability that abatacept was the least costly biologic for second-line biologic DMARD therapy of polyarticular JIA. Given that the model was simple and that the number of simulations for the PSA was only 1000, these analyses would have been simple and quick to perform. It would have been especially informative to do this for the tocilizumab cost-sensitivity analyses. No analyses looked at subgroups of patients, and there was no discussion of potential subgroups.

The PSA results using 1000 simulations were within 5% of the base-case analysis results. Abatacept was the least costly option in 67% of simulations, whereas etanercept was the least costly option in the remaining 33% of simulations. Not all distributions used in the sensitivity analysis were appropriate. For the infusion costs and subcutaneous administration costs, a normal distribution was used for the cost data, which could lead to simulations with negative cost values; a gamma or log-normal distribution would be more appropriate. The drug cost data do not appear to have been subjected to uncertainty. Given that there is a PAS for tocilizumab, using a lower than average cost value for tocilizumab and subjecting it to PSA could have been an alternative approach to conducting only a deterministic analysis for tocilizumab. This would have given a more realistic estimates of the cost uncertainty between treatments.

Critique of the company's submission

The company constructed a cost-minimisation model, assuming that there were no differences between the biologic DMARDs in clinical effectiveness, AEs and discontinuation rates. Patients do not discontinue or switch treatments, which does not reflect current clinical practice or the available evidence.

Overall, the model is limited for decision-making owing to factors such as inadequate time horizon and structural limitations. However, the methods for integrating variable dosing over time used within the model may be useful for building a more comprehensive model.

Review of the Roche submission to the National Institute for Health and Care Excellence (tocilizumab)

The CS includes an economic model and reports the total costs, the QALYs gained and cost-effectiveness of tocilizumab in the treatment of polyarticular JIA.[78] The model evaluates the lifetime costs and benefits for tocilizumab compared with adalimumab. The perspective of the analysis is that of the NHS and Personal Social Services (PSS).

Modelling approach

A de novo Markov state-transition decision model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) with three health states (uncontrolled disease/off treatment, on treatment and dead). The model has 6-month cycles and a time horizon of 25 years. Costs and benefits are discounted at 3.5%. Patients entering the model have active JIA and have previously experienced an inadequate response to, or were intolerant of, methotrexate. Patients in the model have a mean age of 11 years and are based on those in the CHERISH RCT.[68]

Patients start with uncontrolled disease at cycle 0 then move to first-line biologic treatment. Once all lines of treatment are exhausted, patients move into the uncontrolled disease health state. Mortality is included in the model and assumes a 1% 6-month mortality rate across all years. The model includes the occurrence of SAEs. The mortality rate used in the model is about 100 times higher than the annual mortality rate for the general paediatric population of 0.02%. We consider that a lower mortality rate should be used in the model.

Assumptions

The CS states that, owing to differences in terms of trial design, patients, methods of imputation and quality, only adalimumab and tocilizumab could be compared. The CS states that an indirect comparison of safety was not possible and so the risk of SAEs was assumed to be the same for both biologic DMARDs. The model assumes that patients discontinue at a rate proportional to their ACR response [i.e. no response (ACR Pedi < 30), moderate response (ACR Pedi-30–ACR Pedi-70) and good response (ACR Pedi ≥ 70)].

Critical appraisal of model

The submission meets all of the requirements for methodological quality and generalisability, except that it did not fully explore uncertainty or provide any evidence that the economic model had been validated.

The evaluation provided a clear statement of the decision problem to be addressed, including the population, which appeared to follow the scope for the appraisal issued by NICE. The comparators included (adalimumab and tocilizumab) were appropriate, as these are being routinely used or considered for use within the NHS in England and Wales. The model also included etanercept in an exploratory analysis but did not include abatacept, and the CS states that this was not possible owing to differences in trial design, patients, methods of imputation and quality. The 25-year time horizon reflects the chronic nature of the disease and allows for all relevant costs and benefits to be included. The model structure was clearly presented with a description and justification of the key assumptions and data inputs used. Benefits for the model are measured in QALYs using the HUI3 for measuring utility. All benefits and costs are discounted at 3.5% as required by NICE.[130] The CS does not assess uncertainty in sensitivity analysis. It was unclear if the model had been fully validated, as no details were provided.

Estimation of effectiveness

The company reported a systematic review of biologic DMARDs in the treatment of JIA. The CS states that it was possible to compare adalimumab and tocilizumab only by indirect comparison, as these two treatments had greater similarities in trial design, patients, methods of imputation and quality. Results from each study were combined using a hierarchical Bayesian indirect treatment comparison, using an ordered probit model in WinBUGS software to estimate the relative treatment effects and achieving different levels of ACR response. The ACR response rates were estimated for the biologic DMARDs with and without methotrexate and are shown in *Table 44*. The response is generally similar for adalimumab and tocilizumab (both with methotrexate).

TABLE 44 American College of Rheumatology Pediatric response rates from Roche submission (CS table 21)

Response rates		ACR Pedi-30, %	ACR Pedi-50, %	ACR Pedi-70, %	ACR Pedi-90, %
Without methotrexate	Placebo	31	28	25	12
	Tocilizumab	62	59	54	35
	Adalimumab	52	49	44	26
With methotrexate	Methotrexate	52	51	41	25
	Tocilizumab	72	70	61	44
	Adalimumab	76	75	66	49

The discontinuation rate used in the model was derived according to ACR response from the Dutch ABC register.[124] An exponential distribution was fitted to the data for no response (ACR Pedi response < 30), moderate response (ACR Pedi response > 30 and < 70) and good response (ACR Pedi response ≥ 70). The 6-month discontinuation rate was 0.126 for no response, 0.09 for moderate response and 0.042 for good response.

Estimation of quality-adjusted life-years

The company conducted a literature review that identified one study reporting utility values suitable for use in the model (Prince and colleagues[124]). This study reported utility scores obtained using the HUI3 questionnaire to JIA patients starting treatment with etanercept in the Dutch ABC register. Based on these data, the company used values at time 0 for the patients who are off treatment (utility of 0.53), and used values at time 1 year for patients on treatment (utility of 0.73).

The assessment group identified some errors in the Roche model with regard to estimation of QALYs. First, utility values for patients have been applied as if patients were on treatment for some time after finishing the first-line biologic treatment, when these patients should have been assigned the off-treatment utility. Second, utility values have been incorrectly calculated as the utility value for 1 year has been assigned to each cycle of 6 months. (For corrections to these errors, see *Table 47*.)

Estimation of costs

The costs associated with each health state was obtained from Prince and colleagues,[124] who report costs data from the Dutch ABC register for the year before and after starting etanercept. The total 6-month health-state cost for patients on treatment is £912.33 and off treatment is £1591.43. Treatment unit costs and doses were reported. Tocilizumab was provided with a confidential PAS discount (CiC information has been removed). The model included costs for both intravenous infusion and for subcutaneous injection, as required by the treatment. The administration cost of an infusion (for tocilizumab) was £152.24, using inflated costs from Barton and colleagues.[140] The cost of an administration of a subcutaneous injection was £6.10 for children and £3.05 for a young person, assuming that a proportion of these patients would require nurse assistance.

Cost-effectiveness results

Tables 45 and *46* show the cost-effectiveness results from the CS for tocilizumab compared with adalimumab when used in combination with methotrexate or as a monotherapy. The CS states that the results indicate that both treatments are of similar clinical effectiveness and cost-effectiveness, regardless of

TABLE 45 Roche base-case results: combination therapy

Outcome	Adalimumab + methotrexate	Tocilizumab + methotrexate	Incremental difference	ICER (£ per QALY)
Total QALYs	18.76	18.72	–0.0303	
Total cost, £	81,827	70,707	–11,120	South-west quadrant[a]

a Adalimumab vs. tocilizumab has an ICER of £367,551.

TABLE 46 Roche base-case results: biologic DMARD monotherapy

Outcome	Adalimumab	Tocilizumab	Incremental difference	ICER (£ per QALY)
Total QALYs	18.65	18.7	0.0455	
Total cost, £	74,576	68,560	–6015	Dominant

whether they are used in combination with methotrexate or as a monotherapy. The company urges caution in the interpretation of the QALY estimates, but concludes that tocilizumab is less expensive and therefore represents better value to the NHS.

The CS does not include any sensitivity analyses. It includes an exploratory analysis with etanercept. This analysis assumed a class effect across antiTNFs in polyarticular JIA.

Critique of the company's submission

There are some concerns over the reliability of the model results in the Roche submission owing to errors found by the assessment group in the calculation of QALYs.

The assessment group has corrected the errors in the Roche model by applying the off-treatment utility values when patients finished the first-line biologic treatment and assigning the 6-month utility value to each cycle. In addition, the mortality rate has been reduced to 0.03% per cycle to reflect that of the general population. The results for this analysis are shown in *Table 47*. The corrected results show reduced QALYs and increased costs for adalimumab and tocilizumab in combination with methotrexate compared with the base-case results. However, the incremental QALYs and costs between the tocilizumab and adalimumab are similar in the corrected results to the base-case results.

Review of the AbbVie submission to the National Institute for Health and Care Excellence (adalimumab)

The company did not provide a systematic review of cost-effectiveness studies or an economic evaluation.[77] They discussed the interventions in the NICE scope: adalimumab, etanercept, abatacept, tocilizumab and methotrexate. In sections 5.8–5.10 of the CS, the company provides justifications for not conducting an economic evaluation. Other sections of the CS provide details on what the company would consider important in conducting an economic evaluation in JIA, including an evaluation of the costs associated with surgeries and vision loss.

The company states that an economic evaluation was not conducted owing to a lack of appropriate utility data for HRQoL, heterogeneity in study methods and populations between the interventions that complicated indirect comparisons, and a lack of long-term effectiveness data. The company identified one HRQoL study (Prince and colleagues[124]), which collected HUI3 utilities in addition to other JIA clinical variables, such as the CHAQ score. The data collected from Prince and colleagues[124] were deemed unsuitable to map the CHAQ to HUI3 owing to insufficient sample size, but were considered the most suitable source of utility data by the company. The CS discusses the use of an algorithm by Khan and colleagues[141] that mapped the Pediatric Quality of Life Inventory instrument to EQ-5D in secondary school pupils. The company notes the potential limitations in the use of this method in JIA, as Pediatric Quality of Life data were not collected in any of the JIA biologic DMARD RCTs. The company considers that the biologic DMARD trial populations and study methods were not sufficiently similar to allow indirect comparison through network meta-analysis. The CS concluded that using current data and methods would lead to 'untenable' uncertainty (CS page 90).

TABLE 47 Corrected Roche model results: combination therapy

Outcome	Adalimumab + methotrexate	Tocilizumab + methotrexate	Incremental difference	ICER (£ per QALY)
Total QALYs	10.10	10.05	–0.05	
Total cost, £	95,761	83,593	–12,168	South-west quadrant[a]

a Adalimumab vs. tocilizumab has an ICER of £251,208.

Review of the Pfizer submission to the National Institute for Health and Care Excellence (etanercept)

Pfizer did not submit any cost-effectiveness evidence.[97] The CS notes the limitations raised in the previous submissions for NICE of etanercept TA35[43] and tocilizumab TA238.[44] These relate to the limitations in the HRQoL data and the limited evidence on the long-term outcomes and the effectiveness of the treatments. The CS states that any cost-effectiveness evidence would be associated with considerable and unresolvable uncertainty. The company submitted a cost analysis that compared the annual costs for the first year of treatment based on etanercept against adalimumab and tocilizumab in patients with polyarticular JIA. The CS states that the cost analysis showed that etanercept is the biologic DMARD with the lowest acquisition cost compared with list prices for tocilizumab and adalimumab.

Comparison of economic models in company submissions

The CSs differ in the approach to providing economic evidence for biologic DMARDs for JIA. Only one company (Roche) constructed an economic model for tocilizumab that included both costs and outcomes. Two companies (BMS for abatacept and Pfizer for etanercept) submitted cost analyses and assumed that the biologic DMARDs were equivalent, whereas the remaining company (AbbVie for adalimumab) considered there to be too many limitations with any potential analysis and, therefore, did not submit an economic analysis.

Although AbbVie has raised valid concerns about uncertainty in the data available for conducting an economic evaluation, we consider that concerns about uncertainty are an insufficient justification for not building an economic model. A model provides a representation of current knowledge in a subject and uncertainty is part of that current knowledge. A model, even an uncertain one, with limitations noted by the company, gives a more transparent description of available knowledge and enables more informed decision-making than simply presenting clinical trial data from trials that represent only a highly selected subgroup of the drug licences. Modelling also allows the exposure of the most valuable areas for future research enquiries.

Bristol-Myers Squibb and Pfizer consider that all of the treatments are equivalent. It is noted that the available evidence base consists of small trials that lack the statistical power to justify this assumption, and Otten and colleagues[79] do not conclude that there is equivalent efficacy between the treatments, but that the treatments are similar.

Briggs and O'Brien[142] argue that a cost-minimisation analysis should be conducted only when equivalence of comparators has been statistically demonstrated. Dakin and Wordsworth[143] argue that the limitations of a cost-minimisation analysis do not allow for an appropriate assessment of uncertainty or for the value of future research and may lead to biased conclusions. It is also the case that equivalence of one clinical outcome does not mean equivalence of all clinical outcomes. Patients may have the same QoL on treatment but have different adherence and discontinuation or different AEs, for example. For these reasons, a cost-minimisation analysis is generally forgone in favour of a cost-effectiveness analysis and/or a cost–utility analysis.

Roche have provided a cost–utility analysis that compared two of the biologic DMARDs (adalimumab and tocilizumab). The model appears to be a reasonable attempt at modelling JIA, albeit in only two of the biologic DMARDs. However, we have noted errors in the calculation of QALYs in the model, which limit the credibility of the results.

Independent economic evaluation

The models described in our systematic review of economic evaluations (see *Systematic review of cost-effectiveness evidence*) had certain methodological limitations and were not wholly generalisable to the NHS. Furthermore, the economic evaluation used to inform the NICE appraisal of tocilizumab for systemic JIA (NICE TA238) was subject to a number of concerns from the Appraisal Committee, in particular with regard to the estimation of HRQoL.[44] Given the limitations of existing available models, we therefore constructed a de novo economic model to inform this current appraisal.

The model estimates the costs, benefits and cost-effectiveness of the four biologic DMARDs in patients with JIA and inadequate responses to, or intolerance of, methotrexate. The model compares the biologic DMARDs (in combination with methotrexate, where permitted) with a DMARD (e.g. methotrexate), as specified in the NICE scope. The model does not compare the biologic DMARDs with best supportive care (e.g. NSAIDS; corticosteroids) for patients who cannot tolerate a DMARD, as there are limited data available to make this comparison. Furthermore, patients who are intolerant to a DMARD such as methotrexate would be offered a biologic DMARD rather than best supportive care, particularly to avoid any potential adverse effects of long-term corticosteroid use.[144]

The evidence used in the model was taken from data sources such as the RCTs of biologic DMARDS (in which a number of JIA subtypes were represented, with polyarticular-course JIA being the predominant subtype), and data sources such as registry studies comprising mixed JIA populations (primarily comprising polyarticular and oligoarthritis JIA patients, but also small proportions of patients with ERA, PA and systemic JIA). However, there was insufficient evidence available for all input parameters to permit a cost-effectiveness subgroup analysis for each of the respective types of JIA within the scope of the appraisal. Therefore, the modelled patient population is people with JIA, with the results of particular relevance to people with polyarticular course JIA (EO, and RF +ve and RF –ve polyarthritis). The biologic DMARDs are assessed in this report within their licensed indications (e.g. the cost-effectiveness estimates for some of the biologic DMARDs cannot be applied to JIA subtypes for which they are not licensed, such as abatacept and tocilizumab for the treatment of ERA and PA).

The model was populated with clinical effectiveness data from the included RCTs in our systematic review of clinical effectiveness (see *Chapter 4*), HRQoL data from our systematic review of HRQoL studies (see *Systematic review of health-related quality-of-life studies*) and cost data derived from published studies (where available), as well as national and local NHS unit costs.

The economic evaluation was from the perspective of the NHS and Personal Social Services, with only these direct costs included. The model estimates the long-term costs and benefits from each of the treatments. The costs and benefits were discounted at 3.5%, as recommended by NICE.[130] The base price year for the costs was 2014. The intervention effect, in terms of reducing disease flare, was derived from the systematic review of clinical effectiveness reported in *Chapter 4*. The outcome of the economic evaluation is reported as incremental cost per QALY gained.

Methods for independent economic analysis

A Markov model was developed in Microsoft Excel to assess the cost-effectiveness of the biologic DMARDs. The model contains health states for 'on treatment', 'off treatment', 'remission off treatment' and 'death'. A diagram of the model is shown in *Figure 8*. The model uses 3-month cycles to be consistent with the usual time between outpatient appointments for JIA patients. A time horizon of 30 years was modelled as the base case, with shorter and longer horizons tested in sensitivity analyses. This time horizon was considered sufficiently long to capture the costs and effects of biologic DMARDs for paediatric patients, given the uncertainty around the long-term clinical outcomes for adults with JIA. The model structure is based upon the clinical pathway of patients who participated in the withdrawal RCTs,

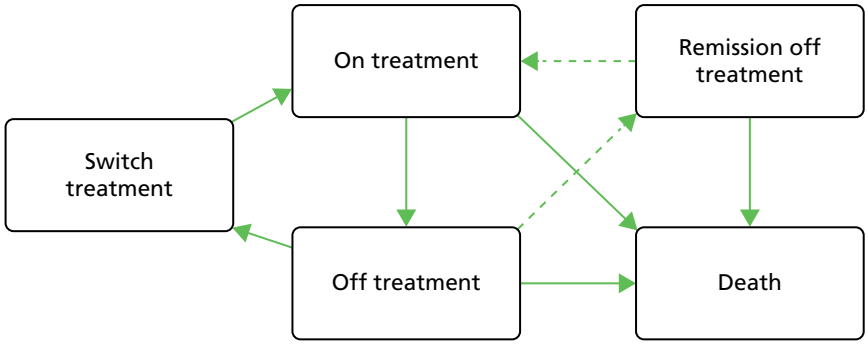

FIGURE 8 Schematic of the SHTAC JIA model structure.

described in *Chapter 4*, the natural history of JIA described in registry data and discussions with clinical experts. The starting age of patients in the model is 11 years, based upon the mean age of patients in the RCTs. Patients' heights and weights are assumed to be similar to those in the general population.

Patients treated with a biologic DMARD continue on treatment unless they die or withdraw from treatment owing to adverse effects, loss of efficacy or clinical remission off treatment. Patients with clinical remission who have their treatment discontinued may relapse and resume treatment with a biologic DMARD. Based on clinical advice, we assumed that clinicians would be reluctant to stop treatment with a biologic DMARD as a result of remission because of the risk of relapse, and so, for the base-case analysis we assume that no patients discontinue treatment owing to remission. We investigate discontinuation attributable to remission in more detail in a scenario analyses. Therefore, for the base-case analysis, no patients enter the 'clinical remission off treatment' health state and this is indicated in *Figure 8* by dotted lines for this health state.

In the base-case analysis, patients treated with adalimumab, etanercept and tocilizumab receive only one line of biologic DMARD treatment. Patients treated with abatacept receive two lines of biologic DMARD treatment, as abatacept is licensed for use only after a preceding antiTNF. Following withdrawal from these biologic DMARDs, patients continue on a standard treatment regimen that does not contain a biologic DMARD.

In a scenario analysis (scenario V), we investigate multiple lines of treatment with biologic DMARDs, which reflects the range of strategies used in clinical practice. Patients continue on the subsequent treatments until they die or withdraw from treatment as a result of AEs, loss of efficacy or clinical remission. Following withdrawal from the final biologic DMARD, patients continue on a standard treatment regimen that does not contain a biologic DMARD.

Patients treated with methotrexate only (i.e. those not receiving a biologic DMARD) are assumed to continue on treatment unless they die or withdraw from treatment owing to AEs or loss of efficacy.

The model incorporates disease flares to estimate the clinical effectiveness of treatment. This was the primary outcome measure in the RCTs of the biologic DMARDs. Patients who have a disease flare continue in their current health state in the model but are allocated a HRQoL disutility and an additional health-care cost during that cycle.

The costs in the model comprise drug treatment, consultation and monitoring costs and costs for treating AEs. Costs used in the model are described in more detail in *Data sources*. HRQoL is estimated according to each health state.

In each cycle, the total costs and QALYs are calculated by multiplying the individual costs and HRQoL by the number of people in the cohort still alive for each of the treatments. The total long-term costs and QALYs are calculated by aggregating the costs and QALYs for all cycles. The total discounted QALY gain and cost of treatments are calculated and compared to give the cost-effectiveness of the treatments.

Assumptions are applied to all treatment options unless explicitly stated otherwise. These assumptions have been made owing to an absence of data and have been informed by discussion with our clinical advisors. The model includes the following main assumptions:

- There are few studies for biologics, other than for etanercept, that report long-term discontinuation owing to AEs and inefficacy. The discontinuation rate is assumed to be similar for each of the biologic DMARDs.
- Our clinical effectiveness review concluded that there is no evidence of a difference in efficacy between biologics and, therefore, we assumed that the QoL utility values are the same for all biologic DMARDs ('on treatment').
- It is currently unclear whether or not the effectiveness of subsequent lines of biologic DMARDs would be reduced or remain the same. The effectiveness of the biologic DMARDs is assumed to be similar taken as a first- or subsequent-line biologic treatment. This applies to abatacept as a second-line biologic DMARD in the base case, and to the scenario analysis that models three lines of biologic DMARD treatment (scenario V).

Evaluation of uncertainty

The evaluation of the cost-effectiveness of JIA treatment is based on uncertain information about variables such as clinical effect, HRQoL and resource use. This uncertainty was evaluated using deterministic and PSA. One-way deterministic sensitivity analyses were conducted to evaluate the influence of individual parameters on the model results and to test the robustness of the cost-effectiveness results to variations in the structural assumptions and parameter inputs (see *Results of the independent economic analysis*). Where possible, the parameters were varied according to the ranges of the CIs of these parameters based on the published estimates. Where these data were not available an alternative range was chosen.

Multiparameter uncertainty in the model was addressed using PSA (*Results of the independent economic analysis*).[145] In the PSA, probability distributions are assigned to the parameter point estimates used in the base-case analysis. The model is run for 1000 iterations, with a different set of parameter values for each iteration by sampling parameter values at random from their probability distributions.

The uncertainty surrounding the cost-effectiveness of the treatment is represented on a cost-effectiveness acceptability curve according to the probability that the intervention will be cost-effective at a particular willingness-to-pay threshold. *Appendix 11* reports the parameters included in the PSA, the form of distribution used for sampling each parameter and the upper and lower limits assumed for each variable.

Model validation

The model was validated by checking the model structure, calculations and data inputs for technical correctness by another researcher. The structure was reviewed by clinical experts from the advisory group for its appropriateness for the disease and its treatment. A senior health economist from the advisory group reviewed the methods and assumptions of the economic evaluation. The robustness of the model to changes in input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude.

Data sources

Effectiveness data

Disease flare

The risk of disease flare was included in the model as a RR compared with methotrexate (*Table 48*), as derived from our systematic review of clinical effectiveness [*Chapter 4, Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus placebo (with methotrexate where permitted)*]. The baseline risk of flare for methotrexate was a weighted average of the risk of flare estimates from the placebo arms of the abatacept, adalimumab and tocilizumab trials, converted to a 3-month cycle risk. For each biologic DMARD, the risk of flare was derived using the RR for that treatment compared with methotrexate from the relevant RCT, multiplied by the baseline risk.

Treatment discontinuation

Treatment discontinuation was assumed to be attributable to AEs, lack of efficacy or clinical remission. Estimates for treatment discontinuation were identified through a literature search of trial and registry data. The first model cycle has certain different treatment discontinuation parameters because it was designed to represent the open-label lead-in phase of the RCTs.

The estimates for the first model cycle were taken from the RCTs of the biologic DMARDs[42,57,61,68] for the open-label lead-in period (*Table 49*). For the period after the treatment lead-in, the clinical trials of the biologic DMARDs also include other categories of withdrawal (such as patient/guardian consent or physician decision), but it is unclear whether these categories would also apply to clinical practice or were particular to the trials. As a result, the discontinuation rate after the first model cycle was not taken from these clinical trials but from Tynjala and colleagues[146] who conducted a retrospective observational study on JIA patients in Finland taking etanercept or infliximab with a 4-year follow-up.

There were few long-term data on treatment discontinuation identified except for etanercept and, hence, we assumed that the discontinuation rate would remain constant over time and would be the same for all biologic DMARDs (based on data for from Tynjala and colleagues[146]). The discontinuation rate was 7% for AEs and 28% for inefficacy over 4 years. The discontinuation rate for inefficacy for methotrexate was taken from a retrospective analysis of the German Methotrexate Registry,[147] which collected data on the

TABLE 48 Risk of disease flare

Drug	Risk of flare per cycle	Source
Methotrexate	0.25	Ruperto *et al.* (2008),[57] Lovell *et al.* (2008)[61] Brunner *et al.* (2015)[68]
Abatacept	0.09	Ruperto *et al.* (2008)[57]
Adalimumab	0.14	Lovell *et al.* (2008)[61]
Etanercept	0.09	Lovell *et al.* (2000)[42]
Tocilizumab	0.14	Brunner *et al.* (2014)[68]

TABLE 49 Discontinuations during the trials' lead-in time (first cycle)

Parameter	Abatacept[57]	Adalimumab[61]	Etanercept[42]	Tocilizumab[68]
AE, %	0.5	1.8	1.4	1.6
Loss of efficacy, %	9.5	3.5	2.9	8.0
Total discontinuation, %	10.0	5.3	4.3	9.6

efficacy and safety of methotrexate treatment since 2005. The discontinuation rate for inefficacy used in the model was 0.4% per cycle. The STRIVE registry (see *Review of cost-effectiveness in company submissions to the National Institute for Health and Care Excellence*) reported a methotrexate discontinuation rate for AEs of 2.3% per year and this was converted to a 3-month rate and used in the model.[77]

Mortality Patients are assumed to have the same mortality rate as for the general population. Mortality was taken from age-related statistics from the Office for National Statistics.[21]

Health-related quality of life Our systematic review of HRQoL studies identified two potentially relevant studies that reported generic preference-based HRQoL studies of people with JIA who received a biologic DMARD.[124,136] Furthermore, none of the clinical trials of the biologic DMARDs under review collected HRQoL data that could be used as health-state utility values. We investigated methods for mapping HRQoL to treatment response, for example from CHAQ or ACR Pedi to HUI3, but concluded that the data available were insufficient to provide a reliable fit for modelling. Therefore, the utility values used in the model were taken directly from the Dutch ABC Registry by Prince and colleagues,[124] as this study was considered to be of most relevance from the available literature. This study is described in more detail above (see *Systematic review of health-related quality-of-life studies*). It consists of patients who have polyarticular-course JIA and in whom the response to the maximum dose of methotrexate is insufficient. The utility value for patients who had not yet received etanercept in that study is assumed to be representative of those patients with uncontrolled disease not currently receiving a biologic DMARD (i.e. those patients in the methotrexate-only arm and those patients who discontinue biologic DMARD therapy). In the study by Prince and colleagues,[124] most of the patients were still receiving methotrexate. In the absence of any other utility data, we assumed that all biologic DMARDs would have the same utility values as each other and that this would increase over time, as seen in the Prince and colleagues study.[124] For simplicity, for the scenarios with additional lines of biologic treatments (scenario V), we assumed that treatment with the biologic DMARD would have a constant utility value of 0.74 (i.e. the value after 15 months of treatment for second- and third-line biologic DMARD treatment). The annual health-state utility values used are shown in *Table 50*.

Patients with a disease flare are assumed to have an associated disutility. We assumed that patients with a disease flare would have a similar HRQoL to patients with uncontrolled disease, but with appropriate treatment would recover from their disease flare within 3 months (one model cycle). Assuming that patients recovered HRQoL at a constant rate over the model cycle, the average HRQoL for these patients during that cycle would be 0.655, and converting this to an annual disutility would be equivalent to 0.03 per flare.

TABLE 50 Health-related quality-of-life utility values

HRQoL utility values	Per year	Source
No treatment	0.53	Prince *et al.* (2011)[124]
Treatment with first-line biologic, 0–3 months	0.53	Prince *et al.* (2011)[124]
Treatment with first-line biologic, 3–15 months	0.69	Prince *et al.* (2011)[124]
Treatment with first-line biologic, 15–27 months	0.74	Prince *et al.* (2011)[124]
Treatment with first-line biologic, 27+ months	0.78	Prince *et al.* (2011)[124]
Treatment with second- and third-line biologics	0.74	Prince *et al.* (2011)[124]
Disutility for disease flare	0.03	Assumption

Caregiver disutility We conducted a literature search of studies reporting the quality-of-life impact on caregivers of patients with JIA and did not identify any studies that reported HRQoL as utility values. The precise quality-of-life impact on primary caregivers of patients with JIA, in terms of change in HRQoL utility values, is unclear. A study by Bruns and colleagues[148] examined the HRQoL and disease burden of primary caregivers of 70 patients with JIA. They used the CHAQ, Short Form questionnaire-36 items and the psychiatric screening questionnaire (the Self-Reporting Questionnaire-20 items). The burden of disease on the caregivers was measured by the Caregiver Burden Scale. They concluded that there was a high prevalence of psychoemotional disturbance in JIA caregivers and that the burden of disease on the caregivers was primarily related to patients' emotional status (rather than to their physical status).

In the absence of suitable HRQoL data for caregiver disutility, we assumed in the base-case analysis that there was no utility benefit for parents of children and young people and varied this assumption in a scenario analysis (scenario IV).

