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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

RoActemra® (tocilizumab) for the treatment of systemic juvenile idiopathic arthritis (sJIA)

Specification for manufacturer/sponsor submission of evidence

Roche NICE STA Submission to the
National Institute for Health and Clinical Excellence
5th April 2011

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Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Disease Background

Systemic idiopathic juvenile arthritis (sJIA) is a subtype of juvenile idiopathic arthritis (JIA), characterised by systemic manifestations of disease in addition to arthritis. It occurs at all ages with some predilection for children less than 5 years of age. Currently JIA is diagnosed with a minimum disease duration of 6 weeks. There are no pathognomonic features for sJIA but diagnosis is usually made after 2 weeks of daily high fever spikes and transient rash. Importantly development of arthritis may lag behind by months. Other manifestations of the disease may include hepatosplenomegaly, lymphadenopathy and serositis. sJIA accounts for 10-20% of all JIA cases (See section A, Decision Problem).

Important complications of the disease are disability, joint damage and joint replacement, hospitalisations due to uncontrollable disease, osteoporosis, growth retardation, secondary amyloidosis and anaemia. A life-threatening complication occurring in about 5% of cases is the so-called macrophage-activation syndrome (MAS) which is an overwhelming systemic inflammatory reaction. About 50% of patients develop an unremitting course, and about a quarter of patients develop severe arthritis with significant disability.

Current Treatment Strategies

There are currently no licensed treatments for sJIA, therefore treatment is mainly empirical. Yet to date there have been few controlled trials to help guide treatment choices.

Tocilizumab, upon being granted approval by the European Medicines Agency (EMA), will be the first licensed drug treatment for sJIA.

Current treatment options encompass non-steroidal anti-inflammatory drugs (NSAIDs) but are usually not sufficient and high dose corticosteroids are added initially and for exacerbations. Because of the known side effects of corticosteroid treatment, methotrexate (MTX) is recommended as disease modifying therapy although it appears to be less effective than in oligoarticular and polyarticular JIA. Less commonly azathioprine is used. None of these DMARDs have been approved in sJIA by the EMA. Cyclosporine A and thalidomide have also been reported to be efficacious in patients with ongoing disease activity despite treatment with corticosteroids and MTX. Etanercept is approved for polyarticular JIA but appears to have markedly lower efficacy in sJIA, (registry study, Ann Rheum Dis. 2004;63:1638–44), and is not approved in this indication (Etanercept Summary of Product Characteristics, February 2011). Adalimumab is approved for polyarticular JIA and used off-label for sJIA, anakinra is currently used off-label and mainly uncontrolled studies support its use, and clinical studies are ongoing for canakinumab and rilonacept. Patients with refractory disease have been subjected to autologous stem cell transplantation.

Tocilizumab

Tocilizumab is a humanised monoclonal antibody directed against the IL-6 receptor. Due to the implication of IL-6 in the pathogenesis of sJIA,

tocilizumab, as an IL-6 receptor inhibitor, offers a unique treatment choice for these patients after failure of NSAIDs and corticosteroids.

Tocilizumab, the active substance of RoActemra, in combination with MTX, is currently indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNFα) antagonists/inhibitors. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

The acquisition cost (excluding VAT) of RoActemra is £102.40 for the 80mg vial and RoActemra is administered as an intravenous infusion over 1 hour and once every 2 weeks in sJIA. The recommended posology is 8mg/kg in patients weighing greater than or equal to 30kg or 12mg/kg in patients weighing less than 30kg (Section A).

The regulatory application for tocilizumab in sJIA was completed in October 2010 with anticipated approval in 2011.

Clinical Effectiveness

There are no head-to-head studies which directly compare tocilizumab with the comparators in the 2 populations outlined in the Decision Problem. However, the pivotal Phase III TENDER study (WA18221) (De Benedetti et al. 2010) has been identified as relevant to the Decision Problem. (Section 5 Clinical Evidence). This is supplemented by data from relevant non randomised studies and an indirect comparison with other biologics. (Section 5)

In summary, TENDER was a pivotal randomised double-blind, placebo controlled trial which compared current standard of care + tocilizumab versus current standard of care + placebo. This design is the preferred choice for the demonstration of efficacy because there are no licensed therapies in sJIA and an actively controlled study would be difficult to compare due to ethical issues in this patient population.

Short term (12 week) and longer term (up to 72 weeks) efficacy has been conclusively demonstrated in this trial. Findings within the trial and compared to the supportive studies show a consistent clinically relevant effect.

The primary endpoint from TENDER was the proportion of patients with at least 30% improvement in the JIA American College of Rheumatology (ACR) core set (JIA ACR30 response) at week 12 and absence of fever (no temperature recording ≥ 37.5°C in the preceding 7 days). 85.3% (64/75) of tocilizumab treated patients and 24.3% (9/37) of placebo treated patients achieved this endpoint. These proportions were highly significantly different ($p<0.0001$)

Clinical remission in children is the aim of any sJIA treatment and results from TENDER show that tocilizumab is highly effective in treating sJIA, as shown by the clinically relevant JIA ACR 70 and ACR90 responses, irrespective of baseline characteristics of patients such as active joint disease, fever, high platelet count, and previous biologic therapy (Section 5).

The qualitative safety profile of tocilizumab in children also appears to be generally comparable to adults.

Clinical evidence on comparators and indirect comparison analysis

The comparison versus methotrexate is performed using evidence from the head-to-head clinical trial data from TENDER (described above).

A systematic review was conducted to identify relevant clinical data on the additional comparators (anakinra and anti-TNFα treatment). Only one study was identified with a systemic JIA population. Due to the lack of clinical evidence in systemic JIA, the dataset was augmented with evidence from a rapid review. The additional review has a broader scope and is performed with objective to identify all pivotal trials in juvenile arthritis regardless of subtype. One RCT was identified with similar study design to TENDER and was included in the indirect comparison analysis.

The indirect comparison focuses on efficacy of treatments as reflected by ACR response. This is selected as it is the most common efficacy outcome across all comparator trials. The summary measure selected for this analysis is the relative risk (RR). The efficacy of tocilizumab, anakinra and anti-TNFα treatments (infliximab as proxy) is indirectly compared using placebo as a common comparator, following the method developed by Bucher at al. [1997]. Given data are only available in one study for each treatment there is no need for meta-analysis.

The analysis shows that patients on tocilizumab are significantly more likely to reach an ACR30 response than patients on anakinra. They are also numerically more likely to reach the combined outcome of ACR30 response and absence of fever. Compared to patients on infliximab, patients treated with tocilizumab are also significantly more likely to reach an ACR30, 50 and 70 response.

Table 1: Results of the indirect comparison analysis

Comparison	Outcome	RR	95% CI
TCZ vs ANK	ACR30	2.37	1.10, 5.10
	ACR30 and absence of fever	1.91	0.84, 4.37
TCZ vs INF	ACR30	2.87	1.49, 5.55
	ACR50	5.35	1.91, 14.97
	ACR70	4.61	1.16, 18.38

Economic evidence literature review

A systematic review was conducted to identify existing economic evaluations relevant to the STA Decision Problem. Of the 949 citations retrieved 49 were selected and included in the review. The included studies were stratified according to study type. Of the 49 studies retrieved there were 6 economic evaluations, 9 cost studies and 34 focusing on quality of life (QoL). Of the economic evaluations, none consisted of a cost-effectiveness or cost-utility analysis of tocilizumab versus methotrexate or anti-TNFα treatment. The identified studies were reviewed to provide relevant evidence on cost and utilities for a de-novo economic evaluation.

De-novo economic evaluation

The economic evaluation is designed around the population of the TENDER trial and in line with the final scope of the technology appraisal. The analysis employs a Markov chain to evaluate costs and effectiveness of the compared strategies under both populations of interest:

1. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids.

2. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate.

Both of the above populations reflect the proposed licensed indication of tocilizumab. In essence, the two populations greatly overlap; that is, the second population is a subgroup of the first. In practice, since treatment with MTX is not very effective in patients with systemic disease, MTX-IR is not considered important in the stratification of patients.

The structure of the model is developed to closely reflect real practice. The design allows the comparison of two clinical pathways for a cohort of patients with sJIA. The results of the model reflect the cost-effectiveness of the first treatment in either sequence. The additional treatment lines allow the assessment of all relevant costs and health related quality of life (HRQL) impairment resulting from unsuccessful care.

The treatment regimens presented in the economic evaluation, were derived after consultation with clinical experts and review of the comparator summary product characteristics.

The model health states reflect the condition of patients after having tried treatment for a period of 12 weeks. Each health state represents a change in patients' condition from baseline to week 12 as determined by changes in CHAQ score; a functional status measure used in TENDER. The time horizon is designed to capture the life of patients 2-18 years old.

The economic evaluation uses ACR response rates as indication of treatment efficacy. The economic model uses the above ACR data to allocate patients to different health states based on level of response. Patients that don't achieve response are assigned to the next treatment line where a similar process follows.

Discontinuation of treatment is assumed to be determined by a constant risk of withdrawal. The withdrawal risk is applied universally to all biologic treatments. A higher risk is used for methotrexate. Due to lack of data to determine elevated mortality risk dependent on the patient condition, the model assumes a constant mortality risk. The mortality risk is applied universally to all health states and across both model arms.

Due to lack of evidence on HRQL from the trials and the literature a mapping mechanism was employed. Roche acknowledges that the assumptions on the mapping of QALYs have no evidence basis. It is solely due to lack of other available data that this mapping method is preferred for the analysis in order

to derive QALYs for the economic model. Due to lack of evidence to vary HRQL of patients over time the model assumes patients sustain the applied utility at health state entry until transitioning to a different health state. This is supported from the clinical evidence.

A synthesis of HRG from the NHS reference costs and data from secondary sources is used for costing in the economic evaluation. Treatment cost is derived from the relevant SPCs and BNF61. Wastage is included in the calculations. Evidence for resource use according to health state membership is derived from clinical expert opinion and the literature.

Economic model results

The main drivers of the economic evaluation results are treatment cost and assumptions around the cost of inpatient stay. Treatment cost, is also influenced by the duration of the model; therefore, assumptions on the starting age of individuals and the model timeframe have an impact on cost-effectiveness results. The mean costs, QALYs and incremental results are presented in the tables below.

Table 2: Base-case cost-effectiveness results: comparison with methotrexate

	Strategy TCZ	Strategy MTX	Incremental
LY with ACR 30 response	6.4341	3.8270	2.6071
QALYs	5.4465	4.7161	0.7304
Treatment cost	£89,554.10	£40,529.21	£49,024.89
Health state cost	£52,161.99	£85,989.50	-£33,827.51
Total cost	£141,716.09	£126,518.71	£15,197.38
ICER (£/QALY)			£20,806.31

Table 3: Base-case cost-effectiveness results: comparison with anakinra

	Strategy TCZ	Strategy ANK	Incremental
LY with ACR 30 response	6.1284	4.3486	1.7797
QALYs	5.3223	4.8185	0.5038
Treatment cost	£82,619.87	£47,808.17	£34,811.71
Health state cost	£56,307.34	£79,421.62	-£23,114.28
Total cost	£138,927.21	£127,229.78	£11,697.43

ICER (£/QALY)			£23,219.02

Conclusions

To date there is currently no market authorised intervention for the treatment of systemic Juvenile idiopathic arthritis. Due to the dearth of evidence on the treatment comparators required a number of assumptions were required to complete data on costs and utilities for the economic model. The analysis demonstrates that tocilizumab is a cost-effective alternative to current treatments below a threshold of £25,000 per QALY.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

The RoActemra SPC is attached.

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

RoActemra (tocilizumab), immunosuppressant, interleukin inhibitors (RoActemra Summary of product characteristics, 2010)

1.2 What is the principal mechanism of action of the technology?

Tocilizumab binds specifically to both soluble and membrane-bound IL 6 receptors (sIL 6R and mIL 6R). Tocilizumab has been shown to inhibit sIL 6R and mIL 6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia (RoActemra Summary of product characteristics, 2010).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No. The regulatory application for tocilizumab use in systemic juvenile idiopathic arthritis (sJIA) was completed in October 2010. The approval date was 1 August 2011.

1.4 **Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).**

1.5 As part of the EU Centralised License, all healthcare professionals who are expected to prescribe/use Tocilizumab will be provided with educational materials on macrophage activation syndrome (MAS).

1.6 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Tocilizumab, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Tocilizumab is also indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tocilizumab can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

1.7 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

A two year extension data lock of the TENDER trial (De Benedetti et al. 2010) (which forms the basis of this submission) will be completed in July 2011, with the EU submission of these data in December 2011. These data will provide long term safety follow up and efficacy measures including:

- Further corticosteroid reduction/cessation
- Achievement of inactive disease/clinical remission
- Growth and development endpoints
- Improvement in physical function
- An analysis of radiographic progression

1.8 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Tocilizumab is available in the UK for use in rheumatoid arthritis as per the existing licence (RoActemra Summary of product characteristics, 2010). Therefore tocilizumab should be immediately available for use in sJIA following the licence in August 2011.

1.9 Does the technology have regulatory approval outside the UK? If so, please provide details.

Tocilizumab is licensed for use in sJIA in Japan and India

1.10 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

There are currently no ongoing health technology assessments in the UK for tocilizumab in sJIA.

[redacted]

For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4: Unit costs of technology being appraised

Pharmaceutical formulation	Solution for infusion
Acquisition cost (excluding VAT)	80mg - £102.40
Method of administration	Intravenous infusion over 1 hour
Doses	The recommended posology is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg.
Dosing frequency	Once every 2 weeks
Average length of a course of treatment	N/A – ongoing treatment
Average cost of a course of treatment	30kg patient = £7987.20 per year 25kg patients = £9984 per year
Anticipated average interval between courses of treatments	N/A – ongoing treatment
Anticipated number of repeat courses of treatments	N/A – ongoing treatment
Dose adjustments	Dose interruptions of tocilizumab for laboratory abnormalities are recommended in sJIA patients and are similar to what is outlined for RA patients in the Tocilizumab Summary of Product Characteristics

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

As recommended for other biological treatments, in RA and sJIA, patients should be screened for latent tuberculosis (TB) infection prior to starting Tocilizumab therapy. Patients with latent TB should be treated with standard

anti-mycobacterial therapy before initiating Tocilizumab. Treatment should not be initiated in patients with active, severe infection and it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of Tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents (tocilizumab Summary of Product Characteristics).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), neutrophil and platelet levels should be monitored at the second infusion and thereafter according to good clinical practice (tocilizumab Summary of Product Characteristics).

Assessment of lipid parameters should take place 4 to 8 weeks following the initiation of treatment (tocilizumab Summary of Product Characteristics).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

In line with the main Phase III trial (TENDER, De Benedetti et al, 2010) stable doses of methotrexate and NSAIDs may be continued. Corticosteroid doses may also be continued and tapered.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the Decision Problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Juvenile idiopathic arthritis (JIA) is a term that covers a heterogeneous group of syndromes in which the onset of inflammatory arthritis occurs before the age of 16 years and lasts for more than 6 weeks. JIA is characterised by persistent joint swelling, pain and limitation of movement. The cause of JIA is poorly understood, but may relate to genetic and environmental factors.

A classification system for JIA has been developed by the International League of Associations for Rheumatology (ILAR). There are seven categories of JIA: systemic, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified (types that do not correspond to any, or to more than one, category) (Petty et al., 2004). The clinical manifestations and severity of the different sub-types varies considerably. sJIA is a multiorgan disease characterised by arthritic symptoms, fever, transient rash, liver and spleen enlargement. It is distinct from other subtypes and is often resistant to treatment. The overall outcome of the disease is poor with a high risk of long-term functional impairment. Macrophage activation syndrome (MAS) is a severe, life threatening complication to sJIA which affects around 7% of children, which is associated with serious morbidity and sometimes death (Yokota et al., 2010).

Abnormal expression of proinflammatory cytokines including interleukin-6 (IL-6) is apparent in sJIA patients. Serum IL-6 and IL-6 receptor levels have shown correlation with disease activity and the extent and severity of joint involvement (Yokota et al., 2010).

2.2 How many patients are assumed to be eligible? How is this figure derived?

JIA is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1000 children per year, equivalent to 1000 children diagnosed per year. The prevalence is in the order of 1 per 1000 children, and about 10,000 children in the UK are affected. Approximately 10% of children diagnosed with JIA have systemic disease. Of these patients, those who have had an inadequate response to NSAIDs and corticosteroids and are 2 years of age and older will be eligible for Tocilizumab treatment.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There are currently no specific NICE guidance documents or national protocols for the treatment of sJIA. NICE issued guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis in March 2002 (NICE Technology appraisal 35, March 2002). Etanercept is licensed specifically in polyarticular JIA (Etanercept Summary of Product Characteristics, Jan 2011). Additionally, NICE reviews for abatacept and adalimumab in JIA were suspended in June 2008. The British Society for Paediatric and Adolescent Rheumatology (BSPAR) have issued standards of care for children and young people with juvenile idiopathic arthritis (2009) (BSPAR Clinical Affairs subcommittee; Standards of care for children and young people with juvenile idiopathic arthritis, 26/01/2009), as well as standard assessments for juvenile arthritis (BSPAR standard assessment for juvenile idiopathic arthritis. March 2002), however, these do not provide any treatment recommendations. This lack of definitive best practice in the treatment of JIA has been recognised in a recent review of standards of care in the disease (Sandborg et al., 2010).

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new

technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

At present there are no licensed therapies for the treatment of sJIA. The current clinical pathway of care for the pharmacological treatment of sJIA includes sequential NSAIDs, corticosteroids (intra-articular, intravenous or oral) and disease modifying anti-rheumatic drugs (DMARDs) – specifically methotrexate (NICE Technology appraisal 35, March 2002). Following failure of these treatments patients move onto biologic DMARDs including etanercept (NICE Technology appraisal 35, March 2002) which is licensed and recommended by NICE for polyarticular JIA and other anti- TNFα therapies and immunosuppressive drugs, which are also not licensed for use in sJIA (BSPAR Clinical Affairs subcommittee; Standards of care for children and young people with juvenile idiopathic arthritis, 26/01/2009). Due to the implication of IL-6 in the pathogenesis of sJIA, tocilizumab as an IL-6 receptor inhibitor, will offer a unique treatment choice for these patients after failure of NSAIDs and corticosteroids.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Tocilizumab will represent the first licensed drug for sJIA. Currently treatment for sJIA includes the off-licence use of DMARDs and biologic DMARDs including tocilizumab.

2.6 Please identify the main comparator(s) and justify their selection.

The comparator for population one: (*Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids*) is methotrexate. The current UK standard of care in sJIA patients who have had an inadequate response to NSAIDs and

corticosteroids, is off-label treatment with methotrexate. Tocilizumab (+/- methotrexate) in population 1 will be used in place of methotrexate alone.

The comparator for population two: (*Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate)* is TNF inhibitors (for example, etanercept and infliximab) and anakinra. The current UK standard of care in sJIA patients who have had an inadequate response to NSAIDs, corticosteroids and methotrexate, is off-label treatment with biologic DMARDs. Tocilizumab (+/- methotrexate) in population 2 will be used in place of other biologic DMARDs.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of tocilizumab. Appropriate therapy may be required in the event of infection, for example antibiotics and anti-virals (RoActemra Summary of product characteristics, 2010).

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Tocilizumab treatment should be initiated by healthcare professionals (e.g. paediatric consultant rheumatologists) experienced in the diagnosis and treatment of sJIA in a routine hospital setting.

Tocilizumab is dosed according to bodyweight and is administered as an intravenous infusion over 1 hour and dosing is repeated at 2 week intervals. Hence the main resource use will be administration of intravenous biologic drugs to paediatric patients normally in a children's hospital setting and the nursing/healthcare professional care associated with this (e.g. screening for

latent TB prior to treatment; monitoring patients for any possible hypersensitivity or anaphylactic reactions during the infusion; laboratory monitoring of ALT/AST/neutrophils/platelets at the time of the 2nd infusion and thereafter according to good clinical practice, assessment of lipid parameters 4 to 8 weeks following initiation of treatment).

2.9 Does the technology require additional infrastructure to be put in place?

No

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

None

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

n/a

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	1. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids. 2. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate.	Yes Yes	N/A N/A
Intervention	Tocilizumab with or without methotrexate	Yes	N/A
Comparator(s)	1. For children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids: ▪ **methotrexate**	This is addressed to some extent in the submission. The pivotal trial WA18221 (TENDER) (De Benedetti et al. 2010), was designed to compare tocilizumab versus placebo.	The pivotal trial WA18221 (TENDER) (De Benedetti et al. 2010) was a randomised, double-blind, placebo controlled trial. This compared tocilizumab + standard of care versus placebo + standard of care This design is the preferred choice for the demonstration of efficacy because there are no licensed therapies in sJIA and an actively controlled study would be difficult to compare due to ethical issues in this patient

	2. For children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate: ▪ **TNFα inhibitors (for example, etanercept and infliximab)** ▪ **anakinra**	This is addressed to some extent in the submission, but there is very limited appropriate comparison that can be made in the absence of any head-to-head studies involving tocilizumab, and limited RCTs involving other biologics in sJIA.	population. No studies currently exist directly comparing tocilizumab with TNFα inhibitors and anakinra, hence no/very limited appropriate comparisons can be made.
Outcomes	Outcomes to be considered include: ▪ disease activity ▪ physical function ▪ joint damage ▪ pain ▪ steroid sparing ▪ mortality ▪ adverse effects of treatment ▪ health-related quality of life	Yes, although joint damage as assessed by radiographic progression is not currently available from the 12 week data from TENDER (De Benedetti et al. 2010) due to the short timeframe. 'Fever' is also an outcome which will be addressed	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should reflect the chronic nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.	Yes	N/A
Subgroups to be considered		N/A	N/A
Special considerations, including issues related		N/A	

to equity or equality			

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A systematic search was carried out using the DataStar Web platform. Studies were indentified using relevant MeSH and EmTree terms and free text searches. There were no restrictions in place at this stage such as language or publication. The search strategy is detailed in Appendix 2. These searches were carried out on 15.03.2011.

Databases searched include:

- EMBASE – 1993 to date (EMYY)
- EMBASE alert – latest 8 weeks (EMBA)
- MEDLINE – 1993 to date (MEYY)
- MEDLINE in progress – latest 8 weeks (MEIP)
- BIOSIS previews – 1993 to date (BIYY)
- BIOSIS previews – last update (BIOX)

The following searches were also carried out:

- Cochrane library search including: Cochrane reviews, clinical trials, technology assessments and Cochrane groups
- Manual hand search of relevant review and trial reference lists
- Manual screen of internal databases
- Manual screening of relevant publication e-alerts for the period 16.03.2011-submission date
- Conference abstracts including (2005-2010):
    - American College of Rheumatology (ACR)
    - The European League Against Rheumatism (EULAR)

5.2 Study selection

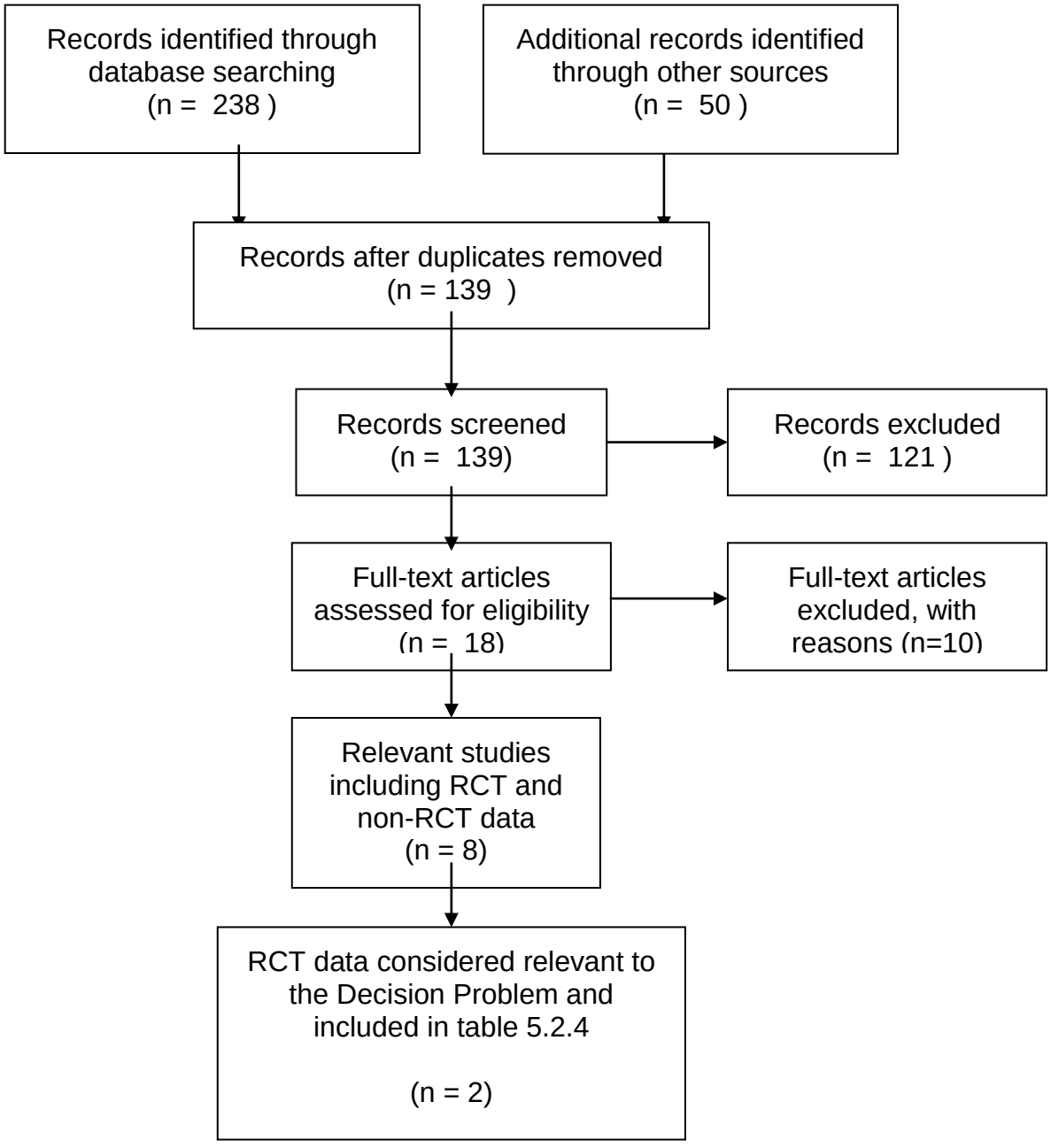
5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table 5: Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	**Population** Patients with systemic juvenile idiopathic arthritis (sJIA) or systemic juvenile rheumatoid arthritis **Interventions** Tocilizumab, interleukin-6 receptor inhibitor **Outcomes** Disease activity, physical function, joint damage, pain, steroid sparing, mortality, adverse effects of treatment, health-related quality of life, fever **Study design** No restrictions **Language restrictions** No restrictions
Exclusion criteria	No exclusion criteria were used at database level searches. The following exclusions were used during hand screening of results **Population** Patients with JIA subtypes other than systemic ie, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified **Interventions** Studies that do not include tocilizumab **Outcomes** None excluded **Study design** None excluded **Language restrictions** Languages other than English

Please note that a more detailed search of all relevant comparators in sJIA (not just focusing on tocilizumab as the intervention) is captured in Section 5.7 (Indirect comparison)

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The TENDER study (De Benedetti et al. 2010) was published in abstract form at the ACR and EULAR congresses in 2010. For the purposes of this document the ACR abstract will be used as the most recent publication, [redacted]

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 6: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
WA18221 TENDER (De Benedetti et al. 2010) Phase III	Tocilizumab 12 mg/kg < 30 kg or 8 mg/kg ≥ 30 kg every 2 weeks for 12 weeks (69% of patients received concomitant methotrexate)	Placebo (70% of patients received concomitant methotrexate)	112 patients with active sJIA and a previous inadequate response to NSAIDs and corticosteroids (ages 2-17) 37 received placebo 75 received tocilizumab	De Benedetti et al. Arthritis Rheum 2010;62(10 Supple 1):S596 (Presented at ACR congress 2010) [redacted]
MRA316JP (Yokota et al. 2008) Phase III	Tocilizumab 8mg/kg every 2 weeks 6 week open-label lead-in phase followed by a 12 week randomised double-blind, placebo controlled, withdrawal, phase III trial (Concomitant methotrexate therapy not permitted)	Placebo (Concomitant methotrexate therapy not permitted)	56 patients with active sJIA and a previous inadequate response to conventional treatments (ages 2-19) received tocilizumab, in the open-label lead-in phase 23 received placebo 20 received tocilizumab, in double-blind phase	Yokota et al. Lancet 2008;371:998-1006 [redacted]

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

There are no head-to-head studies which directly compare tocilizumab with the comparators in the 2 populations outlined in the Final scope.