Estimation of costs

Drug costs

Drug unit costs and doses were based on the *British National Formulary for Children* 2015.[149] A summary of the dose and unit cost of treatment for each of the comparators is given in *Table 51*. The manufacturers of abatacept and tocilizumab have provided a confidential PAS. Cost-effectiveness results for these treatments presented in *Results of the independent economic analysis* are based on the drug list price, whereas a CiC separate appendix to this report available only to the NICE Appraisal Committee presents results with the confidential PAS discount applied. Patient height, weight and body surface area were taken from the *British National Formulary* and reflect the increase in children's heights and weights as they

TABLE 51 Drug acquisition costs and dosages (source: *British National Formulary for Children*[149])

Parameter	Methotrexate	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug dose	10–15 mg/m^2	10 mg/kg	24 mg/m^2 (maximum 40 mg) aged 4–13 years 40 mg (aged 13–18 years)	0.4 mg/kg (up to a maximum of 25 mg per dose)	10 mg/kg for patients < 30 kg; 8 mg/kg for patients > 30 kg
Method	Subcutaneous injection/oral	Intravenous infusion	Subcutaneous injection	Subcutaneous injection	Intravenous infusion
Dosing schedule	Once weekly	Infusions given at weeks 0, 2, 4, 8, 12, 16	Every other week	Twice weekly	Every 4 weeks
Unit cost	Oral: 2.5 mg 24-tab pack = £2.22; 28-tab pack = £2.60 Subcutaneous: Metoject (Medac GmbH, Wedel, Germany) pre-filled syringe. 50 mg/ml: 0.15 ml = £14.85; 0.2 ml = £15.29; 0.3 ml = £16.57; 0.4 ml = £17.84; 0.5 ml = £18.48; 0.6 ml = £18.95	250-mg vial = £302.40	40-mg prefilled pen or prefilled syringe = £352.14	10-mg vial = £35.75; 25-mg vial = £89.38; 25-mg prefilled syringe = £89.38	3 ml (80-mg vial) = £102.40; 10 ml (200-mg vial = £256; 20 ml (400-mg vial) = £512.00
Administration cost, £	0	154	0	0	154

grow older.[150] The administration costs for an intravenous infusion was £154 based on a HTA monograph of disease-modifying drugs in the treatment of rheumatoid arthritis (Stevenson and colleagues[139]). We assumed that for patients taking methotrexate, half would receive oral and half subcutaneous administration, based upon clinical advice.

Patients taking biologic DMARDs also receive concomitant methotrexate treatment as shown in *Table 52*. These values have been taken from the RCTs or registries for these treatments. Patients receiving etanercept in the model do not also receive methotrexate, according to etanercept's marketing authorisation. It was assumed that 20% of patients in the methotrexate comparator arm would be intolerant to methotrexate and therefore would not receive it.[124]

Resource use

We conducted a literature search for costing studies in patients with JIA and identified two relevant studies. Thornton and colleagues[153] examined the resources used and associated patient-based costs during the first year after diagnosis for JIA patients in the UK. Prince and colleagues[124] analysed the costs of treatment for patients in the Dutch ABC Register before and after receiving etanercept. There are limitations to both studies: the patients in the Thornton and colleagues[153] study are likely to have different resources and costs in the first year after diagnosis than the patients included in this assessment report; for example, they may have had less severe disease. The resources used by patients in the Prince and colleagues study[124] are not reported and it is unclear how different Dutch health-care costs would be to the NHS. Our clinical experts commented that the resources for monitoring patients costs were not substantially different between the patients treated with methotrexate only or with a biologic DMARD, and were broadly similar to those in the Thornton and colleagues[153] study. We therefore used the resources described by Thornton and colleagues in the base case and explored the costs used by Prince and colleagues[124] in a scenario analysis (scenario II). The assumed resources used by patients are shown in *Table 53*. Blood tests consisted of the combined cost of full blood count, CRP, urea and electrolytes and a liver function test. Clinical imaging consisted of the combined cost of magnetic resonance imaging scan, dual-energy X-ray absorptiometry scan, ultrasound and radiography. The total health-care cost for patients on biological treatment and off biologic treatment using the resources shown in *Table 53* was £724 per cycle.

Patients who experienced a disease flare received one or more injections of intra-articular steroids and were treated as paediatric rheumatology inpatient cases at a cost of £429.97.[152]

Adverse events

The database of studies from our systematic review was searched for studies reporting any AEs or discontinuation. In addition, the CSs were consulted for any relevant data. Although the types and frequencies of AEs were reported, no cost data were identified in any of the studies that reported SAEs or discontinuation rates, or in observational studies reported in the CSs. In order to identify data, previous NICE TAs were searched. Neither of the JIA technology appraisals, TA35 and TA238, contained data on the cost of SAEs.[43,44]

TABLE 52 Concomitant biologic DMARD and methotrexate use

Drug use	Methotrexate only	Abatacept	Adalimumab	Etanercept	Tocilizumab
Methotrexate use, %	80	80	69	0	82

TABLE 53 Resource use and unit costs

Resource per year	Resource use per year: Off biologic treatment	Resource use per year: On biologic treatment	Unit cost, £	Reference
General practitioner visit	10	10	46.00	PSSRU (2013)[151]
Hospital appointments				
Rheumatology paediatric consultant	5.58	5.58	234.86	National reference costs 2013/14[152] (OP code 262)
Ophthalmologist	2.69	2.69	114.73	National reference costs 2013/14[152] (OP code 216)
Specialist nurse	7.00	7.00	40.00	PSSRU 2013[151]
Physiotherapist	4.00	4.00	16.50	PSSRU 2013[151]
Occupational therapist	0.65	0.65	16.50	PSSRU 2013[151]
Podiatry	0.61	0.61	43.59	National Reference Costs 2013/14[152] (OP code 653)
Hospital tests				
Blood tests	1	1	46.27	Thornton *et al.* (2008),[153] updated to 2013/14 values using PSSRU HCHS Index
Clinical imaging	1	1	386.42	
Disease flare				
Inpatient treatment per disease flare			429.97	National Reference Costs 2013/14[152] (non-elective short stay. Weighted average codes HD23D–HD23JK)

HCHS, Hospital and Community Health Services; PSSRU, Personal Social Services Research Unit.

Owing to the paucity of data relating to JIA, TAs of rheumatoid arthritis were also assessed. Of the six TA publications available on the NICE website,[154–159] only one contained data for the cost of an AE, namely TA195: *Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis after the Failure of a TNF Inhibitor*.[158] A Pfizer CS provided the only relevant cost data in TA195. Pfizer assumed that a SAE involved two general practitioner visits, 7 days of hospitalisation and a utility decrement of 0.05, with a total cost of £1181. No specific AEs were identified by Pfizer. Further details on the types of SAE experienced by JIA patients are given in *Chapter 4, Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus placebo (with methotrexate where permitted)* and in *Appendix 2*. The most common SAEs were serious infections and infestations, but SAEs also included autoimmune diseases and malignancies. All independent analyses in rheumatoid arthritis conducted by assessment groups to this point have been based on the Birmingham Rheumatoid Arthritis Model,[140] which assigns a cost to increases in HAQ scores. In JIA, it is not possible to model SAE costs in this way owing to lack of HAQ in the RCTs.

In order to model the cost of SAEs, health-care resource group codes for intermediate and severe paediatric infections were consulted. In addition, a study in etanercept patients by Otten and colleagues[160] indicated that the median length of hospitalisation for SAEs was 9 days (IQR 2–12). Given this, we estimated inpatient costs by averaging all spells for intermediate and major paediatric infections (£1532.87).

A summary of the input parameters used in the model are shown in *Table 54*.

TABLE 54 Summary of the input parameters used in the SHTAC economic model

Parameter	Mean	Higher value	Lower value	Source
Starting age, years	11	15	6	Assumption, based on RCTs
Time horizon, years	30	10	70	Assumption
Discount rate (costs), %	3.5	6	1.5	NICE reference case[130]
Discount rate (benefits), %	3.5	6	1.5	NICE reference case[130]
Utility values, per cycle				
No treatment	0.13	0.15	0.11	Prince *et al.* (2011)[124]
Treatment after 3 months	0.17	0.20	0.15	Prince *et al.* (2011)[124]
Treatment after 15 months	0.19	0.21	0.16	Prince *et al.* (2011)[124]
Treatment after 27 months	0.20	0.23	0.16	Prince *et al.* (2011)[124]
Disease flare disutility	0.03	0.04	0.02	Assumption
Disease flare, per cycle				
Placebo	0.25	0.34	0.16	Ruperto *et al.* (2008),[57] Lovell *et al.* (2008),[61] Brunner *et al.* (2015)[68]
Abatacept	0.09	0.16	0.05	Ruperto *et al.* (2008)[57]
Adalimumab	0.14	0.23	0.09	Lovell *et al.* (2008)[61]
Etanercept	0.09	0.17	0.04	Lovell *et al.* (2000)[42]
Tocilizumab	0.14	0.20	0.09	Brunner *et al.* (2015)[68]
AEs, first cycle, %				
Abatacept	0.53	1.51	0.00	Ruperto *et al.* (2008)[57]
Adalimumab	1.75	3.71	0.00	Lovell *et al.* (2008)[61]
Etanercept	1.45	4.19	0.00	Lovell *et al.* (2000)[42]
Tocilizumab	1.60	3.36	0.00	Brunner *et al.* (2015)[68]
Loss of efficacy, %				
Abatacept	9.47	13.59	5.36	Ruperto *et al.* (2008)[57]
Adalimumab	3.51	6.25	0.76	Lovell *et al.* (2008)[61]
Etanercept	2.90	6.82	0.00	Lovell *et al.* (2000)[42]
Tocilizumab	7.98	11.90	4.06	Brunner *et al.* (2015)[68]
Further-line treatment, %				
AEs, biologic DMARD	0.43	0.82	0.04	Tynjala *et al.* (2009)[146]
Loss of efficacy biologic DMARD	2.00	2.59	1.41	Tynjala *et al.* (2009)[146]
AEs, methotrexate	0.58	0.82	0.34	STRIVE (2015)[77]
Loss of efficacy methotrexate	0.42	0.79	0.05	Klein *et al.* (2012)[147]
Costs, £				
On biologic DMARD cost	724	940.92	506.65	National Reference Costs 2013/14[152] PSSRU 2013[151]
Off biologic DMARD cost	724	940.92	506.65	
SAE cost	1533	1993	1073	National Reference Costs 2013/14[152]
Disease flare cost	430	301	559	National Reference Costs 2013/14[152]

PSSRU, Personal Social Services Research Unit.

Results of the independent economic analysis

This section reports the cost-effectiveness results for a person with JIA who received treatment with a biologic DMARD in combination with methotrexate (where permitted) compared with those who received methotrexate only. Results for costs and QALYs are presented for each treatment, with costs and benefits discounted at 3.5%. The results are presented for biologic DMARDs licensed for use as a first-line biologic treatment (i.e. adalimumab, etanercept and tocilizumab) and are then presented for abatacept as a second-line biologic treatment following previous treatment with an antiTNF. The results shown in this section are for the drug list price, and the results with the confidential PAS discount for abatacept and tocilizumab are presented in a separate CiC appendix to this report available only to the NICE Appraisal Committee.

Licensed first-line biologics: adalimumab, etanercept and tocilizumab

The undiscounted summary results of the analyses for adalimumab, etanercept and tocilizumab compared with methotrexate for the treatment effects are shown in *Tables 55–57*. In the base case, total undiscounted QALYs vary between 14.98 for methotrexate and 17.99 for tocilizumab (see *Table 55*). Patients on methotrexate have higher QALYs only in the off-biologic-DMARD health state than the patients on biologics, as they spend more time in this health state. The summary results of the undiscounted drug costs are shown in *Table 56*. The total undiscounted drug acquisition cost of the biologic DMARDs varied between £103,497 and £128,071 for treatment first with etanercept and tocilizumab, respectively, compared with a total undiscounted cost of £7029 for patients treated with methotrexate only. The total patient costs varied between £107,299 and £225,797 for methotrexate only and tocilizumab, respectively. As noted earlier, patients taking etanercept do not receive methotrexate, which partially explains the lower costs for the etanercept regimen.

TABLE 55 Summary of the total undiscounted QALYs in each health state for treatment with first-line biologic compared with methotrexate

	Health-state QALYs			
Treatment	On biologic DMARD	Off biologic DMARD	Disease flare	Total
Methotrexate only	N/A	15.9	–0.9	14.98
Adalimumab	8.6	9.9	–0.8	17.77
Etanercept	8.5	10.0	–0.7	17.81
Tocilizumab	9.2	9.5	–0.8	17.99

N/A, not applicable.

TABLE 56 Summary of the total undiscounted costs in each health state for treatment with first-line biologic compared with methotrexate

	Total undiscounted costs, £				
Treatment	Medical	Drug	AEs	Flare	Total
Methotrexate only	86,938	7029	498	12,834	107,299
Adalimumab	86,938	114,701	248	10,805	212,693
Etanercept	86,938	103,497	254	9766	200,454
Tocilizumab	86,938	128,071	269	10,519	225,797

TABLE 57 Cost-effectiveness of first-line biologic DMARDs vs. methotrexate only

Treatment[a]	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£ per QALY gained) vs. methotrexate[b]
Methotrexate only	67,426	9.35			
Adalimumab	145,047	11.40	77,513	2.0	38,127
Etanercept	134,868	11.44	67,334	2.1	32,526
Tocilizumab	150,530	11.52	82,995	2.1	38,656

a Abatacept was not included in this analysis as the marketing authorisation is not for first-line biologic DMARD.
b Results presented compared with methotrexate; no incremental analysis presented.

The base-case discounted cost-effectiveness results are shown in *Table 57*. Each of the biologic DMARDs is more expensive than methotrexate only, with the incremental cost ranging from £77,513 to £82,995 for etanercept and tocilizumab, respectively. The ICER versus methotrexate only for adalimumab, etanercept and tocilizumab is £38,127, £32,256 and £38,656 per QALY gained, respectively. The results are not presented as an incremental analysis of the biologic DMARDs, as the costs and QALYs for each biologic DMARD are generally similar and it has been previously discussed in *Chapter 4* that the biologic DMARDs may be regarded as similar in effectiveness.

Licensed second-line biologic: abatacept

Abatacept is licensed for use after at least one previous antiTNF biologic DMARD. The results are shown for abatacept, adalimumab, etanercept and tocilizumab compared with methotrexate. For each biologic comparator, patients are assumed to have been treated initially with etanercept as the first-line biologic. The summary results of the non-discounted treatment effects are shown in *Table 58*. In the base case, total undiscounted QALYs vary between 14.98 for methotrexate and 20.07 for abatacept. The summary results of the undiscounted costs are shown in *Table 59*. The total undiscounted drug acquisition cost of the DMARDs varied between £7029 for methotrexate only to £222,533 for abatacept. The total patient costs varied between £107,299 and £317,097 for methotrexate only and abatacept.

The base-case discounted cost-effectiveness results are shown in *Table 60*. The costs and QALYs are different from those for the first-line biologic cost-effectiveness analysis (see *Table 57*) because this analysis includes the costs and QALYs of two lines of biologics. The cost-effectiveness of abatacept compared with methotrexate is £39,536 per QALY. The results are not presented as an incremental analysis, as the costs and QALYs for the biologic DMARDs are similar.

TABLE 58 Summary of the total undiscounted QALYs in each health state for treatment with second-line biologics compared with methotrexate

	QALYs			
Treatment	On biologic DMARD	Off biologic DMARD	Disease flare	Total
Methotrexate only	N/A	15.9	–0.9	14.98
Abatacept	15.8	4.8	–0.5	20.07
Adalimumab	15.1	5.3	–0.6	19.80
Etanercept	15.0	5.4	–0.5	19.82
Tocilizumab	15.7	4.8	–0.6	20.00

N/A, not applicable.

TABLE 59 Summary of the total undiscounted costs in each health state for treatment with second-line biologic DMARDs compared with methotrexate

	Costs, £				
Treatment	Medical	Drug	AEs	Flare	Total
Methotrexate only	86,938	7029	498	12,834	107,299
Abatacept	86,938	222,533	502	7124	317,097
Adalimumab	86,938	184,594	433	8118	280,082
Etanercept	86,938	179,686	440	7311	274,374
Tocilizumab	86,938	205,174	457	7840	300,409

TABLE 60 Cost-effectiveness of second-line biologic DMARDs compared with methotrexate using list price

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£ per QALY gained) vs. methotrexate[a]
Methotrexate only	67,534	9.37			
Abatacept	203,276	12.80	135,742	3.4	39,536
Adalimumab	183,387	12.65	115,853	3.3	35,284
Etanercept	179,580	12.67	112,045	3.3	33,948
Tocilizumab	194,263	12.76	126,728	3.4	37,363

a Results presented compared with methotrexate; no incremental analysis presented.

Sensitivity analysis

Deterministic sensitivity analysis

Tables 61–64 show the results of the deterministic sensitivity analyses for each of the biologic DMARDs versus methotrexate for the most influential parameters. Other parameters, such as time horizon, cost and frequency of disease flare, complete response rate and utility values were varied in the sensitivity analyses but were found to have only a negligible effect on the results. For each of the treatments, the models are most sensitive to the utility values chosen while on biologic DMARD treatment. They are also sensitive to the discount rate and the health-state costs.

TABLE 61 Deterministic sensitivity analysis for adalimumab vs. methotrexate only

Adalimumab vs. methotrexate	High 95% CI, £	Low 95% CI, £	Range, £
Base-case ICER: £38,127			
Utility treatment, long term[a]	26,571	67,470	40,898
Utility no treatment	59,814	27,982	31,832
Discount rate benefits	45,936	32,123	13,813
Discount rate costs	31,919	45,016	13,097
On biologic DMARD cost	41,630	34,624	7006
Off biologic DMARD cost	34,624	41,630	7006
Disease flare methotrexate	35,871	40,598	4727
AE adalimumab	37,983	33,308	4675

a After treatment for > 27 months with biologic DMARD.

TABLE 62 Deterministic sensitivity analysis for etanercept vs. methotrexate only

Etanercept vs. methotrexate	High 95% CI, £	Low 95% CI, £	Range, £
Base-case ICER: £32,526			
Utility (treatment, long term)[a]	22,886	56,196	33,310
Utility (no treatment)	50,511	23,986	26,525
Discount rate (costs)	26,909	38,783	11,874
Discount rate (benefits)	39,075	27,478	11,598
Start age	35,045	26,173	8873
Off biologic DMARD cost	29,118	35,934	6817
On biologic DMARD cost	35,934	29,118	6817
Disease flare methotrexate	30,566	34,668	4102

a After treatment for > 27 months with biologic DMARD.

TABLE 63 Deterministic sensitivity analysis for tocilizumab vs. methotrexate only

Tocilizumab vs. methotrexate	High 95% CI, £	Low 95% CI, £	Range, £
Base-case ICER: £38,656			
Utility (treatment, long term)[a]	26,835	69,092	42,257
Utility (no treatment)	58,865	28,777	30,088
Discount rate costs	31,360	46,904	15,545
Discount rate benefits	47,140	32,196	14,943
Start age	42,589	32,993	9596
On biologic DMARD cost	42,130	35,182	6948
Off biologic DMARD cost	35,182	42,130	6948
Disease flare methotrexate	36,395	41,130	4735

a After treatment for > 27 months with biologic DMARD.

TABLE 64 Deterministic sensitivity analysis for tocilizumab vs. methotrexate only

Abatacept vs. methotrexate	High 95% CI, £	Low 95% CI, £	Range, £
Base-case ICER: £39,536			
Utility (treatment, long term)[a]	31,529	52,995	21,467
Discount rate costs	30,512	50,137	19,625
Utility treatment 15–27 months	32,110	51,430	19,319
Discount rate benefits	49,908	31,906	18,002
Utility no treatment	50,345	32,549	17,796
Start age	42,187	33,234	8952
On biologic DMARD cost	43,094	35,978	7117
Off biologic DMARD cost	35,978	43,094	7117

a After treatment for > 7 months with biologic DMARD.

The deterministic sensitivity results for adalimumab versus methotrexate are shown in *Table 61* and varied between £26,571 and £67,470 per QALY gained.

The deterministic results for etanercept versus methotrexate only varied between £22,886 and £56,196 per QALY gained (see *Table 62*).

The deterministic sensitivity results for tocilizumab versus methotrexate only varied between £26,835 and £69,092 per QALY gained (see *Table 63*).

The deterministic sensitivity analysis results for abatacept versus methotrexate only varied between £31,259 and £52,995 per QALY gained (see *Table 64*).

Scenario analysis

We conducted several scenario analyses to investigate uncertainty for specific aspects of the modelling. The results of these analyses are presented for the first-line biologics.

Discontinuation of treatment owing to clinical remission (scenario I)

Patients with clinical remission off medication are at high risk of relapse. Baszis and colleagues[161] conducted a retrospective chart review in a cohort of 171 patients with JIA (of a range of subtypes but predominantly polyarticular course) in the USA treated with TNFα antagonists. They found that 12 months after stopping treatment only 33% of patients still had clinical remission. Similarly, a retrospective chart review of 437 JIA patients from centres in the USA and Italy by Wallace and colleagues[162] estimated that 6% of patients who had discontinued methotrexate therapy with clinical remission had persistent remission after 5 years off treatment.

The rate of discontinuation of biologic treatment varies between studies. In a retrospective observational study by Tynjala and colleagues,[146] patients receiving etanercept were followed up for 4 years and 10% of patients had discontinued treatment owing to inactive disease. In the study by Baszis and colleagues,[161] 80% of patients discontinued TNFα antagonist treatment owing to inactive disease. We varied the discontinuation rate between that seen by Tynjala and colleagues[146] (used in the base case) and that seen by Baszis and colleagues.[161]

We assumed a relapse rate from Baszis and colleagues[161] of 67% for that analysis and a 40% relapse rate as seen in Wallace and colleagues[162] for the Tynjala and colleagues[146] analysis. We assumed that no patients on the methotrexate-only arm would discontinue, as fewer patients on methotrexate would be in remission.

The results for the scenario with patients discontinuing treatment for clinical remission is shown in *Table 65* for first-line biologics compared with methotrexate only. In the scenario with the highest discontinuation rate, the cost-effectiveness of the biologics improves from the base case by about £4000 per QALY.

TABLE 65 Cost-effectiveness for first-line biologics vs. methotrexate only with patient discontinuation of treatment for clinical remission

Analysis	Remission off treatment (per cycle), %	Relapse rate, %	ICER (£/QALY) vs. methotrexate		
			Adalimumab	Etanercept	Tocilizumab
Base case	0		38,127	32,526	38,656
Baszis *et al.* (2011)[161]	7.8	67	33,744	28,580	34,214
Tynjala *et al.* (2009)[146]	0.66	40	37,512	31,970	38,028

Health-state costs from Prince and colleagues[124] (scenario II)

The base-case analysis uses health-state costs estimated by a UK study by Thornton and colleagues[153] of patients during the first year after diagnosis. However, as stated earlier, this may not necessarily reflect the patient group in this economic evaluation as patients in that study were newly diagnosed. The Roche CS cost-effectiveness analysis uses health-state costs based on the Prince and colleagues study.[124] Assuming that hospital admissions would be for disease flare only, the health-state costs per cycle are £589.51 and £408.91 for the off-treatment and on-treatment health states, respectively (compared with £724 in the base case). In this analysis, the biologic DMARDs are slightly more cost-effective and the ICER decreases by approximately £2900 per QALY compared with the base-case analysis (e.g. the ICER for adalimumab decreases to £35,214 per QALY) (*Table 66*).

Discount rates used in the National Institute for Health and Care Excellence appraisal of etanercept (scenario III)

The previous NICE appraisal of etanercept (NICE TA35[43]) used a discount rate of 6% for costs and 1% for benefits[123] (which were the recommended rates at the time). We ran the analysis for etanercept using those discount rates. *Table 67* shows ICERs that are much reduced compared with the base case in the current assessment report, namely £21,718 per QALY. Using this discount rate, etanercept would be cost-effective at a willingness-to-pay threshold of £20,000–30,000 per QALY.

TABLE 66 Summary of the cost-effectiveness for adalimumab, etanercept and tocilizumab vs. methotrexate only using health-state costs from Prince and colleagues[124]

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	57,306	9.37			
Adalimumab	128,894	11.40	71,589	2.0	35,214
Etanercept	118,771	11.44	61,465	2.1	29,691
Tocilizumab	134,097	11.52	76,792	2.1	35,767

TABLE 67 Cost-effectiveness for etanercept vs. methotrexate using a discount rate of 6% for costs and 1% for benefits

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	51,494	12.96			
Etanercept	107,200	15.53	55,707	2.6	21,718

Caregiver benefit (scenario IV)

We were unable to find HRQoL utility values associated with caring for a child or young person with JIA and assumed in the base-case analysis no disutility benefit for parents and caregivers. A study by Kuhlthau and colleagues[163] compared the well-being of parents of children with and without activity limitations. This list of conditions includes medical conditions that would commonly be considered disabling (e.g. paraplegia and blindness) as well as typically less disabling but chronic conditions (e.g. attention deficit hyperactivity disorder and asthma). They estimated the disutility for these parents to be 0.07 using the EQ-5D. Values from caregivers' disutility for patients with multiple sclerosis, from a study by Gani and colleagues,[164] indicate that the caregiver disutility is small (< 0.02) until patients reach a health state with significant mobility limitations.[164]

Patients receiving a biologic DMARD have a better HRQoL than those eligible for a biologic who have not yet received one. It follows that this improvement in HRQoL may also improve the HRQoL of caregivers, although the magnitude of any improvement is unclear. In this scenario, we assume that the disutility of caregivers is half that for patients on a biologic DMARD compared with those on methotrexate only and vary the disutility according to the values in the studies by Kuhlthau and colleagues[163] and Gani and colleagues.[164]

The results for the scenario including a disutility for caregivers are shown in *Table 68* for first-line biologics compared with methotrexate only. In the scenario with the highest disutility for caregivers, cost-effectiveness improves, with the ICER for etanercept reducing to £28,619 per QALY.

Three lines of biologic therapy (scenario V)

In the base-case analysis, patients treated with adalimumab, etanercept and tocilizumab received one line of biologic DMARD treatment, and those treated with abatacept received two lines of biologic DMARDs to account for the licensed indication for that drug. In this scenario, patients can receive three lines of biologic DMARDs to allow for treatment switching as happens in clinical practice. We included a scenario in which patients received etanercept as the first-line biologic, adalimumab as the second-line biologic and tocilizumab as the third-line biologic. These were the most common first-line and second-line treatments in an analysis of the UK Childhood Arthritis Prospective Study.[23] We also presented an alternative analysis with a third-line biologic of abatacept instead of tocilizumab.

The cost-effectiveness of the two scenarios varied between £36,982 and £38,152 per QALY (*Table 69*). The cost-effectiveness of three-line biologic therapy is similar to that seen in the base-case analysis for one line of biologic therapy (see *Table 57*).

TABLE 68 Cost-effectiveness for first-line biologics vs. methotrexate only with inclusion of disutility for caregivers

	Disutility for caregivers		ICER (£/QALY)		
Scenario	On biologic	Off biologic	Adalimumab	Etanercept	Tocilizumab
Base case	0	0	38,127	32,256	38,656
Higher disutility[163]	–0.035	–0.07	33,436	28,619	33,933
Lower disutility[164]	–0.01	–0.02	36,658	31,305	37,178

TABLE 69 Cost-effectiveness for three lines of biologic therapy

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	67,534	9.37			
Etanercept, adalimumab, tocilizumab	207,565	13.16	140,031	3.8	36,982
Etanercept, adalimumab, abatacept	212,562	13.17	145,028	3.8	38,152

Younger biologic disease-modifying anti-rheumatic drug starting age (scenario VI)

Adalimumab, etanercept and tocilizumab have a licensed indication from 2 years of age for patients with polyarticular arthritis, and abatacept has a licensed indication from ≥ 6 years. In this scenario we investigated the cost-effectiveness of the biologics with a starting age of 6 years old (in the base case the starting age is 11 years). The results of the analysis for first-line biologics are shown in *Table 70*. These indicate that there is minimal difference in the cost-effectiveness for adalimumab but a decrease of about £6000 in the cost-effectiveness of etanercept and tocilizumab.

The results of the analysis for second-line biologics are shown in *Table 71*. These indicate a similar improvement in the cost-effectiveness and there is a reduction in the cost-effectiveness of abatacept of £6302 per QALY.

Probabilistic sensitivity analyses

In the PSA, all parameters were sampled probabilistically from an appropriate distribution using similar ranges as used in the deterministic sensitivity analyses. The parameters sampled were: treatment effectiveness, discontinuation rate, health-state costs, disease flare parameters and HRQoL. The distribution assigned to each variable included in the PSA and the parameters of the distributions are reported in *Appendix 11*.

First-line biologics

A total of 1000 simulations were run. The PSA results are presented in *Table 72* for first-line biologics and show similar results to the deterministic analyses (see *Table 58*). The cost-effectiveness for biologics versus methotrexate only varied between £32,554 and £38,744 per QALY for tocilizumab.

TABLE 70 Cost-effectiveness of first-line biologics with a starting age of 6 years

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	67,492	9.39			
Adalimumab	145,089	11.42	77,597	2.0	38,124
Etanercept	121,737	11.46	54,245	2.1	26,173
Tocilizumab	138,421	11.54	70,929	2.1	32,993

TABLE 71 Cost-effectiveness of second-line biologics with a starting age of 6 years

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	67,492	9.39			
Abatacept	181,776	12.83	114,285	3.4	33,234
Adalimumab	170,364	12.68	102,872	3.3	31,283
Etanercept	163,006	12.69	95,514	3.3	28,895
Tocilizumab	176,066	12.78	108,575	3.4	31,961

TABLE 72 Summary of the probabilistic sensitivity results for first-line biologics vs. methotrexate only

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	67,531	9.38			
Adalimumab	145,933	11.43	78,402	2.05	38,181
Etanercept	135,803	11.48	68,272	2.10	32,554
Tocilizumab	151,800	11.55	84,269	2.18	38,744

The cost-effectiveness acceptability curve is shown in *Figure 9* and indicates that at the £20,000 and £30,000 willingness-to-pay thresholds methotrexate has the highest probability of being cost-effective, at 0.98 and 0.62, respectively.

Second-line biologics

The PSA results are presented in *Table 73* for second-line biologics and show similar results to the deterministic analyses (see *Table 61*). The cost-effectiveness of abatacept in the PSA is £39,608 per QALY.

The cost-effectiveness acceptability curve is shown in *Figure 10* and indicates that at the £20,000 and £30,000 willingness-to-pay thresholds methotrexate has the highest probability of being cost-effective, at 0.99 and 0.71, respectively.

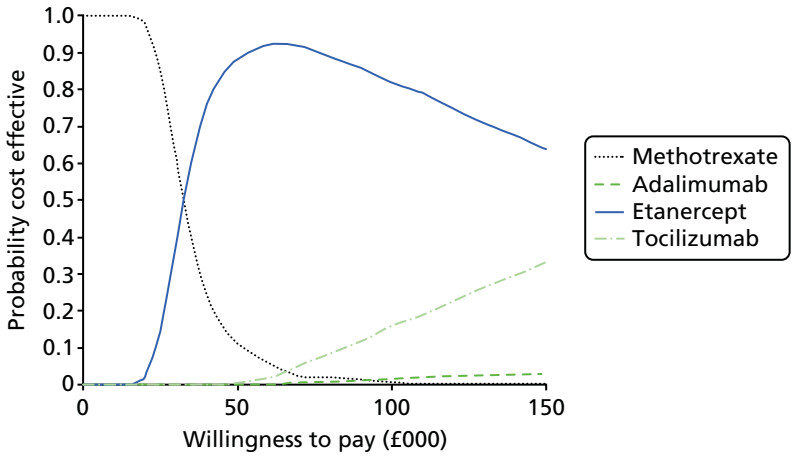

FIGURE 9 Cost-effectiveness acceptability curve from the PSA for first-line biological treatments compared with methotrexate.

TABLE 73 Summary of the probabilistic sensitivity results for second-line biologics vs. methotrexate only

Treatment	Costs, £	QALYs	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Methotrexate only	67,168	9.35			
Abatacept	203,396	12.81	136,041	3.43	39,608
Adalimumab	183,563	12.66	116,208	3.29	35,366
Etanercept	179,807	12.67	112,452	3.30	34,053
Tocilizumab	194,464	12.77	127,109	3.39	37,443

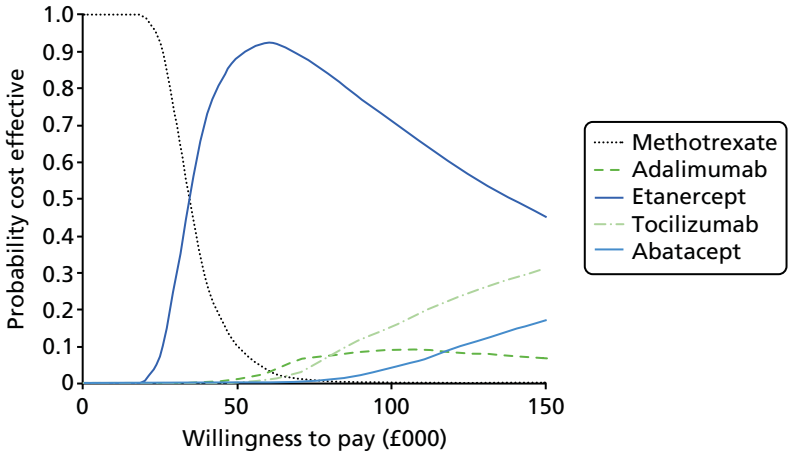

FIGURE 10 Cost-effectiveness acceptability curve from the PSA for second-line biological treatments compared with methotrexate.

Subgroups

There are a number of potential subgroups that were within the NICE scope, including the subtypes of JIA (EO, polyarticular arthritis, ERA and PA) and patients with extra-articular manifestations such as uveitis. As stated earlier, subgroup analyses by subtype of JIA was not possible owing to insufficient evidence for input parameters to support modelling. The modelled patient population is therefore people with JIA, with the results of particular relevance to those with polyarticular-course JIA (EO, and RF+ve and RF–ve polyarthritis).

In considering the potential for modelling the clinical effectiveness and cost-effectiveness of biologic DMARDs in patients with JIA-associated uveitis, a draft NHS clinical commissioning policy on the use of antiTNFα agents in paediatric patients with severe refractory uveitis was consulted.[29] The policy discusses the cost-effectiveness of treatment and the elements of an economic evaluation are given, although the full results from such an economic evaluation have not been reported.

The report states that infliximab and adalimumab in combination with methotrexate are widely used worldwide for the treatment of refractory uveitis, and that etanercept is not recommended for use in this patient group. The report also cites evidence from a systematic review by Simonini and colleagues[96] (see *Chapter 4, Juvenile idiopathic arthritis-associated uveitis*), which shows that, based on a pooled analysis of observational studies, the proportion of children with improved intraocular inflammation (responders) was 87% for adalimumab, 72% for infliximab and 33% for etanercept. Potential modelling of the clinical effectiveness and cost-effectiveness in JIA-associated uveitis in this report would therefore apply only to adalimumab, as this is the only one of the four biologic DMARDs within the scope of the appraisal recommended for treating this patient subgroup.

With regard to QoL, the clinical commissioning policy assumes that loss of vision causes detrimental effects on utility based on the results of a study of age-related macular degeneration by Reeves and colleagues.[165] This study measured HRQoL changes associated with loss of vision using data from the SF-6D and best corrected visual acuity. This population is quite different from JIA-associated uveitis, and the data do not capture aspects of JIA related to arthritic joints.

In our model, we have used utility data derived using the HUI3 generic preference instrument from the study by Prince and colleagues.[124] This instrument is appropriate for conditions that involve vision impairment, as it includes a domain for vision. HUI3 is not compatible with the SF-6D and the instruments will produce different QoL estimates. Attempting to combine data from Reeves and colleagues[165] and Prince and colleagues[124] would be inappropriate owing to the differences in the populations of the studies and the incompatibility of SF-6D and HUI3. Moreover, if it is assumed that adding vision loss to the other QoL decrements owing to advancing JIA even partially decreases patient QoL, then it follows that adalimumab will be more cost-effective in JIA patients with uveitis and joint inflammation than it is in JIA patients without uveitis.

Likewise, if most of the costs related to uveitis relate to the management of vision loss, as stated in the clinical commissioning policy,[29] then any reduction of these costs attributable to improving vision would increase cost-effectiveness in the subgroup of JIA patients with uveitis. Any additional analysis of cost-effectiveness in a JIA uveitis population that is refractory to methotrexate, as is indicated in the licensing for adalimumab, is therefore likely to have predictable results.

As discussed *Chapter 4*, the SYCAMORE trial of adalimumab and methotrexate in JIA-associated uveitis patients has recently closed early following an interim analysis that showed a favourable effect for treatment.[87] The trial also includes a cost-effectiveness analysis, the results of which would be likely to concur with the logical implications discussed above.

Comparison of the economic models

The cost-effectiveness of biologic DMARDs estimated in this report varies between £30,000 and £40,000 per QALY gained compared with methotrexate only. This is higher than estimated by the previous NICE appraisal for etanercept in patients with JIA, which estimated an ICER of £16,082 per QALY gained.[123] The NICE Appraisal Committee accepted that the ICER for etanercept was likely to be in the region of £15,000–30,000 per QALY.[43] The model used in that NICE appraisal is not fully described and so it difficult to compare with the current model developed for this report. However, the discount rate for that appraisal was 6% for costs and 1% for benefits. Using these discount rates in the independent model in this assessment report gives cost-effectiveness estimates of between £20,000 and £30,000 per QALY gained.

A cost–consequence analysis conducted by Prince and colleagues[124] in the Netherlands did not estimate the cost-effectiveness of etanercept. We have estimated the cost-effectiveness of etanercept compared with methotrexate from that study, by aggregating the costs and QALYs in each time period reported, to be £32,590 (€43,300).

Comparing the results from the independent model in this assessment report with those submitted by the companies was complicated by differences in structure between the models. Roche, who manufacture tocilizumab, was the only company that submitted a full economic analysis to NICE, including costs and QALYs and with a 25-year time horizon. BMS, who manufacturer abatacept, submitted a model with a 20-year time horizon with only drug and administration costs. In addition, in one company model, patients receive oral methotrexate (Roche), and in another company model, patients receive subcutaneous methotrexate (BMS). It was therefore only possible to compare drug costs between the three models with a 20-year time horizon and with discounting applied to allow a level comparison between the models independent of structural assumptions. *Table 74* shows the comparison with the Roche model with patients using oral methotrexate, whereas *Table 75* shows the comparison with the BMS model with patients using subcutaneous methotrexate.

It should be noted that the Roche analysis has not compared the biologic DMARDs against methotrexate in its submission but has compared adalimumab with tocilizumab; however, this analysis was present in the economic model.

As can be seen, there was variation in costs between the models. The Roche model has lower drug costs and total costs than the assessment report model. This is because their model uses a higher discontinuation rate so patients remain on the biologic for a shorter duration, and with lower health-state costs. The BMS model does not include discontinuation for any cause, which explains why it has the highest drug costs of

TABLE 74 Comparison of the drug costs in the assessment report model with the Roche CS model (20-year discounted, no PAS) (CiC information has been removed)

	Assessment report model (using oral methotrexate)		Roche model	
Treatment	Drug costs, £	Total costs, £	Drug costs, £	Total costs, £
Methotrexate	393	49,178	CiC information has been removed	CiC information has been removed
Adalimumab	71,992	119,269	CiC information has been removed	CiC information has been removed
Etanercept	65,396	111,941	CiC information has been removed	CiC information has been removed
Tocilizumab	74,578	121,725	CiC information has been removed	CiC information has been removed

TABLE 75 Comparison of the drug costs in the assessment report model with the BMS CS model (20-year discounted, no PAS) (CiC information has been removed)

	Assessment report model (using subcutaneous methotrexate)		BMS model	
Treatment	Drug costs, £	Total costs, £	Drug costs, £	Total costs, £
Methotrexate	8012	56,798	CiC information has been removed	CiC information has been removed
Adalimumab	81,804	129,081	CiC information has been removed	CiC information has been removed
Etanercept	70,368	116,914	CiC information has been removed	CiC information has been removed
Tocilizumab	85,312	132,459	CiC information has been removed	CiC information has been removed

the above models. Overall, the differences between the model results may be explained by differences in model structures and choices with regard to discontinuation, AEs and other costs.

Discussion

- A systematic search of the literature found four relevant economic evaluations of biologic DMARDs for patients with JIA. Two of the studies were presented as cost–utility studies,[123,125] one was a cost-effectiveness study[126] and the other was a cost–consequence study.[124] The evaluations were published between 2002 and 2012 in the UK, the Netherlands, Russia and Canada. One of the studies was the previous NICE appraisal of etanercept.[123] The studies varied in design and structure, time horizons and the comparators included. The limitations in the methodological quality in all the studies identified include limited reporting of model parameters and assumptions.
- A systematic search of the literature found two HRQoL studies in children and adolescents with JIA. One study assessed the effectiveness of a foot care programme in a RCT setting,[136] whereas the other evaluated QoL in a cohort of patients from the Dutch ABC Registry before and after treatment with etanercept.[124,137]
- Four pharmaceutical companies submitted evidence to NICE for consideration in this appraisal. Only one company (Roche) constructed a cost–utility analysis that included both costs and outcomes.[78] Two companies (BMS[85] and Pfizer[97]) submitted cost analyses and assume that the biologic DMARDs were equivalent in effectiveness, whereas AbbVie[77] did not submit an economic analysis owing to limitations identified with any potential analysis. Roche submitted a Markov state-transition model with health states for uncontrolled/off treatment, on treatment and dead. The model compared treatment with adalimumab to tocilizumab. The base-case results from the submission conclude that tocilizumab is of similar effectiveness and is less expensive than adalimumab.
- We developed an independent cost–utility model comparing the biologic DMARDs to methotrexate alone. From this model, the incremental cost-effectiveness of adalimumab, etanercept and tocilizumab versus methotrexate only is estimated at £38,127, £32,526 and £38,656 per QALY gained, respectively. An analysis comparing second-line biologics with methotrexate only estimated a cost-effectiveness ratio of £39,536 per QALY gained. The model results are most sensitive to changes to the HRQoL utility values.

Chapter 6 Assessment of factors relevant to the NHS and other parties

Etanercept was recommended by NICE in 2002,[131] and it is known that adalimumab, abatacept and tocilizumab are commonly used in practice (as well as infliximab – although not in the scope of this NICE appraisal).[144] It is unlikely that any positive NICE recommendations for the use of these biologic DMARDs will significantly increase the number of patients requesting treatment and thus affect budget impact.

Given that biologic DMARDs are currently used in the management of patients with JIA in the NHS, it is unlikely that substantial modifications will be needed to services, such as infrastructure development or increased staff training. However, a survey of services for children, young people and families living with JIA in the UK by the National Rheumatoid Arthritis Society found that, among the 13 specialist (tertiary) centres surveyed, there was a shortfall of staff to adequately cover the services required.[166] These included paediatric rheumatology consultants and clinical nurse specialists, clinical psychologists, occupational therapists and physiotherapists. Further recruitment and training of professionals to make up the multidisciplinary teams needed to provide effective treatment and care of JIA patients would seem to be necessary.

A long-term condition such as JIA can have a significant impact on children and young people's education. They may need to miss lessons to attend health-care appointments and may be absent for longer periods of time while experiencing symptoms (including disease flares) or if joint or other surgery is required. This can have a negative impact on educational attainment and, in turn, on their ability to gain employment in adulthood. It may also affect their social and psychological health, through a reduced ability to participate in social and leisure activities and sport, and the general burden of a serious health condition during the sensitive period of adolescence. The effect of this may, therefore, widen socioeconomic and health inequalities in this group. Only one of the RCTs included in the systematic review of clinical effectiveness reported the impact of treatment (abatacept)[58] on missed school days. This outcome was not formally included in our review, but it was found that treated patients experienced a statistically significantly higher increase in school days (1.9 days) than placebo patients (0.9 days). This indicates the potential for biologic DMARDs to improve education as well as health outcomes, although further evidence is required, particularly in a UK context.

Schools and health services are required to liaise to ensure appropriate care for children and young people with JIA. The National Rheumatoid Arthritis Society survey of 13 specialist centres found that all centres liaise with schools by letter or telephone, but fewer than half were unable to visit schools or provided only a limited service.[166] However, there were some examples of greater involvement, such as in one centre where the clinical nurse specialist will visit schools and give talks if required. Effective liaison between health services and schools is important to ensure that the needs of children with JIA receiving biologic DMARDs are adequately met.

The impact of JIA on parents and caregivers can also be significant. For example, they may have to pay for child care, take time away from work, or even cease employment altogether to provide care. This will negatively affect their income and may increase dependency on welfare benefits (where available). Again, this is likely to increase socioeconomic inequalities. The inability of parents and caregivers to work may have a negative impact on society and the economy, through reduced productivity, less income tax collection and, in some professions, a shortage of skilled workforce capacity. The impact of treating JIA on parents and caregivers was generally not assessed by the RCTs in the systematic review of clinical effectiveness. However, one of the RCTs (abatacept)[58] reported improvements in the number of days of normal activity per month missed by parents, including work and non-work activities, compared with placebo. The number of days on which paid care was required remained stable in both trial arms (following an initial decline in the open-label lead-in phase with abatacept treatment). Further evidence on the impact of biologic DMARD treatment on parents and carers would be useful to gauge the full potential benefits of treatment beyond the patients themselves.

Chapter 7 Discussion

Statement of principal findings

Clinical effectiveness

The systematic review of clinical effectiveness conducted for this report found that biologic DMARDs are superior to placebo (with methotrexate where permitted) across a number of outcome measures in children with JIA (predominantly polyarticular course) and an insufficient response to previous DMARD treatment. With the exception of the etanercept trial, the majority of patients in the trials received methotrexate in addition to the biologic DMARD/placebo. Biologic DMARD-treated patients had fewer arthritis flares, a longer time to disease flare (applicable to abatacept, adalimumab and etanercept), were more likely to achieve a treatment response as defined by the ACR Pedi criteria and were more likely to have inactive disease (measured only in the abatacept and tocilizumab trials). This last outcome can be considered to be the most clinically significant, as absence of disease activity (e.g. no joints with active arthritis; PGA indicates no disease activity, etc.) is a key treatment goal. Treatment was associated with reduced pain scores, although this was reported as statistically significant in only one study (tocilizumab). HRQoL as measured by the CHAQ appeared to be higher for treated patients, although this was not always statistically significant.

The percentage of patients achieving ACR Pedi-30 in the open-label lead-in phases of the RCTs ranged from 65% to 94% across the trials. It should be acknowledged that owing to the withdrawal design of the RCTs, in which only patients achieving an ACR Pedi-30 response during the open-label lead-in phase are eligible for randomisation, the results of the double-blind randomised phase of the trials are therefore applicable only to patients who have achieved an initial degree of treatment benefit. The effects seen during the double-blind period in the placebo group may not necessarily be the same for a placebo group who had not received a biologic DMARD prior to randomisation. However, expert clinical opinion suggests that ACR Pedi-30 can be considered an inadequate or partial response threshold, and higher rates, such as ACR Pedi-70 or above, are considered more clinically significant. In this respect, the patients responding to ACR Pedi-30 in the open-label lead-in phase (and eligible to be randomised) may not necessarily be considered atypical of patients eligible for treatment in clinical practice, as both would have active disease.

The clinical significance of the ACR Pedi-30 results of the randomised phases of the trials may also be questioned. ACR Pedi-30 response rates varied from 63% to 80% across the trials and declined with increasing response thresholds. Nonetheless, at ACR Pedi-70 (the highest threshold for which data were available across all four RCTs), the response rate varied from 44% to 65% and remained higher in biologic DMARD-treated patients than placebo patients in all trials. Research is under way to further develop the JADAS tool as a clinically useful measurement tool,[35–37] although clinical trials are continuing to use the ACR Pedi criteria, albeit with effectiveness judged at thresholds higher than ACR Pedi-30.

In the longer term, treatment effectiveness, in terms of ACR Pedi response, appears to be sustained, as reported in the observational OLE studies for all four included RCTs. The longest follow-up available is for etanercept, where ACR Pedi responses were maintained up to 8 years after treatment.

The occurrence of AEs was generally similar between biologic DMARD- and placebo-treated patients, based on reported non-statistically significant differences. A range of AEs were reported, including viral and upper respiratory tract infections, injection-site reactions and nasopharyngitis. Serious AEs were uncommon. Discontinuations attributable to AEs were also uncommon (< 3% patients). In the lead-in phase of the RCTs, discontinuations attributable to AEs were low, ranging from 0.5% to 1.8%. The incidence of AEs and SAEs during open-label long-term follow-up did not appear to be excessive. The safety profile of the biologic DMARDs, therefore, appears to be relatively favourable.

Subgroup analyses were reported in only one of the included RCTs (tocilizumab).[68] Patients receiving methotrexate background therapy had higher ACR Pedi response rates than those not receiving it, as did patients receiving background glucocorticoids. Patients who had received previous treatment with a biologic agent had lower ACR Pedi responses than those who were naive to biologic DMARDs. It is not clear whether these subgroup analyses were pre-planned or post hoc, so caution is advised in their interpretation.

Two recently published systematic reviews of the effectiveness of biologic DMARDs were identified during the production of this report.[167,168] Both of these included a range of biologic DMARDs, including the four relevant to the scope of this assessment. However, none of these reviews identified any additional RCT evidence to this assessment report. The only other relevant published systematic review of biologic DMARDs that we are aware of is by Otten and colleagues,[79] (most recent search date January 2012). As discussed earlier in this report [see *Chapter 4, Assessment of clinical effectiveness: biologic disease-modifying antirheumatic drugs versus each other (with methotrexate where permitted)*], Otten and colleagues[79] conducted an adjusted indirect comparison of adalimumab, abatacept and etanercept, using the same RCTs as included in this assessment report. We replicated the indirect comparison, extending it to include the tocilizumab RCT,[68] which was not published during the timescale of the Otten and colleagues[79] review. Our results and conclusions match those of Otten and colleagues,[79] namely that the biologic DMARDs appear similar in effectiveness in polyarticular-course JIA, in terms of ACR Pedi response and preventing disease flares. Otten and colleagues[79] also share some of the caveats made in this assessment report about the limitations of the data included in the indirect comparison, namely, the small number of trials (and patient numbers), and differences between the trials in key patient characteristics and in treatment duration.

The conclusion that biologic DMARDs may be similar in clinical effectiveness was supported by the expert advisers to this assessment report. In their experience, there is similarity in effects between the drugs at a population level. However, it is noted that interpatient variation in effects may occur, and comparative effectiveness of the biologic DMARDs may potentially vary between JIA subtypes. Currently, there are a lack of clinical trial data to confirm this. Experts suggested that future trials of biologic DMARDs should stratify by disease phenotype to assess the differential effects of each treatment.

As noted earlier in this report, the RCTs of the biologic DMARDs included a mixture of JIA subtypes, broadly under the classification of polyarticular-course JIA (including EO). The trials did not appear to include patients with ERA or PA; thus, we reviewed available evidence from trials in progress (see *Chapter 4, Ongoing trials*) and from non-randomised studies (see *Chapter 4, Additional supporting evidence*) to gauge the effectiveness of biologic DMARD treatment in these groups. Much of the evidence is for etanercept (licensed for ERA and PA) with some available for adalimumab (licensed for PA). A broad comparison of the results of these studies with those of the RCTs included in this assessment report suggests that effectiveness is generally similar between these JIA subtypes. For example, ACR Pedi-70 response rates for biologic DMARDs were in the range of 44–65% across the RCTs (see *Table 14*), compared with around (CiC information has been removed) across the JIA subtypes in the CLIPPER study of etanercept[99] (see *Table 34*) (notwithstanding differences in study variables such as length of follow-up). Evidence from trials in progress will provide greater clarity regarding the efficacy and safety of biologic DMARDs in these JIA subtypes. At present, there do not appear to be any studies of the comparative effectiveness of biologic DMARDs in these subtypes (e.g. adalimumab vs. etanercept).

All of the RCTs were multinational, with only one specifying that it included patients from the UK. The distribution of JIA subtypes within the trials, as far as reported (see *Table 11*), appears reasonably similar to that seen in UK registry studies (see *Table 2*), although this comparison may be limited by different reporting classifications used between studies. In addition, clinical practice in the RCTs (e.g. the oldest one published in 2000[42]) may not necessarily reflect current NHS care. The generalisability of the RCTs to the NHS is considered uncertain.

Cost-effectiveness

A systematic search of the literature found four economic evaluations of biologic DMARDs for patients with JIA. Two of the studies were presented as cost–utility studies, one was a cost-effectiveness study and the other was a cost–consequence study. The evaluations were published between 2002 and 2012 in the UK, the Netherlands, Russia and Canada. One of the studies was the assessment report which informed the previous NICE appraisal of etanercept (NICE TA35).[123] The studies varied in design and structure, time horizons and the comparators included. There were limitations in the methodological quality in all the studies identified, and limited reporting of model parameters and assumptions.

A systematic search of the literature found two HRQoL studies in children and adolescents with JIA. One study assessed the effectiveness of a foot care programme in a RCT setting, whereas the other evaluated the QoL in a cohort of patients from the Dutch ABC Registry before and after treatment with etanercept.

Four drug companies submitted evidence to be considered as part of the NICE appraisal. Only one company (Roche) constructed a cost–utility analysis that included both costs and outcomes. Two companies (BMS and Pfizer) submitted cost analyses and assumed that the biologic DMARDs were equivalent in effectiveness, whereas another company (AbbVie) did not submit an economic analysis owing to suggested methodological limitations with any potential analysis. Roche submitted a Markov state-transition model with health states for uncontrolled/off treatment, on treatment and dead. The model compared treatment with adalimumab to that with tocilizumab. The base-case results from the submission conclude that tocilizumab is of similar effectiveness and is less expensive than adalimumab.

We developed an independent cost–utility model comparing the biologic DMARDs to methotrexate only. From the model, the incremental cost-effectiveness versus methotrexate only for adalimumab, etanercept and tocilizumab is estimated at £38,127, £32,526 and £38,656 per QALY gained, respectively. The incremental cost-effectiveness for abatacept as a second-line biologic was £39,536 per QALY gained. The model results are most sensitive to changes to the HRQoL utility values.

The cost-effectiveness of biologic DMARDs estimated in this report is associated with some uncertainty owing to the limitations of the evidence base. For this reason, assumptions have had to be made to simplify the modelling. There was limited evidence on HRQoL, in particular with regard to disease progression. The HRQoL utility values were taken from a small Dutch registry study of patients receiving etanercept. The HRQoL values for patients treated with methotrexate were assumed to be constant over time. Patients with JIA who do not receive a biologic will experience disease progression and, therefore, their HRQoL will decline over time. In the model, we have assumed a constant HRQoL utility value for patients receiving methotrexate only and so the biologic DMARDs would be more cost-effective than estimated by the economic model.

The model has not considered the underlying disease progression in terms of joint damage for patients with JIA. These patients may have sustained permanent damage to one or more joints, thereby affecting their physical function and HRQoL into adulthood and potentially requiring joint surgery. The model has not considered the cost of this surgery and this assumption implies that biologic DMARDs have no impact on long-term disease progression in terms of joint damage. However, a prospective registry-based cohort study by Minden and colleagues[169] showed improved long-term prognosis for adult JIA patients who received etanercept during childhood. Furthermore, the AbbVie CS suggests that the reduction in orthopaedic surgery in JIA patients has been attributable to the increase in the use of immunomodulatory agents among children in recent decades and so DMARDs and biologic agents may have successfully prevented end-stage joint damage, based upon historical data that have shown a reduction. Therefore, biologic DMARDs are likely to reduce long-term damage compared with treatment with methotrexate, and they would potentially be more cost-effective than estimated by the independent economic model.

The cost-effectiveness of biologic DMARD treatment of patients with JIA-associated uveitis has not been formally estimated in this economic evaluation, owing to a lack of suitable input parameter data. The current evidence base comprises mainly small retrospective observational studies and suggests that adalimumab and infliximab are clinically effective in terms of improving intraocular inflammation and vision impairment.[96] A US cohort study of children with JIA compared those with JIA-associated uveitis with those without JIA-associated uveitis.[170] It reported that vision-related HRQoL was worse in uveitis patients, but general HRQoL was similar to that of JIA patients without uveitis.[170] It can be assumed that biologic DMARD treatment in JIA-associated uveitis patients will result in bigger overall HRQoL improvement (including vision-related HRQoL) and therefore would be more cost-effective in this group than in JIA patients without uveitis.

It was also reported that significant predictors of uveitis were persistent oligoarthritis and younger age at JIA diagnosis.[170] As discussed in *Chapter 1*, persistent oligoarthritis accounts for up to 48% of JIA cases in the UK and is regarded as a milder form of JIA. In contrast, EO accounts for between 6% and 17% of JIA cases in the UK and results in more severe symptoms and disease progression. Only EO was explicitly included in the NICE scope for this appraisal, and, therefore, it can be considered that uveitis is less likely to affect the patient subtypes that are relevant to the appraisal.

The economic model does not include the wider societal costs associated with JIA, which are described in more detail in *Chapter 6*. In the base-case analysis we have not included caregiver benefits associated with biologic DMARD treatment. A scenario analysis showed an improvement in cost-effectiveness for the biologic DMARDs when incorporating a utility disutility for patient caregivers.

The base-case analysis includes only one line of biologic DMARD treatment; however, in clinical practice some patients may switch to second- or third-line DMARDs. A scenario analysis that included a sequence of biologic treatments that most resembles current clinical practice was performed. The cost-effectiveness of multiple lines of biologic therapy is similar to that seen in the base-case analysis for one line of biologic therapy. There are many other possible treatment sequences but these have not been modelled, as they were considered to be less likely to occur in clinical practice and the results for these sequences are similar to those presented. In clinical practice, infliximab is often used but this has not been included as a treatment in the economic model, as it is licensed for this indication.

The cost-effectiveness results in this report are consistent with those from an earlier NICE technology appraisal for etanercept for patients with JIA (NICE TA35[43]). The previous appraisal used a discount rate of 6% for costs and 1% for benefits.[123] We ran the analysis for etanercept using these discount rates and the cost-effectiveness of etanercept improved to £21,718 per QALY. Using these discount rates, etanercept would be cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Strengths and limitations of the assessment

The systematic reviews and economic evaluation in this report have been carried out independently of any competing interest, and the results are presented in a consistent and transparent manner.

The systematic reviews of clinical effectiveness, cost-effectiveness and HRQoL have been undertaken following an established methodology and principles for conducting a systematic review.[52] The methods used were reported in a research protocol, which defined the decision problem in line with the NICE scope and set out the inclusion and quality assessment criteria, data extraction process and the other methods to be employed during the evidence synthesis.

A multidisciplinary advisory group has informed the review from its initiation. The research protocol was informed by comments received from the advisory group. The group also commented on a draft of the final report.

A de novo economic model has been developed following recognised guidelines. The model structure and data inputs are clearly presented in this report. The economic model is based upon data identified from systematic searches for clinical effectiveness, cost-effectiveness and QoL evidence, and other best available data.

This report is subject to certain limitations. The lack of head-to-head trials meant performing an indirect comparison of the biologic DMARDs, which is subject to a number of caveats due to heterogeneity between the trials (e.g. patient characteristics, treatment duration).

Limited HRQoL data were available for children with JIA, with none of the RCTs of biologic DMARDs reporting health utility data. The model results were based upon one Dutch registry study for patients treated with etanercept. It was necessary to make assumptions about the QoL of patients treated with other biologic DMARDs. Owing to the scarcity of the HRQoL data, it was not possible to link effectiveness data from the RCTs, in terms of ACR Pedi or CHAQ score, to a HRQoL utility measure. Furthermore, no HRQoL data were identified to inform the estimate of disutility of disease flare or the caregiver burden.

There were limited data available for the long-term discontinuation rates for patients for some of the biologic DMARDs, and it was necessary to assume that the discontinuation rates for the biologic DMARDs were the same as each other.

The economic analysis has compared biologic DMARDs against methotrexate only, for patients with an insufficient response to previous methotrexate. The NICE scope also includes best supportive care (e.g. NSAIDs, corticosteroids) as a comparator in patients who cannot tolerate a DMARD (e.g. methotrexate), but this has not been included in the analysis owing to a lack of available data to make a comparison with best supportive care. Such patients would be likely to be offered a biologic DMARD rather than receiving best supportive care; therefore, this comparison is not necessarily clinically relevant.

The model consists of a simple structure that does not incorporate the natural history of the disease in terms of long-term disease progression. JIA causes joint disease that requires joint operations and is associated with other comorbidities. It is unclear from the current evidence how biologic DMARDs affect the natural history of the disease and the occurrence of these outcomes.

Uncertainties

The RCTs included in our systematic review of clinical effectiveness did not report the impact of treatment on extra-articular manifestations. Uveitis is the most common of these manifestations and, if not identified and adequately controlled, can lead to permanent vision loss. Current guidance is to treat JIA patients with uveitis who have not responded to steroids or methotrexate with either adalimumab or infliximab, both of which are antiTNF drugs (of these, only adalimumab is within the scope of this assessment).[29] The guidance[29] states that etanercept is not suitable for the treatment of JIA patients with uveitis.