However, the Phase III TENDER study (WA18221) (De Benedetti et al. 2010), as detailed below, has been identified as most relevant to the Decision Problem.

In summary, this was a pivotal randomised double-blind, placebo controlled trial which compared current standard of care + tocilizumab versus current standard of care + placebo. This standard of care backbone therapy design is the preferred choice for the demonstration of efficacy of tocilizumab, because there are no licensed therapies in sJIA. An actively controlled trial would be difficult to evaluate fairly because no other therapies have been appropriately investigated in sJIA, thus placebo (+ standard of care) is an acceptable comparator.

As stated in Section A (Decision Problem) of this submission, in the absence of head-to-head data, using the TENDER trial, Roche will attempt to compare tocilizumab with the 2 comparator groups in the 2 populations (namely methotrexate and TNFα inhibitors/anakinra) by reference to relevant sub-analyses results from TENDER and from an indirect comparison analysis (see Section 5.7).

Population:

Inclusion criteria for the TENDER (WA18221) study population included an inadequate response to previous treatment with NSAIDs and corticosteroids.

In TENDER, all patients had evidence of active disease at baseline which was at least 6 months after a definite diagnosis of sJIA. Inadequate response to previous treatment was determined by the treating physician's clinical assessment.

A total of 108/112 (96%) patients had been treated with oral corticosteroids (CS) (see below), 78/112 (67%) with MTX (see below) and 92/112 (82%) with biologic agents prior to study entry.

Oral corticosteroids at baseline: Four patients did not have a history of oral CS treatment recorded. All four patients had a disease duration of greater than 1 year. Three of the four patients had been treated with biologic therapy. Two of these patients were receiving NSAIDs and two were receiving MTX and continued to take these medications during study participation.

Oral MTX at baseline: Of the 112 patients enrolled in TENDER,

78 patients had background MTX use at baseline (36 of these entered the study on MTX that had been previously stopped then restarted, 42 of these patients were on their first course of MTX which was ongoing).

29 patients had no background MTX at baseline but did receive and stop MTX previously

5 patients had never received MTX, and could be considered MTX naive.

Thus, in TENDER, all children fulfilled the protocol requirements for active disease, had a definite diagnosis of sJIA for at least 6 months prior to baseline and had an inadequate response to previous treatments.

As highlighted above, due to the nature of the trial design and heterogeneity of the patients with respect to varying previous treatments at baseline (e.g. some patients received MTX previously and stopped, some patients received MTX that was stopped and subsequently restarted, some patients had ongoing MTX, and some patients who had never received MTX), TENDER was not designed to provide clear analysis directly comparing tocilizumab with the comparators specified in the 2 populations outlined in the Decision Problem.

However, it is apparent from TENDER and the general management of patients with sJIA, that the treatment pathway and choice of drugs such as NSAIDs, CSs, MTX or biologics is varied and subject to careful assessment by the treating physician which may not necessarily follow

a linear treatment pathway/algorithm per se (as was suggested by the Decision Problem).

As such, by viewing only the inclusion criteria, the TENDER population matches population 1: children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids.

However, on closer analysis of patients' treatment histories on joining TENDER, the study most accurately reflects population 2: children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate. This is because ~70% of patients (all with prior inadequate response to NSAIDs and corticosteroids) at baseline were still receiving methotrexate, yet had active disease (a further entry requirement for the study), thus could be considered to be failing on methotrexate alone.

Comparator:

The 2 populations in the Decision Problem have distinct comparators. Population 1 compares to methotrexate and population 2 compares to TNFα inhibitors or anakinra. Whilst the comparator in this study was placebo, 70% of the placebo patients (and tocilizumab arm) at baseline were also receiving methotrexate. Therefore a post-hoc analysis comparing the tocilizumab treatment arm to the 70% of patients in the placebo group receiving methotrexate will be carried out to address the comparator for population 1.

The TENDER trial does not specifically address the comparators for population 2, TNFα inhibitors or anakinra. However, in TENDER, a post hoc analysis was performed investigating efficacy outcomes in the tocilizumab group by prior biologic use, as presented at ACR in 2010 by the study authors. To date there have been no RCTs which directly compare

tocilizumab against these therapies as stated in the Decision Problem, hence an indirect comparison will be performed (section 5.7).

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

The MRA316JP study (Yokota et al. 2008) has been excluded from further discussion. This is due to the study design and population. The study was initiated with a 6 week open-label led-in phase. Patients with an ACR Pedi 30 response and CRP levels below 5mg/L were then randomised in a double-blind manner to receive either placebo or tocilizumab for a further 12 weeks, with rescue therapy available if necessary. This was followed by an open-label extension period for at least 48 weeks. Methotrexate treatment was not permitted throughout the duration of the study. The comparator was placebo, and as such this study does not address either population in the Decision Problem.

Additionally the MRA316 study was carried out in Japan and so the patient population may not be reflective of a European population.

Consequently, the long term extension studies (MRA317JP and MRA324JP) from the above will also be excluded.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be

provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

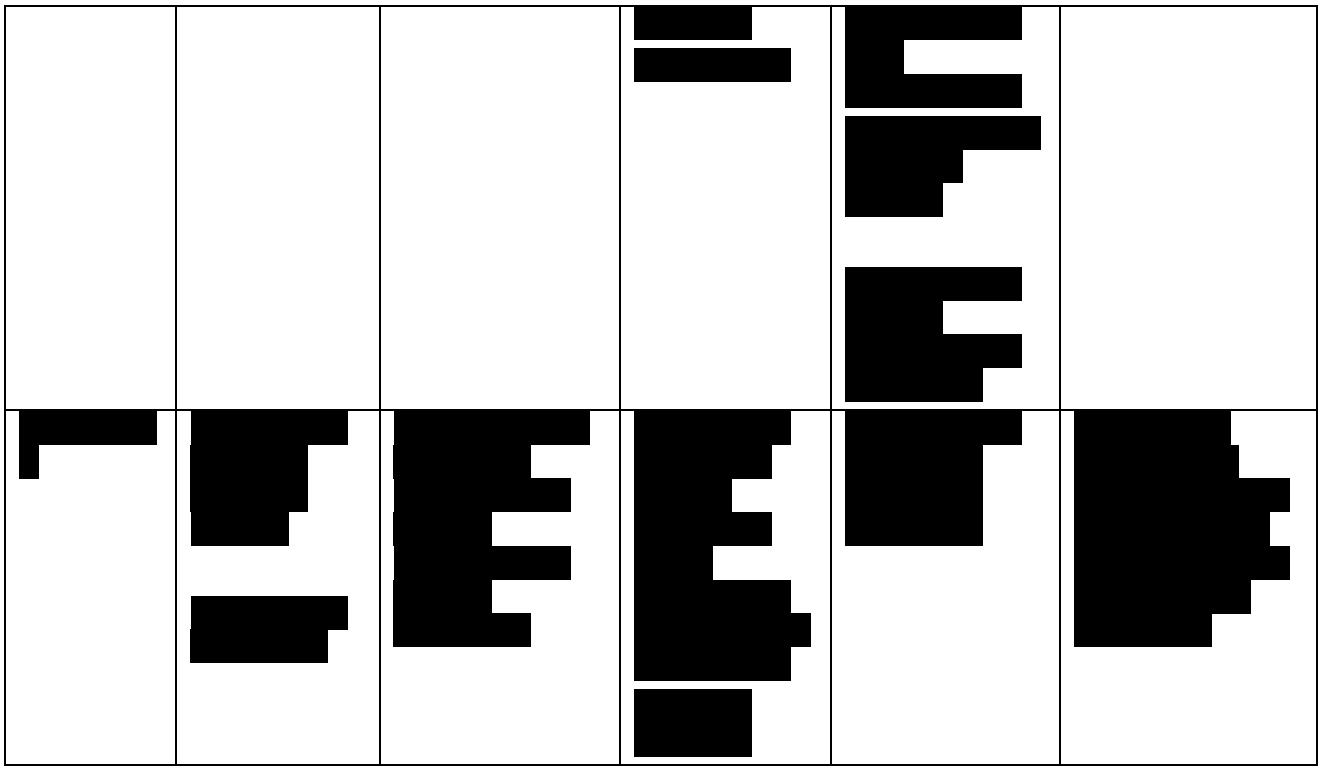
Table 7: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
[redacted]					
[redacted]					

The Results of the 1 year interim analysis from Part II of the TENDER study will be included in section 5.8. [redacted] No other non-RCTs will be included in the submission.

The table below outlines non-RCTs highlighted by the search with justification for their exclusion.

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for exclusion
LRO320 (Woo et al. 2005)	Tocilizumab 2, 4, or 8 mg/kg every 2 weeks followed for 4, 6 and 8 weeks respectively 6 patients per cohort	18 patients with active sJIA for ≤3 months despite receiving <0.2mg/kg/day corticosteroid (ages 2-17) (12/18 of patients received concomitant methotrexate)	ACR Pedi 30, 50 and 70 Systemic features were also recorded	Woo et al. Arthritis-Res-Ther. 2005; 7(6):1281-1288	This was a single arm, single dose study. 12/18 patients received a dose below 8mg/kg, which does not reflect the Decision Problem
MRA011JP	Tocilizumab 2mg/kg every 2 weeks x3 If disease flare occurred 4mg/kg every 2 weeks x3 If further disease flare occurred 8mg/kg every 2 weeks x3	11 patients with active sJIA with a previous inadequate response to NSAIDs, corticosteroids, cyclosporine, methotrexate or any combination of these (ages 3-18)	ACR Pedi 30, 50 and 70	Yokota et al. Arthritis-Rheum. 2005; 52(3):818-25	This is a phase II dose ranging study with a Japanese population. 8/11 of the patients received a dose below 8mg/kg and so are not equivalent to the Decision Problem
Inaba et al.	Tocilizumab 8mg/kg every 2 weeks with mean follow up 56 months	7 sJIA patients with active disease (ages 3-10)	Growth abnormalities in the large joints (shoulders, elbows, hips, knees and ankles)	Inaba et al. Ann Rheum Dis (2011). doi: 10.1136/ard. 2010.145359	This was an open-label, single arm study with small patient numbers
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Please note the non-RCT studies outlined in Table 7 are single arm studies only. As such they do not provide comparator data to address the Decision Problem and will not be included in the submission. These studies provide supplementary, background data as the populations are similar and provide in some instances extended data or outcomes not provided in the RCTs.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Much of the background and results information from the TENDER study has been taken from the Clinical Study Report [redacted]

5.3.1.1 TENDER (WA18221): Introduction

Background and rationale

sJIA is a subset of juvenile idiopathic arthritis (JIA) that is characterized by the presence of arthritis, intermittent fever, and rash. In the new International League Against Rheumatism (ILAR) (Petty, 2001) nomenclature this subset, sJIA, formerly called Still's disease or systemic onset Juvenile Rheumatoid Arthritis (JRA), comprises between 10 and 20 percent of all cases of JIA (Hashkes et al., 2005 and Yokota et al., 2007). This subset of JIA may be especially challenging to diagnose and treat, as a diagnosis of arthritis may not be present at the onset of the disease (necessary for the definitive diagnosis of sJIA), systemic disease manifestations may be difficult to exclude from other differential diagnoses, and complications of the disease need to be closely monitored.

Both sexes are equally affected with a peak incidence between the ages of 1 to 5 years old (Woo, 2006 and Behrens et al., 2008). Although patients with this illness are distributed throughout childhood, the definition of sJIA requires disease onset before the age of 16 years (Petty, 2001). Children with sJIA may present with a variety of articular and extraarticular features. Arthralgias and arthritis constitute the majority of articular complaints in sJIA patients and may involve any number of joints including the knees, wrists, and ankles as well as the temporal-mandibular joints. Fever is the most frequent extraarticular manifestation and is required for the diagnosis of sJIA.

Associated manifestations of sJIA include cardiac disease (including pericarditis, myocarditis, and endocarditis), symptomatic pleuritis, hepatosplenomegaly, splenomegaly, lymphadenopathy, fever and rash. There

is no specific diagnostic laboratory test for sJIA, but characteristic laboratory findings may include anemia, leucocytosis, and thrombocytosis. Growth development is impaired in active sJIA and macrophage activation syndrome (MAS) is the most frequent life-threatening complication of sJIA. sJIA is associated with significant morbidity as a consequence of the disease itself in addition to the effects of current therapies (Yokota, 2010).

The treatment of patients with sJIA remains a challenge as the therapeutic modalities available for sJIA are limited and represents an area of unmet medical need. NSAIDs alone may be effective for some children with mild disease. Moderate to high dose of corticosteroids are often used with temporary responses. Tapering or weaning patients from corticosteroids may be extremely difficult, exposing patients to the long-term side effects of corticosteroids (osteoporosis, growth retardation)(Ravelli A and Martini A, 2009).

Second line agents such as methotrexate may be considered, but their efficacy in sJIA appear to be very limited. Anti-tumor necrosis factor (TNFα) therapy offers limited benefit in sJIA patients (Yokota, 2010). Given the lack of efficacious and licensed therapeutic approaches, unremitting sJIA is the most severe form of JIA.

The pathogenesis of sJIA is not clear. However, the circulating levels of pro-inflammatory cytokines and soluble receptors, especially IL-6 and soluble Interleukin-6 Receptor (sIL-6R), but not TNFα or IL-1β, were shown to play a significant role as inflammatory mediators. An IL-6/sIL-6R complex in serum is able to associate with gp130; mediating intracellular signaling to induce prominent febrile events, acute phase reactants (APRs), and hematopoietic responses. Serum IL-6 and sIL-6R levels in children with sJIA were correlated with disease activity and with the extent and severity of joint involvement. As a result, IL-6 was deemed the most important cytokine in sJIA(De Benedetti et

al., 2001 and 2004 and 2005, Prieur et al. 1996, Keul et al., 1998, Yilmaz et al., 2001).

RoActemra (tocilizumab) is a recombinant humanized anti-human monoclonal antibody of the IgG1 sub-class directed against the IL-6 receptor (IL-6R). It inhibits the function of IL-6 (RoActemra Summary of Product Characteristics 2011) tocilizumab (RoActemra, 8 mg/kg IV) was approved in the EU for the treatment of patients with RA on 16th of January 2009. An anti-IL-6R monoclonal antibody such as tocilizumab clearly may have an important role to play, not only in relieving the systemic features of the disease, but also in preventing the progression of joint damage.

Study WA18221 (TENDER, De Benedetti et al. 2010) is an ongoing three-part, 5 year, Phase III study with Part I consisting of a 12-week randomized, double blind, placebo-controlled, parallel, 2-group study to evaluate the efficacy and safety of tocilizumab in patients with active sJIA. The results of Part I (12-week study) are reported in this submission, in addition to some early data from the 1 year interim analysis of Part II of the study.

Objectives

Part I: Primary Objectives

The primary objective of the TENDER study was to evaluate the efficacy (JIA ACR 30 + absence of fever) of tocilizumab versus placebo in combination with stable ongoing therapy at 12 weeks, in sJIA patients with persistent disease activity and an inadequate response to NSAIDs and systemic corticosteroids. Also, to evaluate the short term safety of tocilizumab versus placebo with regard to adverse events (AEs) and laboratory assessments in this population.

Part I: Secondary Objectives

Secondary objectives of the randomized 12 week phase of the TENDER study were:

1. To assess the efficacy (JIA ACR 50/70/90) of tocilizumab versus placebo in combination with stable ongoing therapy, in sJIA patients with persistent activity and an inadequate response to NSAIDs and corticosteroids;

2. To assess the efficacy of treatment with tocilizumab to permit concomitant corticosteroids reduction;

3. To explore the immunogenicity and pharmacodynamic (PD) properties of tocilizumab in this patient population;

4. To investigate, by a population analysis approach, the pharmacokinetics (PK) of tocilizumab in sJIA patients.

Part I: Exploratory Objectives

Finally, a number of exploratory objectives were considered in the TENDER study population, these were:

1. To assess the effect of treatment on quality of life (QoL), using Childhood Health Assessment Questionnaire (CHQ-PF50)

2. To examine the pharmacodynamics of tocilizumab action on serum IL-6, sIL-6R, C-reactive protein (CRP) levels, Erythrocyte Sedimentation Rate (ESR) and Serum Amyloid A (SAA), as well as other pertinent markers of IL-6R signaling blockade (eg, ferritin, hemoglobin [Hgb], reticulocyte count, serum hepcidin, lipid

subfractions, urinary ß-2 microglobulin, markers of bone turnover and markers of IGF-1 action);

3. To assess the development of anti-tocilizumab antibodies (HAHA);

4. To explore the relationship between tocilizumab exposure and efficacy and safety parameters;

5. To assess the effect of treatment on other less frequent systemic features of sJIA at Week 12 compared to Baseline.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Overview

The TENDER study is an ongoing, three-part, 5 year Phase III study with Part I consisting of a 12-week randomized, double blind, placebo-controlled, parallel, 2-group study to evaluate the efficacy and safety of tocilizumab in patients with active sJIA. Part II is a 92-week single group open-label extension to examine the long-term use of tocilizumab on:

- Safety (including immunogenicity);
- Efficacy (including unblinded assessment of joint counts and objective measurements and high sensitivity C-Reactive Protein [hsCRP], fever, and Hgb);
- The ability to reduce corticosteroids dosage to clinically significant levels.

Part III of the study is a three year single group open-label continuation of the study to assess the efficacy and long-term safety of tocilizumab in patients with active sJIA.

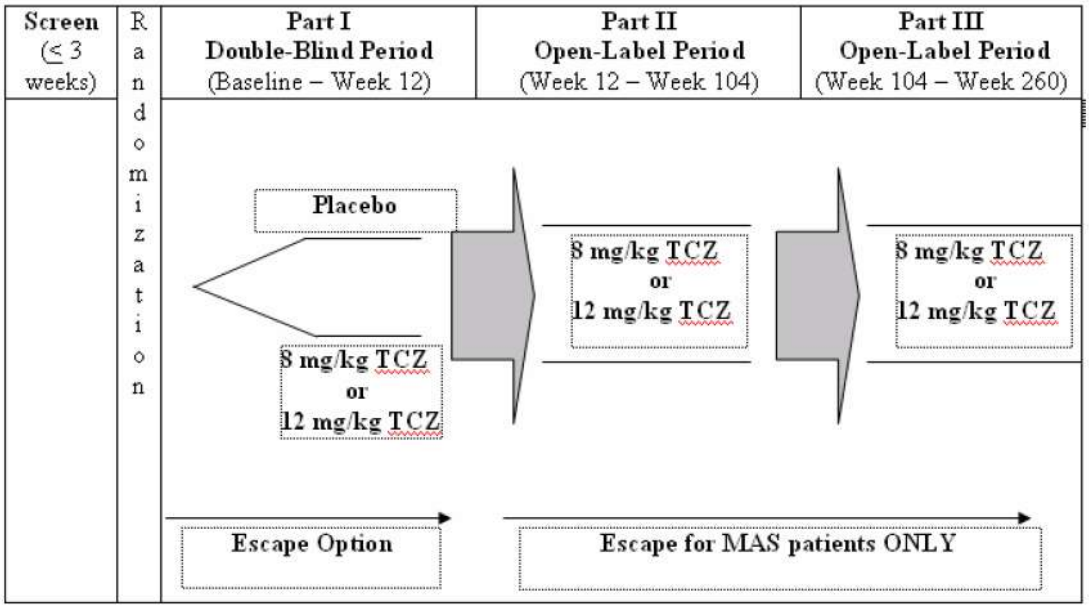
Study Design

The overall design of the study is depicted in the figure below. Following screening, eligible patients were randomized into Part I of the study and received either tocilizumab or placebo by IV infusion in a 2:1 ratio respectively. In the tocilizumab group, patients < 30 kgs received a dose of 12 mg/kg and patients ≥ 30 kgs received a dose of 8 mg/kg every two weeks for six doses. In Part I of the study, the dose assigned at saseline could not be adjusted for any changes (gain or loss) in body weight (BW) (< 30 kgs to/from ≥ 30 kgs).

Patients could have their corticosteroids tapered following corticosteroids Guidelines at Week 6 and/or Week 8 if they acquired a JIA American College of Rheumatology (ACR) 70 response, had a normal ESR, and absence of fever *(defined as no temperature measurement ≥ 37.5° C in the preceding seven days)* prior to taper. Corticosteroids reduction was not permitted at Week 10.

Patients who completed the first six scheduled visits in Part I of the study had the option to enter into the Part II of the study where all patients would receive open-label tocilizumab. Patients who entered escape during Part I and who were benefiting from receiving tocilizumab were also able to enter Part II. Throughout the study, patients were assessed a minimum of every two weeks for clinical efficacy and safety. Patients who received prohibited therapy were withdrawn from study medication. The end of the study will occur when the last participating patient completes the last scheduled visit of Part III.

Figure 1: Overview of Study Design



The proposed parallel group study design provided a robust assessment of both efficacy and safety of tocilizumab. It also offered an opportunity to acquire control data without exposing patients to undue risk of flares of systemic symptoms including arthritis. In addition, the study design permitted the early tapering of corticosteroids beginning at Week 6. The JIA ACR30 response is a well established endpoint for JIA studies. There were no pivotal studies published for sJIA alone at the time of designing the TENDER study, thus no established endpoint specifically for sJIA. Given that a key concern for sJIA is the systemic nature of the disease, the primary endpoint included “the absence of fever”.

A 12-week double blinded treatment period with the assessment of the primary endpoint (proportion of patients achieving a JIA ACR 30 response and absence of fever) at Week 12 was sufficient to characterize the primary efficacy endpoint based on the rapid response noted in previous studies. (Chugai 56 patient study ref).

The parallel group design with inclusion of a placebo group was practical and ethical. The trial had a maximum placebo duration of 12 weeks during the double-blind period, including a provision for escape in patients who met the

criteria for escape. The parallel group design was preferred over the withdrawal design for a number of reasons. Due to the prolonged half-life of tocilizumab, this design was felt to provide more rigorous safety and efficacy data comparisons between the placebo and tocilizumab groups than a randomized withdrawal trial. In addition, it was felt that the safety concerns could be more easily evaluated in this subset of sJIA patients with treatment-resistant disease by the addition of study drug onto stable existing therapy, rather than in a withdrawal design.

The use of escape was felt to offer a more cautious safety net for those children with inadequate control of either systemic or arthritis symptoms than a withdrawal trial design would provide. This design permitted the tapering of corticosteroids beginning at Week 6. The effects of tocilizumab on baseline corticosteroids dose was felt to be important and clinically meaningful. These children with persistent disease frequently have complications related to corticosteroids use including growth abnormalities, osteoporosis, cataracts, and diabetes. Moreover, there is a potential for severe disease flare (and possibly MAS) to occur in patients who have sJIA therapy withdrawn.

[redacted]

[redacted]

[redacted]

[redacted]

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility

criteria for when there is more than one RCT. Highlight any differences between the trials.

The target population for TENDER trial included patients with sJIA (from age 2 onward at screening) as classified by the ILAR Criteria, and symptoms of persistent disease for at least 6 months with inadequate response to NSAIDs and systemic corticosteroids as a requirement. The study enrolled a total of 112 patients unequally randomized (tocilizumab: placebo = 2:1), which provided 75 tocilizumab-treated patients and 37 placebo-treated patients.

The 112 patients were enrolled at 43 centers in 17 countries including Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Germany, United Kingdom, Greece, Italy, Mexico, Netherlands, Norway, Poland, Slovakia, Spain, and United States.

The first patient was screened on 9 May 2008, the first patient was randomized on 21 May 2008, and the date of the last patient who completed Week 12 was on 2 September 2009.

Other major features of the study population included the following:

- Children age 2 up to and including age 17 with active sJIA;
- Documented sJIA disease duration of ≥ 6 months;
- ≥ 5 active joints or ≥ 2 active joints with fever > 38° C for any 5 out of 14 days during screening;
- Patients taking NSAIDs, corticosteroids, or methotrexate were permitted but had to enter the study on a stable dose of these medications;
- Patients had to have active arthritis at screening;
- Patient had to have persistent disease activity for at least 6 months with inadequate response to NSAIDs and corticosteroids due to toxicity or lack of efficacy. Under no circumstances were randomized patients in this study permitted to be re-randomized to this study again for a

second course of treatment. Under selected circumstances permission could be granted by Roche for one re-screen of a patient who had not been randomized. Patients were not eligible for enrollment in the study if there was a history of any other auto-immune, rheumatic disease, or overlap syndrome other than sJIA.

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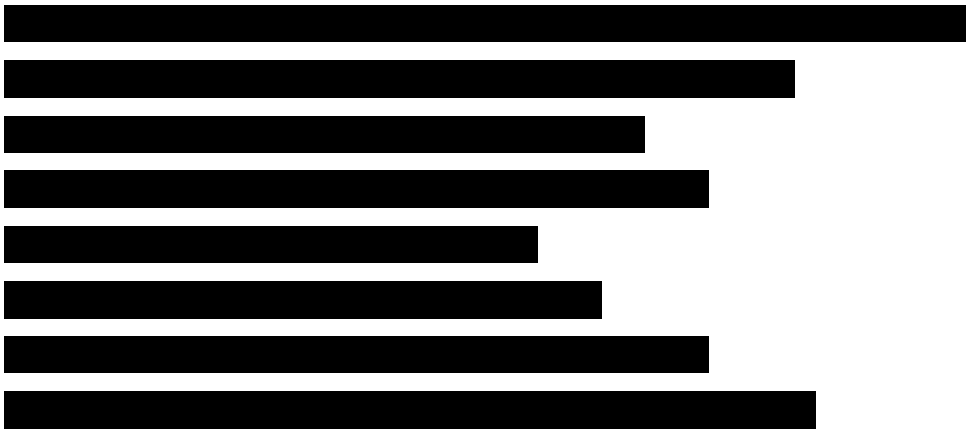

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The baseline characteristics of patients in the TENDER study are presented below. Patients were well balanced and similar between the two groups with respect to most characteristics, apart from bodyweight and age, which varied between the 8mg/kg and 12mg/kg tocilizumab groups, as would be expected.

[redacted]

Outcomes

5.3.20 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.22 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Two key sub-analyses were a post-hoc background methotrexate analysis, investigating whether the use of methotrexate in combination with tocilizumab affected the efficacy outcomes for patients with respect to JIA ACR 30/50/70 and 90 scores.

Also, a post-hoc analysis presented at ACR in 2010 investigating prior use of biologic therapy, and its effect on tocilizumab in patients with sJIA.

An exploratory analysis to investigate the possible influence of patient characteristics at baseline on the probability of achieving the primary endpoint and JIA ACR30/50/70/90 endpoints at Week 12 was performed using logistic regression. The characteristics tested were; weight, disease duration, background oral corticosteroid use, background methotrexate use, sex, age, ethnicity, region, and CRP.

A step-wise model fitting approach was performed and this showed that the main analysis method with adjustment for the stratification factors used at randomization was sufficient and adjustment was not required for any other covariate. In addition, the treatment by baseline characteristic interactions were tested for the primary endpoint. It should be noted that some of the interaction and subgroup analyses performed in this exploratory analysis involve small numbers of patients and, therefore, are not statistically powered or adjusted for multiplicity.

In exploratory analyses the efficacy endpoints were investigated according to patient baseline characteristics and the subgroups included:

• Sex (male, female);
• Age (2-5 years, 6-12 years, 13-18 years);
• Ethnicity (Hispanic, Non-Hispanic);
• Region (Europe, North America, South America, Rest of World);
• Number of joints with active arthritis (0 - < 10, 10 - < 30, ≥ 30);
• Number of joints with limitation of movement (0 - < 10, 10 - < 30, ≥ 30);
• ESR (0 - < 40 mm/hr, 40 - < 80 mm/hr, ≥ 80 mm/hr);
• BW (< 30 kgs, ≥ 30 kgs);
• Duration of disease (< 4 years, ≥ 4 years);
• Background Oral corticosteroids dose (< 0.3 mg/kg/day, ≥ 0.3 mg/kg/day);
• Background methotrexate use (yes, no);
• Previous Anakinra use (yes, no);
• Fever status in last 7/14 days (present, absent/free);
• Rash status in last 14 days (present, free).

Participant flow

5.3.23 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The disposition of patients within the TENDER study is outlined below. Of the 112 patients enrolled into the study, 37 were randomized to placebo, 37 to tocilizumab 8 mg/kg, and 38 to tocilizumab 12 mg/kg. A total of 21 patients received escape therapy with 20 placebo patients (9 treated with open-label tocilizumab 8 mg/kg and 11 treated with open-label tocilizumab 12 mg/kg) and one tocilizumab 8 mg/kg patient. All but three patients completed all 12 weeks of Part I of the study. The majority of escaping placebo patients (13 or 65.0%)

escaped early at the Week 2 visit. The main reasons for escape were fever for ≥ 3 consecutive days or JIA ACR30 Flare.

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5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

Critical Appraisal of the TENDER study

- Was the method used to generate random allocations adequate?

Yes, the patient randomization numbers generated by Roche or its designee were given to the investigator over the telephone at the time of individual patient enrollment. The investigator or designee entered a pre-defined patient number in the electronic case report form (eCRF) and entered the corresponding patient randomization number for allocation to the treatment groups in the appropriate place on each patient's eCRF. The patient randomization numbers were allocated sequentially in the order in which the patients were enrolled according to the specification document agreed with the external randomization company for allocation to the treatment groups.

- Was the allocation adequately concealed?

Yes, this was a blinded study, with the sponsor, investigators, and patients/parents unaware of the treatment assignment of each patient at randomization into Part I. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication or independent pharmacological analysis of biological samples was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment. Unblinding was performed by means of the interactive voice response system (IVRS). Written documentation followed any verbal request to unblind a patient's treatment.

As per regulatory reporting requirement, Roche unblinded the identity of the study medication for all suspected unexpected SAEs that were considered by the investigator to be related to study drug as per safety reference documents; Investigators Brochure, Core Data Sheet, and Summary of Product Characteristics (SmPC).

Any unblinding for independent pharmacological analysis of biological samples including any PK, PD data, or ongoing safety monitoring by a DSMB were performed according to procedures in place to ensure integrity of the data. All other individuals directly involved in this study at Roche remained blinded until after the database lock of study Part I.

- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

Yes, the demographic characteristics at baseline in the placebo group and the all tocilizumab group were similar.

In each treatment group, patients were evenly split between male and female patients and they were predominately Caucasian. As expected as a result of the two different doses < or ≥ body weight (BW) 30 kgs, the mean age, BW, height, and body surface area (BSA) were higher in the tocilizumab 8 mg/kg

group in comparison to the tocilizumab 12 mg/kg group. However, these characteristics were similar between the all tocilizumab group and the placebo group.

Overall the disease characteristics between the placebo and the tocilizumab group were comparable. The six components of the JIA ACR core set at Baseline were similar but with a slightly higher disease burden in the tocilizumab patients. There were higher proportions of patients with fever (within 7 and 14 days prior to Baseline) and sJIA rash (within 14 days prior to Baseline) in the placebo group compared with the all tocilizumab group. The mean and median CRP was lower in the placebo group compared with the all tocilizumab group but three patients in the tocilizumab groups had very high CRPs that distorted the mean/median values. In addition, this acute phase reactant is not used in the JIA ACR core set.

As expected as a result of the two different tocilizumab dosing groups, the number of previous biologics and DMARDs were higher in the tocilizumab 8 mg/kg group compared to the tocilizumab 12 mg/kg group.

The stratification factors used in randomization; BW, disease duration, background corticosteroids dose, and background methotrexate use had approximately 50% of patients in each of the binary categories for both the placebo and all tocilizumab group. There were however a high proportion of patients with background methotrexate use at Baseline.

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

This was a blinded study, with the sponsor, investigators, and patients/parents or care providers unaware of the treatment assignment of each patient at randomization into Part I. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication or independent pharmacological analysis of biological samples was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment, therefore would have been unlikely to bias the results.

- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

There were a small number of withdrawals which are discussed in detail in section 5.3.8

- Is there any evidence to suggest that the authors measured more outcomes than they reported?

No, the outcomes reported here are taken directly from the clinical study report. All intended outcomes are discussed in detail in the methods section. Not all of these outcomes have necessarily been reported at the end of 12 week randomised stage (Part I) however, more analyses will be conducted during the later open label stages.

- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Yes. the TENDER study was analysed using the intent-to-treat (ITT) population. This was an appropriate population to use in analysing the study, and the results of the primary endpoint were confirmed by a second analysis using the per-protocol population, and only including completers of therapy for

both of the arms. No patients were excluded from the study at the end of week 12 (the randomized phase). Missing data was handled using the last observation carried forwards method.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

Please see section 9.3 for more information

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 8: Quality assessment results for RCTs

Trial no. (acronym)	**Trial 1 - TENDER**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, no missing data at end of 12 week randomised phase.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination	

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

Results of TENDER

A top-line summary of the efficacy data from the TENDER Study is presented in this section is as follows:

• The TENDER study met its primary endpoint of a JIA ACR30 response and absence of fever at Week 12 with 85.3% of the tocilizumab patients responding in contrast to 24.3% of the placebo patients, a statistically significant difference ($p<0.0001$);
• Tocilizumab patients had a greater chance of achieving JIA ACR30/50/70/90 responses at Week 12 in comparison with the placebo patients. The differences in proportions of each JIA ACR response level were statistically significantly different ($p<0.0001$);
• Significantly positive effects were shown on joint inflammation, systemic effects, laboratory endpoints, and physical function in tocilizumab-treated patients compared to patients treated with placebo ($p<0.05$);
• The PK between the two treatment groups of tocilizumab, 8 mg/kg and 12 mg/kg, revealed similar serum concentrations over time and similar mean posthoc estimated PK exposures (AUC2weeks, Cmin, and Cmax) at Week 12 indicating that the weight-based dosing regimen was appropriate for this patient population.

• The changes of inflammatory markers (CRP, ESR, and SAA) and markers of the tocilizumab mechanism of action (IL-6 and sIL-6R) were similar between both treatment groups (12mg/kg and 8mg/kg tocilizumab) confirming that the BW based dosing regimen was appropriate for this patient population. All efficacy endpoints were analyzed using the ITT population. All patients who qualified for escape were termed non-responders for the purpose of the primary efficacy evaluation and in other categorical endpoints. The patients who continued in the study but entered escape were treated with open-label tocilizumab treatment in addition to standard of care, which could include parenteral corticosteroids, methotrexate, NSAIDs, cyclosporine, or increased doses of oral corticosteroids above the Baseline dose.

Primary Endpoint Analysis

Sixty-four tocilizumab patients and nine placebo patients met the primary endpoint of a JIA ACR30 response and absence of fever at Week 12. Of the tocilizumab patients, 85.3% responded in contrast to 24.3% of the placebo patients demonstrating a statistically significant difference (p<0.0001) (in the Table below.

Table 9: Summary and Analysis of the Percentage of Patients with a JIA ACR30 Response and Absence of Fever at Week 12 – All tocilizumab vs Placebo (ITT Population)

	Placebo (n=37)	Tocilizumab, all patients (n=75)
Number of Responders (%) (95% confidence intervals)	9 (24.3%) (10.5; 38.1)	64 (85.3%) (77.3; 93.3)
Weighted difference vs. Placebo (95% confidence intervals) p-value		61.5 (44.9; 78.1) **<0.0001**

Responders are patients who had a JIA ACR30 response at Week 12 and absence of fever (temperatures <37.5C) in the 7 days preceding the Week 12 assessment day. Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at Baseline.
Treatment comparisons are vs. Placebo.

Looking at response in the individual tocilizumab groups, and vs. placebo, twenty-eight patients treated with tocilizumab 8 mg/kg and 36 tocilizumab 12 mg/kg patients met the primary endpoint, the proportions were contrasting with 75.7% and 94.7% of patients in the respective groups (in the Table below). This study was not powered to detect differences between the tocilizumab 8 mg/kg and tocilizumab 12 mg/kg doses for any efficacy endpoint and thus, no statistical testing was performed on the comparison between the two doses of tocilizumab.

Table 10: Summary and Analysis of the Percentage of Patients with a JIA ACR30 Response and Absence of Fever at Week 12 (ITT Population)

	Placebo (n=37)	Tocilizumab, 8mg/kg (n=37)	Tocilizumab, 12mg/kg (n=38)
Number of Responders (%) (95% confidence intervals)	9 (24.3%) (10.5; 38.1)	28 (75.7%) (61.9; 89.5)	26 (94.7%) (87.6; 100.0)

Responders are patients who had a JIA ACR30 response at Week 12 and absence of fever (temperatures <37.5C) in the 7 days preceding the Week 12 assessment day. Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at Baseline.
Treatment comparisons are vs. Placebo.

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Secondary Endpoint analysis

Of the secondary endpoints specified in the study design, one of the most relevant to clinical practice and the Decision Problem was the proportion of patients achieving a JIA ACR 30, 50, 70, 90 or better response at week 12. The results of this secondary endpoint presented in the Table below, and in Figure below.

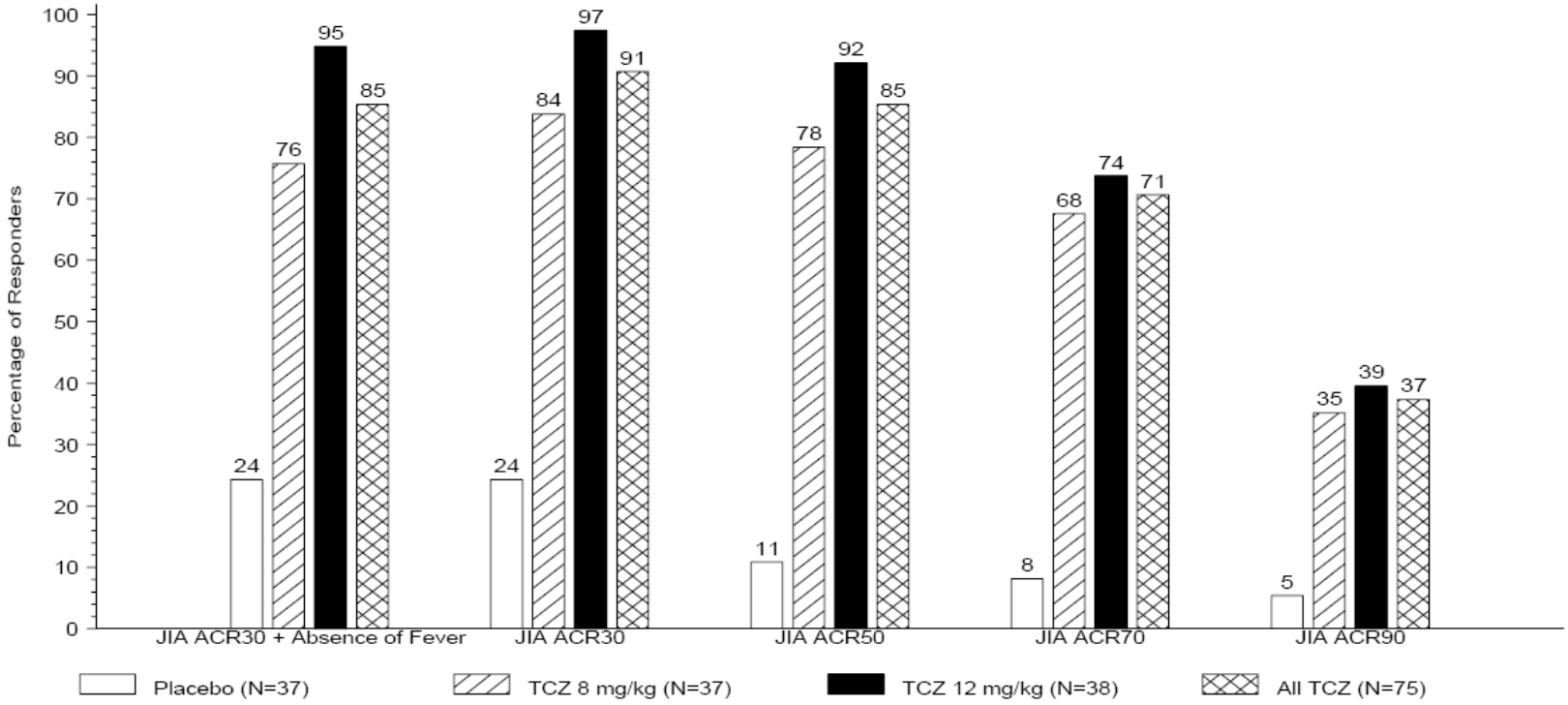
The tocilizumab treated group had a significantly higher proportion of patients achieving JIA ACR30/50/70/90 responses at Week 12 in comparison with the placebo group. The difference in proportions for each JIA ACR response level was statistically significantly different ($p<0.0001$), as shown in Table below. The proportion of responders was higher in the tocilizumab 12 mg/kg patients in comparison to the tocilizumab 8 mg/kg patients.

Table 11: Summary and Analysis of the Percentage of Patients with JIA ACR30/50/70/90 Responses at Week 12 (ITT Population)

Response	Placebo (n=37)	Tocilizumab, 8mg/kg (n=37)	Tocilizumab, 12mg/kg (n=38)	Tocilizumab, all patients (n=75)	Weighted diff. All tocilizumab patients vs. Placebo
JIA ACR 30					
n	9	31	37	68	**66.8**
(%)	(24.3%)	(83.8%)	(97.4%)	(90.7%)	
(95% CI)	(10.5; 38.1)	(71.9; 95.7)	(92.3; 100.0)	(84.1; 97.3)	(50.7; 92.9)
p-value					**<0.0001**
JIA ACR 50					
n	4	29	35	64	**74.0**
(%)	(10.8%)	(78.4%)	(92.1%)	(85.3%)	
(95% CI)	(0.8; 20.8)	(65.1; 91.6)	(83.5; 100.0)	(77.3; 93.3)	(57.9; 90.1)
p-value					**<0.0001**
JIA ACR 70					
n	3	25	28	53	**62.9**
(%)	(8.1%)	(67.6%)	(73.7%)	(70.7%)	
(95% CI)	(0.0; 16.9)	(52.5; 82.7)	(59.7; 87.7)	(60.4; 81.0)	(46.1; 79.7)
p-value					**<0.0001**
JIA ACR 90					
n	2	13	15	28	**33.3**
(%)	(5.4%)	(35.1%)	(39.5%)	(37.3%)	
(95% CI)	(0.0; 12.7)	(19.8; 50.5)	(23.9; 55.0)	(26.4; 48.3)	(16.8; 49.7)
p-value					**<0.0001**

Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.
Cochran-Mantel-Haenszel analysis adjusted for the randomization stratification factors applied at Baseline.
Treatment comparisons are vs. Placebo.
CI = Confidence Interval.

Figure 2: Bar Chart of the Proportion of JIA ACR30 Responders with Absence of Fever and JIA ACR30/50/70/90 Responders at Week 12 (ITT Population)



Responders are patients who had a JIA ACR30 response and absence of fever or JIA ACR30/50/70/90 responses at Week 12.
Absence of fever (temperatures <37.5C) in the 7 days preceding the Week 12 assessment day.
Patients who withdrew, received escape medication, or for whom the endpoint could not be determined are classified as non-responders.
LOCF rule applied to missing JIA ACR core set components at Week 12.

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Summary of all secondary Endpoint data

All 22 secondary endpoints were statistically significant (p<0.05) in favour of tocilizumab, and are briefly summarized below:

JIA ACR Responses:

• The proportion of patients with JIA ACR30 response at Week 12. tocilizumab = 90.7% vs placebo = 24.3% (p<0.0001);
• The proportion of patients with JIA ACR50 response at Week 12. tocilizumab = 85.3% vs placebo = 10.8% (p<0.0001);
• The proportion of patients with JIA ACR70 response at Week 12. tocilizumab = 70.7% vs placebo = 8.1% (p<0.0001);
• The proportion of patients with JIA ACR90 response at Week 12. tocilizumab = 37.3% vs placebo = 5.4% (p<0.0001).

JIA ACR Core Components:

• The percentage change from Baseline in number of joints with active arthritis at Week 12. tocilizumab adjusted mean = -70.6 vs placebo adjusted mean = -37.2 (p=0.0012);
• The percentage change from Baseline in number of joints with limitation of movement at Week 12. tocilizumab adjusted mean = -51.6 vs placebo adjusted mean = -22.5 (p=0.0192);
• The percentage change from Baseline in physician's global assessment of disease activity VAS at Week 12. tocilizumab adjusted mean = -69.6 vs placebo adjusted mean = -41.1 (p=0.0005);

• The percentage change from Baseline in parent/patient's global assessment of overall well-being VAS at Week 12. tocilizumab adjusted mean = -65.8 vs placebo adjusted mean = -1.4 (p<0.0001);
• The percentage change from Baseline in CHAQ-DI score at Week 12. tocilizumab adjusted mean = -45.6 vs placebo adjusted mean = -10.3 (p=0.0148);
• The proportion of patients with a minimally important improvement in the CHAQ-DI by Week 12. tocilizumab = 77.3% vs placebo = 18.9% (p<0.0001);
• The percentage change from Baseline in ESR Week 12. tocilizumab adjusted mean = -88.2 vs placebo adjusted mean = 33.6 (p<0.0001);
• The proportion of patients receiving oral corticosteroids with JIA ACR70 response at Week 6 or Week 8 who reduced their oral corticosteroids dose by at least 20% without subsequent JIA ACR30 flare or occurrence of systemic symptoms at Week 12. tocilizumab = 24.3% vs placebo = 3.2% (p=0.0280);
• The proportion of patients with JIA ACR30 response at Week 12 adjusted for oral corticosteroids dose modifications (p<0.0001).

Systemic Features:

• The proportion of patients with fever due to sJIA at Baseline who are free of fever at Week 12. tocilizumab = 85.4% vs placebo = 20.8% (p<0.0001);
• The proportion of patients with rash characteristic of sJIA at Baseline who are free of rash by Week 12. tocilizumab = 63.6% vs placebo = 11.1% (p=0.0008);
• The change from Baseline in the pain VAS at Week 12. tocilizumab adjusted mean = -41.0 vs placebo adjusted mean = -1.1 (p<0.0001).

Laboratory Parameters:

• The proportion of patients with an elevated CRP at Baseline who have normal CRP at Week 12. tocilizumab = 98.6% vs placebo = 5.9% (p<0.0001);
• The proportion of patients with anemia at Baseline who have normal Hgb at Week 12. tocilizumab = 80.0% vs placebo = 6.9% (p<0.0001);
• The proportion of patients with anemia at Baseline who increase Hgb by ≥ 10 gm/dL at Week 6. tocilizumab = 88.0% vs placebo = 3.4% (p<0.0001);
• The proportion of patients with anemia at Baseline who increase Hgb by ≥ 10 gm/dL at Week 12. tocilizumab = 88.0% vs placebo = 3.4% (p<0.0001);
• The proportion of patients with thrombocytosis at Baseline who have a normal platelet count at Week 12. tocilizumab = 90.4% vs placebo = 3.8% (p<0.0001).
• The proportion of patients with leucocytosis at Baseline who have a normal total WBC count at Week 12. tocilizumab = 75.0% vs placebo = 9.5% (p<0.0001).

Statistical testing was not performed between the two tocilizumab groups but descriptive statisticorticosteroids showed that patients treated with tocilizumab 12 mg/kg had better improvement, with higher proportions of responders and greater changes from Baseline in endpoints, than patients treated with tocilizumab 8 mg/kg. Although in the case of the JIA ACR response endpoints, the differences diminished at the harder to attain endpoints. The analyses of the efficacy endpoints for those patients who escaped demonstrated an improvement in responses following the change from placebo treatment to open-label tocilizumab.

Sub Analyses Relevant to the Decision Problem

A sub-analysis conducted in the TENDER study that is particularly relevant to the Decision Problem concerned the concomitant use of methotrexate in both arms, and showed that the effect of concomitant methotrexate on the JIA ACR responses observed in patients was limited. As outlined below, at Week 12

the JIA ACR 30/50/70/90 responses were similar whether patients were receiving MTX at Baseline or not, in both the tocilizumab and placebo arms.

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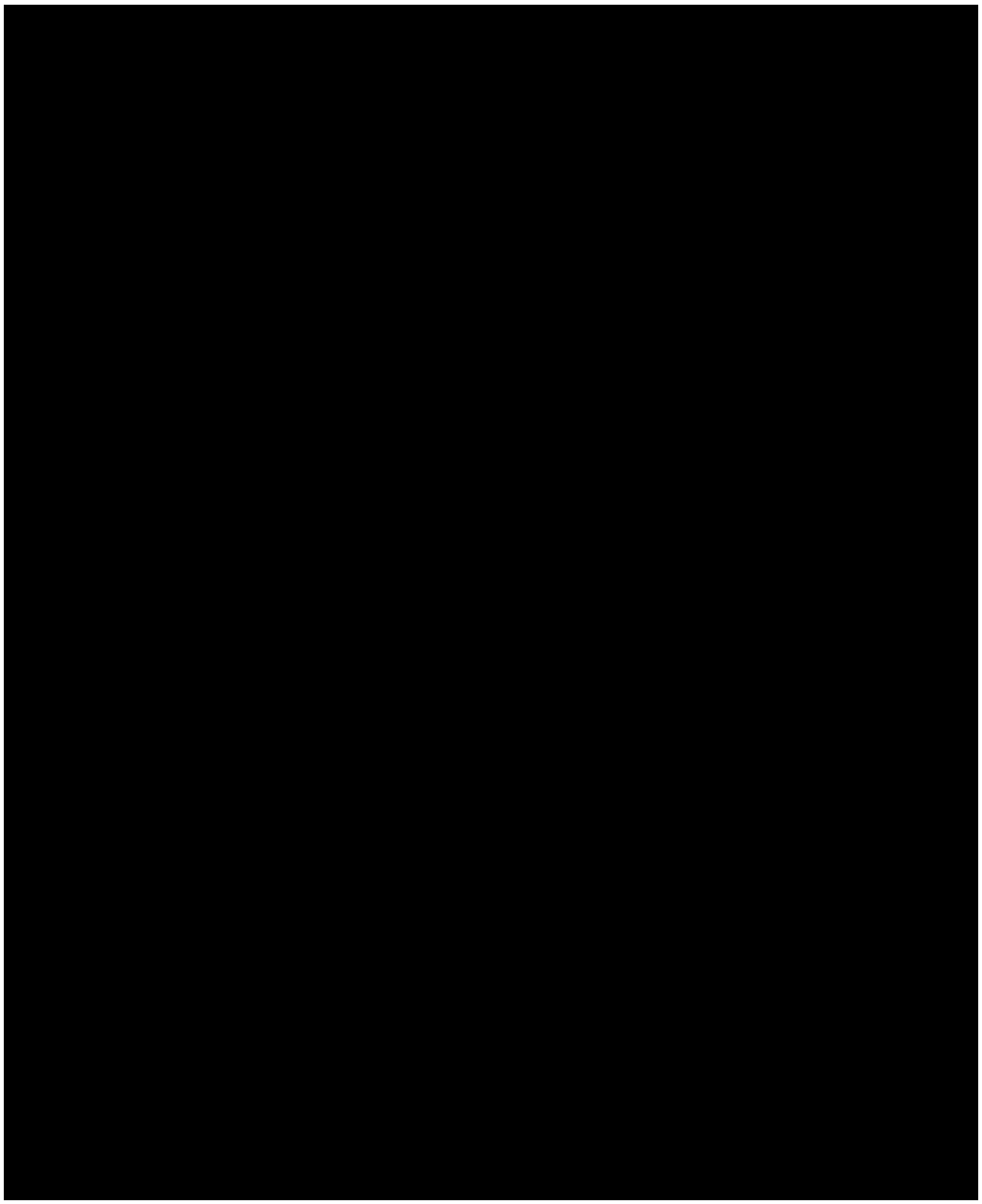


In conclusion, MTX as add-on therapy did not have a significant impact on the JIA ACR responses observed in the tocilizumab arms in the TENDER study.

Post-hoc Analysis - prior Biologic use

A further post-hoc analysis of the 12 week TENDER data was conducted, looking at prior Biologic therapy use, and was presented as a oral presentation at the American College of Rheumatology meeting in Atlanta, GA, USA, November 2010.