Furthermore, no HRQoL utility values for the impact of uveitis on the HRQoL in children with JIA were identified in our systematic review of QoL. The paucity of good-quality evidence for the effectiveness of biologic DMARDs means that the clinical effectiveness and cost-effectiveness of treating JIA patients with uveitis is currently uncertain. However, it could be assumed that if biologic DMARD treatment of uveitis is effective in reducing sight impairment in addition to improving general JIA symptoms, then the cost-effectiveness estimates generated in the independent economic evaluation in this assessment report would be improved. The SYCAMORE RCT of adalimumab in combination with methotrexate for JIA-associated uveitis (funded by the NIHR HTA programme and Arthritis Research UK) has recently completed recruitment and will include an assessment of cost-effectiveness.[87]

The lack of available, suitable, published cost–utility models necessitated building a new model which aimed to resemble clinical practice but also to utilise the effectiveness data from the RCTs. The design of the RCTs does not necessarily represent clinical practice (e.g. there would not be a lead-in phase with a biologic DMARD).

The model has not incorporated the impact of biologic DMARD treatment on disease progression and assumes that the HRQoL of patients treated with methotrexate is constant over time. The results may, therefore, underestimate the cost-effectiveness of treatment.

The model has assumed that treatment is equally effective for subsequent lines of biologic DMARD treatment as for the first line of treatment. If effectiveness is seen to be reduced in subsequent lines of therapy for particular switching regimens, then cost effectiveness may be reduced compared with the results presented in this report (relating to abatacept as a second-line treatment, and the scenario analysis of three lines of treatment).

The model has been modelled with a 30-year time horizon in the base-case analysis. There are a lack of long-term outcome data for JIA patients. In addition, there are often differences in the management of JIA patients as adults, which may affect patient outcomes. However, there are few empirical data available on the management of adult patients with JIA.

Chapter 8 Conclusions

Implications for service provision

Given that biologic DMARDs are currently used in the treatment of JIA, any recommendation supporting their use is unlikely to have significant implications for service provision (e.g. in terms of changes to infrastructure and staff training). However, further recruitment and training of staff is required to address workforce capacity shortages in some specialist centres.

Suggested research priorities

Randomised head-to-head comparisons of biologic DMARDs are necessary to establish comparative effectiveness. Currently, they are assumed to be equivalent based on indirect comparisons of a small number of trials with relatively small patient numbers. Trials should be sufficiently powered, with long-term follow-up of safety and efficacy, and should include an economic evaluation to assess cost-effectiveness. Treatment response should be assessed at a threshold that is considered clinically significant (e.g. ACR Pedi-70 or higher) and should also include measures of disease inactivity. Additional instruments to the ACR Pedi criteria should be used, such as the JADAS instrument.[35–37] Future trials of biologic DMARDs should stratify by disease phenotype to assess the differential effects of each treatment. Where possible, trials should measure the impact of treatment on children's educational and social outcomes, such as time away from school/college when experiencing symptoms and for health-care management, and the ability to participate in leisure and social activities.

Randomised controlled trials are also required for subtypes of JIA for which evidence is currently lacking, including ERA and PA. As mentioned, the SYCAMORE trial of adalimumab in patients with JIA-associated uveitis[87] has recently closed for recruitment early, following interim analysis showing that adalimumab is favourable in the treatment of JIA-associated uveitis.

Further research is needed to establish the HRQoL benefits associated with biological treatment in children with JIA and their caregivers. Validated child-appropriate instruments should be used to assess HRQoL, including generic preference-based tools to enable utilities to be estimated to inform cost-effectiveness analyses.

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Contributions of authors

Jonathan Shepherd (Principal Research Fellow, evidence synthesis) project-managed the study, developed the research protocol, contributed to drafting the background section, assisted in the development of the search strategy, assessed studies for inclusion, performed data extraction and critical appraisal of included clinical effectiveness studies, synthesised evidence, assessed the company submissions, and drafted and edited the final report.

Keith Cooper (Senior Research Fellow, health economics) developed the research protocol, assessed cost-effectiveness and HRQoL studies for inclusion, synthesised evidence, led the development of the economic evaluation, assessed the company submissions and drafted the final report.

Petra Harris (Research Fellow, evidence synthesis) developed the research protocol, contributed to drafting the background section, assessed studies for inclusion, performed data extraction and critical appraisal of included clinical effectiveness studies, synthesised evidence, assessed the company submissions and drafted the final report.

Joanna Picot (Senior Research Fellow, evidence synthesis) developed the research protocol, contributed to drafting the background section, assessed studies for inclusion, performed data extraction and critical appraisal of included clinical effectiveness studies, synthesised evidence, assessed the company submissions and drafted the final report.

Micah Rose (Research Fellow, health economics) contributed to the development of the economic evaluation, assessed the company submissions and drafted the report.

Data sharing statement

All available data relating to the systematic reviews are included in this report and its appendices. Some confidential data were provided that are not in the public domain and this information has been redacted in this report and cannot be shared by the review authors.

The Assessment Group has presented the results of its economic modelling using the drug list prices for abatacept, adalimumab, etanercept and tocilizumab in this report. A separate confidential appendix reporting the results incorporating the confidential PASs for abatacept and tocilizumab has been prepared by the Assessment Group for NICE. The confidential appendix will not be released publicly. The economic model associated with this document is protected by intellectual property rights, which are owned by the University of Southampton. Anyone wishing to modify, adapt, translate, reverse engineer, decompile, dismantle or create derivative work based on the economic model must first seek the agreement of the property owners.

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Appendix 1 Search dates and example MEDLINE search strategies for clinical effectiveness, cost-effectiveness and health-related quality of life

Databases searched for the systematic reviews of clinical effectiveness, cost-effectiveness and HRQoL are presented below. Clinical effectiveness searches were updated on 5 May 2015 and cost-effectiveness and HRQoL searches were updated on 6 May 2015.

		Cost-effectiveness searches
Database searched (host)	Clinical effectiveness searches	HRQoL searches
BIOSIS Previews (Web of Science)	Searched to 29 October 2014	1956–11 November 2014
		1956–2 December 2014
Cochrane Central, CDSR, Cochrane DARE, Cochrane HTA and Cochrane Methods (The Cochrane Library)	Searched to 4 November 2014	
Cochrane Central, Cochrane DARE, Cochrane Economic Evaluations and Cochrane Methods (The Cochrane Library)		HRQoL: searched to 9 December 2014
Centre for Reviews and Dissemination databases: DARE, HTA and NHS EED (CRD)	Searched to 4 November 2014	All available years to 11 November 2014
		All available years to 9 December 2014
CPCI-S (Web of Science)	1990–29 October 2014	1970–11 November 2014
		1970–2 December 2014
DELPHI		Costs: searched to 10 November 2014
EMBASE (Ovid)	All available years to 29 October 2014	Searched to 10 November 2014
		1974–1 December 2014
MEDLINE (Ovid)	Searched to 29 October 2014	1946 to October week 5 2014
		1946 to November week 2 2014
MEDLINE In-Process & Other Non-Indexed Citations (Ovid)	Searched to 29 October 2014	Searched to 10 November 2014
		Searched to 25 November 2014
PsycINFO (EBSCO*host*)		HRQoL: 1954–9 December 2014
Science Citation Index Expanded (SCI-EXPANDED) (Web of Science)	1970–29 October 2014	1970–11 November 2014
		1970–2 December 2014
Zetoc (Mimas)	Searched to 4 November 2014	

CDSR, Cochrane Database of Systematic Reviews; CPCI–S, Conference Proceedings Citation Index – Science; DARE, Database of Abstracts of Reviews of Effects; NHS EED, NHS Economic Evaluation Database.

Searched for ongoing trials (all searched on 13 May 2015)

National Institute for Health Research Clinical Research Network (NIHR CRN Portfolio, formally the UKCRN website).

Clinical trials.gov.

World Health Organization' ICTRP.

ISRCTN.

MEDLINE search strategies for clinical effectiveness, cost-effectiveness and HRQoL are shown here. These were adapted for other databases and are available on request.

Clinical effectiveness MEDLINE search strategy

1. Arthritis, Juvenile/
2. JIA.tw.
3. exp Arthritis/
4. (arthriti* or oligoarthriti* or polyarthriti* or polyarticula*).tw.
5. Rheumatoid Factor/
6. "rheumatoid factor".tw.
7. or/3-6
8. (juvenile* or child* or teen* or adolescen* or youth* or "young person" or "young people" or pediatric* or paediatric*).tw.
9. exp Child/ or Adolescent/
10. 7 and (8 or 9)
11. 1 or 2 or 10
12. (etanercept or enbrel).mp.
13. (abatacept or orencia).mp.
14. (adalimumab or humira).mp.
15. (tocilizumab or toclizumab or RoActemra).mp.
16. or/12-15
17. 11 and 16
18. limit 17 to English language
19. limit 18 to humans
20. (letter or editorial or comment).pt.
21. 19 not 20

Cost-effectiveness MEDLINE search strategy

1. Arthritis, Juvenile/
2. JIA.tw.
3. exp Arthritis/
4. (arthriti* or oligoarthriti* or polyarthriti* or polyarticula*).tw.
5. Rheumatoid Factor/
6. "rheumatoid factor".tw.
7. or/3-6
8. (juvenile* or child* or teen* or adolescen* or youth* or "young person" or "young people" or pediatric* or paediatric*).tw.
9. exp Child/ or Adolescent/
10. 7 and (8 or 9)
11. 1 or 2 or 10
12. (etanercept or enbrel).mp.
13. (abatacept or orencia).mp.
14. (adalimumab or humira).mp.
15. (tocilizumab or toclizumab or RoActemra).mp.
16. or/12-15
17. 11 and 16
18. limit 17 to English language
19. limit 18 to humans
20. (letter or editorial or comment).pt.
21. 19 not 20
22. exp economics/
23. exp economics hospital/
24. exp economics pharmaceutical/
25. exp economics nursing/
26. exp economics medical/
27. exp "Costs and Cost Analysis"/
28. Cost Benefit Analysis/
29. exp models economic/
30. exp fees/ and charges/
31. exp budgets/
32. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*).tw.
33. (value adj1 money).tw.
34. budget$.tw.
35. or/22-34
36. ((energy or oxygen) adj cost).tw.
37. (metabolic adj cost).tw.
38. ((energy or oxygen) adj expenditure).tw.
39. or/36-38
40. 35 not 39
41. (letter or editorial or comment or historical article).pt.
42. 40 not 41
43. 21 and 42

Health-related quality-of-life MEDLINE search strategy

1. Arthritis, Juvenile/
2. JIA.tw.
3. exp Arthritis/
4. (arthriti* or oligoarthriti* or polyarthriti* or polyarticula*).tw.
5. Rheumatoid Factor/
6. "rheumatoid factor".tw.
7. or/3-6
8. (juvenile* or child* or teen* or adolescen* or youth* or "young person" or "young people" or pediatric* or paediatric*).tw.
9. exp Child/ or Adolescent/
10. 7 and (8 or 9)
11. 1 or 2 or 10
12. CHAQ.tw.
13. childhood health assessment questionnaire.tw.
14. child health questionnaire.tw.
15. CHQ.tw.
16. CHU 9D.tw.
17. PedsQL.tw.
18. "Paediatric Quality of Life Inventory".tw.
19. "Pediatric Quality of Life Inventory".tw.
20. "juvenile arthritis disease activity score".tw.
21. JADAS*.tw.
22. value of life/
23. quality adjusted life year/
24. quality adjusted life.ti,ab.
25. (qaly* or qald* or qale* or qtime*).tw.
26. disability adjusted life.ti,ab.
27. daly*.ti,ab.
28. health status indicators/
29. eq 5d 3l.tw.
30. (euroqol or euro qol or eq5d or eq 5d).tw.
31. (hql or hqol or "h qol" or hrqol or "hr qol").tw.
32. (hye or hyes).tw.
33. health* year* equivalen*.ti,ab.
34. health utilit*.ab.
35. (hui or hui1 or hui2 or hui3).ti,ab.
36. disutil*.ti,ab.
37. rosser.ti,ab.
38. "quality of well being".tw.
39. "quality of wellbeing".tw.
40. qwb.tw.
41. "willingness to pay".tw.
42. "standard gamble*".tw.
43. "time trade off".tw.
44. "time tradeoff".tw.
45. tto.tw.
46. (index adj2 "well being").mp.
47. (quality adj2 "well being").mp.
48. (health adj3 utilit*).mp.
49. ((multiattribute* or "multi attribute*") adj3 ("health ind*" or theor* or "health state*" or utilit* or analys*)).mp.

50. "quality adjusted life year*".mp.
51. (15D or "15 dimension*").mp.
52. (12D or "12 dimension*").mp.
53. "rating scale*".mp.
54. "linear scal*".mp.
55. "linear analog".mp.
56. "visual analog*".mp.
57. (categor* adj2 scal*).mp.
58. or/12-57
59. 11 and 58
60. (comment or editorial or letter).pt.
61. 59 not 60
62. limit 61 to English language

Appendix 2 Screening phase 1: titles and abstracts for systematic review of clinical effectiveness

TABLE 76 Titles and abstracts for systematic review of clinical effectiveness

Language	
Non-English language	Exclude
Intervention	
• Abatacept (Orencia) (with or without methotrexate) • Adalimumab (Humira) (with or without methotrexate) • Etanercept (Enbrel) • Tocilizumab (RoActemra) (with or without methotrexate)	Can be either with or without methotrexate (will check usage is as per licensed indication at full-paper screen)
Participants	
JIA • EO • Polyarthritis (onset or course) • Enthesitis related • Psoriatic • Undifferentiated	For mixed populations (e.g. including systemic or oligoarthritis), include only if the proportion of the unwanted type(s) is < 33% (i.e. two-thirds of the population should meet the inclusion criteria) Exclude systemic arthritis (unless NO active systemic symptoms in the previous 6 months); exclude persistent oligoarthritis
Comparators	
• DMARDs (e.g. methotrexate, azathioprine, cyclosporin, penicillamine, sulphasalazine and gold preparations) • Best supportive care if DMARDs not tolerated (e.g. NSAIDs, corticosteroids) • Interventions compared with each other	
Outcomes	
One or more of: • disease activity • disease flares • physical function • joint damage • pain • corticosteroid-reducing regimens • extra-articular manifestations (e.g. uveitis) • body weight and height • mortality • AEs of treatment • HRQoL	Do not exclude at title and abstract screening stage on outcome. Get full paper to check
Design	
RCT	If NO but data may not be available from RCTs (e.g. long-term AEs, height and growth)
Systematic review	If YES (or possibly Yes) and cannot exclude on P, I or C, RETRIEVE for full-paper screen and possible reference list check if meets criteria
Abstracts/conference presentations	
Published 2011 or earlier	Exclude
Published 2012 or later: are sufficient details presented to allow appraisal of methodology and assessment of results?	If cannot definitely exclude on P, I, C or D RETRIEVE (for full-text screen and possible tie up with full papers or ongoing studies)

C, comparator; I, intervention; P, population.

Appendix 3 Screening phase 2: full papers for systematic review of clinical effectiveness

Study name or number

Design				
RCT	Yes	Unclear	No	
	↓	↓	↓	
	Next Q	Next Q	Exclude	
Abstracts/conference presentations				
Published 2012 or later	Yes	Unclear	No	
	↓	↓	↓	
	Next Q	Next Q	Exclude	
Intervention				**Comments**
• Abatacept (Orencia) • Adalimumab (Humira) • Etanercept (Enbrel) • Tocilizumab (RoActemra)	Yes (Y)	Unclear (U)	No (N)	Etanercept should be monotherapy (not with methotrexate)
	↓	↓	↓	
	To drug-specific section (row below)	Skip to comparator section	Exclude	

Abatacept (Orencia)			Adalimumab (Humira)						Etanercept (Enbrel)									Tocilizumab (RoActemra)		
JIA subtype polyarthritis with insufficient response to other DMARDs including at least one TNF inhibitor			JIA subtype polyarthritis with inadequate response to 1 or more DMARDs			JIA subtype ERA with inadequate response/intolerance to conventional treatment			JIA subtype polyarthritis (including RF+ve or RF–ve and EO) with inadequate response/intolerance to methotrexate			JIA subtype PA with inadequate response/intolerance to methotrexate			JIA subtype ERA with inadequate response/intolerance to conventional treatment			JIA subtype polyarthritis (including RF+ve or RF–ve and EO) in patients not responding to other NSAIDs or corticosteroids		
Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N
↓	↓	↓	↓	↗	↗	↓	↓	↓	↓	↗	↗	↓	↗	↗	↓	↓	↓	↓	↓	↓
Next Q	Next Q	Exclude	Next Q	Next Q	Next Q	Next Q	Age Qs	Exclude	Next Q	Next Q	Next Q	Next Q	Next Q	Next Q	Next Q	Age Qs	Exclude	Next Q	Next Q	Exclude
Participant age 6 years			***Participant age 2 years***			***Participant age 6 years***			***Participant age 2 years***			***Participant age 12 years***						***Participant age 2 years***		
Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y		U		N		Y	U	N
↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		↓		↓		↓	↓	↓
Comp	Comp	Ex	Comp	Comp	Ex	Comp	Comp	Ex	Comp	Comp	Ex	Comp		Comp		Ex		Comp	Comp	Ex
Comments:			Comments:			Comments:			Comments:			Comments:						Comments:		

Comparators (Comp)		
• A DMARD (e.g. methotrexate, azathioprine, cyclosporin, penicillamine, sulphasalazine and gold preparations) • Best supportive care if DMARDs not tolerated (e.g. NSAIDs, corticosteroids) • Interventions compared with each other	Yes ↓ Next Q	Unclear ↓ Next Q	No ↓ Exclude	Note what the comparator is

Outcomes			
Any one or more from the list below: Disease activity; disease flares; physical function; joint damage; pain; corticosteroid-reducing regimens; extra-articular manifestations (e.g. uveitis); body weight and height; mortality; AEs of treatment; HRQoL	Yes ↓ Next Q	Unclear ↓ Next Q	No ↓ Exclude
Abstracts/conference presentations			
Published with sufficient detail to allow appraisal of methodology and assessment of results	Yes ↓ Make final decision	Unclear ↓ Make final decision	No ↓ Exclude
Final decision	**INCLUDE**	**UNCLEAR (discuss)**	**EXCLUDE**

Comp, comparator; Ex, exclude; N, no; Q, question; U, unclear; Y, yes.

Appendix 4 Table of excluded and unclear studies from systematic review of clinical effectiveness

TABLE 77 Excluded and unclear studies from systematic review of clinical effectiveness

Excluded study	Primary reason for exclusion (comments)
Amarilyo G, Tarp S, Foeldvari I, Cohen N, Pope TD, Woo JMP, *et al*. Efficacy and safety of biologic agents in patients with poly-articular juvenile idiopathic arthritis: network meta-analysis of randomized controlled withdrawal trials. *Arthritis Rheum* 2013;**65**:S922–3	Design (NMA)
Anink J, Otten MH, Spronk S, van Suijlekom-Smit LW. Efficacy of biologic agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. *Arthritis Rheum* 2012;**64**:S490	Design (SR and indirect comparison)
Canadian Agency for Drugs and Technologies in Health. *Common Drug Review: Clinical Review Report for Tocilizumab (Actemra, intravenous) for the Treatment of Signs and Symptoms of Active Polyarticular Juvenile Idiopathic Arthritis.* 2014. URL: www.cadth.ca/media/cdr/clinical/SR0343_Actemra%20pJIA_CL_Report_e.pdf (accessed May 2015)	Design (SR)
Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. *Health Technol Assess* 2002;**6**(17)	Design (SR and economic evaluation)
Decelle K, Horton ER. Tocilizumab for the treatment of juvenile idiopathic arthritis. *Ann Pharmacother* 2012;**46**:822–9	Design (SR)
Foster CS, Tufail F, Waheed NK, Chu D, Miserocchi E, Baltatzis S, *et al.* Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol* 2003;**121**:437–40	Population (adults)
Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008;**27**:67–76	Design (SR)
Kemper AR, Van Mater HA, Coeytaux RR, Williams JW Jr, Sanders GD. Systematic review of disease-modifying antirheumatic drugs for juvenile idiopathic arthritis. *BMC Pediatr* 2012;**12**:29	Design (SR)
Kingsbury D, Quartier P, Arora V, Kalabic J, Kupper H, Mozaffarian N. Safety and effectiveness of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to < 4 years or > = 4 years weighing < 15 kg. *Ann Rheum Dis* 2013;**72**:A729	Design
Kingsbury D, Quartier P, Arora V, Kalabic J, Kupper H, Mozaffarian N. PReS-FINAL-2161: Safety and effectiveness of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to < 4 years or > = 4 years weighing < 15 kg. *Pediatr Rheumatol* 2013;**11**:P173	Design
Kingsbury DJ, Quartier P, Arora V, Kalabic J, Kupper H, Mozaffarian N. Safety and effectiveness of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to < 4 years or > = 4 years weighing < 15 kg. *Arthritis Rheum* 2013;**65**:S117	Design
Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. *JAMA Intern Med* 2013;**173**:1416–28	Design (SR and MA)
Martini A. Etanercept improves active polyarticular juvenile rheumatoid arthritis. *Clin Exp Rheumatol* 2001;**19**:122–4	Design (commentary)
Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, *et al.* Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011;**63**:939–48	Population (adults)
Mori M, Takei S, Imagawa T, Imanaka H, Nerome Y, Kurosawa R, *et al.* Etanercept in the treatment of disease-modifying anti-rheumatic drug (DMARD)-refractory polyarticular course juvenile idiopathic arthritis: experience from Japanese clinical trials. *Mod Rheumatol* 2011;**21**:572–8	No comparator

continued

TABLE 77 Excluded and unclear studies from systematic review of clinical effectiveness (*continued*)

Excluded study	Primary reason for exclusion (comments)
Mori M, Takei S, Imagawa T, Imanaka H, Nerome Y, Higuchi R, *et al.* Safety and efficacy of long-term etanercept in the treatment of methotrexate-refractory polyarticular-course juvenile idiopathic arthritis in Japan. *Mod Rheumatol* 2012;**22**:720–6	Design (open-label part)
Otten MH, Anink J, Spronk S, van Suijlekom-Smit LWA. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. *Ann Rheum Dis* 2013;**72**:1806–12	Design (review)
Pato E, Munoz-Fernandez S, Francisco F, Abad MA, Maese J, Ortiz A, *et al.* Systematic review on the effectiveness of immunosuppressants and biological therapies in the treatment of autoimmune posterior uveitis. *Semin Arthritis Rheum* 2011;**40**:314–23	Design (review)
Sawyer L, Diamantopoulos A, Brunner HI, Benedetti F, Ruperto N, Dejonckheere F, *et al.* PReS-FINAL-2070: efficacy of biologic treatments in juvenile idiopathic arthritis with a polyarticular course: an indirect comparison. *Pediatr Rheumatol* 2013;**11**:P82	Design (indirect comparison)
Sawyer L, Diamantopoulos A, Brunner H, De Benedetti F, Ruperto N, Dejonckheere F, *et al.* Efficacy of biologic treatments in juvenile idiopathic arthritis with a polyarticular course: an indirect comparison. *Ann Rheum Dis* 2013;**72**:740–1	Design (indirect comparison)
Sawyer L, Diamantopoulos A, Brunner HI, De Benedetti F, Ruperto N, Dejonckheere F, *et al.* Efficacy of biologic treatments in juvenile idiopathic arthritis with a polyarticular course: an indirect comparison. *Arthritis Rheum* 2013;**65**:S119	Design (indirect comparison)
Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor alpha treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. *Arthritis Care Res* 2014;**66**:1073–84	Design (review)
Simonini G, Katie D, Cimaz R, Macfarlane GJ, Jones GT. Does switching anti-TNFalpha biologic agents represent an effective option in childhood chronic uveitis: the evidence from a systematic review and meta-analysis approach. *Semin Arthritis Rheum* 2014;**44**:39–46	Design (review)
Ungar WJ, Costa V, Burnett HF, Feldman BM, Laxer RM. The use of biologic response modifiers in polyarticular-course juvenile idiopathic arthritis: a systematic review. *Semin Arthritis Rheum* 2013;**42**:597–618	Design (review)
Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, *et al.* The effects of early aggressive therapy in JIA: results of the TREAT study. *Pediatr Rheumatol* 2012;**10**:32	Abstract (methods)
Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, *et al.* Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum* 2012;**64**:2012–21	Unclear population
Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, *et al.* Predictors and sustainability of clinical inactive disease in polyarticular juvenile idiopathic arthritis given aggressive therapy very early in the disease course. *Arthritis Rheum* 2013;**65**:S334–5	Abstract (methods)
Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, *et al.* Clinically inactive disease in a cohort of children with new-onset polyarticular juvenile idiopathic arthritis treated with early aggressive therapy: time to achievement, total duration, and predictors. *J Rheumatol* 2014;**41**:1163–70	Unclear population
Wallace CA, Bonsack J, Spalding SJ, Brunner H, O'Neil KM, Milojevic D, *et al.* Results of a 24 month extension study in patients who participated in the trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum* 2013;**65**:S116	Abstract (methods)

MA, meta-analysis; NMA, network meta-analysis; SR, systematic review.

Unclear studies
Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, *et al.* A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18–23

Appendix 5 Clinical effectiveness data extraction tables

Data extraction: abatacept

Reference and design	Intervention and comparator	Participants	Outcome measures
Study identifier: Ruperto *et al.* (2008),[57] Ruperto *et al.* (2010),[58] Ruperto *et al.* (2010),[59] Lovell *et al.* (2012)[60] **Study acronym:** AWAKEN **Study design:** withdrawal RCT (4-month open-label lead-in phase, 6-month double-blind randomised phase, OLE phase) **Country or countries:** Europe (none from the UK), Latin America, USA **Number of centres:** 45 **Recruitment dates:** February 2004 to June 2006 (date of last treatment, recruitment likely to be finished before then) **Funding:** BMS	**Intervention:** 4-month open-label lead-in phase (days 1–113) ABA (10 mg/kg according to weight; maximum dose 1000 mg) on days 1, 15, 29, 57 and 85 **Double-blind phase:** ABA given at doses of 10 mg/kg at randomisation and at about 28-day intervals thereafter for 6 months (days 114–283) or until a flare of arthritis **Comparator:** matching placebo **Other interventions used:** all DMARDs except MTX (stable dose) withdrawn and prohibited during the trial (wash-out period of at least 4 weeks for any DMARD other than MTX, before the first dose of study medication). Oral corticosteroids were stabilised 4 weeks before enrolment NSAIDs or analgesics permitted for pain control Folinic acid or folic acid permitted. 140/190 (74%) received MTX concomitantly	OL lead-in phase, number enrolled: $n = 190$. Those achieving ACR Pedi-30 response randomised in double-blind phase (limited data extracted for this phase) Double-blind withdrawal phase **Number of randomised participants:** ABA: $n = 60$ Placebo: $n = 62$ OLE study [up to day 1681 (year 5.5) efficacy, and up to 7 years safety][59,60] Non-responders to ABA during OL phase: $n = 36$ ABA treated patients in double-blind phase: $n = 58$ Placebo treated patients in double-blind phase: $n = 59$ Total in OLE: $n = 153$ **Inclusion criteria:** JIA (EO, polyarticular positive or negative for RF, or systemic without systemic manifestations) Aged 6–17 years At least five active joints (those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion); inadequate response to, or intolerance to, at least one DMARD including biologic agents (e.g. etanercept,	**Primary outcome(s):** time to disease flare **Secondary outcomes:** proportion of patients at the end of 6-month double-blind phase who had disease flare; changes from baseline in each of the six ACR core variables; pain; assessment of safety and tolerability; HRQoL (sleep and missed school days reported but not extracted here) **Method of assessing outcomes:** disease flare defined as worsening of 30% or more in at least three of the six ACR core-response variables for JIA, and at least 30% improvement in no more than one variable during the double-blind period. If a global assessment by either physician or parent was used, flare was defined as a worsening of 20 mm or more on the 100-mm VAS. If the number of active joints or joints with limited range of motion was used for assessment, it was defined as worsening in two or more joints Improvement defined as an improvement of 30% or more in at least three of six ACR core-response variables and at least 30% worsening in not more than one variable. Improvements were also defined by 50%, 70% and 90% improvements in the ACR paediatric criteria CHAQ used to assess physical, emotional and social aspects of HRQOL. Higher scores indicate better HRQoL, 0–100 scale. CHAQ disability index is scored 0–3,

Reference and design	Intervention and comparator	Participants	Outcome measures
		infliximab and adalimumab). (Previous anti-TNF therapy reported in 57/190 patients during OL lead in.) **Exclusion criteria:** active uveitis, major concurrent medical conditions, pregnant or lactating	with a higher score indicating greater disability. CHQ used to assess pain on 100-mm VAS. Higher score indicates more severe pain **Length of follow-up:** end of double-blind period (day 169), plus assessments made for OLE at ≥ 21 months (day 589) (efficacy and safety), and at day 1681 (study year 5.5 – efficacy and safety, and study year 7 (safety). It is presumed that these time points are in relation to the start of the OL lead-in

Baseline characteristics (double-blind period)	ABA ($n = 60$)	Placebo ($n = 62$)	Comments
Age (mean), years (SD)	12.6 (3)	12.0 (3)	
Sex female, *n* (%)	43 (72)	45 (73)	
Ethnic origin, *n* (%)			
White	46 (77)	49 (79)	
Black	5 (8)	4 (7)	
Other	9 (15)	9 (15)	
Type of JIA			
Persistent oligoarthritis	0	2 (3)	
EO	9 (15)	7 (11)	
Polyarthritis (RF+ve)	14 (23)	12 (19)	
Polyarthritis (RF–ve)	26 (43)	28 (45)	
Systemic	11 (18)	12 (19)	
RF+ve, *n* (%)	19 (32)	12 (19)	
RF–ve, *n* (%)	41 (68)	50 (81)	
Duration of JIA (mean), years (SD)	3.8 (3.7)	3.9 (3.5)	
Previous anti-TNF therapy discontinued, *n* (%)	8 (13)	13 (21)	
Lack of efficacy	7 (12)	11 (18)	
For financial reasons	1 (2)	2 (3)	

Results (for double-blind period,[57] unless otherwise stated)

Primary outcome	ABA ($n = 60$)	Placebo ($n = 62$)	*p*-value
Time to flare (median, months)	Not reached	6	0.0002

Comments: Kaplan–Meier survival curves are presented, but the survival probabilities can be read-off only from the curves and have not been extracted here. IQR could not be calculated for the placebo group as there were too few events

Secondary outcomes	ABA ($n = 60$)	Placebo ($n = 62$)	p-value
Disease activity, *n* (%)[a]			
ACR Pedi-30	49 (82)	43 (69)	0.1712
ACR Pedi-50	46 (77)	32 (52)	0.0071
ACR Pedi-70	32 (53)	19 (31)	0.0185
ACR Pedi-90	24 (40)	10 (16)	0.0062
Inactive disease[b]	18 (30)	7 (11)	0.0195
Disease flares, *n* (%)	12 (20)	33 (53)	0.0003
Disease flares, hazard ratio	0.31 (95% CI 0.16 to 0.59)		NR
Core-response variables, mean (SD)			
PGA (VAS: 100 mm)	14.7 (18.9)	23.2 (21.8)	0.0004
Parent's global assessment (VAS: 100 mm)	17.9 (22.2)	23.9 (21.6)	0.6992
Physical function (CHAQ disability index: 0–3)	0.8 (0.9)	0.8 (0.7)	0.0388
Number of active joints	4.4 (7.0)	6.0 (5.8)	0.0245
Number of joints with limited range of motion	8.8 (12.8)	8.6 (12.0)	0.0128
ERS (mm per hour)	25.1 (26.4)	30.7 (30.1)	0.9562
CRT (mg/l)	0.16 (0.25)	0.29 (0.54)	0.0255
Pain (mean parent global assessment of pain, CHAQ 100-mm VAS)	15[c]	21[c]	0.105
Corticosteroid-reducing regimens	NR		
Extra-articular manifestations	NR		
Body weight and height	NR		
Mortality	NR		
HRQoL			
CHQ physical summary score	43.6	41[d]	0.666
CHQ psychosocial summary score	51.7	47[d]	0.056
AEs (for double-blind period, unless otherwise stated)			
Total SAEs, *n* (%)	0	2 (3)	0.50
Total SAEs, OLE, *n* (%)[e]	23 (15)		
Total AEs, *n* (%)[f]	37 (62)	34 (55)	0.47
Infections and infestations, *n* (%)	27 (45)	27 (44)	1.00
Gastrointestinal disorders, *n* (%)	10 (17)	9 (15)	0.81

Secondary outcomes	ABA ($n = 60$)	Placebo ($n = 62$)	p-value
General disorders and administration site conditions, n (%)	4 (7)	9 (15)	0.24
Nervous system disorders, n (%)	3 (5)	2 (3)	0.68
Respiratory, thoracic and mediastinal disorders, n (%)	6 (10)	3 (5)	0.32

p-values for the core-response variables were based on the difference in the adjusted mean percentage change from day 113 to day 282.

a After 6 months of double-blind treatment or at the time of flare for patients who did not complete this period. In addition to the ACR Pedi overall response, data for the respective six ACR Pedi core response variables are reported at the start and end of the double-blind period. Only the number of active joints, number of joints with limited range of motion and the CHAQ disability index (physical function) are data extracted here.

b Defined as no joints with active arthritis, a PGA of ≤ 10 on a 100-mm VAS, and a normal ESR.

c Read-off from graph by reviewer. Number of patients in the trial arms not clear. Abatacept-treated patients ($n = 52$) had improved scores for 14 of the 15 subscales and placebo-treated patients ($n = 34$) for 6 of the 15 subscales ($p > 0.05$ for abatacept vs. placebo for all subscales; details not data extracted).

d Abatacept-treated patients ($n = 52$) had improved scores for 14 of the 15 subscales of the CHQ from start to end of double-blind period ($p > 0.05$ for abatacept vs. placebo for all subscales). Placebo-treated patients ($n = 34$) had improved scores for 6 of the 15 subscales.

e SAEs during the OLE (by day 589) occurred in 23/153 patients including an arthritis flare ($n = 6$), arthralgia ($n = 2$), foot deformity ($n = 2$), pyrexia ($n = 2$) and vomiting ($n = 2$). At 7-year follow-up, 30/153 (19.6%) patients had SAEs. Most were unrelated and were primarily musculoskeletal or infectious events. The incidence rate (per 100 patient-years) of SAEs in the OLE (5.6/100 patient-years) did not increase vs. the 6-month double-blind rate (6.8/100 patient-years).

f AEs that occurred in at least 5% of patients in the open-label and double-blind phases.