Figure 4: TENDER Post hoc: 12-week Efficacy Outcomes in the TCZ Group by Prior anakinra use

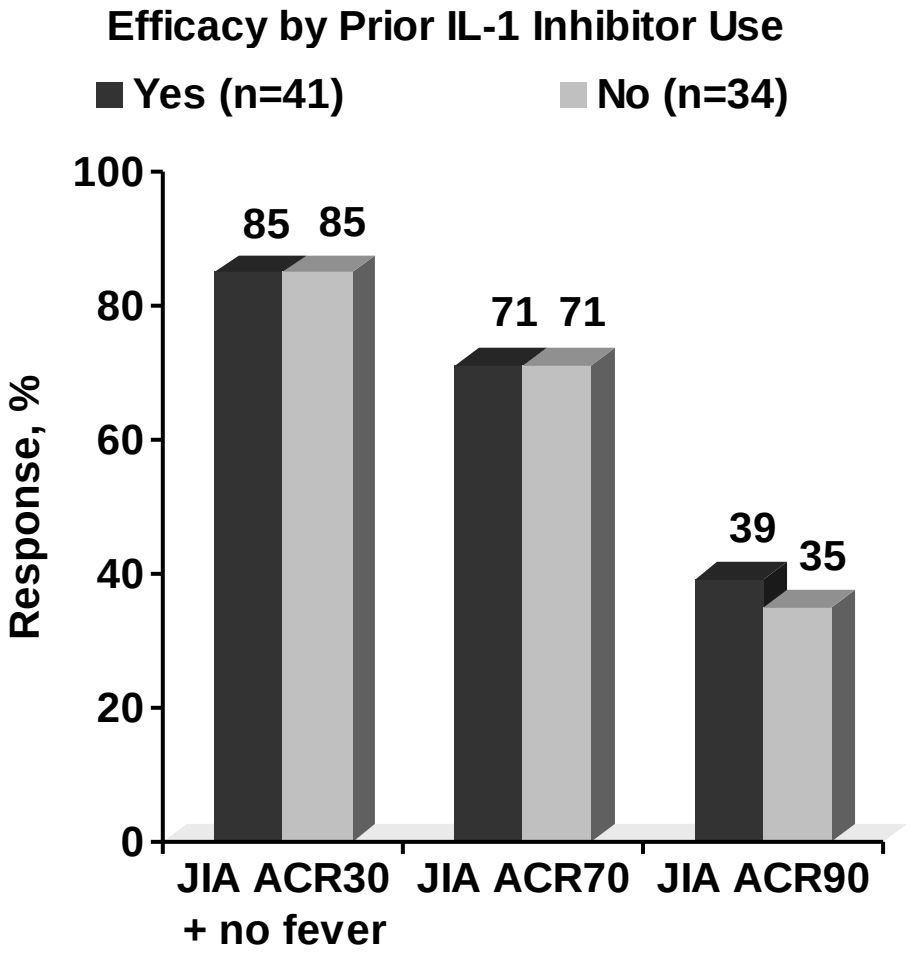
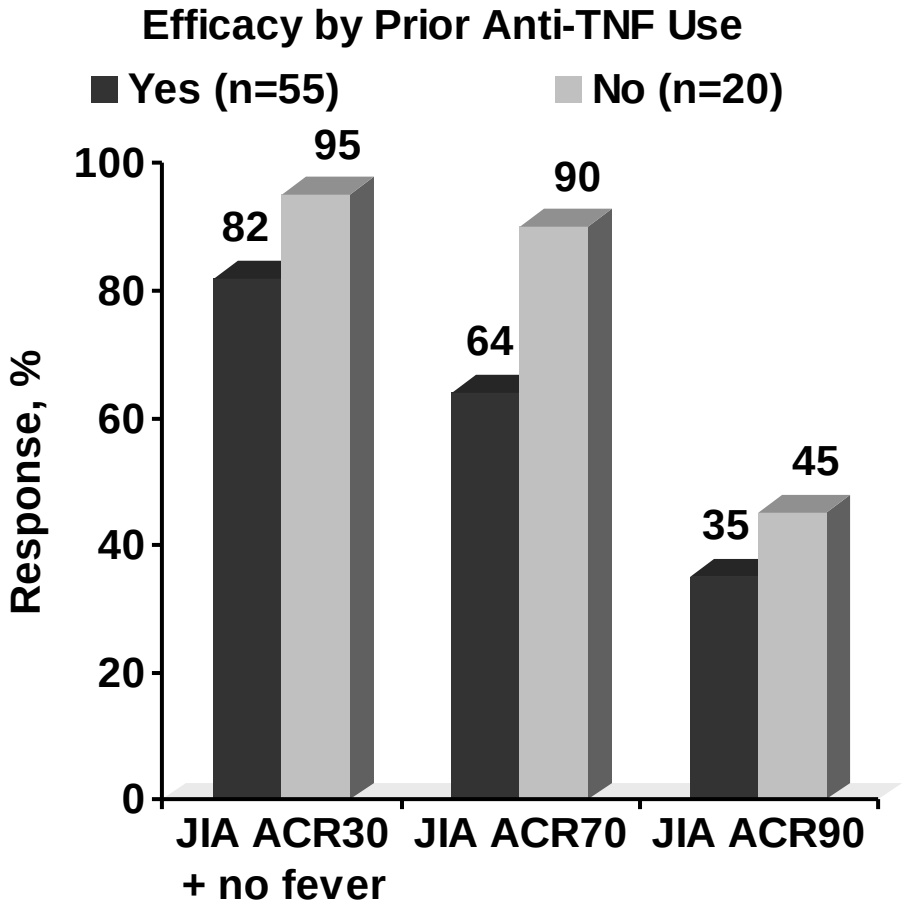


Figure 5: TENDER Post hoc: 12-week Efficacy Outcomes in the TCZ Group by prior Anti-TNFα Use



These results show that tocilizumab is highly effective in treating sJIA, as shown by the clinically relevant JIA ACR responses above, irrespective of previous anakinra use (see Figure above). However, there does appear to be some trendwise difference when prior anti-TNFα use is taken into account, with a numerical reduction in response to tocilizumab in patients receiving prior anti-TNFαs (see Figure above). The statistical significance of these findings was not explored via prospective analyses.

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

Not applicable. Graphical data used to support relevant sections in Question 5.5.1

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.

- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Units of measurement, with hazard ratio and 95% confidnence intervals where available, have been used in reporting all outcomes in section 5.5, along with the number of particpants in the respective arms.

All data is taken from the 12 week randomised phase of the TENDER study, except where longer term data is specified.

A number of the endpoints could be considered clinically significant, based on the nature of sJIA and severity of symptoms, including potential for morbity and mortality. Also, given the burden of some of the current treatments upon patients, such as systemtic corticosteroid use. Finally, the use of established JIA ACR endpoints based on core clinical component scores means that any Improvements seen with tocilizumab use should be expected to related directly to a clinical improvement in patients health.

Relevant sub-and-exploratory analyses have been included in seciton 5.5, with prospective vs post-hoc status specified.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT

results are heterogeneous, try to provide an explanation for the heterogeneity.

- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No meta-analysis is conducted in this submission.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

There is no need for meta-analyses in this submission due to the lack of evidence available. This analysis is based on 3 studies, each of them comparing one of the treatments of interest to placebo. Given data on each comparison are only available in one study, there is no need to calculate a pooled estimate and results of each individual study will be used as such in the analysis.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

This point is not applicable to the analysis presented in this submission.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

A systematic review was conducted to identify relevant clinical data on the analysis comparators

The following resources were used to identify relevant studies:
Searches of the following bibliographic databases were performed using the datastar platform unless otherwise stated:

- MEDLINE; 1949 – 28/03/2011
- EMBASE; 1974 – 28/03/2011
- Medline (R) In Process; (latest 8 weeks) ~ January 2011 – 28/03/2011
- The Cochrane Library via Cochrane; the search was conducted on the 28/03/2011.

Evidence identification was with a focus on the disease area of sJIA with no restrictions on population age or disease severity. The objective of the search was to identify randomised controlled trials with ACR response rates for

adalimumab, anakinra, etanercept and infliximab. Finally, articles were included in the review if the abstract was in the English language.

A summary of the inclusion criteria for the search were as follows:

- **Study design** to include RCTs
- **Disease area** to include all sJIA
- **Population** (no restrictions by age or disease severity)
- **Treatments** to include adalimumab, anakinra, etanercept and infliximab

The search strategy is included in Appendix 4, free-text and Medical Subject Headings were included, where appropriate. The search terms focused on population, study type and treatments as follows:

- Population terms included;
    - juvenile arthritis
    - rheumatoid arthritis
    - systemic arthritis
- Study type terms included all possibilities to retrieve studies reporting randomised controlled trials only.
- The following treatments of interest were included as terms in the search using both brand names and generic names; etanercept, anakinra, adalimumab and infliximab.

The search strategy contained restrictions by publication type such that certain publication types e.g. letters and editorials were not retrieved. The searches were limited to humans. Identified citations were transferred and managed in a Refman12 file.

Study selection:
Included citations were indicated by “Inc”. Excluded citations were indicated by “Exc” and the reason for exclusion provided as follows:

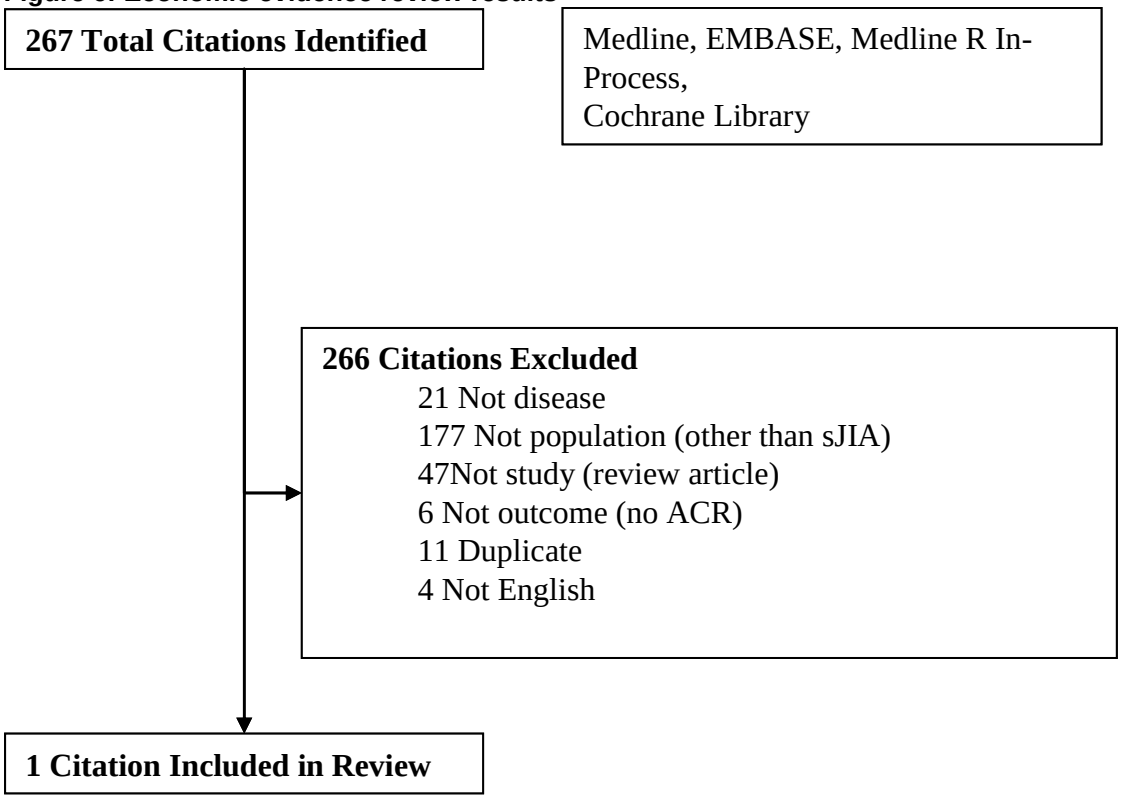
- “Not study” not an RCT

- "Not population" not sJIA population
- "Not outcome" no ACR response rates reported
- "Not disease" other than arthritis
- "Duplicate" duplicate reference in the database
- "Not English" language of publication is other than English

Studies Reviewed

The search on bibliographic databases was performed on 28/03/2011. The search retrieved 267 citations that were compiled in a single electronic file, comprising all records retrieved via the database searches, by exporting records from the respective platforms and importing them into a Reference Manager database file. Of the 267 citations only one, recently published, study was selected [Quartier et al. 2010].

Figure 6: Economic evidence review results



Due to the dearth of clinical evidence in systemic JIA, Roche augmented the dataset with evidence from a rapid review performed with objective to identify all pivotal trials in juvenile arthritis regardless of subtype.

Clinical experts [PC Westhovens R 02/03/2011, Wright S 16/03/2011], stressed the differences between a systemic JIA population and other subtypes and advised against comparing evidence from different populations.

The broader population review was not conducted in a systematic way given that evidence from it would not fall within the scope of this submission. Furthermore, and based on clinical expert opinion, evidence from the rapid review would be used only as an alternative to data found in the systematic review in the absence of other data. The results of non-systemic JIA population trials would require adjustment for the differences in populations.

The methods of the rapid review are presented below. The inclusion criteria differ from the systematic search above. The criteria are broader to include all JIA population subtypes and biologic treatments. A hand search technique was applied whereby recently published systematic reviews were consulted. All relevant references were identified and retrieved and their reference lists also searched for further studies.

The following systematic reviews were searched:

- Shenoi et al. [2010]
- Gartlehner et al. [2008]
- Hashkes et al. [2005]

The disease area was juvenile arthritis with no restrictions on subtypes or population age or severity. Studies with any of the biologic interventions (anakinra, adalimumab, abatacept, infliximab, etanercept) were retrieved and considered appropriate. References that were not of full articles (for example abstracts only) were not included in the review.

A summary of the inclusion criteria for the review is presented below:

- **Study types** to include all reporting clinical data, RCTs, uncontrolled studies, prospective, retrospective studies
- **Disease area** to include all juvenile arthritis
- **Interventions** to include the following biologics: anakinra, adalimumab, abatacept, infliximab and etanercept

The review identified one study for each of the biologic treatments containing evidence on ACR response rates. With the addition of the identified study for anakinra [Quartier et al. 2010] the dataset for the biologics includes the following studies:

- Abatacept: Ruperto et al. 2008
- Adalimumab: Lovell et al. 2008
- Anakinra: Quartier et al. 2010
- Etanercept: Lovell et al. 2000
- Infliximab: Ruperto et al. 2007

The key characteristics of these studies are summarised in section 5.7.2. and 5.7.3.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The identification and selection of relevant RCTs has been highlighted in the above section. The following is a summary of the methodology, quality assessment and presentation of the results from the identified RCTs.

Table 12: Comparative summary of methodology of the RCTs

Trial no. (acronym)	**Trial 1 Ruperto et al. 2007 (Infliximab +MTX)**	**Trial 2 Lovell D et al., 2000 (Etanercept)**	**Trial 3 Lovell D et al., 2008 (Adalimumab)**	**Trial 4 Quartier P et al., 2010 (Anakinra)**	**Trial 5 Ruperto N et al., 2008 (Abatacept)**
Location	North America South America Europe	North America	North America Europe	North America Europe	North America South America Europe
Design	Phase III, International, multicentre, randomised, placebo-controlled, double-blind study.	Phase III, multicentre, randomised, placebo controlled, double blind study.	Phase III, multicentre, randomised, placebo-controlled double-blind, stratified, medication withdrawal study.	Phase III, multicentre, randomised, placebo-controlled, double-blind,	Phase III, multi-centre, randomised, placebo-controlled, double-blind, withdrawal trial.
Duration of study	14 week Randomised phase 44 week active treatment extension	3 month open label lead in Four month ranomised phase	16 week open label lead in phase 32 week double blind withdrawal phase	1 month double-blind phase 11 month open label phase.	4 month open label lead in period 6 month double blind phase
Method of randomisation	Not stated	A blocked randomization scheme with stratification accordingto study center and number of active joints («2 vs. >2) at the end of month 3	Blinded, stratified, 1:1 randomisation conducted by sponsor.	Computer generated randomisation, stratified by centre.	Computer generated randomisation based on sequential number allocation on enrollment
Method of blinding (care	Double Blind	Double blind	Double blind; study co-ordinator,	Double blind; investigators, other	Double blind

provider, patient and outcome assessor)			assessor, patients and parents.	assessors, patients and their parents were blinded.	
Intervention(s) (n =) and comparator(s) (n =)	n=62 (59 included in ITT) n=60 (58 included in ITT)	n=69 (Open Label phase) n=25 (etanercept) n=26 (placebo	n=191 enrolled in lead in phase (85 receiving MTX, 86 no MTX). **+MTX arm:** n=37 placebo n=38 adalimumab **-MTX arm:** n=28 placebo n=30 adalimumab	n=12 patients randomised to anakinra n=12 patients randomised to placebo.	n=190 open label lead in. 170 completed. n=60 randomised to abatacept n=62 randomised to placebo
Primary outcomes (including scoring methods and timings of assessments)	Proportion of patients meeting ACR Pedi 30 criteria based on JIA core set parameters	Number of patients with a disease flare at the end of 4 month ranomised phase	Percentage of patients not receiving MTX who had a disease flare during weeks 16-48.	Efficacy after one months treatment with anakinra based on ACR Pedi 30 score, absense of fever and normalisation of CRP and ESR values.	Time to flare of arthritis
Secondary outcomes (including scoring methods and timings of assessments)	ACR Pedi 50 and 70	N/A	ACR Pedi 30,50. 70 and 90 responses throughout the study	ACR Pedi 30,50. 70 and 90 responses throughout the study	proportion of patients who has disease flare changes in the 6 ACR variables

Duration of follow-up	52 weeks	7 months (end of randomised phase)	104 weeks.	1 year.	6 months (end of randomised phase)

Table 13: Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Trial 1 **Ruperto et al. 2007 (Infliximab +MTX)**	Patients aged 4 to 18 years Diagnosis of JRA Suboptimal response to MTX after => 3 months treatment ≥ 5 active joints No active systemic symptoms	Active Uveitis Serious infection including tuberculosis Malignancy Prior treatment with any TNFα inhibitor Disease modifying drugs other than MTX and intraarticular corticosteroids in the 4 weeks prior
Trial 2 **Lovell D et al., 2000** **(Etanercept)**	Patients 4 to 17 years of age active polyarticular juvenile rheumatoid arthritis During first 6 months of disease, some patients had pauciarticular, polyarticular or systemic systems. Active disease despite treatment with NSAIDs ir MTX at least 10mg/m^2	Not specified.
Trial 3 **Lovell D et al., 2008** **(Adalimumab)**	Patients 4 to 17 years of age active polyarticular juvenile rheumatoid arthritis in at least 5 swollen jounts, 3 with limitation of movement Patients no responding adequately to NSAIDs. Methotrexate naïve or unsuitable (due to AEs or lack of response)	Clincally significant deviations in hematologic, hepatic or renal indicators Ongoing infection or recent infection requiring hospitalisation or I.V. antibiotics Recently received live or attenuated vaccines. Previous treatment with other biologic agents or recently treated with IVIg or cytotoxic drugs, DMARDs other than methotrexate or investigational drugs, Corticosteroids via Intraarticular, I.M or IV route.
Trial 4 **Quartier P et al., 2010**	Patients aged 2 to 20 years Diagnosis of sJIA More than 6 months disease duration	Previous treatment with an IL-1 inhibitor Any condition contr-indicative to treatment I.V or intraarticular steroids

(Anakinra)	Active Systemic disease – disease related fever or CRP > 20mg/l or first hour ESR > 20. 3 of 6 core ACR compoments scores indicative of active disease.	Immunosuppressive drugs and DMARDs within the month before initiation
Trial 5 **Ruperto N et al., 2008** **(Abatacept)**	Patients aged 6 to 17 years At least 5 active joints Active disease Inadequate response, or intolerance to at least one DMARD including biological agents such as etanercept, infliximab and adalimumab.	Active uveitis Major concurrent medical condition pregnant or lactating Live vaccines within 3 months of study and throughout
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Characteristics of participants in the RCTs

Table 14: Trial 1, Ruperto et al., 2007 Infliximab + MTX; Baseline demographic and clinical characteristics of the JRA patients*

	Treatment randomization	
	Placebo/infliximab 6 mg/kg + MTX (n = 62)	Infliximab 3 mg/kg + MTX (n = 60)
Age at study entry, years	11.1 ± 4.0	11.3 ± 4.0
Disease duration, years	3.6 ± 3.4	4.2 ± 3.6
Age subgroup, no. (%)		
≥4 years, <8 years	14 (22.6)	13 (21.7)
≥8 years, <12 years	18 (29.0)	14 (23.3)
≥12 years, <18 years	30 (48.4)	33 (55.0)
Female, no. (%)	49 (79.0)	53 (88.3)
White, no. (%)	53 (88.3)	50 (86.2)
JRA onset subtype, no. (%)		
Systemic onset	8 (13.1)	11 (18.3)
Pauciarticular onset with polyarticular course	15 (24.6)	13 (21.7)
Polyarticular onset	38 (62.3)	36 (60)
Physician's global assessment of disease activity, 10-cm VAS	4.9 ± 1.9	5.2 ± 2.0
Parent's assessment of overall well-being, 10-cm VAS	4.1 ± 2.2	4.5 ± 2.2
C-HAQ score, 0–3 scale	1.2 ± 0.7	1.2 ± 0.7
No. of joints with active arthritis	18.5 ± 11.5	19.5 ± 12.3
No. of joints with limited range of motion	17.6 ± 12.0	18.4 ± 13.6
Erythrocyte sedimentation rate, mm/hour	32.0 ± 26.9	33.0 ± 25.0
Rheumatoid factor positive, no. (%)	14 (23.7)	13 (21.7)
Oral corticosteroid treatment, no. (%)	21 (34.4)	26 (43.3)
Prior DMARD treatment other than MTX, no. (%)	19 (31.1)	24 (40.0)
Weekly MTX dosage, mg/m^2 (range 10–15)	12.2 ± 2.2	12.2 ± 2.4
Duration of MTX therapy, no. (%)		
>6 months	37 (60.7)	35 (58.3)
≤6 months	8 (13.1)	9 (15.0)
Unknown†	16 (26.2)	16 (26.7)

* All patients had involvement of multiple joints. Except where indicated otherwise, values are the mean ± SD. JRA = juvenile rheumatoid arthritis; MTX = methotrexate; VAS = visual analog scale; C-HAQ = childhood Health Assessment Questionnaire; DMARD = disease-modifying antirheumatic drug.
† Exact duration of therapy unknown, but known to be ≥3 months per study inclusion criteria.

Table 15: Trial 2, Lovell et al., 2000 Etanercept. Baseline demographic and clinical characteristics of patients

CHARACTERISTIC	OPEN-LABEL STUDY (N=69)	DOUBLE-BLIND STUDY		
		TOTAL (N=51)	PLACEBO (N=26)	ETANERCEPT (N=25)
Mean age — yr	10.5	10.6	12.2	8.9
Age group — no. (%)				
4–8 yr	25 (36)	18 (35)	5 (19)	13 (52)
9–12 yr	14 (20)	9 (18)	4 (15)	5 (20)
13–17 yr	30 (43)	24 (47)	17 (65)	7 (28)
Sex — no. (%)				
Female	43 (62)	34 (67)	15 (58)	19 (76)
Male	26 (38)	17 (33)	11 (42)	6 (24)
Race or ethnic group — no. (%)				
White	52 (75)	37 (73)	23 (88)	14 (56)
Black	6 (9)	4 (8)	1 (4)	3 (12)
Hispanic	9 (13)	8 (16)	2 (8)	6 (24)
Other	2 (3)	2 (4)	0	2 (8)
Type of onset of JRA — no. (%)				
Pauciarticular	7 (10)	3 (6)	1 (4)	2 (8)
Polyarticular	40 (58)	31 (61)	17 (65)	14 (56)
Systemic	22 (32)	17 (33)	8 (31)	9 (36)
Mean duration of JRA — yr	5.9	5.8	6.4	5.3
Positive for rheumatoid factor — no. (%)	15 (22)	12 (24)	8 (31)	4 (16)
Previous methotrexate therapy — no. (%)	69 (100)	51 (100)	26 (100)	25 (100)
DMARDs at washout — no. (%)	51 (74)	35 (69)	19 (73)	16 (64)
Methotrexate	50 (72)	34 (67)	18 (69)	16 (64)
Hydroxychloroquine	13 (19)	9 (18)	7 (27)	2 (8)
Concomitant therapy at washout — no. (%)				
Corticosteroids	25 (36)	19 (37)	13 (50)	6 (24)
NSAIDs	66 (96)	49 (96)	24 (92)	25 (100)
Mean dose of corticosteroids — mg/day	5.6	5.8	5.5	6.5

*Percentages may not total 100, because of rounding. JRA denotes juvenile rheumatoid arthritis, DMARDs disease-modifiying antirheumatic drugs, and NSAIDs nonsteroidal antiinflammatory drugs.

Table 16: Trial 3, Lovell et al., 2008. Adalimumab. Baseline demographic and clinical characteristics of patients

Characteristic	Open-Label Lead-in Phase		Double-Blind Phase			
	Methotrexate	No Methotrexate	Methotrexate		No Methotrexate	
	adalimumab (N=85)	adalimumab (N=86)	placebo (N=37)	adalimumab (N=38)	placebo (N=28)	adalimumab (N=30)
Age — yr	11.4±3.3	11.1±3.8	10.8±3.4	11.7±3.3	11.3±3.8	11.1±4.1
Age group — no. (%)						
4–8 yr	19 (22)	21 (24)	12 (32)	6 (16)	8 (29)	8 (27)
9–12 yr	30 (35)	32 (37)	10 (27)	17 (45)	7 (25)	10 (33)
13–17 yr	36 (42)	33 (38)	15 (41)	15 (40)	13 (46)	12 (40)
Female sex — no. (%)	68 (80)	67 (78)	30 (81)	30 (79)	20 (71)	23 (77)
Race — no. (%)†						
White	81 (95)	76 (88)	36 (97)	36 (95)	27 (96)	26 (87)
Black	0	3 (3)	0	0	1 (4)	1 (3)
Other	4 (5)	7 (8)	1 (3)	2 (5)	0	3 (10)
Body weight — kg	43.8±18.3	40.9±19.3	44.3±18.9	42.1±17.9	45.4±24.4	41.3±17.3
Negative for rheumatoid factor — no./total no. (%)	64/83 (77)	67/85 (79)	30/36 (83)	27/37 (73)	21/27 (78)	24/30 (80)
Duration of juvenile rheumatoid arthritis — yr	4.0±3.7	3.6±4.0	4.0±3.5	4.3±4.1	2.9±3.3	3.6±4.0
Previous medication use — no. (%)						
Methotrexate	85 (100)	18 (21)	37 (100)	38 (100)	4 (14)	8 (27)
Other disease-modifying antirheumatic drugs	8 (9)	8 (9)	7 (19)	1 (3)	3 (11)	4 (13)
Methylprednisolone	4 (5)	2 (2)	2 (5)	2 (5)	1 (4)	0

* Plus–minus values are means ±SD.
† Race was determined by the patient or the parent.

Table 17: Trial 4, Quartier et al., 2010. Anakinra. Baseline demographic and clinical characteristics of patients

Characteristics	Anakinra (n = 12)	Placebo (n = 12)	All patients (n = 24)
Demographic features			
Female, n (%)	7 (58)	8 (67)	15 (63)
Age, mean value, years (SD)	9.5 (5.19)	7.5 (3.73)	8.5 (4.54)
Disease mean duration, years (SD)	4.2 (3.33)	3.2 (1.95)	3.7 (2.73)
Systemic features			
Fever (>38°C), no. of patients (%)	4 (33.3)	5 (41.7)	9 (37.5)
CRP, mg/l (n≤6), mean value (SD)	66 (64.40)	84 (65.74)	75 (64.35)
ESR first hour (n≤10), mean value (SD)	44 (23.37)	57 (27.85)	50 (25.89)
SAA, mg/l (n≤6.4), mean value (SD)	366 (262)	368 (229)	367 (241)
High serum ferritin*, no. of patients	2	3	5
Joint assessment			
Active joints, mean no. (SD)	16 (13.12)	16 (15.84)	16 (14.23)
Joints with LOM, mean no. (SD)	16 (14.88)	17 (14.91)	17 (14.57)
Global assessments			
Physician's VAS, mean value (SD)	63 (20.57)	57 (29.74)	60 (25.21)
Parent's global VAS, mean value (SD)	50 (24.39)	55 (26.51)	52 (25.04)
Parent's pain VAS, mean value (SD)	50 (25.73)	53 (25.89)	51 (25.28)
CHAQ, mean value (SD)	1.67 (0.845)	1.44 (0.625)	1.55 (0.736)
Treatment with steroids (predniso(lo)ne)			
Duration, mean, years (SD)	3.9 (2.93)	2.7 (2.10)	3.3 (2.56)
Daily dose, mean, mg/kg (SD)	0.52 (0.237)	0.66 (0.373)	0.59 (0.313)
Previous treatments with DMARDs, biological agents			
DMARD and/or biological agent, no. of patients	8	11	19
DMARD, no biological agent, no. of patients	3	3	6
DMARD and biological agent, no. of patients	5	8	13
Methotrexate, no. of patients	8	11	19
Etanercept, no. of patients	5	8	13
Others, no. of patients (no. of DMARDs)	4 (7†)	4 (6‡)	8 (13)

*Ferritin level was highly variable and it was elevated (>100 μg/l in patients <13 years, >200 in female patients >13 years and >300 in male patients >13 years) in only five patients (range 347–3135 μg/l), with low glycosylated ferritin (<40%) in these five patients (range 14–30%).
†Thalidomide (n=2), tocilizumab (n=2, one single infusion, phase II trial), azathioprine (n=1), ciclosporin (n=1), leflunomide (n=1).
‡Azathioprine (n=2), thalidomide (n=1), tocilizumab (n=1, one single infusion, phase II trial), ciclosporin (n=1), intravenous immunoglobulins (n=1).
CHAQ, Childhood Health Assessment Questionnaire (0–3); CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; LOM, joints with limitation of passive motion; SAA, serum amyloid A; VAS, visual assessment (0–100 mm scale) of disease activity by the physician, disease effect on overall wellbeing and pain by the parents.

Table 18: Trial 5, Ruperto et al., 2008. Abatacept. Baseline demographic and clinical characteristics of patients

	4-month, open-label lead-in period	6-month double-blind period	
	Abatacept (n=190)	Abatacept (n=60)	Placebo (n=62)
Age (years)	12·4 (3)	12·6 (3)	12·0 (3)
Sex (female)	137 (72%)	43 (72%)	45 (73%)
Ethnic origin			
White	147 (77%)	46 (77%)	49 (79%)
Black	15 (8%)	5 (8%)	4 (7%)
Other	28 (15%)	9 (15%)	9 (15%)
Duration of juvenile idiopathic arthritis (years)	4·4 (3·8)	3·8 (3·7)	3·9 (3·5)
Number of active joints	16·2 (12·7)	18·2 (11·5)	14·7 (12·8)
Fewer than five active joints	24 (13%)	4 (7%)	8 (13%)
Five or more active joints	166 (87%)	56 (93%)	54 (87%)
Number of joints with limited range of motion	16·3 (14·5)	17·3 (13·2)	14·3 (13·7)
CHAQ disability index*	1·3 (0·8)	1·3 (0·7)	1·2 (0·8)
Parent global assessment†	44·5 (24·6)	41·8 (22·5)	39·9 (24·7)
Physician global assessment†	54·2 (20·3)	53·5 (17·8)	52·7 (21·1)
Juvenile idiopathic arthritis subtype			
Persistent oligoarthritis	3 (2%)‡	0	2 (3%)
Extended oligoarthritis	27 (14%)	9 (15%)	7 (11%)
Polyarthritis (positive for rheumatoid factor)	38 (20%)	14 (23%)	12 (19%)
Polyarthritis (negative for rheumatoid factor)	84 (44%)	26 (43%)	28 (45%)
Systemic	37 (20%)	11 (18%)	12 (19%)
Erythrocyte sedimentation rate (mm per hour)	32 (26·8)	30·8 (26·9)	31·4 (27·7)
C-reactive protein (mg/L)	0·32 (0·44)§	0·29 (0·46)	0·27 (0·34)¶
Rheumatoid factor			
Negative	149 (78%)	41 (68%)	50 (81%)
Positive	41 (22%)	19 (32%)	12 (19%)
Antinuclear antibodies			
Missing	6 (3%)	3 (5%)	2 (3%)
Negative	129 (68%)	40 (67%)	39 (63%)
Positive	55 (29%)	17 (28%)	21 (34%)
Anti-double-stranded DNA			
Missing	5 (3%)	3 (5%)	1 (2%)
Negative	159 (84%)	50 (83%)	50 (81%)
Positive	26 (14%)	7 (12%)	11 (18%)
Methotrexate dose (mg/m^2 per week)	13·2 (4·7)‖	13·5 (4·5)**	12·9 (4·0)††
Previous anti-TNF therapy discontinued	57 (30%)	8 (13%)	13 (21%)
Because treatment not effective	51 (27%)	7 (12%)	11 (18%)
For financial reasons	4 (2%)	1 (2%)	2 (3%)
Because family member had tuberculosis	1 (0·5%)	0	0
Unknown reason	1 (0·5%)	0	0

Data are number (%) or mean (SD), unless otherwise indicated. CHAQ=Childhood Health Assessment Questionnaire. TNF=tumour necrosis factor. *CHAQ scale of 1–3. †Visual analogue scale; 0–100. ‡n=187. §n=189. ¶n=61. ‖n=140. **n=48. ††n=46.

Table 19: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Trial 1 **Ruperto et al. 2007 (Infliximab +MTX)**	were evaluated by the same assessor at each visit. The primary end point of the trial was the proportion of patients meeting the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) criteria for improvement at week 14, defined as improvement of ~30% in at least 3 of 6 core variables, with no more than 1 of the remaining variables worsened by ~30% Null not specified	Cochran-Mantel-Haenszel chi-square test for categorical data and the van der Waerden test for continuous data. Ninety-five percent confidence intervals were calculated.	It was determined that each treatment group would have to include at least 60 patients, to provide ~79–97% power to detect a difference in the proportions of patients achieving the ACR Pedi 30 (_ _ 0.05, 2-sided) if the infliximab group had a frequency of response of at least 55–60% and the placebo group had a frequency of response of 25–30%.	Not specified.
Trial 2 **Lovell D et al., 2000** **(Etanercept)**	The primary efficacy end point, which was evaluated in the double-blind study, was the number of patients with disease flare. Null not specified	The percentages of patients with a response to therapy who had disease flare while receiving placebo or etanercept in the doubleblind study were compared by Mantel–	Not specified	Patients who withdrew early without disease flare were counted in the analysis with those who continued to have a response. To evaluate any bias introduced by the withdrawal assumption in

		Haenszel methods. The percentages of patients with a response who continued to have a response after receiving etanercept or placebo in the double-blind study were compared by Mantel–Haenszel methods. All tests were two-sided, with a significance level of 0.05.		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. In all summaries of measures of disease activity, a last-observation-carried-forward approach was used for missing data or visits and for patients who withdrew early.

Trial 3 **Lovell D et al., 2008** **(Adalimumab)**	The primary efficacy end point was the percentage of patients not receiving methotrexate who had a disease flare during the double-blind phase of the study (weeks 16 to 48). A disease flare was defined as a worsening of 30% or more in at least three of the six core criteria for juvenile rheumatoid arthritis and an improvement of 30% or more in no more than one of the criteria. Null not specified.	Continuous variables were compared by means of analysis of covariance. Categorical data, including those used for the primary end-point analysis, were analyzed with either the Pearson chi-square test or Fisher's exact test, as appropriate.	On the assumption of a 70% rate of response to adalimumab, 42 patients would need to enroll in the open-label lead-in phase to yield the 29 patients needed in each treatment group in the double- blind phase. This estimate was based on a 40% difference in the rate of flare between the placebo and the adalimumab groups and provided a power of 80% at an alpha level of 0.05.	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 nonresponses. ACR Pedi response rates during the open-label extension phase were calculated by using the last observation carried forward for missing values.
Trial 4 **Quartier P et al., 2010** **(Anakinra)**	The primary objective was to compare the effi cacy after 1 month's treatment with anakinra (2 mg/kg subcutaneously daily, maximum 100 mg) or placebo in the two groups of	Qualitative and quantitative data were compared using Wilcoxon test and Fisher exact test, respectively. The R statistical software was used for	We expected at least 60% difference in the percentage of patients obtaining improvement in the anakinra-treated group (group 1) compared with the control	Not Specified

	patients. To be responders to a modifi ed American College of Rheumatology Pediatric (ACRpedi) 30 score built for the purpose of the trial. No null specified	statistical analysis.	group (group 2), with no more than 10% patients improving in group 2. Given a 5% type I error, a 20% type II error and a two-sided Fisher exact test, 12 patients per group were required. An intention-to-treat analysis was retained.	

Trial 5 **Ruperto N et al., 2008** **(Abatacept)**	The primary endpoint was time to flare of juvenile idiopathic arthritis. Flare was defi ned as worsening of 30% or more in at least three of the six ACR core-response variables for juvenile idiopathic arthritis, and at least 30% improvement in no more than one variable during the double-blind period. No null specified.	For the primary endpoint, Kaplan–Meier survival curves were used to estimate the distribution of time to disease flare for each group in the 6-month double-blind phase. We used a log-rank test 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 fl are of arthritis between the two groups. Secondary analyses included comparison of the rate of disease fl are between the abatacept and placebo groups (using a two-sided continuity-corrected χ^2 test at the 5% significance level).	estimated that we would need to enrol 200 patients into 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% signifi cance). 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 diff erence of 35%, assuming a fl are rate of 65% in placebo controls and a dropout rate of 10% for the double-blind phase.	Missing values in the double-blind phase were imputed with the last-observation carried forward method in the analysis of the individual components of the six ACR paediatric response variables, the ACR responses, and inactive disease status.

Table 20: Quality assessment results for RCTs

Trial no. (acronym)	**Trial 1** **Ruperto et al. 2007 (Infliximab +MTX)**	**Trial 2** **Lovell D et al., 2000 (Etanercept)**	**Trial 3** **Lovell D et al., 2008 (Adalimumab)**	**Trial 4** **Quartier P et al., 2010 (Anakinra)**	**Trial 5** **Ruperto N et al., 2008 (Abatacept)**
Was randomisation carried out appropriately?	yes	yes	yes	yes	yes
Was the concealment of treatment allocation adequate?	yes	yes	yes	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	not clear	yes	yes	yes	yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	yes	yes	yes	yes	yes
Were there any unexpected imbalances in drop-outs between	no	no	not clear	not clear	no

groups?					
Is there any evidence to suggest that the authors measured more outcomes than they reported?	not clear	not clear	not clear	not clear	not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes ITT used Not clear on withdrawal/missing data accounting	not clear	yes	yes	not clear
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination					

The results of the relevant RCTs are summarised in the table below with respect to the JIA ACR responses, which is the basis of the indirect comparison analysis which follows.

Table 21: Relevant JIA ACR responses from the RCTs

	Study phase	JIA ACR 30 n (%) p-value	JIA ACR 50 n (%) p-value	JIA ACR 70 n (%) p-value	JIA ACR 90 n (%) p-value
Trial 1 Ruperto et al. 2007 (Infliximab +MTX)	Double-blind led-in	37/58 63.8% P=0.12	29/58 50% P=0.078	13/58 22.4% P=0.130	
	Placebo	29/59 49.2%	20/59 33.9%	7/59 11.9%	
	Open-label		78/112 69.6%	58/112 51.8%	
Trial 2 Lovell D et al. 2000 (Etanercept)	Open-label led-in	51/69 74%	44/69 64%	25/69 36%	
	Double-blind	20/25 80% P<0.01	18/25 72%	11/25 44%	
	Placebo	9/26 35%	6/26 23%	5/26 19%	
Trial 3 Lovell D et al. 2008 (Adalimumab)	Open-label led-in +MTX	94%	91%	71%	28%
	Open-label led-in –MTX	74%	64%	46%	26%
	Double-blind +MTX	63%	63%	63%	42%

		P=0.03	P=0.03	P=0.002	P=0.17
	Double-blind +MTX placebo	38%	38%	27%	27%
	Double-blind –MTX	57% P=0.06	53% P=0.10	47% P=0.16	30% P=0.28
	Double-blind –MTX placebo	32%	32%	29%	18%
Trial 4 **Quartier P et al. 2010** **(Anakinra)**	Double-blind	11/12 92% 0.059	7/12 58% 0.005	5/12 42% 0.038	
	Placebo	7/12 58%	0	0	
	Open-label extension				
Trial 5 **Ruperto N et al. 2008** **(Abatacept)**	Open-label led-in	65%	50%	28%	13%
	Double-blind	49/60 82% 0.1712	46/60 77% 0.0071	32/60 53% 0.0185	24/60 40% 0.0062
	Placebo	43/62 69%	32/62 52%	19/62 31%	10/62 16%

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table 22: Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Intervention	Comparator B	Comparator C	Comparator D
1	Trial 1	✓		✓	✓
1	Trial 2		✓	✓	✓
2	Trial 3 Trial 4	✓	✓		
1	Trial 5	✓		✓	
Etc.	Etc.	Etc.			
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900					

The literature review identified a number of studies for the comparator treatments. None of the studies for anti-TNFα or abatacept evaluate a population of solely systemic JIA patients. A brief description of the pivotal study for each biologic is presented below:

Ruperto et al. [2008] studied **abatacept** versus placebo. The study permitted MTX use if it was already administered and allowed NSAIDs use for pain control. The investigated population was DMARD-IR (including biologics)[1], containing JIA patients of each of the following subtypes: systemic 19%, polyarthritis negative 44%, polyarthritis positive 21%, oligoarthritis extended 13%, and oligoarthritis persistent 2%. The ACR response rates are reported at 6 months. However, the study design adopted is that of a randomised, double blind, controlled withdrawal trial. Patients in this study are randomised after an open-label phase of 4 months. Due to the design of this study it is not appropriate to compare to TENDER [WA18221 - Roche Clinical Study Report 1035146, 2010].

[1] Please note that a subsequent review refers to this study population as MTX-IR [Ruperto et al. 2010].

Lovell et al. [2008] studied **adalimumab** versus placebo. The study stratified patients to those receiving concomitant treatment with MTX or not. The study population is included MTX naïve and MTX-IR JIA patients. The ACR response rates are reported at 48 weeks. The study design adopted is that of a randomised, double blind, controlled withdrawal trial. Patients in this study are randomised after an open-label phase of 16 weeks. Due to the design of this study it is not appropriate to compare to TENDER [WA18221 - Roche Clinical Study Report 1035146, 2010].

Lovell et al. [2000] studied **etanercept** versus placebo. The population included MTX-IR or intolerant patients consisting of the JIA subtypes as follows: systemic 33%, polyarticular 61%, pauciarticular 6%. The study permitted stable doses of NSAIDs, low doses of CS or both. The ACR response rates are reported at 7 months following an open label period of 3 months in which all patients received etanercept. The study design adopted is that of a randomised, double blind, controlled withdrawal trial. Patients in this study are randomised after the open-label phase of 3 months. Due to the design of this study it is not appropriate to compare to TENDER [WA18221 - Roche Clinical Study Report 1035146, 2010].

Ruperto et al. [2007] studied **infliximab** versus placebo in a population of juvenile rheumatoid arthritis patients described as having suboptimal response to MTX. The study population received concomitant MTX alongside placebo or active treatment. The population contained patients from the following subtypes; systemic 16%, pauciarticular 23%, polyarticular 61%. The study design a randomised double blind placebo controlled trial closely matches that of the TENDER trial with ACR responses reported at 14 weeks. Although this population is different to TENDER [WA18221 - Roche Clinical Study Report 1035146, 2010], it was considered in the indirect comparison analysis due to lack of other anti-TNFα treatment evidence.

In the comparison with **anakinra** Quartier et al. [2010] performed a study focusing on the systemic JIA population. The study included MTX-IR and

DMARD-IR JIA patients and did not permit the administration of any DMARDs for the duration of the trial. The study included 24 patients (12 in each arm) and outcomes of the randomised controlled phase are reported after a 1 month period. Following this first month patients are administered the active treatment. Although this study outcome timeframe is much shorter to TENDER [WA18221 - Roche Clinical Study Report 1035146, 2010], it was considered in the indirect comparison analysis due to lack of other more relevant evidence.

A summary of the evidence identified for all possible comparators reporting ACR responses, is shown in the Table below.

Table 23: Summary of clinical trials considered for the comparison

Study (Author/date)	Treatments compared	Study design as described by Ruperto & colleagues [2010]	Population	ACR Outcomes Reported
Ruperto 2008	Abatacept vs placebo MTX ±, NSAIDS±	Randomized, double blind, controlled withdrawal design	DMARD-IR or intolerant, bDMARD-IR or intolerant	ACR 30, 50,70, 90 (treatment and placebo arms) at 6 months after 4-months of open label .
Lovell 2008	Adalimumab vs placebo MTX ±	Randomized, double blind, controlled withdrawal design	Two subgroups: MTX naive and MTX-IR	ACR Pedi 30, 50, 70,90 (treatment and placebo arms for MTX^- and MTX^+ subgroups) at week 48 after 16-week open label
Quartier 2010	Anakinra vs placebo DMARD – NSAIDS/CS+	Part I: parallel RCT with placebo (1 month). Part II: open label all patients anakinra	Mixed population of DMARD-IR, MTX-IR, naive	ACR 30, 50, 70 at 1 month
Lovell 2000	Etanercept vs placebo MTX – NSAIDS/CS±	Randomized, double blind, controlled withdrawal design	MTX-IR or intolerant	ACR 30, 50, 70 for treatment and control arms at end of 7 months (double blind months 4-7)
Ruperto 2007	Infliximab vs placebo MTX +	Parallel RCT with placebo	Suboptimal response to MTX	Assume reported response at week 14 reflects randomised phase
CSR Roche 2010	Tocilizumab vs placebo, MTX ±	Parallel RCT with placebo	NSAID-IR, CS-IR	ACR 30,50,70,90 at week 12

For the selected trials, provide a summary of the data used in the analysis.

The outcome of interest for the economic evaluation is ACR response. This is selected as it is the most common efficacy outcome across all comparators.

The data used in the analysis are presented in the Table below. The percentages were extracted from the relevant studies [WA18221 - Roche Clinical Study Report 1035146, 2010; Ruperto et al. 2007; Quartier et al. 2010]. The number of patients experiencing each outcome, required to perform the analysis, were derived from these percentages and rounded to the nearest integer.

Table 24: Evidence used in the indirect comparison analysis

Study	Treatment	Response	Total N	ACR only		ACR and absence of fever (<38C)	
				%	n	%	n
TENDER	TCZ +/-MTX	ACR 30	75	0.907	68	0.853	64
	TCZ +/-MTX	ACR 50	75	0.853	64	-	-
	TCZ +/-MTX	ACR 70	75	0.707	53	-	-
	PBO +/-MTX	ACR 30	37	0.243	9	0.243	9
	PBO +/-MTX	ACR 50	37	0.108	4	-	-
	PBO +/-MTX	ACR 70	37	0.081	3	-	-
ANAJIS [Quartier et al. 2010]	ANK	ACR 30	12	0.92	11	0.92	11
	PBO	ACR 30	12	0.58	7	0.5	6
NCT00036374 [Ruperto et al. 2007]	INFL +MTX	ACR 30	58	0.638	37	-	-
	PBO +MTX	ACR 50	58	0.5	29	-	-
	INFL +MTX	ACR 70	58	0.224	13	-	-
	PBO +MTX	ACR 30	59	0.492	29	-	-
	PBO +MTX	ACR 50	59	0.339	20	-	-
	PBO +MTX	ACR 70	59	0.119	7	-	-

Data on the ACR 50 and 70 levels of response are available in the TENDER trial on the ACR outcomes only and in the ANAJIS trial on the combined ACR and absence of fever outcomes only. The comparison with Anakinra is therefore limited to the ACR30 response and no other data are presented.

5.7.4 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The summary measure selected for this analysis is the relative risk (RR). The RR and its precision are calculated for each study and each outcome using the n/N data presented above.

The efficacy of tocilizumab, anakinra and infliximab is indirectly compared using placebo as a common comparator, following the method developed by Bucher at al. [1997]. This indirect comparison is carried out on RRs. Given data are only available in one study for each treatment there is no need for meta-analysis.

The indirect effect of tocilizumab compared to its comparators and its associated 95% bilateral confidence interval are calculated using the formulas below. Due to the mathematical characteristics and distribution of the RRs, it is necessary to perform the analysis on the logarithmic scale and then back-transform (exponentiate) the results.

(1) ln(RR)A vs B= ln(RR)A vs P – ln(RR)B vs P

(2) SE(ln(RR)A vs B) = [Var(ln(RR)A vs P)+ Var(ln(RR)B vs P)]1/2 the 95% CI around the logarithm of the indirect effect is calculated as:

(3) ln (RR)A vs B ± 1.96*(ln(RR)A vs B)

Values for the RRs and confidence intervals were calculated using Stata SE version 8.2. The indirect comparisons were carried out in Excel.

5.7.5 Please present the results of the analysis.

The results of the analysis are presented in the Table below.

Table 25: Results of the indirect comparison analysis

Comparison	Outcome	RR	95% CI
TCZ vs ANK	ACR30	2.37	1.10, 5.10
	ACR30 and absence of fever	1.91	0.84, 4.37
TCZ vs INF	ACR30	2.87	1.49, 5.55
	ACR50	5.35	1.91, 14.97
	ACR70	4.61	1.16, 18.38

This analysis shows that patients on tocilizumab are significantly more likely to reach an ACR30 response than patients on anakinra. They are also numerically more likely to reach the combined outcome of ACR30 response and absence of fever.

Compared to patients on infliximab, patients treated with tocilizumab are also significantly more likely to reach an ACR30, 50 and 70 response.

5.7.6 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Due to the limited amount of data available, no assessment of heterogeneity could be performed.

5.7.7 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

This point is not applicable to the analysis presented in this submission.

5.7.8 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

This point is not applicable to the analysis presented in this submission.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

TENDER study – 1 year abstract data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Results

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

TENDER study – 72 week data cut (May 2010) from regulatory submission (Roche data on file)

[redacted]

[redacted]

[redacted]

[redacted]

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

The search strategy used to identify comparative RCTs in section 5.7 can be found in Appendix 4. This search revealed a RCT for each comparator, although not all were related to the Decision Problem (as previously discussed). These RCTs are included in this section to represent adverse events for each comparator in an RCT setting. Regulatory submissions are also used in this section for the relative therapies with indications in JIA. Details can be found below in 5.9.2.

A search was carried out to identify non-RCT data in the comparators, for example registry data. The search strategy can be found in Appendix 8.

These data are supplemented by Roche's regulatory submission document to the European Medicines Agency, 16 Dec 2010 [redacted]

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

There are currently no licensed therapies for the treatment of sJIA. As such there are limited regulatory and RCT data available for the comparators outlined in the Decision Problem. However 2 of the comparators identified in the Decision Problem, etanercept and adalimumab, are licensed in other JIA subtypes, specifically polyarticular JIA.

Table 26: Summary of adverse event data presented below for the technology and each comparator:

Tocilizumab	Regulatory data in sJIA available from proposed SPC and regulatory submission RCT data in sJIA available
Etanercept	Regulatory data in polyarticular JIA available from current SPC RCT data in polyarticular JIA available Non-RCT data in sJIA available
Adalimumab	Regulatory data in polyarticular JIA available from current SPC. RCT data in polyarticular JIA available No non-RCT data in sJIA available

Infliximab	Not licensed in JIA – no SPC data available RCT data in polyarticular JIA available No non-RCT data in sJIA available
Anakinra	Not licensed in JIA – no SPC data available RCT data in sJIA available Non-RCT data in sJIA available
Methotrexate	Not licensed in JIA – no SPC data available RCT data in sJIA available Non-RCT data in sJIA available

Tocilizumab

Wording from the proposed Summary of Product Characteristics (SPC),

[redacted]

XXXXXXXXXXXXX

[redacted]

[redacted]

Regulatory summaries taken from the SPCs for comparators indicated in polyarticular JIA:

Etanercept: (Etanercept SPC, February 2011)

Indicated in active polyarticular JIA.

Taken from section 4.8 Undesirable effects:

> In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.
>
> The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae, appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.
>
> In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (Part I, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of

patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

There have been reports of inflammatory bowel disease in JIA patients being treated with Enbrel from post-marketing sources, including a very small number of cases indicating a positive rechallenge.

Adalimumab (Adalimumab SPC, February 2011)

Indicated in polyarticular JIA.

Taken from section 4.8 Undesirable effects:

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Adverse events at least possibly causally-related to adalimumab, for clinical studies both clinical and laboratory, are displayed by system organ class and frequency (very common 1/10; common 1/100 to < 1/10; uncommon 1/1,000 to < 1/100, rare 1/10,000 to < 1/1,000 and very rare <1/10,000) in Table 1 below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Approximately 15% of patients can be expected to experience injection site reactions, based on the most common adverse event with adalimumab in controlled clinical studies.