Results OLE

Original group sizes in double-blind phase	ABA ($n = 60$)	Placebo ($n = 62$)
ACR Pedi outcomes OLE at day 589[59]	**Received ABA in double-blind phase ($n = 51$)**	**Received placebo in double-blind phase ($n = 47$)**
ACR Pedi-30	46/51 (90%)	41/47 (87%)
ACR Pedi-50	45/51 (88%)	39/47 (83%)
ACR Pedi-70	38/51 (75%)	35/47 (75%)
ACR Pedi-90	29/51 (57%)	19/47 (40%)
ACR Pedi-100	20/51 (39%)	9/47 (19%)
Inactive disease[9]	22/51 (43%)	11/47 (23%)

Comments: Patients treated with abatacept during the double-blind phase had in total (lead-in, double-blind and OLE phases) received continuous abatacept therapy for a minimum of 31 months (those recruited to the study earliest had been treated longer, the maximum was 52 months at the time of database lock), whereas those who received placebo during the double-blind phase usually received abatacept for a shorter period (length not stated).

An analysis according to prior exposure to biologic agents, ACR Pedi data for those in the OLE who had not taken part in the double-blind phase and information on anti-abatacept and anti-CTLA-4 antibody production is presented but has not been extracted.

g Inactive disease was defined as having no joint with active disease, a PGA of disease severity score < 10 mm, and an ESR ≤ 20 mm/hour.

Methodological comments:

Allocation to treatment groups: patients randomly assigned (1 : 1) to receive either abatacept or placebo. The sequential number for each patient was allocated according to a computer-generated randomisation schedule

Blinding: the main phase of the trial was described as double-blind. Responder and flare status were determined by independent blinded evaluators at the co-ordinating centres

Comparability of treatment groups: appear similar on most variables, although placebo group had a greater proportion of RF–ve patients than ABA group (81% vs. 68%)

Method of data analysis: Kaplan–Meier survival curves used to estimate the distribution of time to disease flare for each group in the 6-month double-blind phase. Log-rank test used to compare the time to disease flare between groups. A Cox proportional hazards model, with treatment as the only covariate, was used to compare the hazard ratio and 95% CIs for flare of arthritis between the two groups. Missing values in the double-blind phase imputed with the LOCF method in the analysis of the individual components of the six ACR paediatric response variables, the ACR responses and inactive disease status. HRQoL analysis (CHQ) based on available data at each time point

Sample size/power calculation: estimated 200 patients needed in the open-label phase to have a sufficient sample size to compare the time to flare over 6 months between the abatacept and placebo groups (with two-sided log-rank tests at 5% significance). Assuming that 64% of patients would respond to treatment (based on experience with rheumatoid arthritis in adults), a sample size of 128 patients would yield 95% power to detect a difference of 35%, assuming a flare rate of 65% in placebo controls and a dropout rate of 10% for the double-blind phase. (The actual flare rate for placebo was 53% and the drop-out rate was 34%, with a difference of 33% between abatacept and placebo in percentage of patients experiencing a flare.)

Attrition/drop-out: 42 (34%) patients discontinued during the double-blind period, 31 (50%) in the placebo group and 11 (18%) in the abatacept group); all but one (abatacept-treated patient) did so because the treatment was not effective. 8 patients (2 ABA, 6 placebo) did not receive treatment in accordance with protocol during the double-blind phase but were included in end-point analysis

General comments:

Generalisability: results applicable to patients aged 6–17 years with JIA (EO, polyarthritis or systemic without systemic manifestations) with an inadequate response to, or intolerance to, at least one DMARD (including biologic agents), receiving background MTX

Outcome measures: appear appropriate

Intercentre variability: not reported, but to minimise variability in joint assessments each centre had at least two certified joint assessors who underwent specific and standardised joint assessment training

Conflict of interests: the first two authors have received funding for research activity from a variety of pharmaceutical companies including BMS, although they have not received funding from companies as personal contribution for assistance during the trial. Three other authors are employees of BMS

ABA, abatacept; MTX, methotrexate; NR, not reported; OL, open label.

Quality criteria (Cochrane Risk of Bias tool) randomised controlled trials[171]

Criteria	Judgement[a]	Support for judgement
Random sequence generation (selection bias)	Yes	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Yes	Centres were informed of the random allocation of patients by an interactive voice-randomisation system run by the central drug management group
Blinding of participants and personnel (performance bias)	Yes	Double-blind phase of the study (after open-label lead in)
Blinding of outcome assessment (detection bias)	Yes	Responder and flare status determined by independent blinded evaluators at the co-ordinating centres
Incomplete outcome data addressed (attrition bias)		Larger proportion of patients dropped out of the placebo group in the double-blind phase than the ABA group (50% vs. 18%). Main reason for drop-out was lack of efficacy
ACR responses, inactive disease status	Yes	Missing values imputed with LOCF method
HRQoL[58]	No	Analyses based on available data (observed analysis)
Selective reporting (reporting bias)	Yes	All outcomes reported on
Other sources of bias	Unclear	Intercentre variability not discussed

ABA, abatacept.
a Yes, low risk of bias; no, high risk of bias; unclear, uncertain risk of bias.

Data extraction: adalimumab

Reference and design	Intervention and comparator	Participants	Outcome measures
Study identifier: Lovell *et al.* (2008),[61] Lovell *et al.* (2012),[62] Ruperto *et al.* (2013),[63] Ruperto *et al.* (2014)[64] **Study acronym:** none **Study design:** medication-withdrawal RCT (16-week randomised open-label, 32-week double-blind randomised withdrawal phase, OLE phase) **Country or countries:** not specifically stated but appear to be Belgium, Czech Republic, France, Germany, Italy, Spain, Slovak Republic and the USA **Number of centres**: 31 (not specified by country) **Recruitment dates:** 19 September 2002 to 13 January 2005	16-week open-label phase: 24 mg ADA per square metre (maximum of 40 mg) subcutaneously EOW **Licence indication:** polyarticular onset JIA: presumed to be the same as polyarticular-course JIA **Double-blind phase:** ADA: as per open-label phase for 32 weeks **Comparator:** placebo **Other interventions used:** MTX: $\geq 10\,mg/m^2$ per week for 3-month prior screening, same dosage during open-label lead-in and double-blind phases **No MTX:** have never received MTX or had discontinued it ≥ 2 weeks prior to study drug	**First randomisation, open-label lead-in phase, number randomised: *n* = 171** MTX: $n = 85$ No-MTX: $n = 86$) (Limited data extracted for this phase.) **Second randomisation, double-blind withdrawal phase:** Number randomised: $n = 133$ MTX/placebo: $n = 37$ MTX/ADA: $n = 38$ No data for ADA ($n = 30$) and placebo ($n = 28$) group not receiving MTX extracted Loss to follow-up: $n = 4$ (5.3%)	**Primary outcome(s):** percentage of patients not receiving MTX with disease flares (week 16–48) **Secondary outcomes:** AEs **Method of assessing outcomes:** every 12 weeks **Disease flare (ACR Pedi responses):** worsening of $\geq 30\%$ in more than three of the six core criteria for JIA and an improvement of $\geq 30\%$ in one or fewer criteria. If the number of joints with active arthritis was used as a criterion of flare, an increase in the number of active joints to two or more was required if there were no initial active joints or only one active joint. The same approach was used if the number of joints with loss of motion was used as a criterion of flare. If either of the global assessments was used as a

Reference and design	Intervention and comparator	Participants	Outcome measures
Funding: research grant from Abbott Laboratories	Stable dosages of NSAIDs and low-dose corticosteroids (≤ 0.2 mg of prednisone or prednisone equivalent per kilogram of body weight per day to a maximum of 10 mg per day) were permitted. Pain medications were allowed except for the 12 hours preceding assessment of the joints	ADA: $n = 3$ (7.9%) Placebo: $n = 1$ (2.7%) **Inclusion criteria:** Aged 4–17 years Polyarticular-course JIA (with any type of onset) with active disease (≥ 5 swollen joints and ≥ 3 joints with LOM) and without adequate response to NSAIDs Either no previous treatment with MTX or previous treatment with MTX and AEs or an inadequate response **Had to have an ACR Pedi-30 response at week 16 to enter double-blind phase** **Exclusion criteria:** Clinically significant deviations in clinically hematologic, hepatic or renal indicators Ongoing infection or recent major infection requiring hospitalisation or intravenous antibiotics Recent live or attenuated vaccines Previously treated with other biologic agents at any time or recent treatment with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered by the intra-articular, intramuscular or intravenous route	criterion of flare, any increase of > 30% in the VAS of 0 to 100 was sufficient and no minimum clinically important increase was required (e.g. an increase of 2–4 would qualify for use of that criterion in the determination of flare) **ACR Pedi criteria:** physician's and patient's/parent's global assessment of overall well-being (both measured with a 100-mm VAS: 0 = no disease activity or 'very well' for overall well-being, 100 = most disease activity or 'very poor' for overall well-being) the number of joints with active arthritis (defined as joints with swelling not caused by deformity or joints, in the absence of swelling, with limitation of passive motion accompanied by pain tenderness, or both), the number of joints with limitation of passive motion, physical function measured by the CHAQ-DI, and a laboratory assessment of inflammation (CRP concentrations) ACR Pedi-50, -70, -90 and -100 levels of response were evaluated, defined as improvements of 50% or more, 70% or more, 90% or more and 100%, respectively, in three or more of the six core criteria for JIA, with worsening of 30% or more in only one criterion **Safety:** physical examinations, laboratory results, vital signs and AEs **Post hoc analysis:** **Clinical outcomes:** 27-joint JADAS27 based on C-creative protein; functional outcome: CHAQ-DI. MDA defined as JADAS-27 < 3.8 and normal function defined as CHAQ-DI < 0.5. Higher scores indicate higher disease activity

Reference and design	Intervention and comparator	Participants	Outcome measures
			Length of follow-up: 70 days after last dose for AEs for all patients who discontinued study medication. Those enrolled in the double-blind phase were eligible to receive open-label treatment with ADA in an extension phase of the study (duration not specified)

Baseline characteristics	ADA ($n = 38$)	Placebo ($n = 37$)	Comments
Age, mean years (SD)	11.7 (3.3)	10.8 (3.4)	
Age group, *n* (%)			
4–8 years	6 (16)	12 (32)	
9–12 years	17 (45)	10 (27)	
13–17 years	15 (40)	15 (41)	
Sex: female, *n* (%)	30 (79)	30 (81)	
Ethnicity, *n* (%)			
White	36 (95)	36 (97)	Determined by the patient or parent
Black	0	0	
Other	2 (5)	1 (3)	
Body weight (mean), kg (SD)	42.1 (17.9)	44.3 (18.9)	
Type of JIA			Reported as poly-articular-course JIA
RF–ve, *n*/N (%)	27/37 (73)	30/36 (83)	
Duration of JIA (mean), years (SD)	4.3 (4.1)	4.0 (3.5)	
Previous medication use, *n* (%)			
MTX	38 (100)	37 (100)	
Other DMARDs	1 (3)	7 (19)	
Methylprednisolone	2 (5)	2 (5)	

Results (double-blind phase, weeks 16–48)

Primary outcome	ADA ($n = 38$)	Placebo ($n = 37$)	*p*-value
Disease flares, *n*/N (%)	14/38 (37)	24/37 (65)	$p = 0.02$
Comments:			

Secondary outcomes	ADA ($n = 38$)	Placebo ($n = 37$)	p-value
Disease activity			
ACR Pedi response week 48 (%)[a]			
30	63	38	$p = 0.03$
50	63	38	$p = 0.03$
70	63	27	$p = 0.002$
90	42	27	$p = 0.17$
Physical function	NR	NR	
Joint damage	NR	NR	
Pain	NR	NR	
Corticosteroid reducing regimens	NR	NR	
Extra-articular manifestations (such as uveitis)	NR	NR	
Body weight and height	NR	NR	
Mortality	See comments AEs		
HRQoL	NR	NR	

a A patient who had a flare according to the protocol definition was classified as having no response (ACR Pedi < 30) from that point forward, regardless of the patient's ACR Pedi response at that time.

AEs, number of events (number of events per patient-year)	ADA ($n = 38$) (18.3 patient-years)	Placebo ($n = 37$) (15 patient-years)	p-value
Any AE	234 (12.8)	155 (10.3)	
Most frequently reported AEs			
Related to injection-site reaction	73 (4.0)	57 (3.8)	
Contusion	12 (0.7)	7 (0.5)	
Nasopharyngitis	5 (0.3)	6 (0.4)	
Upper respiratory tract infection	6 (0.3)	5 (0.3)	
Viral infection	7 (0.4)	3 (0.2)	
Vomiting	4 (0.2)	2 (0.1)	
Excoriation	10 (0.6)	1 (0.1)	
Serious AEs, possibly related to study drug[b]	0	1 (0.1) – gastroduodenitis	
AEs leading to the discontinuation of the drug	0	0	

Comments:
No occurrence of deaths, opportunistic infections, malignant conditions, demyelinating diseases or lupus-like reactions. 27/171 (16%) patients had at least one positive test for anti-ADA antibody during the open-label and double-blind phases [MTX: 5/85 (6%), no MTX: 22/86 (26%)], but development of anti-ADA antibody did not lead to a greater rate of discontinuation of the study drug, nor did it increase the incidence of serious AEs.

b SAEs were death or any event that was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, congenital anomaly or spontaneous or elective abortion, or required medical or surgical intervention to prevent another serious outcome.

First 104 weeks of OLE phase[61]	
ACR Pedi at 104 weeks of OLE, %	**OLE phase ($n = 128$)[c]**
30	89%[d]
50	86%[d]
70	77%[d]
90	59%[d]
100	40%

c Only 71/128 (55%) of this group received MTX during the open-label and double-blind phases of the study and meet the licensed indication for adalimumab (i.e. the 128 includes participants not receiving MTX in the two study arms that do not meet the licensed indication).
d Data extracted from figure using Engauge digitizer software (version 4.1, © Mark Mitchell). Data available for earlier time points in OLE (weeks 8, 16, 24, 56, 104) but not data extracted. For missing values, the last observation was carried forward.

Post hoc analysis: OLE,[64] *n* (%)	**ADA**		**Placebo**		***p*-value[e]**
	week 48	**week 88**	**week 48**	**week 88**	
Minimal disease activity[f]	19 (76)	26 (83.9)	15 (62.5)	14.0 (50.0)	
Minimal disease activity[f] with normal function[g]	17 (68.0)	24 (77.4)	15 (62.5)	14 (50.0)	

e Statistical comparison between ADA with or without MTX vs. placebo with or without MTX only. Post hoc analysis on growth in patients with JIA62,63 reported per MTX or non-MTX group only (not data extracted).
f JADAS27 < 3.8.
g CHAQ-DI < 0.5.
The OLE[61] was ongoing at the time the key effectiveness paper was published and the time period for which events were reported is not clear. SAEs considered possibly related to study drug occurred in seven patients during the OLE (a table in the published paper[61] suggests none was receiving MTX, in which case they were not receiving ADA treatment in accordance with the licensed indication). Three patients discontinued treatment owing to AEs during the OLE.

Methodological comments:

Allocation to treatment groups: randomisation at a 1 : 1 ratio within patients' previous respective strata (stratified according to MTX use), no further details reported

Blinding: double-blind (investigators, study co-ordinators, assessors, patients and parents were unaware of the treatment assignment during the double-blind phase of the study)

Comparability of treatment groups: states no significant differences in baseline characteristics between the placebo and the ADA group within either stratum (MTX or no MTX) – no statistical comparison between the ADA–MTX and placebo–MTX group reported. There were some baseline differences between the later treatment groups: the ADA group had a higher percentage of children in the 9- to 12-year age group than the placebo group; conversely, mean body weight was slightly lower. Mean negative for RF was 10% lower in this group compared with placebo, duration of JIA was slightly lower and previous medication use for other DMARDs was 16% lower than the placebo group

Method of data analysis: efficacy analyses ITT; however, this was defined as all patients who received a ≥ 1 dose of the study drug during the phase of the study for which the analysis was being conducted. For the primary efficacy end point and for all secondary analyses of disease flare, missing values were treated as disease flares. For secondary analyses of ACR Pedi-30, -50, -70 and -90 responses during the open-label lead-in and double-blind phases, missing values were imputed as non-responses. In addition, patients in whom a flare occurred according to the protocol definition during the double-blind phase were classified as having no response (ACR Pedi < 30) at week 48, regardless of their actual ACR Pedi responses

Sample size/power calculation: assumption of a 70% response rate to ADA reported, requiring 42 patients in the open-label lead-in phase to yield the 29 patients needed for each group in the double-blind phase. This estimate was based on a 40% difference in the rate of flare between the placebo and the ADA groups and provided a power of 80% at an alpha level of 0.05. However, it is stated that the study was not statistically powered to detect differences between patients receiving and those not receiving MTX

Attrition/drop-out: Double-blind: $n = 4$ (5.3%); ADA, $n = 3$ (withdrew for other reasons, no further details); placebo, $n = 1$ (withdrew consent). [Loss to follow-up, total: $n = 43$ (25%); open-label, all: $n = 38$ (22%); double-blind all $n = 5$ (3.8%)]

General comments:

Generalisability: limited to polyarticular-course JIA patients aged 4 to 17 years, who have previously received 16 weeks' ADA treatment and treated with MTX, and had an ACR Pedi-30 response at week 16

Outcome measures: appear to be appropriate

Intercentre variability: not discussed

Conflict of interests: authors received various financial support and/or unrestricted continued medical education grants from various pharmaceutical companies including the drug manufacturer. States 'no other potential conflict of interests relevant to this article was reported'. Individuals at JK Associates and Abbott Laboratories provided editorial support, and individuals at Abbott Laboratories helped with data management and statistical analysis

ADA, adalimumab; CHAQ-DI, Disability Index of the Childhood Health Assessment Questionnaire; ITT, intention to treat; MTX, methotrexate; NR, not reported.

Quality criteria (Cochrane Risk of Bias tool) randomised controlled trials[171]

Criteria	Judgement[a]	Support for judgement
Random sequence generation (selection bias)	Unclear	No details reported
Allocation concealment (selection bias)	Unclear	No details reported
Blinding of participants and personnel (performance bias)	Yes	Double-blind, details reported
Blinding of outcome assessment (detection bias)	Yes	Double-blind, details reported
Incomplete outcome data addressed (attrition bias)	Yes	Details reported
Selective reporting (reporting bias)	Yes	All outcomes stated were reported
Other sources of bias	Unclear	Intercentre variability not discussed

a Yes, low risk of bias; no, high risk of bias; unclear, uncertain risk of bias.

Data extraction: etanercept

Reference and design	Intervention and comparator	Participants	Outcome measures
Study identifier: Lovell *et al.*(2000),[42] Lovell *et al.* (2003),[65] Lovell *et al.* (2006)[66] and Lovell *et al.* (2008)[67] **Study acronym:** none **Study design:** medication-withdrawal RCT (3 months open-label lead-in phase, 4-month double-blind randomised withdrawal phase, OLE phase) **Country or countries:** Canada and the USA **Number of centres:** not specifically stated, but appears to be 9[65] **Recruitment dates:** not reported **Funding:** Immunex Corporation[171]	**Intervention:** 0.4 mg of etanercept per kilogram subcutaneously twice weekly until disease flare occurred or 4 months elapsed (includes 33% of patients with systemic onset JIA) **Comparator:** placebo **Other interventions used:** stable doses of NSAIDs, low doses of corticosteroids (≤ 0.2 mg of prednisone per kilogram per day, with a maximum of 10 mg per day) or both. Pain medications were allowed except during the 12 hours before a joint assessment MTX discontinued 14 days and other DMARDs 28 days before receipt of etanercept **OLE:** 0.4 mg/kg etanercept twice weekly (maximum dose 25 mg per injection) or 0.8 mg/kg once weekly (maximum dose of 50 mg/week) subcutaneously	(3 months open- label (OL) lead-in phase: $n = 69$) (limited data extracted for this phase) Double-blind withdrawal phase **Number of randomised participants:** $n = 51$ Etanercept: $n = 25$ Placebo: $n = 26$ OLE: $n = 58$ Loss to follow-up: [Part 1: $n = 5$ (7%)] Part 2-RCT: Etanercept: $n = 6$ (24%); Placebo: $n = 19$ (73%) Part 3: OLE: $n = 38$ (66%) **Inclusion criteria:** children aged 4–17 years with JIA, with active disease (five or more swollen joints and three or more joints with LOM and pain, tenderness, or both) despite treatment with NSAIDs and with MTX at doses of at least 10 mg/m^2 of body-surface area per week **Exclusion criteria:** No intra-articular and soft-tissue corticosteroid injections for 1 month before the trial; patients with major concurrent medical conditions; Pregnant and lactating patients	**Primary outcome(s):** number of patients with disease flare **Secondary outcomes:** not specifically stated **Method of assessing outcomes for Part 2:** physical examinations, measures of disease activity and laboratory tests (hematologic analysis, serum chemical analysis, and urinalysis) on day 1 (before etanercept or placebo) and day 15 and at the end of each month. Final safety assessments 30 days after discontinuation of study drug for withdrawals or at next scheduled visit if withdrawal is attributable to disease flare. Serum at the end of 7 months for testing for autoantibodies (antinuclear antibodies, antibodies to double-stranded DNA, IgG and IgM anticardiolipin antibodies and antibodies to extractable nuclear antigens), and on day 1 before the administration of the study drug and at the end of months 7 for testing for antibodies to etanercept Physician's global assessment of disease severity 0–10 (best-worst); patient's or parent's global assess of overall well-being: 0–10 (best-worst); CHAQ: 0–3 (best–worst); ESR: normal ranges 1–30 mm per hour for females and 1–13 mm per hour for males; articular severity score: 0 (best) to 962 (worst); pain: VAS 0 cm (best) to 10 cm (worst); CRP: normal range is 0–0.79 mg per decilitre. Other: 73 joints were evaluated for the total active-joint count; 71 for LOM with pain, tenderness or both; 66 for swollen joints; and 71 for LOM

Reference and design	Intervention and comparator	Participants	Outcome measures
			Definition of disease flare: change in the core set of response variables from the beginning of the double-blind study: worsening of ≥ 30% in three of six response variables and a minimum of two active joints. Could also have improvement of ≥ 30% in no more than one of six response variables. Global assessments, if used to define flare, had to change by at least 2 units on a scale from 0 to 10 Definition of improvement of disease response was based on changes from baseline values at enrolment, whereas flare was measured from beginning of the double-blind study. For example, 28 active joints at baseline, but only 2 active joints at the time of randomisation – a change to 3 active joints would be considered a flare (at least 30% worse than the condition at the time of randomisation) but would also still be considered improvement (at least 30% improved from baseline) **Length of follow-up:** 4 months (double-blind only); OLE: 8 years[67]

Baseline characteristics: double-blind study	Etanercept ($n = 25$)	Placebo ($n = 26$)	Comments
Mean age, year	8.9	12.2	
Age group, *n* (%)			
4–8 years	13 (52)	5 (19)	$p < 0.02$
9–12 years	5 (20)	4 (15)	
13–17 years	7 (28)	17 (65)	
Sex, *n* (%)			
Female	19 (76)	15 (58)	
Male	6 (24)	11 (42)	

Baseline characteristics: double-blind study	Etanercept ($n = 25$)	Placebo ($n = 26$)	Comments
Ethnicity, *n* (%)			
White	14 (56)	23 (88)	$p < 0.02$
Black	3 (12)	1 (4)	
Hispanic	6 (24)	2 (8)	
Other	2 (8)	0	
Type of JIA, *n* (%)			
Pauciarticular	2 (8)	1 (4)	
Polyarticular	14 (56)	17 (65)	
Systemic	9 (36)	8 (31)	
RF+ve, *n* (%)	4 (16)	8 (31)	
Mean duration of JIA, year	5.3	6.4	
Previous medication, *n* (%)			
MTX	25 (100)	26 (100)	
DMARDs at washout, *n* (%)	16 (64)	19 (73)	
MTX	16 (64)	18 (69)	
Hydroxychloroquine	2 (8)	7 (27)	
Concomitant therapy at washout, *n* (%)			
Corticosteroids	6 (24)	13 (50)	
NSAIDs	25 (100)	24 (92)	
Mean dose of corticosteroids, mg/day	6.5	5.5	
Results: double-blind study			
Primary outcome	**Etanercept ($n = 25$)**	**Placebo ($n = 26$)**	***p*-value**
Disease flare, *n* (%)	7 (28)	21 (81)	$p = 0.003$[a]
Corticosteroid use at baseline[b]			
Yes	3/6 (50)	12/13 (92)	$p = 0.05$
No	4/19 (21)	9/13 (69)	
Time to flare, median days	> 116	28	$p < 0.001$

a $p < 0.001$ after adjustment for baseline characteristics in logistic regression model.
b Authors state that, with the exception of corticosteroid use at baseline ($p = 0.05$), none of the baseline characteristics was significant predictors of flare rates ($p > 0.15$).
Because 13/25 patients were still receiving etanercept at the end of the study (day 116) without disease flare, the median time to flare was greater than 116 days.

Secondary outcomes at 7 months, median	Etanercept ($n = 25$)	Placebo ($n = 26$)	p-value
30% improvement, *n* (%)	20 (80)	9 (35)	$p < 0.01$
50% improvement, *n* (%)	18 (72)	6 (23)	
70% improvement, *n* (%)	11 (44)	5 (19)	
JIA core set criteria, median			
Total number of active joints (out of 73 joints)	7.0	13.0	
Number of joints with LOM and with pain, tenderness, or both (out of 71 joints)	1.0	4.5	
PGA of disease severity	2	5	
Patient/parent's global assess. of overall well-being	3	5	
Score on CHAQ (disability domain)	0.8	1.2	
ESR	18	30	
Articular severity score, median	38	66	
Duration of stiffness (minimum), median	5	38	
Pain (on a VAS), median	1.5	3.5	
CRP, median	0.4	3.0	
Number of swollen joints, median	4.0	11.0	
Number of joints with LOM, median	9	22	
Corticosteroid reducing regimens	NR	NR	
Extra-articular manifestations (such as uveitis)	NR	NR	
Body weight and height	NR	NR	
Mortality	See AEs		

Authors state that in the double-blind study, as compared with the end of the open-label study, a significant proportion of patients who received placebo had shifts from normal levels of CRP and ESR to above-normal values ($p \leq 0.003$ for each variable). LOCF approach for missing data and visits and for early termination.

AEs	Etanercept ($n = 25$)	Placebo ($n = 26$)	p-value
Death, *n*	0	0	
Urticaria, *n*	1[c]	0	
Hospitalisation for serious AEs, *n*			
Depression and personality disorder	1	0	
Gastroenteritis-flu syndrome	1	0	
Injection-site reactions, *n*	1	1	
Tested positive for non-neutralising antibody to etanercept, *n*	2	N/A	

c After first dose of etanercept (responded to oral antihistamines). Other AEs were reported to be of mild-to-moderate intensity, with no significant difference in the frequency of AEs between the treatment groups. There were no laboratory abnormalities requiring urgent treatment in the etanercept group. No patient had persistent elevations in autoantibodies or had signs or symptoms of another autoimmune disease.

APPENDIX 5

Baseline characteristics: OPE, 8-year follow-up[67]	OLE ($n = 58$)	Eighth year of OLE ($n = 26$)
Age, mean years (SD)	10.4 (3.8)	10.8 (3.9)
JRA onset type, *n* (%)		
Pauciarticular	5 (9)	2 (8)
Polyarticular	34 (58)	19 (73)
Systemic	19 (33)	5 (19)
Duration of JRA, mean years (SD)	5.9 (3.2)	6.4 (3.4)
RF+ve, *n* (%)	13 (23) ($n = 56$)	6 (24) ($n = 25$)
Concomitant therapy at enrolment, *n* (%)		
NSAIDs	56 (97)	25 (96)
Corticosteroids	22 (38)	8 (31)
Corticosteroid dosage, mg/day mean (SD)	5.7 (3.2)	4.1 (2.3)

After 1 year of the OLE, the dosages and the use of other medications for JRA (including corticosteroids, intra-articular injections of steroids and NSAIDs) could be adjusted or added at the discretion of the treating physician, without restriction. MTX could be added to the regimen (dosage limited to 10–20 mg/m^2/week).

Results: OLE year 8, mean (SEM)[d]	Completed year 8 ($n = 16$)
Total number of joints with active arthritis ($n = 11$)	2.2 (0.9)
Total number of joints with LOM and tenderness and/or pain on motion ($n = 11$)	0
Total number of joints with LOM ($n = 11$)	11.8 (4.4)
PGA	1.6 (0.3)
Patient's/parent's global assessment	2.0 (0.6)
Pain score	1.8 (0.5)
CHAQ score ($n = 11$)	0.6 (0.2)
CRP[e]	1.1 (0.5)

d 74 joints were assessed for tenderness and/or pain on motion, 71 for LOM and 66 for swelling.
e New high-sensitivity method of analysing CRP levels for year 8 (old method: normal range 0–0.79 mg/dl; new method: normal range 0–0.287 mg/dl).

ACR Pedi response, 8 years (LOCF), % (n/N)	
ACR Pedi-30	83 (40/48)
ACR Pedi-50	77 (36/47)
ACR Pedi-70	61 (28/46)
ACR Pedi-90	41 (19/46)
ACR Pedi-100	18 (8/45)

Year of etanercept treatment from RCT (excluding gaps between RCT and OLE)	SAE[f]		MII[g]	
	Number of events	Number of events/ patient-year	Number of events	Number of events/ patient-year
1 ($n = 69$; 57 patient-years of drug exposure)	5	0.09	2	0.04
9 ($n = 14$; 4 patient-years of drug exposure)	0	0	0	0
Total for all years ($n = 69$; 318 patient-years of drug exposure)	39	0.12	9	0.03

SAEs defined as events that were fatal or life-threatening, required hospitalisation or prolonged an existing hospitalisation, resulted in a persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect.

f SAEs occurring during the study or within 30 days of the last dose of etanercept.

g Defined as MIIs resulting in the need for intravenous antibiotic therapy or hospitalisation. Only one MII reported by patients since report at 4 years (pyelonephritis). The most common new SAEs reported beyond 4 years of drug exposure were a flare or worsening of disease [6/9 SAEs (67%)].

Methodological comments:

Allocation to treatment groups: a blocked randomisation scheme with stratification according to study centre and number of active joints (≤ 2 vs. > 2) at the end of month 3 (in the open-label study) was used to assign patients to their treatment group

Blinding: double-blind (no further details)

Comparability of treatment groups: authors state that the groups were well balanced in the double-blind study, except for age group and ethnicity ($p < 0.02$) and corticosteroid use at baseline ($p = 0.05$) and that the unequal randomisation did not affect the study results. The etanercept group had a significantly higher number of younger patients than the placebo group (4- to 8-year olds: etanercept 52% vs. 19% placebo) and a greater ethnic mix (white: etanercept 56% vs. 88% placebo), whereas the placebo group had a significantly larger use of corticosteroid use at washout (placebo 50% vs. 24% E)

Method of data analysis: statistical methods employed were reported. All tests were two-sided, with a significance level of 0.05. Patients who withdrew early without disease flare were counted in the analysis with those who continued to have a response; a LOCF approach was used for missing data and visits and for early termination. To evaluate any bias introduced by the withdrawal assumption in the primary analysis, an analysis of time to flare (by the log-rank test) was undertaken in which data on patients who withdrew without flare were censored at the time of withdrawal. The effect of baseline characteristics on flare rates was assessed by main-effects logistic regression

OLE: data from patients who reached the age of 18 and discontinued the study and who therefore no longer had valid childhood efficacy measures were not included in efficacy analysis (summary of the last visit using the LOCF method). Adult-specific measures of disease for patients ≥ 18 years of age were not included in analyses ($n = 5$ each at years 7 and 8)

Sample size/power calculation: none reported

Attrition/drop-out: part 1 OL: 64/69 (93%) urticaria with the first dose of etanercept $n = 1$; refusal of treatment $n = 2$; lack of response $n = 2$. Part 2 – RCT: etanercept 6/25 (24%): disease flare $n = 6$; placebo: 19/26 (73%): parental refusal to allow continuation n = 1, disease flare $n = 18$

Part 3 OLE: 38/58 (66%): lack of efficacy $n = 7$ (12%); AEs $n = 4$ (7%); physician decision $n = 5$ (9%); protocol issue $n = 3$ (5%); lost to follow-up $n = 3$ (5%); patient/guardian refusal $n = 5$ (9%); other $n = 8$ (14%). 36% patients ($n = 21$) discontinued during the first 4 years

General comments:

Generalisability: limited to pauciarticular, polyarticular and systemic onset JIA patients aged 4 to 17 years, who did not tolerate or had an inadequate response to MTX and had received 3 months of etanercept treatment

Outcome measures: appear to be appropriate

Intercentre variability: not discussed

Conflict of interests: two authors had served as ad hoc consultants to Immunex

IgM, immunoglobulin M; MTX, methotrexate; N/A, not applicable; NR, not reported; OL, open label; SEM, standard error of the mean.

Quality criteria (Cochrane Risk of Bias tool) randomised controlled trials[171]

Criteria	Judgement[a]	Support for judgement
Random sequence generation (selection bias)	Unclear	Blocked randomisation scheme with stratification, no details about how randomisation was performed
Allocation concealment (selection bias)	Unclear	No details reported
Blinding of participants and personnel (performance bias)	Yes	Double-blind phase of study (after open-label lead in)
Blinding of outcome assessment (detection bias)	Yes	Paper states that study site-staff who were not involved in patient assessments constituted the contents of the vials (etanercept or placebo)
Incomplete outcome data addressed (attrition bias)	Yes	Details reported, but drop-outs are nearly three times higher in the placebo group. Incomplete data appears to have been address with the LOCF method (used for missing data/visits and early terminations)
Selective reporting (reporting bias)	Yes	All outcomes reported on
Other sources of bias	Unclear	Intercentre variability not discussed

a Yes, low risk of bias; No, high risk of bias; Unclear, uncertain risk of bias.

Data extraction: tocilizumab

Reference and design	Intervention and Comparator	Participants	Outcome measures
Study identifier: Brunner *et al.* (2015),[68] Brunner *et al.* (2014),[69] Baildam *et al.* (2014),[70] Brunner *et al.* (2013),[71] De Benedetti *et al.* (2013),[72] Baildam *et al.* (2013),[73] De Benedetti *et al.* (2013),[74] and Brunner *et al.* (2012)[75] **Study acronym:** CHERISH **Study design:** medication-withdrawal RCT (16-week randomised open-label, 24-week double-blind randomised withdrawal phase, OLE phase) **Country or countries:** Australia, Canada, Europe, Latin America, Russia and the USA **Number of centres:** 58 **Recruitment dates:** 14 October 2009 to 31 January 2011 **Funding:** funding for manuscript preparation by F. Hoffmann-La Roche Ltd	**Intervention:** intravenous TCZ at 8 mg/kg (8 mg/kg for < 30 kg group) or 10 mg/kg (10 mg/kg for < 30 kg group) every 4 weeks (based on pharmacokinetic modelling and simulation, doses of 10 mg/kg for patients weighing < 30 kg achieved TCZ exposure comparable to that of 8 mg/kg for patients weighing ≥ 30 kg) **Comparator:** placebo **Other interventions used:** stable doses of NSAIDs and low-dose glucocorticoids (≤ 0.2 mg/kg/day prednisone; daily maximum 10 mg) and MTX (10–20 mg/m^2 body surface area/week)	Randomised, OL lead-in phase: TCZ every 4 weeks until week 16, $n = 188$ – patients randomised to < 30 kg TCZ ($n = 69$) or ≥ 30 kg TCZ ($n = 119$) (Limited data extracted for this phase.) Double-blind withdrawal phase **Number of randomised participants:** $n = 166$ TCZ: $n = 82$: 10 mg/kg < 30 kg body weight: $n = 16$ 8 mg/kg < 30 kg body weight: $n = 11$ 8 mg/kg ≥ 30 kg body weight: $n = 55$ Placebo: $n = 84$: 10 mg/kg < 30 kg body weight: $n = 15$ 8 mg/kg < 30 kg body weight: $n = 13$	**Primary outcome(s):** proportion of patients in whom a JIA-flare occurred during part 2 (up to and including week 40) compared with week 16 **Secondary outcomes week 40:** JIA–ACR 30/50/70/90 responses, change from baseline in JIA-CRVs and clinically inactive disease **Method of assessing outcomes:** 4-weekly assessments JIA–ACR-30 response: defined as ≥ 30% improvement of three or more of six JIA core response variables (JIA–CRVs) without > 30% worsening in one or more of the remaining JIA-CRVs compared with baseline (part 1: patients who had at least one JIA–ACR-30 response entered part 2) Active joints: defined as the presence of swollen joints (or, in the absence of swelling, joints with LOM plus pain on motion and/or tenderness with palpation)

Reference and design	Intervention and Comparator	Participants	Outcome measures
		8 mg/kg ≥ 30 kg body weight: $n = 56$ **Loss to follow-up:** OL: $n = 22/188$ (11.7%) RCT: TCZ $n = 3/82$ (3.7%) Placebo: 3/84 (3.6%). OLE: $n = 5/160$ (3.1%) **Inclusion criteria:** 2- to 17-year olds; Diagnoses of RF+ve or RF–ve Polyarticular-course JIA or EO JIA Disease duration ≥ 6months; Inadequate responses to or intolerant of MTX Five or more active joints, with LOM present in three or more of the active joints No MTX ≥ 4 weeks before and including baseline visit or had been taking MTX ≥ 12 weeks immediately before and including baseline visit and on stable dose of 10–20 mg/m^2 for ≥ 8 weeks before and including baseline visit together with either folic acid or folinic acid No oral glucocorticoids at baseline visit or had been taking oral glucocorticoids at a stable dose for ≥ 4 weeks before and including baseline visit ($n \leq 10$ mg/day or 0.2 mg/kg/day) No NSAIDs at baseline or more than one type of NSAID at a stable dose (less than or equal to the recommended daily dose) ≥ 2 weeks before and including the baseline visit	Clinically inactive disease was defined as PGA indicating no disease activity plus absence of all the following: joints with active arthritis, uveitis and ESR > 20 mm/h Serious infections were defined in accordance with the definition of SAEs in the International Conference on Harmonisation guidelines (reference provided) PGA of disease activity: VAS 0–100 (0 = inactive disease); assessment of patient overall well-being: VAS 0–100 (0 = very poor); physical function measured by the CHAQ-DI: 0–3 (0 = no disability) Patients continued RCT until week 40 unless JIA-flare (> 30% worsening in three of six JIA–CRVs without > 30% improvement in one or more of the remaining JIA–CRVs) compared with week 16. They then entered the OLE study **Length of follow-up:** OL 16 weeks; RCT 24 weeks; total 40 weeks. OLE 64 weeks (total 104 weeks)

Reference and design	Intervention and Comparator	Participants	Outcome measures
		Never been treated with biologics or had been previously treated with biologics and discontinued them for at least the following periods: anakinra: 1 week; etanercept: 2 weeks; rilonacept: 5 weeks; infliximab or adalimumab: 8 weeks; abatacept: 12 weeks; canakinumab:, 20 weeks, before and including the baseline visit **Exclusion criteria:** none in addition to the above	

Baseline characteristics[a]	TCZ 8 mg/kg < 30 kg (*n* = 34)	TCZ 10 mg/kg < 30 kg (*n* = 35)	TCZ 10 mg/kg 30 kg (*n* = 119)
Age, years	7.6 (2.71)	6.9 (3.02)	13.1 (2.78)
Sex, females *n* (%)	24 (71)	30 (86)	90 (76)
Ethnicity	NR		
Type of JIA	NR		
Weight (kg)	22.4 (5.3)	20.7 (5.7)	50.0 (12.6)
RF+ve, *n* (%)	2 (6)	4 (11)	48 (40)
Duration of JIA, years	3.5 (2.57)	3.4 (2.39)	4.7 (4.16)
Previous medication, *n* (%)			
DMARD	26 (76)	21 (60)	87 (73)
Biologic agent[b]	6 (18)	8 (23)	47 (39)
Joints with active arthritis, *n*	21.2 (13.6)	23.9 (18.3)	18.9 (13.0)
Joints with LOM, *n*	17.3 (13.3)	23.1 (19.2)	16.0 (12.7)
Assessment of patient overall well-being, VAS	59.1 (26.2)	51.5 (26.9)	51.6 (24.1)
PGA of JIA activity, VAS	64.7 (18.5)	64.7 (20.5)	59.4 (21.3)
CRP (mg/l) (standard reference range 0–10 mg/l)	26.6 (33.6)	21.8 (32.3)	22.8 (38.8)
CHAQ-DI score	1.8 (0.68)	1.7 (0.71)	1.2 (0.69)
ESR (mm/h) (standard reference range 0–18 mm/h)	36.6 (23.0)	35.1 (24.1)	34.2 (26.7)
Concurrent MTX use, *n* (%)	30 (88)	29 (83)	89 (75)
Dose (mg/m^2/week)	13.8 (2.9)	16.5 (11.1)	11.6 (2.7)
Concurrent glucocorticoid use, *n* (%)[c]	18 (53)	15 (43)	54 (45)
Dose (mg/kg/day)[c]	0.15 (0.038)	0.15 (0.033)	0.12 (0.052)

a All patients randomised in part 1. 15/188 (7.9%) did not achieve JIA-ACR30 response and were not randomised in part 2.
b 9% of patients previously received three or more biologic agents. TNF inhibitors: *n* = 56; anakinra *n* = 5; abatacept *n* = 5; canakinumab (Ilaris®, Novartis) *n* = 1.
c Measured in prednisone equivalents.
Baseline characteristic not given the TCZ vs. placebo groups in Part 2.

***Results, week 40 double-blind study*[68,73,75]**

Primary outcome	TCZ[d] (*n* = 82)	Placebo (*n* = 81)	Difference[d] TCZ vs. placebo (95% CI); *p*-value
Proportion with JIA-ACR30 flare (compared with week 16), *n* (%)	21 (25.6%)	39 (48.1)	–0.21 (–0.35 to –0.08); 0.0024
Secondary outcomes	**TCZ[d] (*n* = 82)**	**Placebo (*n* = 81)**	**Difference[d] TCZ vs. placebo (95% CI); *p*-value**
Proportion of patients with JIA–ACR-30 improvement relative to baseline, *n* (%)	61 (74.4)	44 (54.3)	0.09 (0.05 to 0.33); 0.0084
Proportion of patients with JIA–ACR-50 improvement relative to baseline, *n* (%)	60 (73.2)	42 (51.9)	0.20 (0.06 to 0.34); 0.0050
Proportion of patients with JIA–ACR-70 improvement relative to baseline, *n* (%)	53 (64.6)	34 (42.0)	0.22 (0.07 to 0.37); 0.0032
Change from baseline in number of active joints, adjusted mean	–14.3	–11.4	–2.9 (–5.7 to –0.1); 0.0435
Change from baseline in PGA (VAS), adjusted mean	–45.2	–35.2	–9.9 (–16.5 to –3.4); 0.0031
Change from baseline in the pain (VAS), adjusted mean	–32.4	–22.3	–10.2 (–17.6 to –2.7); 0.0076
Change from baseline in number of joints with LOM, adjusted mean	–9.5	–7.7	–1.8 (–4.1 to 0.5); 0.1229
Change from baseline in ESR (mm/h), adjusted mean	–26.3	–12.0	–14.3 (–19.6 to –9.0)[e]
CHAQ-disability score	–0.8	–0.6	–0.2 (–0.4 to 0.0)[e]
Proportion with JIA-ACR90 improvement, *n* (%)	37 (45.1)	19 (23.5)	0.21 (0.07 to 0.35)[e]
Proportion with inactive disease, *n* (%)	30 (36.6)	14 (17.3)	0.18 (0.05 to 0.32)[e]
Corticosteroid reducing regimens	NR		
Extra-articular manifestations (such as uveitis)	NR		
Body weight and height	NR		
Mortality	0	0	
Change from baseline in patient global assessment of well-being adjusted mean	–32.1	–24.7	–7.4 (–14.8 to 0.0)[e]

d Adjusted for baseline stratification factors (background use of MTX and oral glucocorticoids).
e *p*-values were not provided because they fell below a non-significant parameter in the hierarchical chain to address multiplicity.
Time to JIA–ACR-30 flare reported in a Kaplan–Meier curve, but not presented here.

Proportion of patients in the ITT population with JIA–ACR-70 and JIA–ACR-90 response at week 40 by background MTX, glucocorticoid and previous biologic agent use at baseline[f]

Concomitant therapies and previous exposure to biologic agent, *n*/*N* (% *N*)	Response level	TCZ (*n* = 82)		Placebo (*n* = 81)	
		Yes	No	Yes	No
Background MTX	JIA-ACR70	45/67 (67.2)	8/15 (53.3) 5/15 (33.3)	30/64 (46.9) 18/64 (28.1)	4/17 (23.5)
	JIA-ACR90	32/67 (47.8)			1/17 (5.9)
Background glucocorticoid	JIA-ACR70	23/33 (69.7)	30/49 (61.2) 21/49 (42.9)	4/38 (36.8) 5/38 (13.2)	20/43 (46.5)
	JIA-ACR90	16/33 (48.5)			14/43 (32.6)
Previous biologic agent	JIA-ACR70	13/27 (48.1)	40/55 (72.7) 32/55 (58.2)	2/23 (8.7) 2/23 (8.7)	32/58 (55.2)
	JIA-ACR90	5/27 (18.5)			17/58 (29.3)

f Patients who withdrew or escaped to OL TCZ or for whom the end point could not be determined were classified as non-responders.
Authors report an ad hoc analysis of patients who received TCZ continuously in parts 1 and 2 (not data extracted).

AEs and SAEs

SAEs and AEs occurring ≥ 5% of patients, *n* (%)	TCZ[g] (*n* = 82)	Placebo[g] (*n* = 81)	*p*-value
Duration in study (years)	32.33	27.41	
Patients with ≥ 1 AE	58 (70.7)	60 (74.1)	
Total number of AEs[h]	147	141	
Rate of AEs per 100 patient-years	454.7	514.4	
Most frequent AEs			
Nasopharyngitis	14 (17.1)	9 (11.1)	
Headache	3 (3.7)	0	
Upper respiratory infection	4 (4.9)	2 (2.5)	
Cough	2 (2.4)	1 (1.2)	
Pharyngitis	3 (3.7)	3 (3.7)	
Nausea	2 (2.4)	2 (2.5)	
Diarrhoea	2 (2.4)	3 (3.7)	
Rhinitis	2 (2.4)	1 (1.2)	
Vomiting	3 (3.7)	1 (1.2)	
Abdominal pain	2 (2.4)	2 (2.5)	
Oropharyngeal pain	1 (1.2)	5 (6.2)	
Rash	4 (4.9)	1 (1.2)	
SAEs			
Patients with ≥ 1 SAE	3 (3.7)	3 (3.7)	
Rate of SAEs per 100 patient-years	9.3	10.9	
Patients with ≥ 1 infectious SAE	1 (1.2)	0	
Rates of infectious SAEs per 100 patient-years	3.1	0	

SAEs and AEs occurring ≥ 5% of patients, *n* (%)	TCZ[g] (*n* = 82)	Placebo[g] (*n* = 81)	*p*-value
Pneumonia	1 (1.2)	0	
Upper limb fracture	1 (1.2)	0	
Uveitis	0	1 (1.2)	
Psychosomatic disease	1 (1.2)	0	
Enterocolitis	0	1 (1.2)	
Complicated migraine	0	1 (1.2)	
AEs leading to study drug discontinuation			
Increased blood bilirubin level[i]	1 (1.2)		
Gastroenteritis		1 (1.2)[j]	

g AE data on open-label TCZ escape therapy were excluded.
h Multiple occurrences of the same AE in one individual were counted.
i Highest total bilirubin reading, 50 µmol/l (normal range, 3–24 µmol/l); two consecutive readings > 51 mmol/l mandated withdrawal per protocol. The event resolved without sequelae.
j Occurred 46 days after the last of five doses of placebo.
Exposure to TCZ varied for individual patients, depending on the period from the first dose of TCZ to the date of data cut or withdrawal (maximum exposure 1.8 years). The safety population consisted of all patients who received ≥ dose of study medication. Safety data included full exposure data for each patient.

Results for OLE, 104 weeks

[k]Efficacy endpoints and percentage change from baseline in JIA ACR components (continuous TCZ, *n* = 82)[69,71,74]	Baseline	Week 40	Week 104 (*n* = 160)	Change from baseline to week 104, %
JIA ACR-70 responders, *n* (%)[l]		65 (79.3)	71 (86.6)	
JIA ACR-90 responders, *n* (%)[l]		41 (50.0)	58 (70.7)	
Active joints (0–71), mean (SD)	19.7 (14.0)	4.7 (9.1)	3.3 (9.1)	–87.7 (27.1)
Joints with LOM (0–67), mean (SD)	16.5 (13.8)	5.6 (10.1)	3.6 (7.3)	–81.3 (31.7)
Patient global (VAS 0–100 mm), mean (SD)[m]	45.5 (23.1)	12.2 (19.0)	9.1 (18.4)	–75.4 (43.8)
PGA (VAS 0–100 mm), mean (SD)	57.8 (20.3)	8.8 (10.9)	5.0 (10.5)	–89.7 (23.7)
CHAQ-DI (0–3), mean (SD)	1.2 (0.7)	0.4 (0.5)	0.2 (0.4)	–76.7 (34.7)
ESR (mm/h), mean (SD)	31.7 (22.9)	5.4 (6.3)	5.1 (5.6)	–76.2 (27.3)
Inactive disease, *n* (%)[n]		33 (40.2)	52 (63.4)	
Remission, *n* (%)[o]		5 (6.1)	31 (37.8)	
Minimal disease activity (JADAS-71 < 3.8), *n* (%)	0 (0)	49 (59.8)	60 (73.2)	
Inactive disease (JADAS-71 < 1), *n* (%)	0 (0)	24 (29.3)	48 (58.5)	

k Patients who withdrew because of non-safety reasons are non-responders. Patients who withdrew because of safety are included using LOCF.
l Two abstracts[69,74] contain a table with a footnote to indicate patients who withdrew were excluded, however in the third abstract[71] the table footnote states that patients who withdrew owing to non-safety reasons are non-responders whereas patients who withdrew owing to safety are included using LOCF.
m Parent rated.
n No active joints, no active uveitis, ESR < 20 mm/h and PGA VAS ≤ 10.
o Met criteria for inactive disease at each visit for 6 preceding months.

AEs and SAEs[69–71,74]	Safety population = 188 with 307 patient-years
AEs, rates/100 patient-years	406.5
SAEs, rates/100 patient-years	11.1
Most common AE: infections	151.4
Infections: SAE	5.2
ALT elevations ≥ 3× upper limit of normal, %	6.4
AST elevations ≥ 3× upper limit of normal, %	2.7
Grade 3 lowest neutrophil count, %	5.9
Grade 2/3/4 thrombocytopenia, %	1.6
Low-density lipoprotein cholesterol ≥ 110 mg/dl, %	16.2

Methodological comments:

Allocation to treatment groups: randomly assigned 1 : 1, stratified by background use of MTX and oral glucocorticoid use. OL (Part 1): patients weighing < 30 kg were randomly assigned 1 : 1 to receive intravenous TCZ 8 mg/kg or 10 mg/kg, whereas patients weighing ≥ 30 kg received 8 mg/kg. Double-blind RCT (Part 2): each of the three previous groups was randomised to receive either the existing dose of TCZ or placebo, equating to six groups in total. No further details about randomisation procedure were reported

Blinding: double-blind, no further details of procedure reported. States that JIA ACR response rates and clinically inactive disease status were performed in real time by independent masked evaluators at the co-ordinating centres of the Pediatric Rheumatology International Trials Organisation and Pediatric Rheumatology Collaborative Study Group, according to validated criteria

Comparability of treatment groups: no baseline characteristics for Part 2 (RCT) reported. States that disease characteristics at baseline for the OL (Part 1) were generally similar across the 3 groups with the exception of body weight based dosing regime, but no details are reported for the six groups in the RCT Part 2

Method of data analysis: ITT, however 3/166 patients from the placebo group were excluded as they discontinued without receiving the study drug therefore modified ITT. To control for the type-1 error rate, secondary endpoints were tested in a hierarchical fixed-sequence approach provided the primary endpoint was found to be statistically significant. The robustness of the results of the statistical procedure used for the primary endpoint analysis was assessed by logistic regression analysis of the proportion of patients with JIA–flare in the ITT during Part 2, showed a statistically significant treatment difference in favour of TCZ and was consistent with the primary analysis

Primary endpoint analysis was conducted with the Cochran–Mantel–Haenszel test (also used for secondary endpoints), adjusted for stratification factors; patients who withdrew or for whom the endpoint could not be determined were considered to have experienced JIA flare. Patients who escaped or withdrew or for whom the end point could not be determined were considered non-responders. Continuous variables were evaluated using analysis of variance, adjusted for baseline differences between groups and stratification variables

Ad hoc analysis was conducted in patients continuously treated with TCZ up to week 40, including those who escaped from blinded to OL TCZ, using an ITT approach

Sample size/power calculation: sample size estimation was reported. States that recruitment was planned to ensure that a sufficient number of patients were available for randomisation in Part 2, needing 60 patients in each group to achieve 80% power to detect a significant difference in assumed JIA flare rates (35% TCZ, 65% placebo) between groups using a two-sided significance test with $\alpha = 0.05$. For the results, the three TCZ groups were combined and so were the three placebo groups, giving each combined group sufficient power

Attrition/drop-out: Part 1 lead in – states 10.6% discontinued ($n = 20$), but flow chart shows $n = 22$ (11.7%): lack of JIA ACR-30 response $n = 15$, withdrew consent, $n = 3$, AEs $n = 3$, failure to return $n = 1$

Part 2 RCT: TCZ 3/82 [3.7% (10 mg/kg < 30 kg body weight group: $n = 1$; 8 mg/kg ≥ 30 kg body weight: $n = 2$) – AEs $n = 1$, insufficient therapeutic response $n = 1$, withdrew consent $n = 1$. Placebo $n = 3/84$ (3.6%) – AEs $n = 2$, insufficient therapeutic response $n = 1$]

OLE: 5/160 (3.1%) – reasons not reported[69]

General comments:

Generalisability: to patients aged 2 to 17 years, with diagnoses of RF+ve or RF–ve polyarticular-course JIA or EO JIA, with a minimum disease duration of at least 6 months and had inadequate responses to or were intolerant of MTX, and experienced at least one (JIA ACR-30) response to TCZ

Outcome measures: appear to be appropriate

Intercentre variability: not discussed

Conflict of interests: various authors received funding/support from a variety of pharmaceutical companies

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHAQ-DI, Disability Index of the Childhood Health Assessment Questionnaire; ITT, intention to treat; MTX, methotrexate; NR, not reported; OL, open label; TCZ, tocilizumab.

Quality criteria (Cochrane Risk of Bias tool) randomised controlled trials[171]

Criteria	Judgement[a]	Support for judgement
Random sequence generation (selection bias)	Unclear	Insufficient information
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias)	Yes	Double-blind
Blinding of outcome assessment (detection bias)	Yes	JIA-ACR response rates and clinically inactive disease status were performed in real time by independent masked evaluators at two co-ordinating centres according to validated criteria
Incomplete outcome data addressed (attrition bias)	Yes	Details reported and similar between groups
Selective reporting (reporting bias)	Yes	All outcomes reported on
Other sources of bias	Unclear	Intercentre variability not discussed

a Yes, low risk of bias; no, high risk of bias; unclear, uncertain risk of bias.