Undesirable Effects in Clinical Studies

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections
	Uncommon	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avum complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections, joint infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
Blood and the lymphatic system disorders*	Very common	leucopaenia (including neutropaenia and agranulocytosis), anaemia
	Common	thrombocytopaenia, leucocytosis
	Uncommon	idiopathic thrombocytopaenic purpura

	Rare	pancytopaenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very common	lipids increased
	Common	hypokalaemia, uric acid increased, >blood sodium abnormal, hypocalcaemia hyperglycemia, hypophosphotemia, blood potassium increased
	Uncommon	dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoaesthesia), migraine, sciatica
	Uncommon	tremor
	Rare	multiple sclerosis
Eye disorders	Common	visual impairment, conjunctivitis
	Uncommon	blepharitis, eye swelling, diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular	Common	hypertension, flushing, haematoma

disorders		
	Rare	vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	cough, asthma, dyspnoea
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
Hepato-biliary disorders*	Very common	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very common	rash (including exfoliative rash)
	Common	pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis
	Uncommon	night sweats, scar
Musculoskeletal, connective tissue and bone disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)

	Uncommon	rhabdomyolysis
	Rare	systemic lupus erythematosus
Renal and urinary disorders	Common	haematuria, renal impairment
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very common	injection site reaction (including injection site erythema)
	Common	chest pain, oedema
	Uncommon	inflammation
Investigations *	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury and poisoning	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

** including open label extension studies

Injection site reactions

In the pivotal controlled trials, 15% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 9% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials, the rate of infection was 1.50 per patient year in the Humira treated patients and 1.42 per patient year in the placebo and active control-treated patients. The infections consisted primarily nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on Humira after the infection resolved. The incidence of serious infections was 0.043 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control − treated patients.

In controlled and open label studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 171 patients with an exposure of 192.5 patient years during a Humira trial in juvenile idiopathic arthritis patients. During the controlled portions of pivotal Humira trials at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or psoriasis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.6 (4.0, 10.8) per 1,000 patient-years among 3,917 Humira treated patients versus a rate of 4.2 (1.8, 10.41) per 1,000 patient-years among 2,247 control patients (median duration of treatment was 5.6 months for Humira and 4.0 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 9.9

(6.6, 14.8) per 1,000 patient-years among Humira-treated patients and 2.5 (0.8, 7.9) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.5 (1.1, 5.5) per 1,000 patient-years among Humira-treated patients and 0.8 (0.1, 6.0) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.8 (0.2, 3.3) per 1,000 patient-years among Humira-treated patients and 0.8 (0.1, 6.0) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.4 years including 4,954 patients and over 21,021 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 9.1 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 10.1 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.1 per 1,000 patient years.

In post-marketing experience from January 2003, predominately in patients with rheumatoid arthritis, the reported rate of malignancies other than lymphomas and non-melanoma skin cancers is approximately 1.7 per 1,000 patient years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.4 per 1,000 patient years, respectively.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I − V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres

reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Liver Enzyme Elevations
In all rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis studies, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.

These additional adverse reactions have been reported from postmarketing surveillance or Phase IV clinical trials:

System Organ Class	**Adverse Reaction**
Infections and infestations*	diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	hepatosplenic T-cell lymphoma, leukemia
Immune system disorders*	Anaphylaxis, sarcoidosis
Nervous system disorders*	demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome); cerebrovascular accident
Respiratory, thoracic and mediastinal disorders*	pulmonary embolism pleural effusion, pulmonary fibrosis
Gastrointestinal disorders	intestinal perforation
Hepato-biliary disorders*	reactivation of hepatitis B
Skin and subcutaneous tissue disorders	cutaneous vasculitis, Stevens-Johnson syndrome, angioedema, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders	lupus-like syndrome
Cardiac disorders	myocardial infarction

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

RCT data

Adalimumab RCT in polyarticular JIA (Lovell 2008)

Table 27: Adalimumab adverse event profile

AE	In combination with methotrexate				With no concomitant methotrexate			
	Open label-led in	Double blind phase		Open-label extension	Open label-led in	Double blind phase		Open-label extension
	ADA n=85	Placebo n=37	ADA n=38	ADA n=71	ADA n=86	Placebo n=28	ADA n=30	ADA n=57
Any adverse event	422 (15.5)	155 (10.3)	234 (12.8)	694 (5.4)	447 (15.3)	153 (14.4)	171 (11.9)	581 (5.7)
Most frequently reported adverse events								
Related to injection-site reaction	142 (5.2)	57 (3.8)	73 (4.0)	224 (1.8)	166 (5.7)	20 (1.9)	71 (4.9)	149 (1.4)
Contusion	14 (0.5)	7 (0.5)	12 (0.7)	4 (<0.1)	7 (0.2)	5 (0.5)	2 (0.1)	7 (0.1)
Nasopharyngitis	6 (0.2)	6 (0.4)	5 (0.3)	9 (0.1)	2 (0.1)	5 (0.5)	0	7 (0.1)
Upper respiratory tract infection	9 (0.3)	5 (0.3)	6 (0.3)	32 (0.2)	11 (0.4)	6 (0.6)	6 (0.4)	42 (0.4)
Viral infection	9 (0.3)	3 (0.2)	7 (0.4)	26 (0.2)	8 (0.3)	4 (0.4)	8 (0.6)	9 (0.1)
Vomiting	4 (0.2)	2 (0.1)	4 (0.2)	5 (<0.1)	2 (0.1)	1 (0.1)	0	4 (<0.1)
Excoriation	5 (0.2)	1 (0.1)	10 (0.6)	12 (0.1)	5 (0.2)	2 (0.2)	6 (0.4)	8 (0.1)
Serious adverse events, possibly related to study drug								

Total	3 (0.1)	1 (0.1)	0	0 7 (0.1)	4 (0.1)	0	0	2 (<0.1)
Abdominal pain	0	0	0	1 (<0.1)	0	0	0	0
Bronchopneumonia	0	0	0	0	0	0	0	1 (<0.1)
Gastroduodenitis	0	1 (0.1)	0	0	0	0	0	0
Hematochezia	0	0	0	1 (<0.1)	0	0	0	0
Herpes simplex infection	0	0	0	0	1 (<0.1)	0	0	0
Herpes zoster infection	0	0	0	1 (<0.1)	0	0	0	1 (<0.1)
Hydrocephalus	0	0	0	1 (<0.1)	0	0	0	0
Juvenile rheumatoid arthritis disease flare	1 (<0.1)	0	0	1 (<0.1)	2 (0.1)	0	0	0
Leukopenia	1 (<0.1)	0	0	0	0	0	0	0
Neutropenia	1 (<0.1)	0	0	0	0	0	0	0
Pharyngitis	0	0	0	1 (<0.1)	0	0	0	0
Pneumonia	0	0	0	0	1 (<0.1)	0	0	0

Viral infection	0	0	0	1 (<0.1)0	0	0	0	0
Adverse events leading to discontinuation of drug								
Total	5 (0.2)	0	0	2 (<0.1)	7 (0.2)	0	0	2 (<0.1)
Arthralgia	0	0	0	0	1 (<0.1)	0	0	0
Dizziness	0	0	0	0	1 (<0.1)	0	0	0
Hydrocephalus	0	0	0	1 (<0.1)	0	0	0	0
Juvenile rheumatoid arthritis	1 (<0.1)	0	0	0	4 (0.1)	0	0	2 <0.1)
Leukopenia	1 (<0.1)	0	0	0	0	0	0	0
Alanine aminotransferase elevation	1 (<0.1)	0	0	0	0	0	0	0
Aspartate aminotransferase elevation	1 (<0.1)	0	0	0	0	0	0	0
Neutropenia	1 (<0.1)	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	1 (<0.1)	0	0	0
Viral infection	0	0	0	1 (<0.1)	0	0	0	0

Anakinra RCT in sJIA (Quartier 2010)

Table 28: Anakinra adverse event profile

Adverse event	**Double blind – 1 month**		**Open-label – up to 12 months**
	Anakinra 50% of patients (n = 12)	**Placebo 50% of patients (n = 12)**	**Anakinra 100% of patients (n = 22)**
Total adverse events			
Any AE	14 (14/pt-yr)	13 (13/pt-yr)	89 (15.71/pt-yr)
Serious AE	0	0	5 (0.33/pt-yr)
Infections			
Infections:	2 (2/pt-yr)	2 (2/pt-yr)	44 (2.90/pt-yr)
ENT	1	1	20
Bronchitis	0	0	8
Gastroenteritis	1	1	3
Skin infection	0	0	4
Other	0	0	9
Other			
Vomiting, abdominal pain	0	1	9
Pain at injection site	8 (8/pt-yr)	6 (6/pt-yr)	15 (0.99/pt-yr)
Post-injection erythema	3	1	6 (0.40/pt-yr)
Other AE	0	2 (2/pt-yr)	10 (0.66/pt-yr)

Etanercept RCT in polyarticular JIA (Lovell 2000)

Table 29: Etanercept adverse event profile

Adverse Event	**Open-label lead in phase**	**Double-blind phase**	
	Etanercept 100% of patients (n = 69)	**Etanercept 50% of patients (n = 25)**	**Placebo 50% of patients (n = 26)**
Most common AEs			
Injection site reactions	39%	4%	4%
upper respiratory tract infections	35%	Data not provided	Data not provided
headache	20%	Data not provided	Data not provided
rhinitis	16%	Data not provided	Data not provided
abdominal pain	16%	Data not provided	Data not provided
vomiting	14%	Data not provided	Data not provided
pharyngitis	14%	Data not provided	Data not provided
nausea	12%	Data not provided	Data not provided
Gastrointestinal infection	12%	Data not provided	Data not provided
rash	10%	Data not provided	Data not provided
Serious adverse events with hospitalisation:			
	2 etanercept patients		
Withdrawals			
	1 patient		

Infliximab RCT in polyarticular JIA (Ruperto 2007)

Table 30: Infliximab adverse event profile

Adverse events (%)	**Double blind**	**Double blind: weeks 0-14** **Open-label: weeks 14-52**	**Open label: weeks 14-52**
	Placebo + MTX **(n = 60)**	**Infliximab 3mg/kg + MTX** **(n = 60)**	**Infliximab 6mg/kg + MTX** **(n=57)**
Total adverse events			
Adverse events	49 (81.7)	58 (96.7)	54 (94.7)
Serious adverse events	3 (5.0)	19 (31.7)	5 (8.8)
Adverse events leading to discontinuation of study agent	1 (1.7) Circulatory failure	2 (3.3) Infusion reactions	5 (8.8) Infusions reactions 4 (7.0) Depression 1 (1.8)
Infections			
Infections	28 (46.7)	41 (68.3)	37 (64.9)
Serious Infections	2 (3.3)	5 (8.3)	1 (1.8)
No of infusions with infusion reaction	6/177 (3.4)	46/503 (9.1)	13/313 (4.2)
Infusion reactions	5 (8.3)	21 (35.0)	10 (17.5)
Antinuclear antibodies*	0/30 (0)	8/54 (14.8)	1/46 (2.2)
Anti–double-stranded DNA*	0/30 (0)	7/54 (13.0)	0/46 (0)

*newly positive

RCT in methotrexate in sJIA (Woo 2000)

Table 31: Methotrexate adverse event profile

	n=45 (with sJIA)	
Adverse Event	**Placebo**	**Methotrexate**
Nausea	12	13
Gastrointestinal upset	14	13
Mouth ulcers	8	7
Hair loss	5	4
Mood change	9	7
Pneumonitis	2	1
Bone marrow failure	0	0
Abnormal AST level	6	3
Abnormal AP level	8	6
Abnormal bilirubin level	1	0
Other side effects	5	4
Any other illness	17	17
Withdrawals for all reasons	7	

RCTs in tocilizumab in sJIA

Table 32: Tocilizumab adverse events - RCT data (Yokota 2008)

Adverse event	Open-label led-in phase n=56	Double-blind phase placebo n=23	Double-blind phase TCZ n=20	Open-label extension phase n=50
Withdrawn for AE		1	1	2
Death or MAS	0	0	0	-
Serious AE	2			13
Gastroenteritis	-	4%	5%	29%
Upper-respiratory-tract infectio	-	17%	10%	34%
Mild infusion reactions	18%	-	-	-
Nasopharyngitis	-	-	-	59%
Bronchitis	-	-	-	25%
Increased ALT	-	-	-	29%
Increased AST	-	-	-	21%
Increase LDH	-	-	-	18%

Table 33: Tocilizumab adverse event profile from TENDER trial (De Benedetti 2010)

(Summary presented here – more detail given in later section)

System organ/ class/adverse events	Double-blind		Open-label
	Tocilizumab 67% of patients (n = 75)	Placebo 33% of patients (70%+MTX) (n = 37)	Tocilizumab % of patients (n = 112)
Total adverse events			
Adverse event Patients with at least 1 AE	147 66 (88.0%)	48 23 (62.2%)	
Serious AEs patients with at least 1 SAE	4 3 (4.0%)	0 0	25 (22.3%)*
Infections			
Infection patients with at least 1 infection	55 41 (54.7%)	14 11 (29.7%)	
Serious infection patients with at least 1 serious infection	2 2.7%	0	15**

* 12 SAEs were considered related to tocilizumab. SAE rate 0.23/patient year in the double-blind phase and 0.25/patient year in the open-label phase

** 6 serious infections considered relevant to tocilizumab – none led to discontinuation

As shown above RCTs data are only available in specifically sJIA for the technology and two comparators, namely anakinra and methotrexate.

Therefore a search was conducted to identify non-RCT data in specifically sJIA.

Non –RCT data:

Table 34: **Anti- TNFα adverse events - non-RCT data (Russo 2009)**

	Anti-TNF patients (all combined – etanercept, infliximab, adalimumab) n=45 (47% sJIA)
Drug toxicity	13 (29%)
Discontinuation due to toxicity	7 (16%)

Etanercept adverse events - non-RCT data: (Southwood 2011)

483 patients registered with 77 (16%) systemic JIA. Four (36% of total discontinuations across all JIA subtypes) of these patients discontinued treatment (one restarted). Odds ratio for discontinuation due to inefficacy alone was 2.55 in sJIA (95% CI -1.27, 5.14). No other results were stratified for JIA subtype.

Table 35: Etanercept adverse events - non-RCT data (Kimura 2005)

	Etanercept n=82
Any AE	32
(patients with at least 1 AE)	22 (27%)
Infection	9 (11%)
Injection site reactions	6 (7%)
Somatic complaints (fatigue, headache, myalgias)	6 (7%)

Anakinra adverse event profile:

Table 36: Anakinra adverse events - non-RCT data (Nigrovic 2011)

Adverse event	**Anakinra:** **46 sJIA patients.**
MAS	Observed 5 times in 4 patients while receiving treatment
Injection site reactions	44%
Serious infection	3 in 3 patients
Bronchitis	2 in 1 patient
Recurrent viral respiratory illness	1
Eosinophilic hepatitis	1
Elevation of liver enzymes	2 patients
Mild asymptomatic neutropenia	1

Table 37: Anakinra adverse events - non-RCT data (Lequerre 2008)

Adverse event	**Anakinra** **20 sJIA patients**
Discontinuation	5/20 (25%)
Serious adverse event visceral *Leishmania* infection	 1
Infections: varicella rhinoparyngitis non-extensive labial herpes.	 1 2 1
Local pain/reaction to injection	18/20 (90%)
Inflammation at injection site/pruritus	Common
Headache	2/20 (10%)

Table 38: Anakinra adverse events - non-RCT data (Zeft 2009)

Adverse Event	Anakinra n=32 sJIA
MAS	1 patient
ANC<1.8 x 10^3/(l)	1
Epstein Barr virus*	1
Localised pain/swelling at injection site. Injection site pain leading to discontinuation	17/32 (53%) 7
Discontinuation of treatment	10/32 (31%)
Transient hives	2/32 (6%)

absolute neutrophil count
* patient on high dose anakinra

Table 39: Methotrexate adverse events - non-RCT data (Kocharla 2009)

Adverse event	Methotrexate 24/198 (12%) = sJIA
Persistent LFT > 2 ULN	6/198 total patients 2/6 (33%) with sJIA
Transient LFT > 2 ULN	24/198 total patients 6/24 (25%) with sJIA

LFT: liver function test

Methotrexate adverse events - non-RCT data (Al-Sewairy 1998)

All 18 patients had systemic onset JIA, 10 of these patients with systemic features at study start. There were no gastrointestinal, hepatic, pulmonary or haematological side effects encountered, and none of the patients withdrew

because of toxicity or lack of efficacy at no more than 0.7mg/kg/week methotrexate.

Details from the safety analysis of tocilizumab during the TENDER (De Benedetti) trial can be found below

DETAILS OF ALL IMPORTANT ADVERSE EVENTS IN TOCILIZUMAB

Details of all important adverse events experienced with tocilizumab in relation to the Decision Problem are summarised below and data is taken primarily from Roche's regulatory submission document to the European Medicines Agency, 16 Dec 2010 [redacted] Where additional information is added from a different reference source this is clearly marked.

STUDY WA18221 (12 WEEK TENDER) (De Benedetti 2010)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Immunogenicity

[redacted]

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The qualitative safety profile of tocilizumab in children appears to be generally comparable to adults. However, infections and infestations and neutropenia appear to be more common in paediatric patients than in adults. Of note, there is no clear association of neutropenia and infection. So far no serious opportunistic

infections have been observed. Elevation of transaminases are also observed frequently, the clinical significance of this is still unclear.

Due to lack of any head-to-head data with tocilizumab and the comparators identified in the Decision Problem, it is difficult to accurately compare tocilizumab's safety profile in sJIA in relation to MTX, the TNFα inhibitors and anakinra although the data to date, mainly from TENDER suggest a qualitative safety profile in children similar to what is known about tocilizumab in adult rheumatoid arthritis patients.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The following information relating to safety is also summarised in the draft Summary of Product Characteristics for tocilizumab [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Short term efficacy has been conclusively demonstrated in the pivotal TENDER trial (De Benedetti et al. 2010) which is the main basis for the licence application and the results of which are documented in the proposed SPC for tocilizumab in sJIA. Findings within the trial and compared to the supportive studies show a consistent clinically relevant effect. Long term efficacy data are still limited, and longer follow up may provide a better insight into the longer term effects of tocilizumab treatment in sJIA. Thus far, 1 year and 72 week data from the TENDER study has shown an increased benefit of tocilizumab with extended use.

The qualitative safety profile of tocilizumab in children appears to be generally comparable to adults. However, infections and infestations and neutropenia appear to be more common than in adults.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

As stated previously, there are no head-to-head studies which directly compare tocilizumab with the comparators in the 2 populations outlined in the Decision Problem, and also very few data from RCTs on the efficacy of the comparators in sJIA. However, the TENDER study (De Benedetti et al. 2010) was identified as relevant to the Decision Problem.

In summary, this pivotal randomised double-blind, placebo controlled trial compared current standard of care + tocilizumab versus current standard of care + placebo. This design is the preferred choice for the demonstration of efficacy because there are no licensed therapies in sJIA and an actively controlled study would be difficult to compare due to ethical issues in this patient population. The outcomes from TENDER, including the sub-analyses, presented in section 5.5 are relevant to the clinical needs of UK patients, and effectively demonstrate the benefit that UK patients in clinical practice might expect to receive from tocilizumab.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The data from the TENDER trial (De Benedetti et al. 2010) are the main basis for the licence application, the results of which are documented in the proposed SPC for tocilizumab in sJIA. The choice of eligible patients and doses used in the TENDER trial would also reflect the choice of patients and recommended doses in the proposed SPC [redacted]

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic review was conducted to identify existing economic evaluations relevant to the STA Decision Problem.

The following resources were used to identify relevant studies:

Searches of the following bibliographic databases were performed using the datastar platform unless otherwise stated:

- MEDLINE; 1949 – 18/10/2010
- EMBASE; 1974 – 18/10/2010
- Medline (R) In Process; (latest 8 weeks) ~ 18/08/2010 – 18/10/2010
- NHS Economic Evaluation Database (NHS EED) via Cochrane; the search was conducted on the 21/10/2010.
- HEED Database

Evidence identification was with a focus on the disease area of juvenile arthritis with no restrictions on subtypes, population age or disease severity. Similarly there were no restrictions by treatment; all interventions in the treatment of JIA were considered appropriate and therefore included in the review. Finally, articles were included in the review if the abstract was in the English language.

A summary of the inclusion criteria for the search is presented below:

- **Study design** to include economic evaluations, pharmacoeconomic studies, cost effectiveness and cost utility analysis
- **Disease area** to include all juvenile arthritis (no restrictions by subtype)
- **Population** (no restrictions by age or disease severity)
- **Treatments** (no restrictions by treatment all interventions included)

The search strategy is included in Appendix 10, free-text and Medical Subject Headings were included, where appropriate. The search terms focused on population and study type as follows:

- Population terms included;
    - juvenile arthritis
    - rheumatoid arthritis
    - child
- Outcome terms included possibilities to retrieve studies containing information on modelling methods, cost and or utility data such as:
    - Pharmacoeconomic evaluation
    - Cost-effectiveness evaluation
    - Cost-minimisation study

Treatments were not included as terms in the search. The search strategy contained restrictions by publication type such that certain publication types e.g. letters and editorials were not retrieved. The searches were limited to humans. Identified citations were transferred and managed in a Refman12 file.

Study selection:
Included citations were indicated by “Inc”. Excluded citations were indicated by “Exc” and the reason for exclusion provided as follows:

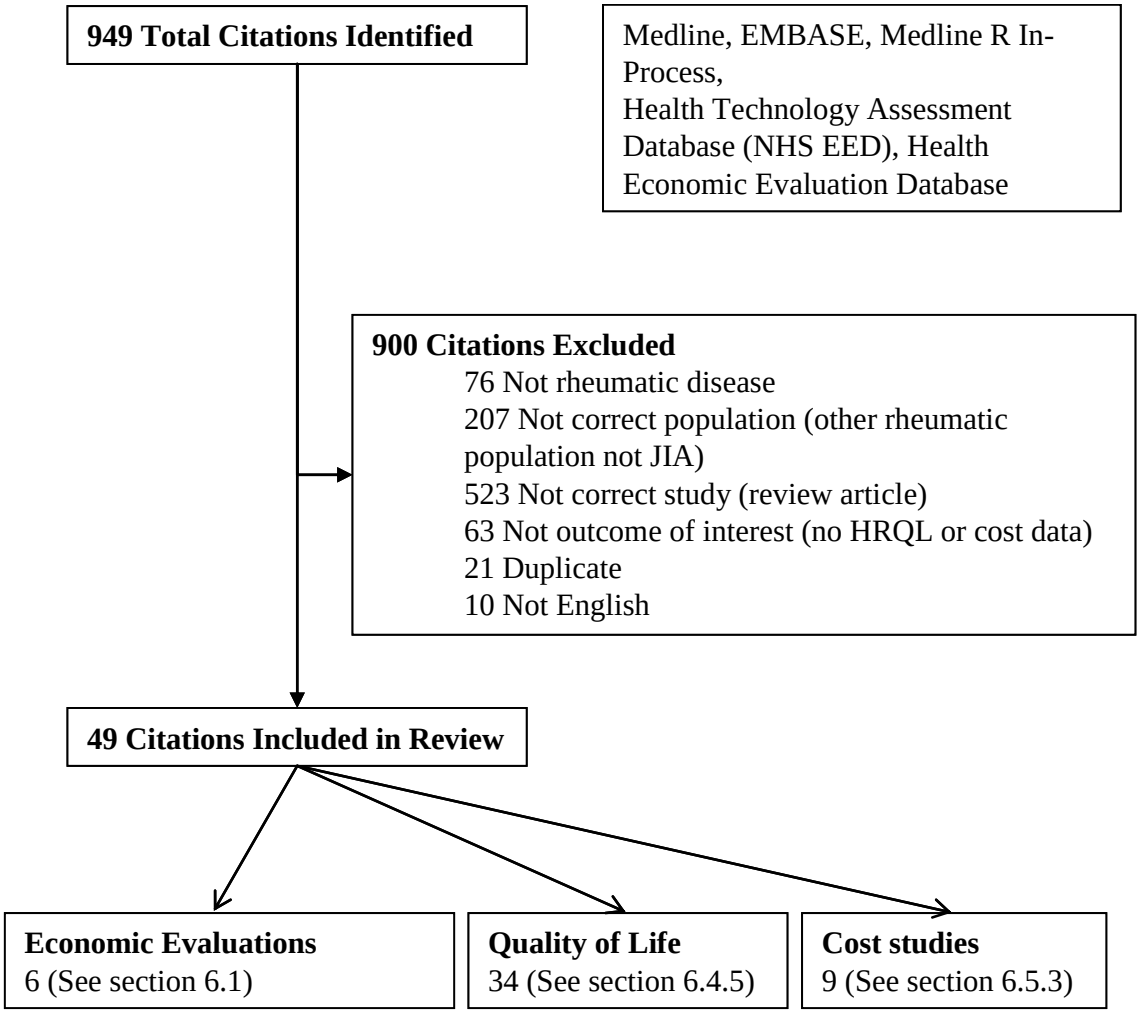
- “Not study” (not an economic or cost/utility study)
- “Not population” (not JIA population)
- “Not disease” (not arthritis related, other disease area)

- "Not outcome" (no cost or utility data reported)
- "Duplicate" (duplicate reference in the database)
- "Not English" (language of publication is other than English)

Studies Reviewed

The search on bibliographic databases was performed on 18/10/2010. The search retrieved 949 citations that were compiled in a single electronic file, comprising all records retrieved via the database searches, by exporting records from the respective platforms and importing them into a Reference Manager database file. Of the 949 citations 49 were selected and included in the review (see Figure below). Table 40 below presents a summary of the search results. The included studies were stratified according to study type. Of the 49 studies retrieved there were 6 economic evaluations, 9 cost studies and 34 focusing on quality of life (QoL).

Figure 7: Economic evidence review results



Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The literature search identified a total of 6 studies that present a synthesis of cost and effects. Of the total of 6 studies that were identified there were 3 cost-utility studies [Cummins et al. 2002, Epps et al. 2005 and Unger et al. 2010], 1 willingness to pay (WTP) study [Barron et al. 2004], 1 decision analysis regarding treatment options for knee monoarthritis [Beukelman et al. 2008] and 1 record that was not clear with regard to many domains including authors and study type [Budapest 2010]. See table below.

Table 40: Study characteristics and results (Economic Evaluations)

Study	Population	Treatment considered	Form of analysis	Type of model	Time-horizon	Main results	Relevance to the Decision Problem
Cummins et al. 2002 (review of Wyeth submission)	JIA	Etanercept vs. Placebo	Cost-utility	Not explicitly determined. Believed to be Markov model.	Lifetime	Base case ICER: £16,082. Sensitivity analysis ICER range: £3,900 - £34,000 Amended model ICER: £24,000	Not very relevant. Some information on resource use in the UK can be used for the C/E model. The model is an RA model adapted for JIA. The model has uncertain validity.
Barron et al. 2004	JIA	Hypothetical medications	WTP	No model considered	N/A	WTP $395 ± $329	Not relevant. The analysis is based on hypothetical interventions and elicits WTP.
Beukelman 2008	JIA	Optimal treatment of knee monarthritis	Decision analysis	Markov decision analysis comparing 3 treatment strategies	6 months	Of 3 most common treatment strategies compared: The number of patients that need to be treated with intraarticular corticosteroid injections is 3.8 with additional cost of 6.7 months of active arthritis	Not relevant.
Budapest University: Etanercept study 2006	JIA	Not clear	Not clear	Not clear	Not clear	Incremental QALY gain per patients is 0,72 QALY. ICER is 9.7million HUF per QALY (265HUF=1€)	No information is provided.
Epps 2005	JIA	Hydrotherapy	Cost utility	Model not defined	6 months	Patients in the combined group (+hydro) had slightly higher mean costs (£20.90) and lower mean QALYs (–0.0478).	Cost data and resource use may be relevant. QALYs specific for hydrotherapy not JIA population.
Ungar et al. 2010	JIA (poly articular)	Biologics in DMARD IR	Cost utility	Decision model	2 consecutive 6 month	The additional costs per additional ACR Ped 30 responder at one year (95% CI) were	Costs specific for Canada setting. Effectiveness combined

Study	Population	Treatment considered	Form of analysis	Type of model	Time-horizon	Main results	Relevance to the Decision Problem
					intervals	$26,061 (17,070, 41,834), $46,711 (30,042, 75,787), $16,204 (11,393, 22,608) and $31,209 (16,659, 66,220), for etanercept, adalimumab, abatacept and infliximab, respectively.	from several RCTs, response data used not QALYs therefore may not be useful.