Appendix 6 Table of excluded studies for systematic review of cost-effectiveness

TABLE 78 Excluded studies for systematic review of cost-effectiveness

Excluded study	Primary reason for exclusion
Haapasaari JE, Kauppi M, Hakala MS, Kautiainen H. Economic evaluation of etanercept therapy in the treatment of re-fractory JIA. *Arthritis Rheum* 2002;**46**:S480	Abstract
Brodszky V, Pentek M, Majer I, Karpati K, Gulacsi L. [Etanercept in patients with juvenile idiopathic arthritis: systematic review and economic evaluation.] Budapest: Unit of Health Economics and Technology Assessment in Health Care; 2006	Abstract
Prince FHM, de Bekker-Grob EW, Twilt M, Van Rossum MAJ, Hoppenreijs EPAH, ten Cate R, *et al.* An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2011;**29**:443	Abstract
Simpson K, Hubert MM, On PV, Cifaldi M, Shaw J. Long-term cost-effectiveness of adalimumab therapy in juvenile idiopathic arthritis: from a Canadian perspective. *J Rheumatol* 2012;**39**:1712	Abstract
Luca N, Burnett H, Ungar W, Beukelman T, Feldman BM, Schwartz G, *et al.* Cost-effectiveness analysis of early biologic treatment in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum* 2012;**64**:S501	Abstract
Luca N, Burnett H, Ungar W, Beukelman T, Feldman B, Schwartz G, *et al.* Cost-effectiveness analysis of early biologic treatment in polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2013;**40**:988	Abstract
Chang S, Sawyer L, Dejonckheere F, van Suijlekom-Smit LW, Anink J, Diamantopoulos A. Tocilizumab in polyarticular juvenile idiopathic arthritis – a cost–utility model for the United Kingdom. *Value Health* 2013;**16**:A564	Abstract
All Wales Medicines Strategy Group. *Adalimumab (Humira®)*. 2013. URL: www.awmsg.org/	Not economic evaluation
All Wales Medicines Strategy Group. *Etanercept (Enbrel®)*. 2013. URL: www.awmsg.org/	Not economic evaluation
All Wales Medicines Strategy Group. *Abatacept (Orencia®)*. 2014. URL: www.awmsg.org/	Not economic evaluation
All Wales Medicines Strategy Group. *Tocilizumab (RoActemra®)*. 2014. URL: www.awmsg.org/	Not economic evaluation
Canadian Agency for Drugs and Technologies in Health. *Tocilizumab (Actemra – Hoffmann-La Roche Limited) New Indication: Polyarticular Juvenile Idiopathic Arthritis*. 2014	Not economic evaluation

Appendix 7 Cost-effectiveness studies: data extraction forms

1	**Study**	Cummins *et al.* (2002)[123]
2	**Research question**	To provide background info and systematic review of JIA, including economic evidence of etanercept compared with other treatment options
3	**Country/setting**	Not stated
4	**Funding source**	Not stated
5	**Analysis type**	Cost–utility analysis
6	**Study type**	Industry submission cost–utility model using results from one JIA trial (Lovell *et al.*[42]). The model assumes response related to health assessment (HAQ) and mortality
7	**Perspective**	Health-care system
8	**Time horizon**	Model cycle length: 3 months, 6 months and 1 year, then yearly intervals over the life-course
9	**Model assumptions**	It is an adaptation of a rheumatoid arthritis model for adults using strong and questionable assumptions, related to health assessment, utility, mortality and costs
10	**Discounting (rate)**	Yes, costs 6% per annum and benefits 1%
11	**Costing year, currency**	2001, £
12	**Population**	Etanercept in children with polyarticular juvenile rheumatoid arthritis Definition of condition: JIA, heterogeneous group of painful conditions involving persistent swelling of the joints with variable presentation and course
13	**Intervention(s), comparator(s)**	Etanercept vs. placebo (placebo effect assumed to last 3 months)
14	**Intervention effect**	Effect size measured in terms of CHAQ and mortality Cost offset per HAQ point £860 38% increase in mortality per point change in HAQ Relative risk of mortality in JIA was 2.98 Placebo and etanercept HAQ progression: responders 0–4 years 0, responders > 4 years 0.034, non-responders 0.0669 Annual withdrawal from responders to non-responders: placebo 50%, etanercept 13%
15	**Health-state utilities**	EQ-5D adults
16	**Intervention cost**	Adult cost
17	**Indirect costs**	N/A

18 **Results**

Discounted/undiscounted	Intervention	Comparator	Incremental	ICER, £
Costs, £	40,624	12,602	28,022	
QALY	15.0	13.3	1.7	16,082

19 **Sensitivity analysis**

Sensitivity analysis varied from £3900 to £34,000 (SF-36 regression used)

20 **Author's conclusions** Insufficient data to construct a model for JIA, and little is known about HRQoL in JIA. The ICER should be viewed with caution

21 **Reviewer's comments** Limited relevance in cost/utilities; adult rheumatoid arthritis cannot be assumed to be the same for JIA in children

N/A, not applicable.

Critical appraisal checklist for economic evaluations (based on Drummond *et al.*)[129]

Item	Y/N?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	Y
3. Is the analytical and modelling methodology appropriate?	N
4. Are all the relevant costs and consequences for each alternative identified?	N
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	Y
8. Are costs and outcomes discounted?	Y
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y
Comments Out of date, not children-specific, relying on very strong assumptions due to lack of evidence. Informative in general terms but not relevant	

?, unclear; N, no; Y, yes.

1	**Study**	Prince *et al*. (2011)[124]
2	**Research question**	To analyse and report the costs and effects of etanercept therapy in patients with JIA
3	**Country/setting**	Netherlands/national ABC register
4	**Funding source**	The Dutch Board of Health Insurances and Wyeth International
5	**Analysis type**	Cost–consequence analysis
6	**Study type**	Trial-based: prospective etanercept effectiveness and safety add-on study with JIA patients in 7 of 9 Dutch paediatric rheumatology centres
7	**Perspective**	Health-care system
8	**Time horizon**	27 months
9	**Model assumptions**	N/A
10	**Discounting (rate)**	No
11	**Costing year, currency**	2008, €
12	**Population**	Dutch JIA patients younger than 18 years of age are eligible for treatment with etanercept if the disease has a polyarticular course and the response to the maximum (tolerated) dose of MTX) is not sufficient Onset subtype JIA ($n = 49$): • Systemic (22%) • Polyarticular RF+ve (8%) • Polyarticular RF–ve (37%) • EO (22%) • ERA (4%) • Juvenile arthritis psoriatica (6%) Concomitant drug use at start of etanercept: • NSAID (92%) • Glucocorticoids systemic (47%) • MTX (80%) • Other DMARD (10%)
13	**Intervention(s), comparator(s)**	Intervention: etanercept (add-on to conventional treatment) Comparator: conventional treatment with synthetic DMARDs, mostly MTX, if required accompanied by anti-inflammatories or systemic glucocorticoids
14	**Intervention effect**	Effect size measured in the study in terms of change in disease activity response variables of the JIA core set and HUI3
15	**Health-state utilities**	HUI3: preference-based HRQoL measure completed by the parents of study participants (eight domains in 15-item parent questionnaire) Valuation using value scores obtained by Feeny *et al.*[172] from the Canadian general population
16	**Intervention cost**	Unit costs for medication were retrieved from the Pharmacotherapeutic Compass provided by the Dutch Board of Health Insurances, and treatment costs were calculated with the exact dose of medication and administration period as reported in the patients' files Etanercept unit cost ≈€10,478/year
17	**Indirect costs**	N/A

18	**Results:**	
19	**Sensitivity analysis:** N/A	
20	**Author's conclusions**	'Although etanercept is expensive, the major utility gain justifies the costs'
21	**Reviewer's comments**	Sound trial-based evaluation of costs and consequences (including disease activity improvement and utility) associated to adding etanercept to conventional care Full incremental cost-effectiveness/utility analysis not performed and there is no indication of the variation from the mean estimates reported nor assessment of uncertainty

Undiscounted	Intervention	Comparator	Incremental
Costs (€) (27 months)	28,075	8370	19,705
Utility	0.78 (27 months)	0.53 (0 months)	0.25

MTX, methotrexate; N/A, not applicable.

Critical appraisal checklist for economic evaluations (based on Drummond *et al.*)[129]

Item	Y/N?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	?
3. Is the analytical and modelling methodology appropriate?	Y[a]
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	N/A
6. Are health outcomes measured in QALYs?	N
7. Is the time horizon considered appropriate?	N
8. Are costs and outcomes discounted?	N
9. Is an incremental analysis performed?	?[a]
10. Is uncertainty assessed?	N

?, unclear; N, no; N/A, not applicable; Y, yes.
a The methodology is appropriate for a cohort-based evaluation; however, a full incremental cost–utility analysis has not been performed.

1	**Study**	Simpson *et al.* (2012)[125]
2	**Research question**	To evaluate the cost-effectiveness of adalimumab vs. non-biologic therapy for the treatment of JIA in Russian children and adolescents
3	**Country/setting**	Russia/health-care system
4	**Funding source**	Not stated
5	**Analysis type**	Cost–utility analysis
6	**Study type**	Markov model; mutually exclusive health states: • Base model (children under 18 years): (1) mild disease activity; (2) moderate disease activity; (3) severe disease activity; (4) remission without movement limitations; (5) remission with movement limitations Second part of the model (adults from 18 years to death): (6) remission; (7) active mild disability; (8) active moderate disability; and (9) active severe disability; (10) death (not clear if children mortality is included)
7	**Perspective**	Health-care system and society
8	**Time horizon**	Lifetime. Model cycle length: 4 months
9	**Model assumptions**	• Adult patients with moderate to severe disability are assumed to have hip and knee prosthetic surgery at the frequency observed in patients[173] • Patients who do not achieve remission after 1 year of treatment had a median time on treatment of 3 years (as observed in DE038) • Mean age of 11 years at start of therapy
10	**Discounting (rate)**	Yes (3% per annum, costs and outcomes)
11	**Costing year, currency**	2011, Russian roubles
12	**Population**	Trial name: randomised double-blinded placebo-controlled trial DE038 (adalimumab + methotrexate vs. placebo + methotrexate) Children aged 4–17 years with JIA
13	**Intervention(s), comparator(s)**	Intervention: adalimumab + methotrexate Comparator: placebo + methotrexate
14	**Intervention effect**	Intervention effect was incorporated in terms of HRQoL and the estimated number of person-years spent in each health state. The HRQoL associated to each health state was obtained from the CHAQ responses in trial DE038
15	**Health-state utilities**	For the base model, HUI2 utilities for each health state were mapped from CHAQ responses from parents of children participating in DE038. HUI2 valuation was derived from survey to the UK general population For the second part of the model, utilities were derived from the literature on adult patients with rheumatoid arthritis[174]
16	**Intervention cost**	Cost of treatment with adalimumab was derived from its expected cost in the List of Vital and Essential Medicinal Products (58,100 roubles for two 40-mg syringes after adjustment for VAT and 10% trade mark-up)
17	**Indirect costs**	A secondary analysis included value of time lost from work to provide care for a sick child. Value and source not reported

18 **Results for base-case lifetime time horizon NHS perspective**

Discounted	Intervention	Comparator	Incremental	ICER
Costs (roubles)	4,116,231	2,753,954	1,362,277	–
QALY	24.80	20.04	4.76	286,267

19 **Sensitivity analysis:** Deterministic univariate lifetime time horizon

Parameter/scenario	Value	ICER, £
Age of treatment initiation	7 years of age	229,744
Discounting rate	0%	119,496
	5%	428,236

Note: results for 11-year time horizon and societal perspective also reported

20 **Author's conclusions** Adalimumab seems to be cost-effective relative to conventional non-biologic therapy. ICERs estimated in the base-case lifetime analyses did not exceed the per-capita gross domestic product for Russia (≈380,000 roubles)

21 **Reviewer's comments** Transition probabilities not reported; poor reporting of sources for the estimates used and their derivation; limited sensitivity analysis without indication of most influential parameters

Critical appraisal checklist for economic evaluations (based on Drummond *et al.*)[129]

Item	Y/N?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	?
3. Is the analytical and modelling methodology appropriate?	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	N
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	Y
8. Are costs and outcomes discounted?	Y
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y
Comments: Limited assessment of uncertainty	

?, unclear; N, no; Y, yes.

1	**Study**	Ungar *et al.* (2011)[127]
2	**Research question**	To determine the incremental costs of biologics per additional responder compared with conventional treatment (methotrexate)
3	**Country/setting**	Canada, secondary care
4	**Funding source**	Ontario Ministry of Health and Long-term Care Drug Innovation Fund
5	**Analysis type**	CEA
6	**Study type**	Decision-analysis model
7	**Perspective**	Societal
8	**Time horizon**	1-year time horizon with two consecutive 6-month cycles
9	**Model assumptions**	Model incorporated probabilities that patients would, based on their response at 6 months, either continue with the same treatment or switch
10	**Discounting (rate)**	Not included
11	**Costing year, currency**	2008 Canadian dollars
12	**Population**	In the base case, a 40-kg patient was assumed, similar to the mean weight in two paediatric RCTs. Patients had JIA with a prior inadequate response or intolerance to DMARDs
13	**Intervention(s), comparator(s)**	Etanercept, adalimumab, abatacept and infliximab vs. MTX
14	**Intervention effect**	The effectiveness measure was the proportion of patients who had a reduction in symptoms at 1 year according to the ACR Pedi-30 criteria Effect size were taken from RCTs: etanercept (Lovell *et al.*, 2000[42]), adalimumab (Lovell *et al.*, 2008[61]), infliximab (Ruperto *et al.*, 2007[135]) and abatacept (Ruperto *et al.*, 2008[57]) For the base case, patients achieving ACR Pedi-30, %

Time	Etanercept	Adalimumab	Abatacept	Infliximab	DTX
6 months	79	80	82	80	30
12 months	79	63	82	79	30

15	**Health-state utilities**	No utility values included
16	**Intervention cost**	Total annual costs for treatment were: abatacept ($14,733), infliximab ($17,259), etanercept ($18,966), adalimumab ($18,654), methotrexate ($952). Treatment costs included medication costs, preparation and administration costs and concomitant medications
17	**Indirect costs**	The costs for abatacept and infliximab included parental time losses of $1875 and $1071. There were no indirect costs for the other treatments

18 **Results**

Intervention vs. MTX

Undiscounted	Etanercept	Adalimumab	Abatacept	Infliximab
Incremental costs, $	11,090	13,107	7,873	12,167
Incremental effectiveness, %	47.6	29.4	49.4	43.2
ICER, £	26,061	46,711	16,204	31,209

19 **Sensitivity analysis**

Deterministic analysis was performed for extreme efficacy with biologic high efficacy and MTX low efficacy and vice versa

Probabilistic sensitivity analyses were conducted for each treatment vs. MTX and cost-effectiveness acceptability curves were calculated. If a decision-maker was willing to pay no more than $30,000 to gain a responder, then the probability that etanercept would demonstrate a net economic benefit would be 95%. The willingness to pay points at which the biologic had a 50% probability of cost-effectiveness were $45,000, $17,000 and $27,500 for adalimumab, abatacept and infliximab respectively

20 **Author's conclusions** JIA patients with a prior suboptimal response or intolerance to MTX may benefit from treatment with biologic for at least 1 year

21 **Reviewer's comments** Results not present in QALYs, which makes results difficult to interpret. Short time horizon used (1 year). Unclear how ICERs are calculated

Critical appraisal checklist for economic evaluations (based on Drummond *et al.*[129])

Item	Y/N?
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y
2. Is the setting comparable to the UK?	N
3. Is the analytical and modelling methodology appropriate?	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	N
7. Is the time horizon considered appropriate?	N
8. Are costs and outcomes discounted?	N
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y

?, unclear; N, no; Y, yes.

Appendix 8 Table of excluded studies for systematic review of health-related quality of life

TABLE 79 Excluded studies for systematic review of HRQoL

Identified studies from titles/abstracts and full papers	Reason for exclusion
Anink J, Prince FHM, Dijkstra M, Otten H, Twilt M, Ten CR, *et al*. Long term functional outcome and quality of life of patients with refractory juvenile idiopathic arthritis treated with etanercept: results of the Dutch arthritis and biologicals in children register. *Pediatr Rheumatol* 2014;**12**(Suppl. 1):P28	Abstract
Duarte-Salazar C, Guzman-Vazquez S, Soto-Molina H, Chaidez-Rosales P, Ilizaliturri-Sanchez V, Nieves-Silva J, *et al.* Disability impact on quality of life in Mexican adults with juvenile idiopathic arthritis and juvenile ankylosing spondylitis. *Clin Exp Rheumatol* 2007;**25**:922–7	No utilities reported
Hendry GJ, Gardner-Medwin J, Turner DE, Woodburn J, Lorgelly PK. *Self-vs Proxy-Reported Health-Related Quality of Life of Patients with Juvenile Idiopathic Arthritis: Implications for a Cost-Utility Analysis of Multidisciplinary Foot Care*. 2011. URL: http://rheumatology.oxfordjournals.org/content/50/suppl_1/i2.full.pdf+html (accessed March 2015)	Abstract
Hendry GJ, Gardner-Medwin J, Steultjens MPM, Woodburn J, Sturrock RD, Turner DE. Frequent discordance between clinical and musculoskeletal ultrasound examinations of foot disease in juvenile idiopathic arthritis. *Arthritis Care Res* 2012;**64**:441–7	No utilities reported
Janse AJ, Uiterwaal CS, Gemke RJ, Kimpen JL, Sinnema G. A difference in perception of quality of life in chronically ill children was found between parents and pediatricians. *J Clin Epidemiol* 2005;**58**:495–502	Irrelevant population
Janse AJ, Sinnema G, Uiterwaal CS, Kimpen JL, Gemke RJ. Quality of life in chronic illness: perceptions of parents and paediatricians. *Arch Dis Child* 2005;**90**:486–91	Irrelevant population
Janse A, Sinnema G, Uiterwaal C, Kimpen J, Gemke R. Quality of life in chronic illness: children, parents and paediatricians have different, but stable perceptions. *Acta Paediatr* 2008;**97**:1118–24	Irrelevant population
Angeles-Han ST, Griffin KW, Lehman TJA, Rutledge JR, Lyman S, Nguyen JT, *et al.* The importance of visual function in the quality of life of children with uveitis. *J Am Assoc Pediatr Opthalmol Strabismus*; 2010;**14**:163–8	Irrelevant population
Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ, *et al.* Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. *Ann Rheum Dis* 2008;**67**:309–14	No utilities reported
Feinstein AB, Forman EM, Masuda A, Cohen LL, Herbert JD, Moorthy LN, *et al.* Pain intensity, psychological inflexibility, and acceptance of pain as predictors of functioning in adolescents with juvenile idiopathic arthritis: a preliminary investigation. *J Clin Psychol Med Settings* 2011;**18**:291–8	No utilities reported
Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Economic comparison of leflunomide and methotrexate in patients with rheumatoid arthritis: an evaluation based on a 1-year randomised controlled trial. *Pharmacoeconomics* 2002;**20**:61–70	Irrelevant population
Matza LS, Boye KS, Feeny DH, Johnston JA, Bowman L, Jordan JB. Impact of caregiver and parenting status on time trade-off and standard gamble utility scores for health state descriptions. *Health Qual Life Outcomes* 2014;**12**:48	Irrelevant population
McTaggart-Cowan HM, Brazier JE, Tsuchiya A. Clustering Rasch results: a novel method for developing rheumatoid arthritis states for use in valuation studies. *Value Health* 2010;**13**:787–95	Irrelevant population
Medrare L, Ngeuleu A, Rkain M, Bouaddi I, Znat F, El KS, *et al.* Is there any relationship between the children health assessment questionnaire (CHAQ) and the european quality of life (EUROQOL) in children suffering from chronic haemophilic arthropathy? *Ann Rheum Dis* 2014;**73**:1099	Irrelevant population

continued

TABLE 79 Excluded studies for systematic review of HRQoL (*continued*)

Identified studies from titles/abstracts and full papers	Reason for exclusion
Mo F, Choi BC, Li FC, Merrick J. Using Health Utility Index (HUI) for measuring the impact on health-related quality of life (HRQL) among individuals with chronic diseases. *Scientific World J* 2004;**4**:746–57	Irrelevant population
Nordvag B-Y, Bernklev T, Slevolden E, Myhr K-M, Stensland E. Norwegian quality registry for biological drugs: The NOKBIL project. *Scand J Rheumatol* 2012;**41**(Suppl. 126):50	Abstract
Osnes-Ringen H, Kvien TK, Henriksen JE, Mowinckel P, Dagfinrud H. Orthopaedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health-related quality of life. *Ann Rheum Dis* 2009;**68**:1596–601	Irrelevant population
Osnes-Ringen H, Kvien TK, Henriksen JE, Dagfinrud H. Patients with inflammatory arthropathies undergo feet surgery later in the disease course than hand surgery. *Clin Exp Rheumatol* 2010;**28**:702–7	Irrelevant population
Osnes-Ringen H, Kvamme MK, Kristiansen IS, Thingstad M, Henriksen JE, Kvien TK, *et al.* Cost-effectiveness analyses of elective orthopaedic surgical procedures in patients with inflammatory arthropathies. *Scand J Rheumatol* 2011;**40**:108–15	Irrelevant population
Shelepina TA, Stepanenko NY, Fedorov ES. Comparative characteristic of quality of life with patients suffering from juvenile idiopathic arthritis (JIA), attending school and taught at home. *Pediatr Rheumatol* 2011;**9**:106	Abstract
Simpson K, Hubert MM, On PV, Cifaldi M, Shaw J. Long-term cost-effectiveness of adalimumab therapy in juvenile idiopathic arthritis: from a Canadian perspective. *J Rheumatol* 2012;**39**:1712	Abstract
Solari N, Viola S, Pistorio A, Magni-Manzoni S, Vitale R, Ruperto N, *et al.* Assessing current outcomes of juvenile idiopathic arthritis: a cross-sectional study in a tertiary center sample. *Arthritis Rheum* 2008;**59**:1571–9	No utilities reported
Sparsa L, Job DC, Quartier P, Kahan A, Wipff J. Quality of life of juvenile idiopathic arthritis cohort at adulthood in a transition program. *Ann Rheum Dis* 2013;**71**(Suppl. 3):432	Abstract
Wade AG, Crawford GM, Pumford N, Koscielny V, Maycock S, McConnachie A. Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation. *BMC Med Res Methodol* 2011;**11**:91	No utilities reported
Wang H-M, Beyer M, Gensichen J, Gerlach FM. Health-related quality of life among general practice patients with differing chronic diseases in Germany: cross sectional survey. *BMC Public Health* 2008;**8**:246	Irrelevant population

Appendix 9 Health-related quality-of-life systematic review: data extraction forms

Reference

Hendry *et al.* (2013)[136]

Study characteristics

Research question

What are the stated objectives of the study?

To evaluate the effectiveness of multidisciplinary foot-care, and to evaluate the methodological considerations of a trial of multidisciplinary care in JIA.

Describe the type of study and study design.

Exploratory randomised controlled trial

Was the sample from (1) the general population; (2) patients with the disease of interest; (3) individuals with knowledge of the disease; (4) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (e.g. > 80 years)?

The sample was drawn from patients with the disease of interest (i.e. children and adolescents with a definitive diagnosis of JIA and inflammatory joint disease affecting the foot/ankle).

The inclusion/exclusion criteria were clearly stated; however, might exclude a proportion of individuals with the disease of interest but whose disease has not affected the foot/ankle.

Patients were included if they satisfied at least one of the following: (1) previously documented arthritis in the foot including small joints derived from medical case notes; (2) previously documented foot arthritis in one or more large joints derived from medical case notes; or (3) current widespread polyarthritis involving large and small foot joints derived from clinical examination by a consultant paediatric rheumatologist. Patients with an unconfirmed diagnosis of JIA, and/or only upper limb, jaw, or neck involvement were excluded.

What are the characteristics of the baseline cohort for the evaluation?

Age, years, mean (SD)	
Intervention arm	10.1(4.22)
Control arm	10.0(3.39)
Male/female, *n*	
Intervention arm	7/14
Control arm	6/17
Race (if appropriate)	NR
Disease subtypes, *n* (%)	
Intervention arm	
Persistent oligoarthritis	7 (33)
EO	4 (19)
Polyarthritis RF–ve	6 (29)
Polyarthritis RF+ve	0 (0)
Psoriatic arthritis	2 (10)
ERA	2 (10)
Undifferentiated	0 (0)
Control arm	
Persistent oligoarthritis	4 (17)
EO	5 (22)
Polyarthritis RF–ve	10 (43)
Polyarthritis RF+ve	2 (9)
Psoriatic arthritis	1 (4)
ERA	0 (0)
Undifferentiated	1 (4)
Sample size, *n*	
Intervention arm	21
Control arm	23
Pharmacological management, *n* (%)	
Intervention arm	
Analgesics	2 (9)
NSAIDs	18 (86)
Methotrexate	7 (33)
Etanercept	1 (5)
Sulphasalazine	0 (0)
Rituximab	5 (24)

Control arm	
Analgesics	3 (13)
NSAIDs	16 (70)
Methotrexate	5 (22)
Etanercept	0 (0)
Sulphasalazine	1 (4)
Rituximab	5 (22)
Combination methotrexate and etanercept	–
QoL instrument	EQ-5D-Y (patients) and EQ-5D-3L (parents/guardians) questionnaires
Utility values (Y/N)	Y
Treatment effect, if reported	Both the treatment groups appeared to improve by one point on the JAFI impairment scale between baseline and 12 months follow up, however, the differences between groups for change scores did not reach statistical significance

Country/setting

What is the country and setting for the evaluation?

Royal Hospital for Sick Children, Glasgow, UK.

Data sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review/synthesis or combination of previous studies, expert opinion?

This single exploratory RCT.

Results

Summarise the results.

There were no significant differences between treatment groups for secondary outcomes at final follow-up.

	Intervention arm	Control arm
Baseline		
Self EQ-5D utility index, mean (SD)	0.57 (0.31)	0.58 (0.35)
Self EQ-5D utility index, median (IQR)	0.62 (0.52–0.76)	0.66 (0.52–0.75)
Proxy EQ-5D utility index, mean (SD)	0.69 (0.29)	0.60 (0.33)
Proxy EQ-5D utility index, median (IQR)	0.69 (0.58–1)	0.62 (0.55–0.82)
Change at 12 months		
Self EQ-5D utility index, median (IQR)	0 (–0.1 to 0.01)	0 (–0.04 to 0.04)
Proxy EQ-5D utility index, median (IQR)	0 (0–0.11)	0 (0–0.1)

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

A valid preference-based instrument was used: EQ-5D-Y and EQ-5D-3L.

Are the levels of missing data reported? How are they dealt with?

For missing data identified at the end of the study, a sensitivity analysis was performed in order to identify the most appropriate method to address this problem (LOCF, mean value imputation, maximum value imputation, minimum value imputation and random value imputation). LOCF was found to be the most conservative method while being less labour intensive; therefore, it was subsequently used to impute all missing data at final follow-up.

Mapping

If a model was used, describe the type of model (e.g. regression) or other conversion algorithm.

Not applicable.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

Integrated multidisciplinary foot care did not result in a significant reduction in disease-related foot impairments and disability.

What are the implications of the study for the model?

In both arms, a proportion of participants received etanercept, so the utility values reported cannot be used in the model for baseline HRQoL with standard of care.

Reference

Prince *et al.* (2011),[124] Prince *et al.* (2010)[137]

Study characteristics

Research question

What are the stated objectives of the study?

To evaluate changes in HRQoL in patients with refractory JIA who are being treated with etanercept.

Describe the type of study and study design.

Prospective study.

Was the sample from: (1) the general population; (2) patients with the disease of interest; (3) individuals with knowledge of the disease; (4) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (e.g. > 80 years)?

JIA patients younger than 18 years treated with etanercept.

What are the characteristics of the baseline cohort for the evaluation?

Study	Prince *et al.* (2010)[137]	Prince *et al.* (2011)[124]
Age	11.9 years (IQR 8.1–14.9)	11.6 years (IQR 7.9–14.9)
Sex, *n* (%)		
Male	20 (38)	20 (41)
Female	33 (62)	33 (59)
Ethnicity (if appropriate)		
Indication/disease, *n* (%)	Systemic 14 (26)	Systemic 11 (22)
	Polyarticular RF+ve 5 (9)	Polyarticular RF+ve 4 (8)
	Polyarticular RF–ve 18 (34)	Polyarticular RF–ve 18 (37)
	EO 11 (21)	EO 11 (22)
	ERA 2 (4)	ERA 2 (4)
	Juvenile PA 3 (6)	Juvenile PA 3 (6)
Other characteristics (sample size)	Sample size 53	Sample size 49
	Median disease duration JIA (years) at start of etanercept 3.0	Median disease duration JIA (years) at start of etanercept 3.6
Quality-of-life instrument	HUI3	HUI3
Utility values (Y/N)	Yes	Yes
Treatment effect, if reported	Significant improvements were shown after 3 months and these continued at least up to 27 months	Significant improvements were shown after 3 months and these continued at least up to 27 months

Country/setting

What is the country and setting for the evaluation?

The Netherlands.

Data sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review/synthesis or combination of previous studies, expert opinion?

Single prospective study.

Results

Summarise the results.

Prince *et al.* (2010)[137]	Baseline	3 months	15 months	27 months
HUI3 mean (SE)	0.53 (0.04)	0.69 (0.05)	0.74 (0.06)	0.78 (0.07)

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes.

Are the levels of missing data reported? How are they dealt with?

Not reported.

Mapping

If a model was used, describe the type of model (e.g. regression) or other conversion algorithm.

Mapping was not used.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

This study shows that the HRQoL of patients with refractory JIA can be substantially improved by the use of etanercept.

What are the implications of the study for the model?

This is a potential source of HRQoL for the SHTAC economic model.

Appendix 10 Cost-effectiveness data extraction forms for the company submissions

Company submission from Abbvie

Reference

AbbVie (2015)[77]

Health technology

Adalimumab

Interventions and comparators

What interventions/strategies were included?

No economic evaluation was conducted; however, reasons for not conducting an economic evaluation were discussed and included the following interventions: adalimumab, etanercept, abatacept, tocilizumab and methotrexate.

Was a no treatment/supportive care strategy included?

No.

Describe interventions/strategies

p. 13 CS: 'The aim of drug therapy in JIA patients is to induce and maintain remission of symptoms, and thus allow a child to achieve normal growth, development, and allow full participation in school, career, sport and all other aspects of normal life. The initial aim is induction of complete disease remission using corticosteroids – either intravenously (IV) or intra-articular. Oral corticosteroids are avoided where possible to avoid side effects (can affect growth or increase risk of osteoporosis) but may be needed for short time periods.'

p. 14 EMA licence: 'Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.'