DMARD IR: Disease modifying anti rheumatic drug inadequate response, ICER: Incremental cost effectiveness ratio, JIA: Juvenile idiopathic arthritis, QALY: quality-adjusted life year, WTP: willingness to pay

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

The instrument used to assess the quality for each of the economic evaluations was as described by Drummond and Jefferson [1996]. The economic evidence review identified a total of 6 studies that were classified as economic evaluations within the broad meaning of the term. Some of the identified studies did not consist of cost-effectiveness analysis. For these studies, the checklist recommended by Drummond and colleagues [1996] may not be appropriate for reasons described below. Although, Barron et al. [2004] and Beukelman et al. [2008] were subjected to the quality assessment process, it was found that many components of the checklist could not be applied. Barron et al. [2004] conducted a willingness to pay study for measuring health care preferences in hypothetical treatments rather than actual treatments. Beukelman et al. [2008] used a Markov decision analysis model for treatments in the area of JIA with the outcome of eradication of disease without an economic element. Although Beukelman et al. [2008] did not include any synthesis of costs in their analysis the study was reviewed to identify examples of disease progression for the de novo economic evaluation.

As a means of scoring and summarizing the quality of the individual studies the table below presents the results of the quality assessment in which the score for

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

each study was deduced by counting the total number of components with a yes response.

Table 41: Quality assessment of economic evidence studies

Author and Year	Score: total Yes out of possible 36 questions
Barron et al. 2004	12
Beukelman et al. 2008	11
Budapest study 2006	0
Cummins et al. 2002 (review of Wyeth submission)	20
Epps et al. 2005	25
Ungar et al. 2010	16

Individual quality assessments for each of the cost effectiveness studies are included in Appendix 11.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The economic evaluation is designed around the population of the TENDER trial [WA18221 - Roche Clinical Study Report 1035146, 2010] and in line with the final scope of the technology appraisal:

3. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids.

4. Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate.

Both of the above populations reflect the licensed indication of tocilizumab. The first group of patients reflects all patients in the TENDER trial. The second population is represented by the majority of patients in the TENDER trial.

With regards to the second population, the TENDER study includes 6 patients (5%) that are MTX naïve and therefore it cannot be inferred whether they would have inadequate response to MTX or not. The remaining 106 patients (95%) are all MTX-experienced and with active disease, and therefore, it can be assumed they have inadequate response to MTX.

In essence, the two populations greatly overlap; that is, the second population is a subgroup of the first. In practice, treatment with MTX is not very efficacious for sJIA patients, response to MTX treatment is not an important factor when stratifying the patient population [Giannini E et al. 1992, Albers H et al. 2009]. A brief overview of the typical patient care pathway is described in section 6.2.3. In the TENDER trial the use of MTX was permitted but not required by the protocol inclusion criteria [WA18221 - Roche Clinical Study Report 1035146, 2010].

The licensed indication of tocilizumab includes both monotherapy and combination with MTX. Use of background MTX in the trial was high at 70% of the patients. The economic evaluation compares tocilizumab with or without MTX (as licensed) versus MTX and versus a biologic (anakinra or etanercept). In the comparison with anakinra the model uses the administration regimen used in Quartier et al. [2010]. In the comparison with etanercept the model uses the same administration regimen with its indication in polyarticular JIA. In the first

comparison the control arm of the TENDER trial is refined to a subgroup of patients that receive both placebo and MTX. In the second comparison, since we have no evidence from the other studies on MTX-IR (see 5.7.3), the ITT population of the TENDER trial is used to indirectly compare tocilizumab to the respective biologics.

The cohort characteristics at the start of the model are summarised in the Table below.

Table 42: Cohort starting characteristics

Parameter	Value	Reference
Starting age	2 years	Assumption based on scope
Starting CHAQ score	1.702	Average CHAQ score at baseline from TENDER
Starting weight	13.25 kgs	Assumption based on data extrapolated by NICE 2001

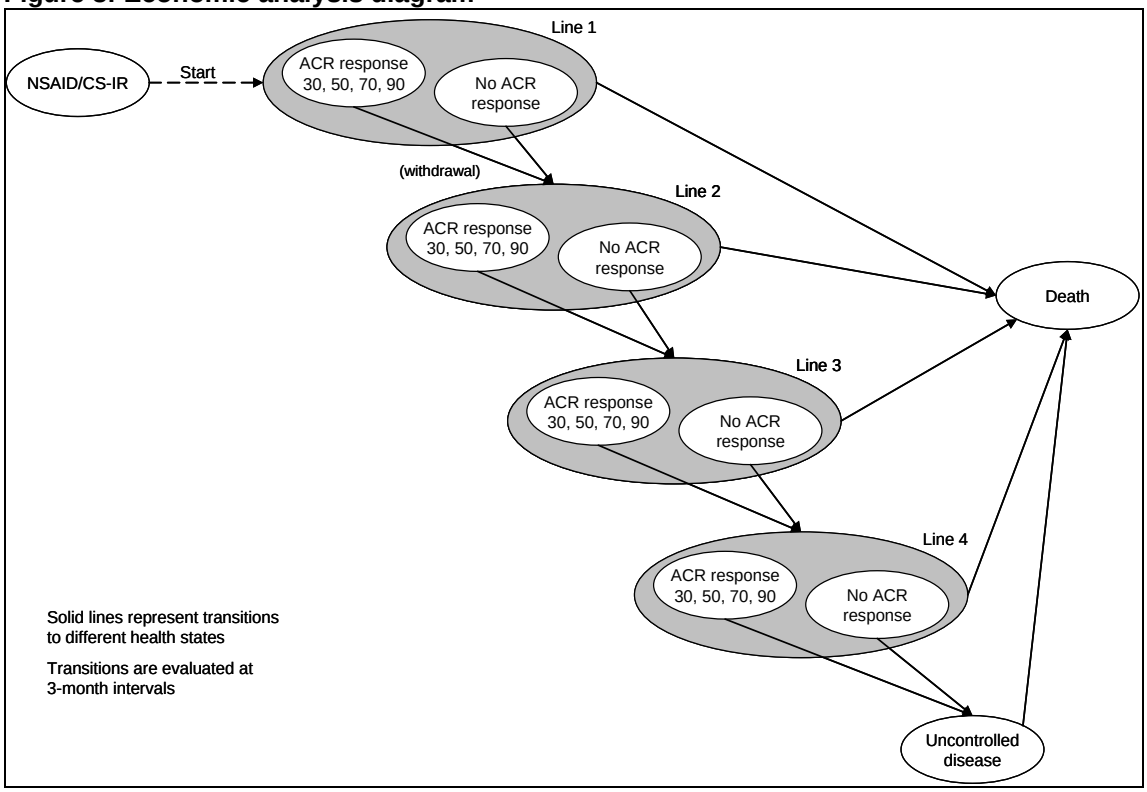
CHAQ: childhood health assessment questionnaire

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

The economic analysis employs a Markov chain to evaluate costs and effectiveness of the compared strategies. Transitions to health states are evaluated at 12-week time increments (cycles). The model outcomes are evaluated by cohort analysis. Half-cycle correction is applied to the model. A diagrammatic representation of the model is presented in the Figure below.

Figure 8: Economic analysis diagram



NSAID/CS-IR: Nonsteroidal anti-inflammatory drugs/corticosteroids-inadequate response, ACR response: American college rheumatology response criteria

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The structure of the model is developed to closely reflect real practice. The design allows the comparison of two clinical pathways for a cohort of patients with systemic JIA. The results of the model reflect the cost-effectiveness of the first treatment in either sequence. The additional treatment lines allow the assessment of all relevant costs and quality of life (QoL) impairment resulting from unsuccessful care.

Advice from clinical experts (Personal communication (PC): Westhovens R 02/03/2011, Wright S 16/03/2011, Woo P 21/03/2011, Baildam E 28/03/2011) determined the following clinical pathway for a typical patient:

First line treatment of patients with sJIA is NSAID or CS. Following inadequate response to NSAIDs and CSs (NSAID-IR, CS-IR), MTX is added. Nevertheless, in practice, in systemic JIA patients the addition of MTX rarely has successful results in their functional status and it is considered by clinicians almost equivalent to placebo treatment [Giannini E et al. 1992, Woo P et al. 2002, Albers H et al. 2009; PC: Wright S. 16/03/2011, Woo P. 21/03/2011].

The following treatment is largely determined by patient symptoms. If systemic symptoms are prevalent, clinicians would start with anakinra. Until recently, anakinra's efficacy in sJIA patients is not determined by solid RCT data (with exception the recently published Quartier et al. 2010), and therefore, it is not recommended for treatment in this population [Anakinra SPC accessed 20/03/2011]. However, its use is based on clinical experience that it has superior effects to other biologics on systemic JIA patients [PC: Westhovens R. 02/03/2011, Wright S. 16/03/2011, Woo P. 21/03/2011].

If arthritis symptoms are more prevalent than systemic ones, clinicians would administer etanercept. Following, inadequate response to etanercept clinicians would subsequently administer another biologic. It was suggested that clinicians would avoid the subsequent use of an anti-TNFα treatment if patients already demonstrated inadequate response to a previous one [PC: Westhovens R. 02/03/2011]. Others considered that clinicians would use biologic treatments that they are familiar with until they exhaust all possible options [PC: Wright S. 16/03/2011, E Baildam 28/03/2011]. Abatacept is recommended for use in polyarticular JIA patients after inadequate response to at least one anti-TNFα, placing it at a later line in the sequence [Abatacept SPC accessed 20/03/2011]. Adalimumab, given its indication in poluarticular JIA, can be used as an alternative to etanercept. However, due to the age of patients adalimumab is indicated for (13 to 17 years old) it can be assumed it is placed on later line in the treatment sequence. Two clinicians from the UK would not use abatacept before adalimumab in systemic patients [PC: Wright S. 16/03/2011, E Baildam

28/03/2011]. Infliximab is not recommended for JIA patients due to insufficient evidence [Infliximab SPC accessed 20/03/2011], nor it is widely used by clinicians as a treatment on systemic JIA patients after NSAID-IR or CS-IR and/or MTX-IR.

Given the above description of a typical patient clinical pathway the analysis considers the following treatment sequence for the first comparison:

	Strategy A	**Strategy B**
Line 1	Tocilizumab	Methotrexate
Line 2	Anakinra	Anakinra
Line 3	Etanercept	Etanercept
Line 4	Adalimumab	Adalimumab
Uncontrolled disease		

For the second comparison the analysis considers the following as base case:

	Strategy A	**Strategy B**
Line 1	Tocilizumab	Anakinra
Line 2	Etanercept	Etanercept
Line 3	Adalimumab	Adalimumab
Line 4	Abatacept	Abatacept
Uncontrolled disease		

and as sensitivity analysis:

(Etanercept scenario)

	Strategy A	**Strategy B**
Line 1	Tocilizumab	Etanercept
Line 2	Anakinra	Anakinra
Line 3	Adalimumab	Adalimumab
Line 4	Abatacept	Abatacept
Uncontrolled disease		

6.2.4 Please define what the health states in the model are meant to capture.

The model health states reflect the condition of patients after having tried treatment for a period of 12 weeks. Each health state represents a change in patients' condition from baseline to week 12 as determined by changes in CHAQ score; a functional status measure used in TENDER.

In essence, ACR response defines the level of improvement of patients based on a number of criteria. An analysis of the TENDER population identified a relationship between ACR response and changes in CHAQ scores. Patient CHAQ observations at baseline and week 12 were analysed to derive the CHAQ change from baseline based on ACR response. One patient, for whom the CHAQ at week 12 was not recorded, was excluded from the analysis. Since, change in CHAQ is assumed to be response-related and not treatment-related all patients were included in the analysis; that is, regardless of them having escaped to active treatment during the 12 weeks randomised period of the trial. The results of CHAQ change from baseline are presented in the Table below.

Table 43: Observed CHAQ changes

	Baseline CHAQ	CHAQ at week 12	Change from baseline	N
Total	1.7017	0.9982	-0.7035	111
Response	1.7055	0.8763	-0.8291	95
ACR 30	1.7727	1.3409	-0.4318	11
ACR 50	2.0250	1.4583	-0.5667	15
ACR 70	1.6708	0.8292	-0.8417	30
ACR 90	1.5902	0.5577	-1.0325	39
No-response	1.6797	1.7221	0.0424	16

CHAQ: childhood health assessment questionnaire, ACR response: American college rheumatology response criteria

The analysis assumes that the cohort enters the model with a starting CHAQ value. Change in patient CHAQ is determined by the level of ACR response after 12 weeks. The base case analysis assumes a starting CHAQ score for the cohort equal to that observed in the TENDER trial; 1.702 [WA18221 - Roche Clinical Study Report 1035146, 2010]. Sensitivity analysis considers alternative starting CHAQ score values. Based on the above starting score the CHAQ score reflected by each of the health states in the base case analysis is presented in the Table below.

Table 44: CHAQ score assumed for each health state

Health state name	CHAQ
No response or uncontrolled disease	1.7442
ACR 30	1.2699
ACR 50	1.1351
ACR 70	0.8601
ACR 90	0.6692

ACR response: American college rheumatology response criteria, CHAQ: Childhood health assessment questionnaire

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As discussed in section 2.1, patients with sJIA suffer from a combination of short term flares of the disease with extreme pain and discomfort, and long-term arthritis complications that can lead to permanent damage of the joints. In the TENDER study patients have already shown inadequate response to NSAID and CS and suffer from persistent symptoms of sJIA where short-term flares are not the only or the primary concern for clinicians.

The analysis adopts a structure that models disease progression based on the efficacy of each administered treatment and assumes no underlying improvement or deterioration of patient condition apart from that triggered by the treatment. There is no evidence to determine the rate of transition between health states of flare and quasi-remission. Moreover, a slow deterioration of patient condition for the proportion of the cohort with uncontrolled disease would be more in line with the population of the TENDER trial. However, the rate of this deterioration is not determined from the evidence. The assumption of no deterioration in uncontrolled disease is conservative against the cost-effectiveness of tocilizumab.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 45: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	16 years	Patient age 2-18 years	Assumption
Cycle length	12 weeks	Duration of randomised period of TENDER trial	[WA18221 - Roche Clinical Study Report 1035146, 2010]
Half-cycle correction	Implemented		NICE 2008
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs		NICE 2008
Discount of 3.5% for utilities and costs	Applied		NICE 2008
Perspective (NHS/PSS)	Applied		NICE 2008
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention (tocilizumab) is assumed to be used as indicated in its EU Summary of Product Characteristics (SPC). Tocilizumab is administrated by intravenous infusion (IV) as monotherapy or in combination with methotrexate (MTX). The analysis assumes concomitant medication with methotrexate for 70% of the model cohort [WA18221 - Roche Clinical Study Report 1035146, 2010].

To date, there is no other treatment indicated directly for patients with systemic JIA. The analysis assumes the comparators would have a similar administration regimen for systemic JIA patients as for other JIA subtype populations currently indicated[4].

Methotrexate is used in children with JIA, started at a dose of 10 to 15 mg/m^2 and is administered weekly, either orally or parenterally (subcutaneously or intramuscularly). The oral route is preferred by most pediatric rheumatologists because of its easier administration and greater child comfort; furthermore, there does not appear to be any advantage related to efficacy or safety with either the oral or parenteral method of administration [Ravelli A, et al. 1998]. Roche has no evidence on the body surface of the typical sJIA patient. The economic analysis assumes a dose of 10mg per administration. Due to the cost difference between methotrexate and the other biologics, the above assumption is not expected to have a notable impact on the cost-effectiveness results.

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNFα inhibitor. Abatacept has not been studied in children under 6 years old [Abatacept SPC accessed 20/03/2011]. The analysis assumes dosing and administration for children with sJIA would be similar to that of children with pJIA:

[4] Anakinra does not have any juvenile arthritis indication

- IV infusion
- Every 4 weeks:
    - 10 mg/kg for patient lighter than 75 kg or 6-17 years old
    - 750mg over 75kgs and <100kgs if patient over 17 years old

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in adolescents aged 13 to 17 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 SPC accessed 20/03/2011]. The analysis assumes dosing and administration for children with sJIA would be similar to that of children with pJIA: 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Concomitant use of methotrexate is assumed to be similar to that observed in the TENDER trial and as applied in the tocilizumab model arm (70% of the cohort) [WA18221 - Roche Clinical Study Report 1035146, 2010].

Anakinra is not recommended for the treatment of children or adolescents due to insufficient evidence. The analysis considers anakinra as the base case analysis given wide use of this treatment amongst physicians based on clinical experience of its efficacy on systemic JIA patients. The model uses the administration regimen used in Quartier et al. [2010] for anakinra: 2mg/kg administered via subcateneous injection.

Etanercept is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of 4 years who have had an inadequate response to, or who have proved intolerant of, methotrexate [Etanercept SPC accessed 20/03/2011]. The analysis assumes dosing and administration for children with sJIA would be similar to that of children with pJIA: 0.4mg/kg twice a week (up to a maximum of 25 mg per dose) via subcateneous injection [Etanercept SPC accessed 20/03/2011].

Infliximab is not recommended for the treatment of children or adolescents with JIA due to insufficient evidence [Infliximab SPC accessed 20/03/2011].

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

This is not applicable; no treatment continuation rule is assumed in the analysis.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Treatment response/no response:

The economic evaluation uses ACR response rates as indication of treatment efficacy. Observed ACR response from the clinical trial is used for the comparison TCZ vs. MTX. As described in section 6.2.1 the control arm of the TENDER trial is refined to a subgroup of patients that receive both placebo and MTX for this comparison.

ACR response rates from the indirect comparison of the TENDER trial, Quartier et al. [2010], and Ruperto et al. [2007] (see section 5.7) are used for the model comparisons versus anakinra and all other biologics.

The economic model uses the above ACR data to allocate patients to different health states based on level of response. Patients that don't achieve response are assigned to the next treatment line where a similar process follows. The analysis assumes that patients try each treatment for 12 weeks before response levels are evaluated. This is consistent with the observed clinical trial data and the indirect comparison results.

Roche acknowledges that the starting age of the model cohort is different to the average baseline age (10 years). This potentially introduces inaccuracy to the model assumptions given that the ACR response probabilities used in the model

reflect patients with age of 10 years rather than 2 years. Due to the small number of patients with age less than 4 years it is not possible to undertake the appropriate heterogeneity analysis for ACR response of the younger population.

Nevertheless, evidence suggests that the peak age of onset of sJIA is between 18 months and 2 years [Woo et al. 2006]. In a UK cohort the peak age was 2 years and 61% of patients had an age of onset of 5 years or below [Fishman et al. 1998]. In the CAPS study, another UK prospective study, the median age of onset is reported to be 6.4 years [Adib et al. 2008], indicating that although there is some variability in the age of disease onset, in the UK in most cases disease onset is below 10 years.

Roche is mindful that existing NICE guidance for adult RA patients define response and stopping rules according to DAS. However, this is not a relevant clinical endpoint for juvenile arthritis patients.

Withdrawal from treatment:

Discontinuation of treatment is assumed to be determined by a constant risk of withdrawal. The withdrawal risk is identified from secondary sources and it is assumed to reflect withdrawal due to lack of efficacy.

In order to obtain this evidence for the model comparators a rapid review was performed. The relevant studies identified from the evidence review were assessed for their coverage of long-term data. Studies with a follow up of less than 4 months and also studies with a sample size of less than 20 patients were excluded. Follow up and treatment duration were recorded for each study where it was available and also any information on number of patients remaining at specified times.

A summary of the data extracted separately for methotrexate and biologic treatments is shown in Table 46 and Table 47 below.

Table 46: Evidence of treatment withdrawal for MTX

Study	Drug	Follow up duration	Outcomes Reported	Sample size	Tx duration	Withdrawal evidence
Woo 2000	MTX vs placebo	4 months	Physicians assessment ESR, joint score, limited joint	88 (45 systemic arthritis, 43 extended oligoarticular)	4 months	Total of 9 patients withdrew. 7 patients in systemic arthritis group withdrew, all except 1 because of exacerbation of systemic disease. 2 of 6 during placebo period, remaining 4 during active period. 2 patients withdrew from extended oligoarticular arthritis group.
Giannini 1992	MTX vs placebo	6 months	No. joints with swelling, no. joints with pain, no. joints with tenderness	Low dose MTX: 46, very low dose MTX: 40, placebo 41 (127 randomised)	6 months (108 completed)	108 completed entire 6 month trial (including 97 (85%) of the 114 in the efficacy subgroup
Giannini 1993 (results from 3 trials)	MTX vs placebo	Study 1:12 months, studies 2 and 3: 6 months	No. active joints	520	Study 3 MTX 15% drop out by 6 months (study 3 as Giannini 1992).	
Silverman 2005	Leflunomide or MTX	16 weeks plus 32 week extension study	No. active joints, no. joints with limited range of motion global assessment physician and patient, CHAQ DI, ESR	Leflunomide (47) Methotrexate (47)	86 completed initial study, 70 entered extension study (37 enter MTX group)	During extension 5 patients in MTX group withdrew
Ruperto 2004	MTX either intermediate or higher dose no placebo control	6 months	ACR 30, 50, 70	Randomised to intermediate dose N=40, Randomised to higher dose N=40	6 dropped from intermediate dose, 11 dropped from higher dose arm	Intermediate dose: n=6 dropped (3 disease flare, 2 adverse events, 1 parents refusal). Higher dose: n=11 dropped (5 adverse events, 3 insufficient effect, 2 parents refusal, 1 lost to follow up)

Tx: Treatment, MTX: Methotrexate

Table 47: Evidence of treatment withdrawal for biologic treatments

Study	Drug	Follow up duration	Outcomes Reported	Sample size	Tx duration	Withdrawal evidence
Ruperto 2010	Abatacept	21 months	ACR 30,50,70,90	153 enter LTE	Median 1069 days, Range 168-1457. 59% patients treated for at least 36 months.	153 entered LTE. 42 patients who entered LTE discontinued treatment (10 patients from treatment group, 16 from placebo group, 16 from group of non responders. 20 of 42 discontinued due to lack of efficacy, 55% (11 of 20) were from the group of non responders. 3 of 42 discontinued due to AEs and the remainder were lost to follow up or discontinued for other reasons.
Lequerre 2008	Anakinra	14.7 months	30,50	20 systemic onset	Mean follow up 14.7 months (2-27 months (range))	2 SJIA patients stopped anakinra treatment during the first 3 months and 3 patients stopped treatment between months 3 and 6. Treatment withdrawal in these 5 patients was either due to intolerance (1 case) or a lack of efficacy (4 cases)
Lovell 2003	Etanercept	2-3 yrs	30,50,70	58	2 years	10 patients discontinued. Patient discontinuations shown during 1st 2 years of extension trial in article. At end of 2 years 83% patients continued in study.
Lovell 2006	Etanercept	4 yrs	30,50,70	58 patients entered LTE study 34 patients remain	4 years	See 8 year data
Lovell 2008	Etanercept	8 yrs	30,50,70	58 patients entered LTE study 26 patients entered 8th year.	8 years	Of 58 patients who enrolled in OLE, 7 (12%) discontinued because of a suboptimal clinical response, 5 (9%) discontinued because of parent or guardian refusal to continue participation, 4 (7%) discontinued because of AEs, and 3 pts each (5% each) discontinued because of patient refusal to continue, because of protocol issues or because they were lost to follow up
Prince 2009	Etanercept	2.5 yrs	30,50,70	146	Median duration of Etanercept therapy was 1.7 yrs (range	Etanercept use (0-80 months)

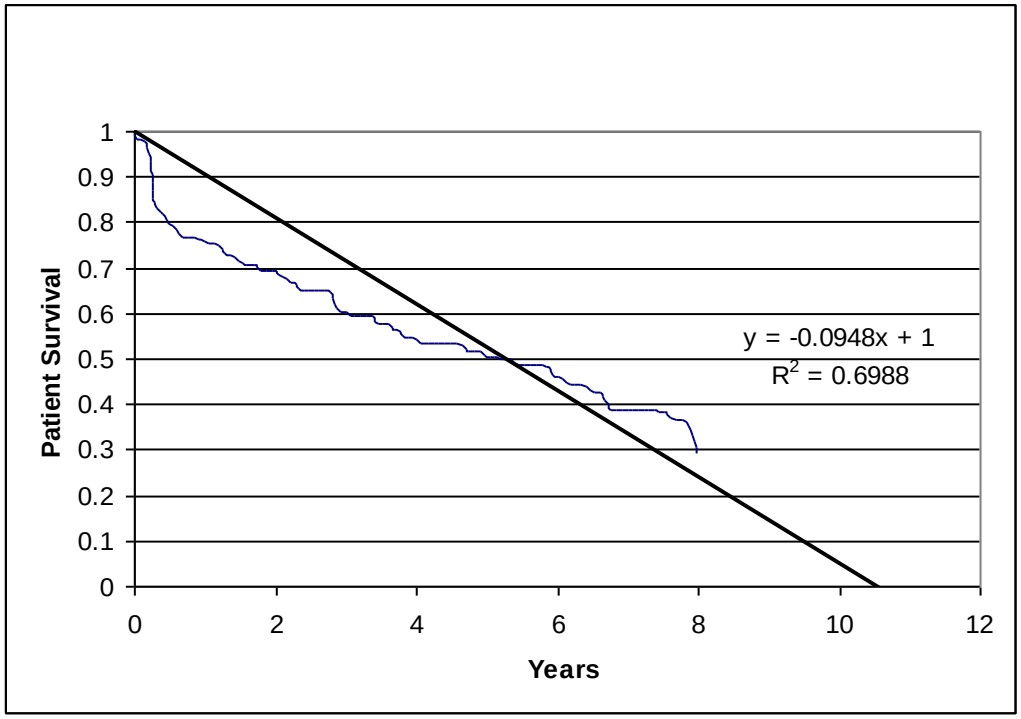
					0.1 to 6.8 yrs).	
Horneff 2004	Etanercept	2 yrs (registry)	30,50,70	322	1-48 months, mean length 13.4 (10.5) months, median 12 months.	287,229,194,139 and 106 patients had been treated for at least 6,12,18, 24 and 30 months respectively

LTE: Longterm extension, AEs: adverse events, OLE: open label extension

For MTX treatment, the most recent evidence is from Ruperto et al. [2004] and Woo et al. [2000]. Evidence from Woo et al. [2000] is selected for the base case analysis as it reflects data for the systemic subtype populations. Woo et al. [2000] is a crossover study, in which it is reported that over a period of 4 months 4 patients out of a sample of 45 withdrew due to exacerbation of systemic condition. The withdrawal risk assumed is 9% for 4 month duration.