Adalimumab is delivered as 24 mg/m^2 body surface area (with varying maximum doses dependent on weight and study protocol) subcutaneous injection with concomitant methotrexate for 24 weeks or more. Patients were allowed to take NSAIDs and prednisone or equivalents to prednisone.

Research question

What are the stated objectives of the evaluation?

No economic evaluation was conducted.

Study type: cost-effectiveness/cost–utility/cost–benefit analysis?

No economic evaluation was conducted.

Study population

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

From pp. 9–10 of the CS: 'Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood and describes a group of conditions that involve joint inflammation which lasts for more than 6 weeks in people under 16 years of age. . . . JIA is an "umbrella" term which covers a number of different subtypes listed below that were proposed by the International League of Associations for Rheumatology (ILAR) in 1995 for the classification of JIA:

- Oligoarticular JIA – Oligoarthritis is the most common type of JIA, accounting for up to 50% of new diagnoses in Europe each year. It is diagnosed when four or fewer joints are affected in the first 6 months of disease.
- Extended Oligoarticular JIA – If oligoarthritis progresses and affects more than four joints during the first 6 months, it is called extended oligoarthritis.
- Poly-Articular JIA (RF –ve or RF +ve) – Polyarticular JIA is diagnosed when five or more joints are affected at presentation, and can be further divided into rheumatoid factor positive arthritis and rheumatoid factor negative disease.
- Systemic-Onset JIA – Systemic JIA accounts for 5–10% of new diagnoses and is diagnosed when arthritis is part of a general illness involving features such as fever, lymphadenopathy, hepatosplenomegaly and serositis. This patient group was not included in the NICE Scope for this project.
- Psoriatic JIA – Psoriatic arthritis accounts for 2–15% of new diagnoses and is diagnosed when there is joint swelling associated with psoriasis, or a family history of psoriasis.
- Enthesitis-Related Arthritis (ERA) – ERA accounts for 2–10% of new diagnoses and is diagnosed in the presence of arthritis or inflammation of tendon attachments to the bones (entheses), in association with two or more other features of spondyloarthropathy.'
- No economic evaluation was conducted, so there is no relevant baseline cohort.

Institutional setting: where is/are the intervention(s) being evaluated usually provided?

Paediatric secondary care.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

No economic evaluation was conducted.

Funding source

AbbVie.

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

No economic evaluation was conducted.

Effectiveness

Were the effectiveness data derived from: a single study, a review/synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation.

No economic evaluation was conducted.

Intervention costs

Were the cost data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation: include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

No economic evaluation was conducted.

Indirect costs (costs attributable to lost productivity, unpaid inputs to patient care)

Were indirect costs included?

No economic evaluation was conducted.

Health-state valuations/utilities (if study uses quality-of-life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

No economic evaluation was conducted.

List the utility values used in the evaluation

No economic evaluation was conducted.

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported: list them if reported.

No modelling was undertaken.

Extract transition probabilities for (natural history/disease progression) model and show sources (or refer to table in text)

No modelling was undertaken.

What is the model time horizon?

No modelling was undertaken.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

No modelling was undertaken.

If no economic evaluation was conducted, state the manufacturer's reasons for this

No economic evaluation was conducted owing to heterogeneity in study methods and populations between the interventions that complicated indirect comparisons, a lack of appropriate utility data for HRQoL and lack of long-term data.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

No economic evaluation was undertaken.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation

No economic evaluation was undertaken.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation

No economic evaluation was undertaken.

Synthesis of costs and benefits: are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results

No economic evaluation was undertaken.

Give results of any statistical analysis of the results of the evaluation

No economic evaluation was undertaken.

Was any sensitivity analysis performed: if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]?

No economic evaluation was undertaken.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

No economic evaluation was undertaken.

Give a summary of the results of the sensitivity analysis: did they differ substantially from the base-case analysis. If so, what were the suggested causes?

No economic evaluation was undertaken.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

No economic evaluation was undertaken.

What are the implications of the evaluation for practice?

No economic evaluation was undertaken.

Southampton Health Technology Assessments Centre commentary

Selection of comparators

Although no economic evaluation was conducted, the comparators listed by the manufacturer were appropriate and in accordance with the NICE scope.

Validity of estimate of measure of benefit

No economic evaluation was undertaken.

Validity of estimate of costs

No economic evaluation was undertaken.

Company submission from BMS

Reference

BMS (2015)[85]

Health technology

Abatacept.

Interventions and comparators

What interventions/strategies were included?

Abatacept, adalimumab, etanercept and tocilizumab.

Was a no treatment/supportive care strategy included?

No.

Describe interventions/strategies

Abatacept is a biologic DMARD that prevents T-cell activation, thus down-regulating the immune response of inflammatory disease. (p. 9). Abatacept is administered intravenously.

p. 9 CS: 'The recommended dose of abatacept for polyarticular JIA patients aged 6 to 17 years (who weigh less than 75 kg) is 10 mg/kg, calculated based on the patient's body weight at each administration. Paediatric patients weighing 75 kg or more should follow the abatacept adult dosing regimen and should not exceed a maximum dose of 1,000 mg. Abatacept should be administered as a 30-minute intravenous infusion. Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, and every 4 weeks thereafter.'

Etanercept is a biologic DMARD that inhibits TNF activation. It is administered subcutaneously. For patients aged 2–18 400 µg/kg (maximum 25 mg twice a week) or 800 µg/kg (maximum 50 mg once a week) was administered. For patients over 18 years of age the dose was 50 mg.

Adalimumab is a biologic DMARD that inhibits TNF activation. It is administered subcutaneously. For patients aged 4–13 24 mg/m^2 (maximum 40 mg) was administered EOW. For patients aged 13 and above the dose was 40 mg.

Tocilizumab is a biologic DMARD. It is a humanised monoclonal antibody that inhibits the cytokine IL-6. It is administered by intravenous infusion. Tocilizumab dose was based on weight. For patients weighing < 30 kg the dose was 10 mg/kg. For patients 30 kg and above the dose was 8 mg/kg (maximum 800 mg). Doses were administered every 4 weeks. All tocilizumab patients were older than 2 years of age.

All drugs were administered with subcutaneous methotrexate. BMS indicated that methotrexate was given every 4 weeks at a dosage of 13.5 mg/m^2.

Research question

What are the stated objectives of the evaluation?

From CS model: 'The model evaluates the cost-effectiveness of abatacept against other biological disease modifying anti rheumatic drugs (bDMARDs) in moderate-to-severe active polyarthritis in paediatric patients from the age of 6 years and who have shown insufficient response to other DMARDs, including at least one anti-TNF.'

BMS reports that this is not in perfect agreement with the NICE Scope, but is in accord with the drug licence. The NICE Scope is broader with no specifications for patient age, or insufficient response on other DMARDs (including failure of at least one TNF inhibitor). The NICE Scope also includes ERA.

Study type: cost-effectiveness/cost–utility/cost–benefit analysis?

BMS has conducted a cost-minimisation analysis with an assumption that there is no difference between the biologic DMARDs in effectiveness. BMS indicated that effectiveness evidence was not considered because it 'would lead to uncertainty within the model'.

Study population

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

'JIA encompasses all forms of arthritis of unknown aetiology that persist for at least 6 weeks and begin in patients younger than 16 years.1 JIA comprises several heterogeneous subtypes (oligoarthritis, polyarthritis, systemic, psoriatic, enthesitis-related and undifferentiated), all presenting with different clinical signs and symptoms.[1,3,14] Overall, JIA is characterised by persistent joint swelling, pain and limitation of movement and has an estimated incidence in the UK of 1 per 10,000 children and a prevalence in the order of 1 per 1,000 children.[2] Polyarticular JIA (classifiable as polyarthritis [rheumatoid factor-positive or -negative]) is characterised by arthritis affecting five or more joints during the first 6 months of the disease,[1,3,14,15] and it affects 13%–37% of patients with JIA.[3]

JIA causes functional impairment due to joint and back pain, heel pain, swelling of joints and morning stiffness, contractures, pain and anterior uveitis leading to blindness.[16] This leads to suboptimal health-related quality of life (HRQL) in patients and parents or carers alike.[17,18] Moreover, as JIA patients reach adulthood, they face possible continuing disease activity, medication-associated morbidity, life-long disability and the risk of emotional and social dysfunction.[16]'

CS p. 8. Reference citations have been reproduced from the CS as supplied

The baseline cohort population was defined as 12-year old 'moderate-to-severe active polyarticular JIA [patients] who have had an insufficient response to other DMARD, including at least one TNF inhibitor' in the decision problem stated by BMS.

Institutional setting: where is/are the intervention(s) being evaluated usually provided?

The institutional setting appears to be paediatric secondary care, but this is not entirely clear. The delivery environment is not specifically referenced.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

The country setting given is the UK. Costs are expressed in pounds sterling (£). Costs were derived from the MIMS database (accessed November 2014). The price year was not explicitly stated.

Funding source

BMS.

Analytical perspective

What is the perspective adopted for the evaluation [health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)]?

The model reports that it adopts an NHS and PSS perspective; however, it appears that only drug and administration costs have been included in the model. The NHS and PSS perspective generally includes costs associated with the disease. This would routinely include hospitalisation costs, costs for physician visits and nurse time, as well as costs for managing AEs. This could also include reductions in costs attributable to temporary dose reductions and interruptions. The NHS and PSS perspectives presented by BMS are much more limited than those commonly presented in NHS economic evaluations.

Effectiveness

Were the effectiveness data derived from: a single study, a review/synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation.

No effectiveness data were used.

Intervention costs

Were the cost data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Intervention costs were derived from MIMS. A PAS was incorporated for abatacept (CiC information has been removed). Sensitivity analyses were run for the price of tocilizumab using various percentage price discounts as a CiC PAS has been agreed for tocilizumab.

Drug	Cost, £	Dose	PAS discount	PAS cost
Abatacept	302.40	250 mg	(CiC information has been removed)	(CiC information has been removed)
Etanercept	35.75	10 mg		
	89.38	25 mg		
	178.75	50 mg		
Adalimumab	352.14	40 mg		
Tocilizumab	102.40	80 mg		
	256.00	200 mg		
	512.00	400 mg		
Methotrexate	14.85	7.5 mg		
	15.29	10 mg		
	16.50	12.5 mg		
	16.57	15 mg		
	17.50	17.5 mg		
	17.84	20 mg		

Administration method	Costs, £
Infusion	154.00
Subcutaneous injection	3.05

Indirect costs (costs attributable to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

No.

Health-state valuations/utilities (if study uses quality-of-life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

No health valuations were undertaken.

List the utility values used in the evaluation

No health valuations were undertaken.

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? List them if reported.

The model is essentially a one-state model where child height and weight change as they age which affects only the cost of drug doses. There are no health states.

Extract transition probabilities for (natural history/disease progression) model and show sources (or refer to table in text)

There was no natural history modelling.

What is the model time horizon?

The base-case model has a 6-year time-horizon. The time-horizon is user adjustable within the model by setting different exit ages.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

A discount rate of 3.5% annually has been applied to costs, in accordance with the NICE Reference Case.

If no economic evaluation was conducted, state the manufacturer's reasons for this

A cost-minimisation analysis was conducted.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

No benefit measure was evaluated.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation

No clinical outcomes nor benefit measures were evaluated.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation

Discounted results for the base case (table 13 in CS)

Results for the base-case model (12 year olds, 6-year time horizon, from Excel model)				
	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug costs	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
Administration costs, £	11,797	871	871	11,646
Total costs	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
Cost savings with abatacept		(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)

Undiscounted results for the base case (table 12 in CS)

Results for the base-case model (12 year olds, 6-year time horizon, from Excel model)				
	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug costs	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
Administration costs, £	13,040	964	964	12,889
Total costs	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)
Cost savings with abatacept		(CiC information has been removed)	(CiC information has been removed)	(CiC information has been removed)

Synthesis of costs and benefits: are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results

A cost minimisation analysis was undertaken, so there was no synthesis of costs and benefits.

Give results of any statistical analysis of the results of the evaluation

There were no statistical analyses of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]

A PSA was undertaken and scenario analyses were undertaken.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

A sensitivity analysis was undertaken wherein the infusion costs for tocilizumab were increased owing to the longer infusion time. This evaluates parameter uncertainty.

The starting age of patients in the model was varied between 6 and 16 years. This related to the structural assumption of starting age. In the biologic DMARD trials, the mean age was 11 years at baseline, but the drug licences were for much younger ages.

The time horizon of the model was varied between 6 months and 20 years. Longer time horizons were meant to represent that one-third of children with JIA will have it continue into adulthood. It was unclear why shorter time horizons were tested.

PAS discount for tocilizumab. This represents parameter uncertainty in the cost of tocilizumab.

Exclude methotrexate from the etanercept arm. This scenario dabbles across all the types of uncertainty. NICE specifies that etanercept probably benefits from methotrexate being given concurrently, but the licence is not for etanercept plus methotrexate, so there is some uncertainty in the appropriateness of methodology recommended by NICE. Changing a comparator is a structural modification and requires new parameter estimates.

Give a summary of the results of the sensitivity analysis: did they differ substantially from the base-case analysis. If so, what were the suggested causes?

Adjusting the starting age of patients downwards favoured etanercept with a starting age of 10 or under resulting in etanercept being cost saving compared with abatacept. Applying a PAS discount of (CiC information has been removed) to tocilizumab makes the costs for the two drugs identical. Excluding methotrexate costs from the etanercept arm made etanercept cost-saving compared with abatacept. There were no suggested causes for any of the analyses, only a statement of the analysis results.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

In the base case, abatacept is the least costly bDMARD and has similar efficacy and safety to other bDMARDs. These results remain stable for a wide range of scenarios.

What are the implications of the evaluation for practice?

There are no implications, because the economic evaluation did not evaluate practice, it only evaluated drug pricing. The model assumes that the drugs will have identical discontinuation rates, AEs and onset of effectiveness and duration of effectiveness. These assumptions are unlikely to be true. Even in an analysis that assumes there is no difference in effectiveness, differences in how the drugs behave in practice should be reflected in the costs.

Southampton Health Technology Assessments Centre commentary

Selection of comparators:

The comparators were consistent with the NICE Scope.

Validity of estimate of measure of benefit:

The assumption of equivalent efficacy was of unclear validity. Although BMS provided justification for assuming equivalence, the nature of the data available may not justify this approach. The trials were small, but generally share many characteristics, and indirect comparisons were referenced by BMS and conducted by BMS. A full evaluation of AEs using data beyond the clinical trials was not undertaken, and no comparisons of discontinuation rates were undertaken. The data from the trials were of insufficient quantity to make equivalency assumptions on event rates over time.

Given that there is a large amount of uncertainty in the effectiveness data, it may have been more appropriate to conduct a full economic evaluation with that uncertainty incorporated.

Validity of estimate of costs:

The costs were derived from appropriate sources, but BMS has assumed that the drugs will have identical AE costs and discontinuation rates (and identical everything else), both of which would lead to costs that have not been captured here. The strong assumption that there are no differences in the behaviour of the drugs in spite of different licences and mechanisms of action lacks face validity.

Critical appraisal checklist of economic evaluation (questions in this checklist based on Philips *et al.*[128] and Drummond *et al.*[129])

	Item	MS 1
1	Is there a clear statement of the decision problem?	Yes
2	Is the comparator routinely used in UK NHS?	Yes
3	Is the patient group in the study similar to those of interest in UK NHS?	Yes
4	Is the health-care system comparable to UK?	Yes
5	Is the setting comparable to the UK?	Yes
6	Is the perspective of the model clearly stated?	Yes
7	Is the study type appropriate?	No
8	Is the modelling methodology appropriate?	No
9	Is the model structure described and does it reflect the disease process?	?[a]
10	Are assumptions about model structure listed and justified?	Yes
11	Are the data inputs for the model described and justified?	Yes
12	Is the effectiveness of the intervention established based on a systematic review?	N/A
13	Are health benefits measured in QALYs?	N/A
14	Are health benefits measured using a standardised and validated generic instrument?	N/A
15	Are the resource costs described and justified?	Yes
16	Have the costs and outcomes been discounted?	No[b]
17	Has uncertainty been assessed?	Yes
18	Has the model been validated?	Yes

N/A, not applicable.
a The model is a single-state cost model with a time horizon from age 12–18 years that includes neither costs nor benefits of disease progression or complications. The model represents only the disease process by having patients take higher doses of drugs as they age.
b The model was a cost model with no measure of benefits; therefore, only costs were discounted.

Company submission from Pfizer

Reference

Pfizer (2015)[97]

Health technology

Etanercept.

Interventions and comparators

What interventions/strategies were included?

No economic evaluations were conducted; however, a cost analysis comparing etanercept, adalimumab and tocilizumab was conducted.

Was a no treatment/supportive care strategy included?

No.

Describe interventions/strategies

No economic evaluation was conducted. The cost analysis included etanercept, adalimumab and tocilizumab. Etanercept is administered by subcutaneous injection at a recommended dose of 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3–4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly.

Research question

What are the stated objectives of the evaluation?

No economic evaluation was conducted.

Study type: cost-effectiveness/cost–utility/cost–benefit analysis?

No economic evaluation was conducted, however a cost analysis was conducted.

Study population

What definition was used for (condition)? What are the characteristics of the baseline cohort for the evaluation?

The cost analysis was undertaken for a cohort with polyarticular JIA.

Institutional setting: where is/are the intervention(s) being evaluated usually provided?

NHS outpatient setting.

Country/currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

No economic evaluation. The cost analysis was conducted in pounds sterling (£) but does not state the price year.

Funding source

Pfizer.

Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

No economic evaluation was conducted.

Effectiveness

Were the effectiveness data derived from: a single study, a review/synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation.

No economic evaluation was conducted.

Intervention costs

Were the cost data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

No economic evaluation was conducted. The cost analysis used drug costs and administration costs for first year of treatment for different patient ages and weights. Cost sources are not given.

Indirect costs (costs attributable to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

No economic evaluation was conducted.

Health-state valuations/utilities (if study uses quality-of-life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

No economic evaluation was conducted.

List the utility values used in the evaluation

No economic evaluation was conducted.

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

No economic evaluation was conducted.

Extract transition probabilities for (natural history/disease progression) model and show sources (or refer to table in text)

No economic evaluation was conducted.

What is the model time horizon?

No economic evaluation was conducted.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

No economic evaluation was conducted.

If no economic evaluation was conducted, state the manufacturer's reasons for this

The CS notes the limitation raised in previous NICE submission TA35 and TA238. These relate to the limitations in the HRQoL data and the limited evidence on the long term outcomes and the effectiveness of the treatments. The company states that any cost-effectiveness evidence would be associated with considerable and unresolvable uncertainty and have therefore not submitted a cost-effectiveness model for this appraisal.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

No economic evaluation was conducted.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation

No economic evaluation was conducted.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation

No economic evaluation was conducted; the cost analysis shows the costs were similar between etanercept, adalimumab and tocilizumab.

	Etanercept[a]	Adalimumab	Tocilizumab[b]
2 years	£1,859.00	£9,155.64	£5,000.19
3 years	£3,718.00	£9,155.64	£5,000.19
4 years	£3,718.00	£9,155.64	£5,665.79
5 years	£3,718.00	£9,155.64	£5,665.79
6 years	£3,718.00	£9,155.64	£6,331.39
7 years	£3,718.00	£9,155.64	£6,331.39
8 years	£3,718.00	£9,155.64	£6,996.99
9 years	£4,647.76	£9,155.64	£6,996.99
10 years	£4,647.76	£9,155.64	£6,996.99
11 years	£9,295.00	£9,155.64	£6,996.99
12 years	£9,295.00	£9,155.64	£8,328.19
13 years	£9,295.00	£9,155.64	£8,993.79
14 years	£9,295.00	£9,155.64	£8,993.79
15 years	£9,295.00	£9,155.64	£8,993.79
16 years	£9,295.00	£9,155.64	£10,324.99
17 years	£9,295.00	£9,155.64	£10,324.99

a Where relevant, the cheapest dosage regimen was assumed to be used in selecting between once-weekly and twice-weekly options.
b Includes cost of administration in hospitals.

To reflect clinical practice and avoidance of drug wastage, doses were rounded down to the nearest available combination of vial strengths to a maximum of 10% variation from estimated dose.

Synthesis of costs and benefits: are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results

No economic evaluation was conducted.

Give results of any statistical analysis of the results of the evaluation

No economic evaluation was conducted.

Was any sensitivity analysis performed: if yes, what type(s) (i.e. deterministic (one-way, two-way, etc.) or probabilistic)

No economic evaluation was conducted.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

No economic evaluation was conducted.

Give a summary of the results of the sensitivity analysis: did they differ substantially from the base-case analysis. If so, what were the suggested causes?

No economic evaluation was conducted.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

No economic evaluation was conducted.

What are the implications of the evaluation for practice?

No economic evaluation was conducted.

Southampton Health Technology Assessments Centre commentary

Selection of comparators:

No economic evaluation was conducted, the cost analysis did not include abatacept.

Validity of estimate of measure of benefit:

No economic evaluation was conducted.

Validity of estimate of costs:

No economic evaluation was conducted. Costs used in the cost analysis appear reasonable.

Company submission from Roche

Reference

Roche (2015)[78]

Health technology

Tocilizumab.

Interventions and comparators

What interventions/strategies were included?

Tocilizumab vs. adalimumab.

Was a no treatment/supportive care strategy included?

No.

Describe interventions/strategies

Tocilizumab + MTX vs. adalimumab + MTX.

Tocilizumab only vs. adalimumab only.

Research question
What are the stated objectives of the evaluation?

To demonstrate the cost-effectiveness of tocilizumab when used in patients with pJIA who had an inadequate response to DMARDs.

Study type: cost-effectiveness/cost–utility/cost–benefit analysis?

Cost utility.

Study population
What definition was used for (condition)? What are the characteristics of the baseline cohort for the evaluation?

Patients entering the model have active JIA and have previously experienced an inadequate response to, or were intolerant of methotrexate. The modelled population is in line with the CHERISH trial population.

Institutional setting: where is/are the intervention(s) being evaluated usually provided?

NHS outpatient care.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

UK. Costs have been taken from sources from year 2011–15 with some costs taken from the Netherlands. Costs have not been inflated to a common base year.

Funding source

Roche.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

UK NHS and PSS.

Effectiveness

Were the effectiveness data derived from: a single study, a review/synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation.

The company completed a systematic review of biologics in the treatment of JIA. The effectiveness data were derived from a WinBUGS indirect comparison with an order probit model. The results were in terms of level of ACR response.

		JIA ACR-30	JIA ACR-50	JIA ACR-70	JIA ACR-90
Without MTX	Placebo	31%	28%	25%	12%
	Tocilizumab	62%	59%	54%	35%
	Adalimumab	52%	49%	44%	26%
With MTX	MTX	52%	51%	41%	25%
	Tocilizumab	72%	70%	61%	44%
	Adalimumab	76%	75%	66%	49%

MTX, methotrexate.

Intervention costs

Were the cost data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

The costs associated with each health state was obtained from Prince *et al.*,[124] who report costs data from the Dutch ABC register for the year before and after starting etanercept. The total 6-month health-state cost for patients on treatment is £912.33 and off treatment is £1591.43.

The source of the treatment acquisition costs was not stated (assumed to be BNF).

Treatment	Dose 1	Frequency	Unit cost (list price), £
Adalimumab (40 mg)	40 mg (assume wastage and all children receive 40-mg vial)	Every 2 weeks	352.14
Etanercept (10 mg)	0.4 mg/kg (maximum 25 mg)	Twice a week	35.75
Etanercept (25 mg)			89.38
Methotrexate (10 mg, oral)	10 mg	Every week	0.56
Tocilizumab (80 mg)	10 mg/kg for patients < 30 kg;	Every 4 weeks	102.40
Tocilizumab (200 mg)	8 mg/kg for patients ≥ 30 kg		256.00
Tocilizumab (400 mg)			512.00

Indirect costs (costs attributable to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

Indirect costs are not included.

Health-state valuations/utilities (if study uses quality-of-life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

The company conducted a literature review that identified one study that reported utility values suitable for use in the model (Prince *et al.*[124]) This study reported utility scores obtained using the HUI3 questionnaire to JIA patients starting treatment with etanercept in the Dutch ABC register.

Based on these data, the company used values at time 0 for the patients who are off treatment, and used values at time 1 year for patients on treatment.

List the utility values used in the evaluation

On treatment: 0.7275.

Off treatment: 0.53.

Dead: 0.

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

A de novo Markov state transition model with three health states (uncontrolled disease/off treatment, on treatment and dead) was developed. The model has 6-month cycles. Patients start with uncontrolled disease at cycle 0 then move to first-line treatment. Patients discontinue from treatment at a rate proportional to their response. Once all lines of treatment are exhausted, patients move into uncontrolled disease health state.

The model uses a 1% 6-month mortality rate.

Extract transition probabilities for (natural history/disease progression) model and show sources (or refer to table in text)

The 6-month discontinuation rate is 0.126 for no response, 0.09 for moderate response and 0.042 for good response.

What is the model time horizon?

25-year time frame. The company states that this reflects the chronic nature of the disease and allows for all relevant costs and benefits to be included in the analysis.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

3.5% for costs and benefits.

If no economic evaluation was conducted, state the manufacturer's reasons for this

Not applicable.

Results/analysis

What measure(s) of benefit were reported in the evaluation?

Cost per QALY gained.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation

Combination therapy

	Adalimumab + MTX	Tocilizumab + MTX
Total QALYs	18.76	18.72

Monotherapy

	Adalimumab + MTX	Tocilizumab + MTX
Total QALYs	18.65	18.7

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation

Combination therapy

	Adalimumab + MTX	Tocilizumab + MTX
Total cost, £	81,827	70,707

Monotherapy

	Adalimumab + MTX	Tocilizumab + MTX
Total cost, £	74,576	68,560

Synthesis of costs and benefits: are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results

	Combination therapy	Monotherapy
Incremental QALYs	0.03	0.0455
Incremental cost, £	11,120	6015
Incremental ICER, £	280,370	Tocilizumab dominant

Give results of any statistical analysis of the results of the evaluation

None reported.

Was any sensitivity analysis performed. If yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]

None reported.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

An exploratory analysis has been performed for tocilizumab versus etanercept. The analysis assumes a class effect across TNFs in pJIA. The analysis found that tocilizumab was a cost-effective alternative to etanercept.

Give a summary of the results of the sensitivity analysis: did they differ substantially from the base-case analysis. If so, what were the suggested causes?

None reported.

Conclusions/implications

Give a brief summary of the author's conclusions from their analysis.

Adalimumab and tocilizumab have similar outcomes for patients with JIA, however tocilizumab is a less expensive alternative to adalimumab.

What are the implications of the evaluation for practice?

None.

Southampton Health Technology Assessments Centre commentary

Selection of comparators:

Results not presented for tocilizumab compared with methotrexate only.

Validity of estimate of measure of benefit:

Based on only utility estimates available for this population.

Validity of estimate of costs:

Based on relevant dataset of costs for patients on etanercept in the Netherlands. May be differences in costs between countries.

Critical appraisal checklist of economic evaluation (questions in this checklist based on Philips *et al.*[128] and Drummond *et al.*[129]).

	Item	Roche
1	Is there a clear statement of the decision problem?	Yes
2	Is the comparator routinely used in UK NHS?	Yes
3	Is the patient group in the study similar to those of interest in UK NHS?	Yes
4	Is the health-care system comparable to UK?	?[a]
5	Is the setting comparable to the UK?	Yes
6	Is the perspective of the model clearly stated?	Yes
7	Is the study type appropriate?	Yes
8	Is the modelling methodology appropriate?	Yes
9	Is the model structure described and does it reflect the disease process?	Yes
10	Are assumptions about model structure listed and justified?	Yes
11	Are the data inputs for the model described and justified?	Yes
12	Is the effectiveness of the intervention established based on a systematic review?	Yes
13	Are health benefits measured in QALYs?	Yes
14	Are health benefits measured using a standardised and validated generic instrument?	Yes
15	Are the resource costs described and justified?	Yes
16	Have the costs and outcomes been discounted?	Yes
17	Has uncertainty been assessed?	No[b]
18	Has the model been validated?	No

a Costs and utilities have been taken from a Dutch registry study.
b An exploratory analysis was conducted against etanercept.

Appendix 11 Parameters used in the independent model probabilistic sensitivity analysis

TABLE 80 Parameters used in the independent model PSA

Parameter	Mean	Higher CI	Lower CI	Standard error	Distribution
Utility values					
No treatment	0.13	0.15	0.11	0.010	Beta
Treatment 3 months	0.17	0.20	0.15	0.013	Beta
Treatment 15-month phase	0.19	0.21	0.16	0.015	Beta
Treatment long term 27+ months	0.20	0.23	0.16	0.018	Beta
Disease flare disutility	0.03	0.04	0.02	0.006	Beta
Disease flare					
Placebo	0.25	0.34	0.16	0.046	Beta
Abatacept	0.09	0.16	0.05	0.021	Beta
Adalimumab	0.14	0.23	0.09	0.028	Beta
Etanercept	0.09	0.17	0.04	0.021	Beta
Tocilizumab	0.14	0.20	0.09	0.025	Beta
AEs first cycle, %					
Abatacept	0.53	1.51	0.00	0.005	Beta
Adalimumab	1.75	3.71	0.00	0.010	Beta
Etanercept	1.45	4.19	0.00	0.014	Beta
Tocilizumab	1.60	3.36	0.00	0.009	Beta
Loss of efficacy, %					
Abatacept	9.47	13.59	5.36	0.021	Beta
Adalimumab	3.51	6.25	0.76	0.014	Beta
Etanercept	2.90	6.82	0.00	0.020	Beta
Tocilizumab	7.98	11.90	4.06	0.020	Beta
Further-line treatment, %					
AEs biologic DMARD	0.43	0.82	0.04	0.002	Beta
Loss of efficacy biologic DMARD	2.00	2.59	1.41	0.003	Beta
AEs MTX	0.58	0.82	0.34	0.001	Beta
Loss of efficacy MTX	0.42	0.79	0.05	0.002	Beta
Costs, £					
On biologic DMARD cost	724	724	941	507	Gamma
Off biologic DMARD cost	724	724	941	507	Gamma
SAE cost	1,533	1,533	1,993	1,073	Gamma
Disease flare cost	430	430	559	301	Gamma

MTX, methotrexate.

EME
HS&DR
HTA
PGfAR
PHR

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