For biologic treatments the review identified a number of sources with evidence on withdrawal; the majority of them based on treatment with etanercept. Due to insufficient evidence to differentiate between treatments, the economic analysis assumes the same withdrawal risk across all biologics. The base case analysis assumes the annual risk of withdrawal is based on Lovell et al. [2008]. Lovell et al. [2008] was selected as the most relevant evidence given duration of the observational data (8 years). A constant risk of withdrawal over a year is assumed to be 9.48% (R^2=0.70). An annual risk of withdrawal around 10% is also supported by clinical expert opinion [PC: Wright S. 16/03/2011, Woo P. 21/03/2011, Baildam E 28/03/2011].

Figure 9: Assumed constant withdrawal risk for biologic treatments

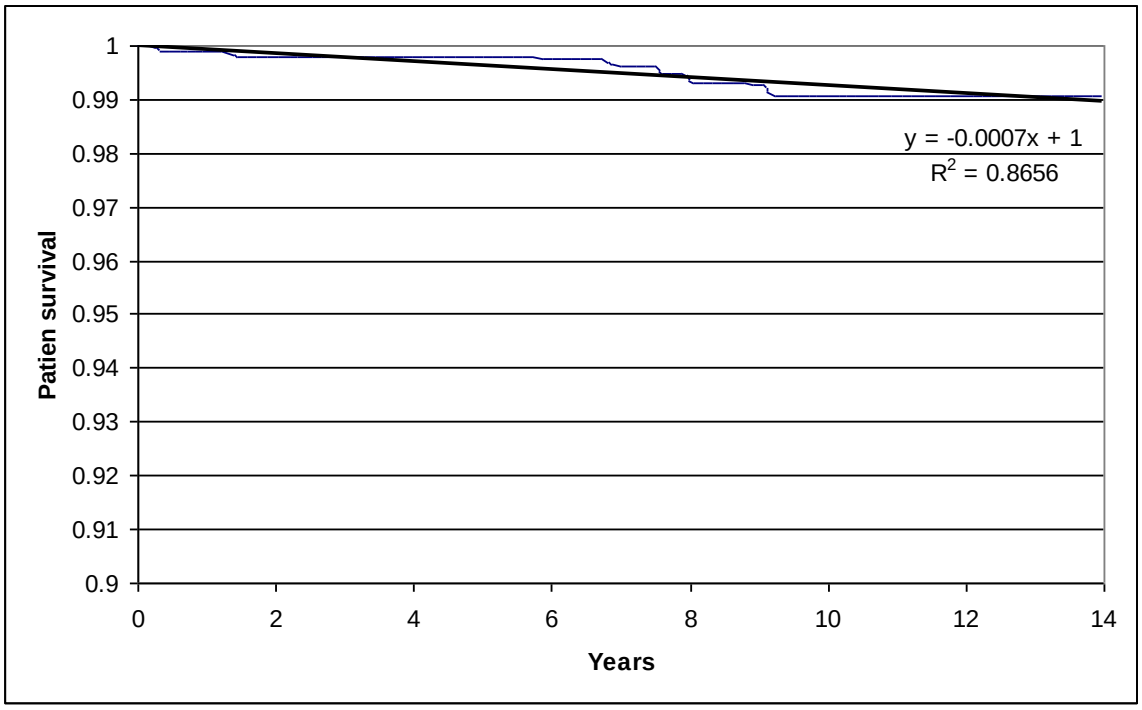


Mortality risk

Due to lack of data to determine elevated mortality risk dependent on the patient condition, the model assumes a constant mortality risk based on evidence from Hashkes et al. [2010]. Hashkes and colleagues [2010] studied records of a paediatric registry in the US (49,000 patients) and provide evidence on the observed survival of patients by subtype of JIA. The study reports that systemic disease is a predictor of higher mortality risk. Nevertheless, the standardised mortality ratio (SMR) reported on 962 patients with systemic JIA is not statistically significant (p=0.15). Evidence from a figure of the observed mortality in sJIA patients, as reported by Hashkes et al. [2010], was extracted and a constant annual risk of mortality was estimated; 0.07% (R^2=0.8656). This risk is applied across all treatments and all health states and is included in the analysis for completion, without having an impact on the incremental cost-effectiveness results. The annual mortality risk is assumed to have a range between 0.000076

(lowest risk in UK population for 2-18 year old patients) [ONS 2011] to 0.001324 (apply equal difference over 0.0007).

Figure 10: Assumed constant mortality risk



6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Probabilities of response/no-response to treatment

In the first comparison (tocilizumab vs. MTX) evidence from the TENDER clinical trial is used for the transitions probabilities for ACR 30, ACR 50, ACR 70, ACR 90 response and no-ACR 30 response. The proportion of the cohort that falls within each response category is obtained by adjusting the reported response rates in order to ensure the categories are non-overlapping. The transformation involves a simple re-expression of these proportions in non-overlapping categories. To obtain the final ACR probability input and avoid the double-counting of patients, the following method was utilised:

1. the proportion of ACR 30 includes ACR 50, ACR 70, and ACR 90

2. subtract from ACR 30 the sum of the other 3 categories

3. continue the same with ACR 50, and ACR 70

Table 48: ACR evidence comparison TCZ vs. MTX

	Methotrexate	Tocilizumab	Reference
ACR 30	0.154	0.907	WA18221 - Roche Clinical Study Report 1035146, 2010
ACR 50	0.077	0.853	
ACR 70	0.077	0.707	
ACR 90	0.038	0.373	

ACR response: American college rheumatology response criteria

Table 49: ACR probabilities: comparison TCZ vs. MTX

	Methotrexate	Tocilizumab	PSA distribution
pACR NR	0.846	0.093	Dirichlet
pACR 30	0.077	0.054	
pACR 50	0	0.146	
pACR 70	0.039	0.334	
pACR 90	0.038	0.373	

ACR response: American college rheumatology response criteria

In the second comparison (tocilizumab vs. anakinra) the result of the indirect comparison (as discussed in 5.7) is used for the transition probability for ACR 30. The RR of ACR 30 for tocilizumab versus anakinra is used to derive the probability of ACR 30 with anakinra treatment, given the probability of ACR 30 with tocilizumab treatment (see Table below).

The ANAJIS study [Quartier et al. 2010] reports evidence for 1 month. The ACR 30 response probability from the indirect comparison could be further adjusted to reflect projected response to anakinra at 12 weeks. A degradation of ACR 30 response probability for anakinra for longer than the trial duration is supported by the reported evidence: around 50% of responders to the modified ACR 30 lost response after 1 month. However, due to lack of evidence to perform this adjustment, the base case analysis assumes no degradation for the anakinra

ACR 30 response. This assumption is conservative against tocilizumab since further degradation of response for anakinra would improve the cost-effectiveness results.

The probabilities of ACR 50, ACR 70 and ACR 90 are derived by applying to the probability of ACR 30 with anakinra the relative difference of ACR 50 to ACR 30, ACR 70 to ACR 30, and ACR 90 to ACR 30 with tocilizumab (see Table below).

Table 50: ACR evidence comparison TCZ vs. ANK

	Tocilizumab	Anakinra	Anakinra rates adjustment
ACR 30	0.907	0.3827	Based on RR= 2.37 (section 5.7)
ACR 50	0.853	0.3599	Adjusted based on difference ACR 50-30 TCZ
ACR 70	0.707	0.2983	Adjusted based on difference ACR 70-30 TCZ
ACR 90	0.373	0.1574	Adjusted based on difference ACR 90-30 TCZ

ACR response: American college rheumatology response criteria, ANK: anakinra, RR: Relative risk TCZ, tocilizumab

Table 51: ACR probabilities: comparison TCZ vs. ANK

	Tocilizumab	Anakinra	PSA distribution
pACR NR	0.093	0.617	Dirichlet
pACR 30	0.054	0.023	
pACR 50	0.146	0.062	
pACR 70	0.334	0.141	
pACR 90	0.373	0.157	

ACR response: American college rheumatology response criteria, ANK: anakinra, RR: Relative risk TCZ, tocilizumab

The ACR response of the other biologics is derived by the indirect comparison of TENDER versus Ruperto et al. 2007. Similarly to the above, the relative risk is used to derive the probability of ACR 30, ACR 50 and ACR 70 for the other biologics. The probability of ACR 90 is derived by applying to the probability of ACR 50 with biologic the relative difference of ACR 90 to ACR 50 with tocilizumab (see Table below).

The ACR response in Ruperto et al. 2007 reflects a JIA population of which only 16% are systemic JIA patients. The indirect comparison results are further

adjusted for the differences in the population subtypes. Data from an observational study by Prince et al. [2009] are used to correct ACR response rates of biologics. Prince and colleagues [2009] report long-term efficacy data from a Dutch registry. The study reports evidence from 146 patients, out of which 27% were systemic JIA. The adjustment factor consists of the difference in the proportion of responders between the total population and the systemic JIA patients (see Table below).

Table 52: Prince et al. 2009 adjustment

	Total patients	sJIA	Adjustment factor	Reference
ACR 30	79%	59%	0.75	Prince et al. 2009
ACR 50	67%	43%	0.65	Prince et al. 2009
ACR 70	51%	27%	0.53	Prince et al. 2009

ACR response: American college rheumatology response criteria,

Table 53: ACR evidence comparison TCZ vs. biologics

	Tocilizumab	Biologics	Biologics rates adjustment
ACR 30	0.907	0.238	Based on RR= 2.87 (section 5.7) with Prince 2009 adjustment
ACR 50	0.853	0.103	Based on RR= 5.35 (section 5.7) with Prince 2009 adjustment
ACR 70	0.707	0.082	Based on RR= 4.61 (section 5.7) with Prince 2009 adjustment
ACR 90	0.373	0.045	Adjusted based on difference ACR 90-50 TCZ

ACR response: American college rheumatology response criteria, RR: relative risk

Table 54: ACR probabilities: comparison TCZ vs. biologics

	Tocilizumab	Biologics	PSA distribution
pACR NR	0.093	0.762	Dirichlet
pACR 30	0.054	0.135	
pACR 50	0.146	0.021	
pACR 70	0.334	0.037	
pACR 90	0.373	0.045	

ACR response: American college rheumatology response criteria, PSA: Probabilistic sensitivity analysis

Withdrawal and mortality risk

The withdrawal risk was adjusted for the duration of the cycle. If the true transition rate is assumed to be constant over the corresponding time period then the probability P_j can be estimated by:

$P_j = 1 - [1 - P_{(t_0, t_j)}]^{1/j}$ where j represents the number of equal time intervals [Miller et al. 1994].

Table 55: Withdrawal probabilities

	Reported risk	Adjusted risk
MTX	0.0889 per 4 months	0.0674 per 12 weeks
All biologics	0.0948 per year	0.0227 per 12 weeks

MTX: methotrexate

A similar adjustment was applied to the mortality risk from 0.0007 per year to 0.000162 per 12 weeks.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Transition probabilities reflecting ACR response are applied at 12 week intervals and reflect the risk of response (or no response) during this period. A time-dependent adjustment (degradation) of response could be appropriate given the chronic characteristics of the disease. The adjustment would degrade response based on time from start of the analysis; effectively assuming a lower chance of response to treatment dependent on disease duration. However, no evidence was identified to introduce such an adjustment to response probabilities.

The withdrawal risk could be expressed as a time-dependent probability based on a function that reflects survival on treatment. Given the evidence on withdrawal risk with MTX and other biologics, it was not possible to differentiate greatly across treatments on this parameter. In particular, the model assumes the same withdrawal risk for all biologic treatments. Given the above assumption, a constant risk was in line with the objectives of the current analysis and model parsimony.

The mortality risk could be expressed as an age-dependent probability based on UK life tables. However, given the availability of evidence on mortality of the analysis population from a recent study on systemic JIA patients it was deemed more appropriate to use disease-specific risk. The use of a constant risk based on Hashkes et al. [2010] is supported by the evidence; R^2=0.8656. In addition, due to lack of data to determine elevated mortality risk dependent on the patient condition, the model assumes the same probability across all treatments and all health states and is included in the analysis for completion, without having an impact on the incremental cost-effectiveness results.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcome measures are linked to final outcomes related to cohort transitions. The CHAQ scores derived from the TENDER trial were used as a surrogate endpoint to calculate utility measurements in the economic analysis.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A structure for an interview with questions on the clinical and economic impact of the condition was prepared by an independent consultant. The interview included questions on the patients of interest, disease management, adverse events, HRQL, disease progression and utilisation and cost.

Four clinicians were selected for the interview process based on their experience in the area of systemic JIA and also familiarity with economic evaluations. A separate telephone interview took place with Professors Rene Westhovens, Patricia Woo and Dr Eileen Baildam dated 2/3/2011, 21/3/2011, and 28/03/2011 respectively. A face to face meeting took place for the interview with S Wright dated 16/03/2011. Although Dr Stephen Wright is the clinical scientist of the TENDER trial the interview did not contain any treatment specific questions so his expertise in the area of systemic juvenile arthritis in the UK is considered relevant and appropriate to be used here.

Given the sequence of the interviews, evidence provided by Professor Westhovens was validated by Dr Wright, Professor Woo and Dr Baildam.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 56: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Starting age of typical patient	2 years	CI N/A; No sampling performed	Section 6.2.1
Starting CHAQ of typical patient	1.702	CI N/A; No sampling performed	Section 6.2.1
Starting weight of typical patient	13.25 kgs	CI N/A; No sampling performed	Section 6.5.5
Children requiring assistance for injection	0.20	Assume CI: 0.0824, 0.3176; Beta	Section 6.5.5
Young persons requiring assistance for injection	0.10	Assume CI: 0.0412, 0.1588; Beta	Section 6.5.5
Young person age	10.00	Assume CI: 7 ,13; Uniform	Section 6.5.5
Discounting	0.035	CI N/A; No sampling performed	Section 6.2.6
Transition probabilities			
ACR30 Abatacept	0.1352	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR30 Adalimumab	0.1352	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR30 Anakinra	0.0228	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR30 Etanercept	0.1352	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR30 Methotrexate	0.0770	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR30 Tocilizumab	0.0540	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR50 Abatacept	0.0213	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR50 Adalimumab	0.0213	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR50 Anakinra	0.0616	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR50 Etanercept	0.0213	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution	Section 6.3.2

		for each ACR category	
ACR50 Methotrexate	0.0000	CI N/A; Dirichlet distribution: assume N=alpha=0.01 of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR50 Tocilizumab	0.1460	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Abatacept	0.0367	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Adalimumab	0.0367	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Anakinra	0.1409	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Etanercept	0.0367	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Methotrexate	0.0390	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR70 Tocilizumab	0.3340	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Abatacept	0.0451	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Adalimumab	0.0451	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Anakinra	0.1574	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Etanercept	0.0451	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Methotrexate	0.0380	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
ACR90 Tocilizumab	0.3730	CI N/A; Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	Section 6.3.2
Withdrawal all biologics	0.0227	Assume CI: 0.0094, 0.0361; Beta	Section 6.3.2
Withdrawal methotrexate	0.0674	Assume CI: 0.0278, 0.1071; Beta	Section 6.3.2
Mortality risk	0.0002	Assume CI: 0.000018, 0.0003; Beta	Section 6.3.2
Utility scores			
uACR30 (annual values)	0.5674	CI N/A; Sampling linked to ACR-No response	Section 6.4.9

uACR50 (annual values)	0.6050	CI N/A; Sampling linked to ACR-No response	Section 6.4.9
uACR70 (annual values)	0.6736	CI N/A; Sampling linked to ACR-No response	Section 6.4.9
uACR90 (annual values)	0.7150	CI N/A; Sampling linked to ACR-No response	Section 6.4.9
uACRNR (annual values)	0.4152	Assume CI: 0.1711, 0.6593; Beta	Section 6.4.9
Unit costs			
Treatment cost Abatacept	£242.17 per 250mg	CI N/A; No sampling performed	Section 6.5.5
Treatment cost Adalimumab	£357.50 per 40mg	CI N/A; No sampling performed	Section 6.5.5
Treatment cost Anakinra	£26.23 per 100mg	CI N/A; No sampling performed	Section 6.5.5
Treatment cost Etanercept	£83.38 per 25mg	CI N/A; No sampling performed	Section 6.5.5
Treatment cost Methotrexate	£0.5649 per 10mg	CI N/A; No sampling performed	Section 6.5.5
Treatment cost Tocilizumab	£102.40 per 80mg, £256 per 200mg, and £512 per 400mg	CI N/A; No sampling performed	Section 6.5.5
Inpatient stay (per day)	£428.32	CI N/A; No sampling performed	Section 6.5.6
GP visit (per visit)	£32.00	CI N/A; No sampling performed	Section 6.5.6
Haematological (per visit)	£91.00	CI N/A; No sampling performed	Section 6.5.6
Radiological (per visit)	£139.55	CI N/A; No sampling performed	Section 6.5.6
Podiatrist (per visit)	£11.00	CI N/A; No sampling performed	Section 6.5.6
Opthalmologist (per visit)	£70.47	CI N/A; No sampling performed	Section 6.5.6
Rheumatology paediatric (per visit)	£266.66	CI N/A; No sampling performed	Section 6.5.6
Psychologist paediatric (per visit)	£89.00	CI N/A; No sampling performed	Section 6.5.6
Orthodontist (per visit)	£101.00	CI N/A; No sampling performed	Section 6.5.6
Occupational therapist (per visit)	£15.00	CI N/A; No sampling performed	Section 6.5.6
Full blood count (per test)	£15.41	CI N/A; No sampling performed	Section 6.5.6

Liver function test (per test)	£8.55	CI N/A; No sampling performed	Section 6.5.6
Erythrocyte sedimentation rate (per test)	£15.41	CI N/A; No sampling performed	Section 6.5.6
C-reactive protein (per test)	£15.41	CI N/A; No sampling performed	Section 6.5.6
Urea, electrolytes and creatinine (per test)	£0.11	CI N/A; No sampling performed	Section 6.5.6
Administration cost per IV infusion	£149.76	Assume CI: £61.70, £237.82; Gamma	Section 6.5.5
Nurse visit cost (per visit)	£13.00	Assume CI: £6.00, £20.00; Gamma	Section 6.5.5
Resource use for response			
Inpatient stay (annual units)			
Number of days	7.50	Assume CI: 5, 10; Gamma	Section 6.5.6
Proportion of pts ACR 30	0.2250	Assume CI: 0.20, 0.25; Beta	Section 6.5.6
Proportion of pts ACR 50	0.1475	CI N/A; Sampling linked to pts with ACR 30 response	Section 6.5.6
Proportion of pts ACR 70	0.0715	CI N/A; Sampling linked to pts with ACR 30 response	Section 6.5.6
Proportion of pts ACR 90	0.0000	CI N/A; Sampling linked to pts with ACR 30 response	Section 6.5.6
GP visit (annual units)			
Number of visits	3.50	Assume CI: 3, 4; Gamma	Section 6.5.6
Haematological (annual units)			
Number of visits	2.00	Assume CI: 0.824, 3.1760; Gamma	Section 6.5.6
Radiological (annual units)			
Number of visits	2.00	Assume CI: 0.824, 3.1760; Gamma	Section 6.5.6
Proportion of patients	0.20	Assume CI: 0.0824, 0.3176; Beta	Section 6.5.6
Podiatrist / foot problems management (annual units)			
Number of visits	1.00	Assume CI: 0.412, 1.588; Gamma	Section 6.5.6
Proportion of patients	0.025	Assume CI: 0.02, 0.03; Beta	Section 6.5.6
Opthalmologist (annual units)			
Number of visits	2.00	Assume CI: 0.824, 3.1760; Gamma	Section 6.5.6
Proportion of patients	1.00	CI N/A; No sampling performed	Section 6.5.6
Rheumatology paediatric			

(annual units)			
Number of visits	3.00	Assume CI: 1.236, 4.764; Gamma	Section 6.5.6
Proportion of patients	1.00	CI N/A; No sampling performed	Section 6.5.6
Psychologist paediatric (annual units)			
Number of visits	1.00	Assume CI: 0.412, 1.588; Gamma	Section 6.5.6
Proportion of patients	0.20	Assume CI: 0.0824, 0.3176; Beta	Section 6.5.6
Orthodontist (annual units)			
Number of visits	1.00	Assume CI: 0.412, 1.588; Gamma	Section 6.5.6
Proportion of patients	0.20	Assume CI: 0.0824, 0.3176; Beta	Section 6.5.6
Occupational therapist / hand problem management (annual units)			
Number of visits	1.00	Assume CI: 0.412, 1.588; Gamma	Section 6.5.6
Proportion of patients	0.20	Assume CI: 0.0824, 0.3176; Beta	Section 6.5.6
Outpatient diagnostic tests (annual units)			
Number of tests	3.00	Assume CI: 1.236, 4.764; Gamma	Section 6.5.6
Resource use for No-response/uncotrolled disease			
Inpatient stay (annual units)			
Number of days	24.50	Assume CI: 21, 28; Gamma	Section 6.5.6
Proportion of patients	0.9	CI Assume range 0.85 – 0.95; Beta	Section 6.5.6
GP visit (annual units)			
Number of visits	20.8	Assume CI: 16.5, 25; Gamma	Section 6.5.6
Haematological (annual units)			
Number of visits	12.00	Assume CI: 5, 19; Gamma	Section 6.5.6
Radiological (annual units)			
Number of visits	2.00	CI: N/A; Sampling linked to response health state value	Section 6.5.6
Proportion of patients	0.90	CI: Assume range 0.85, 0.95; No sampling performed	Section 6.5.6
Podiatrist (annual units)			
Number of visits	1.00	CI: N/A; Sampling linked to response health state value	Section 6.5.6

Proportion of patients	0.10	Assume CI: 0.0412, 0.1588; Beta	Section 6.5.6
Opthalmologist (annual units)			
Number of visits	2.00	CI: N/A; Sampling linked to response health state value	Section 6.5.6
Proportion of patients	1.00	CI N/A; No sampling performed	Section 6.5.6
Rheumatology paediatric (annual units)			
Number of visits	10.00	Assume CI: 4.12, 15.88; Gamma	Section 6.5.6
Proportion of patients	1.00	CI N/A; No sampling performed	Section 6.5.6
Psychologist paediatric (annual units)			
Number of visits	1.50	Assume CI: 1, 2; Gamma	Section 6.5.6
Proportion of patients	0.85	Assume CI: 0.75, 0.95; Beta	Section 6.5.6
Orthodontist (annual units)			
Number of visits	1.00	Assume CI: 0.412,1.588; Gamma	Section 6.5.6
Proportion of patients	0.35	Assume CI: 0.14, 0.56; Beta	Section 6.5.6
Occupational therapist (annual units)			
Number of visits	3.50	Assume CI: 3, 4; Gamma	Section 6.5.6
Outpatient diagnostic tests (annual units)			
Number of tests	18.00	Assume CI: 12, 24; Gamma	Section 6.5.6
Proportion of patients	0.10	CI N/A; Sampling linked to inpatient stay	

ACR: American college rheumatology response criteria, CHAQ: Childhood health assessment questionnaire

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Not applicable.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumptions on clinical parameters and model structure:

- ACR response is the main efficacy measure of each treatment; this is a common approach in economic evaluations of arthritis treatments in adults [NICE 2010] and is used before in children [Cummins et al. 2002]. ACR response is used given wide use amongst clinical trials, allowing a comparison with the majority of available treatments.

- Health states reflect CHAQ status; this is a structural assumption and allows the synthesis of efficacy (ACR) and HRQL evidence. ACR alone is a measure of relative change from baseline. CHAQ is an absolute measure and can be assigned a HRQL value.

- Disease-duration-related response. Due to lack of data to adjust response to treatment based on disease duration, the analysis assumes the same

response to treatment as observed from the TENDER trial or from the indirect comparison results.

- Initial response to treatment is evaluated after 12 weeks; this timeframe is in line with the observed evidence from TENDER and other clinical trials used in the indirect comparison [Ruperto et al. 2007].

- TENDER ITT population is used for the second comparison; see details in 6.2.1. A subgroup analysis addresses this assumption. The changes in the ACR response results and in cost-effectiveness results are minimal.

- Anakinra ACR response is not adjusted; see details in 6.3.2. Given evidence from the anakinra study [Quartier et al. 2010] this is a conservative assumption as the most likely adjustment for anakinra response rates should be degradation.

- Infliximab ACR response is used for the anti-TNFα treatments and abatacept; see details in 5.7.3. A class effect is assumed for other biologics given lack of evidence.

- Anti-TNFα and abatacept ACR response adjusted; see details in 6.3.2. this is a necessary assumption given the differences in populations from the two clinical trials (TENDER vs. Ruperto et al. [2007]).

- Constant mortality risk; see details in 6.3.1 and 6.3.3. Due to lack of data to determine elevated mortality risk dependent on the patient condition, the model assumes a constant withdrawal risk based on evidence from Hashkes et al. [2010] (R^2=0.8656). This is applied universally to all health states, treatment arms without an effect in incremental cost or utility.

- Constant withdrawal risk; see details in 6.3.1 and 6.3.3. Due to lack of evidence on withdrawal risk for the comparators the analysis cannot

differentiate between biologic treatments. This assumption does not have an impact on the economic evaluation objectives and is more appropriate from the viewpoint of parsimony.

- ACR response corresponds to model cohort of 2 years of age; see details 6.3.1. Due to the small number of patients with age less than 4 years it is not possible to undertake the appropriate analysis for ACR response of the younger population. Sensitivity analysis addresses this by assessing the cost-effectiveness of the intervention with different starting age.

- Starting CHAQ is assumed to be equal to the observed baseline CHAQ from TENDER. This assumption is tested in sensitivity analysis.

- Starting weight of patients is assumed to be 13.25kgs. This is estimated based on evidence from a similar exercise performed by NICE [NICE 2001]. In the base-case analysis patients grow up to average weight of 62.5kgs. In sensitivity analysis patient weight is assumed to remain constant once individuals reach a level of 75kgs.

- Changes in CHAQ score are response-related and not treatment-related. This assumption is deemed reasonable as ACR response should trigger changes in CHAQ regardless of treatment.

- Safety profile of comparators is assumed similar; see details in section 5.9.2, 6.4.8, and 6.5.7. This assumption is supported by evidence from the clinical trials considered in this submission. The most notable side-effects observed in the clinical studies are minor with short duration, and non-costly management.

- The model time-horizon is 16 years. This duration covers patient life 2-18 years old. Sensitivity analysis explores different timeframes.

Assumptions on measurement and valuation of health effects:

- A transformation of HRQL data is performed through a mapping mechanism; see details in 6.4.3 and 6.4.4. This is a necessary assumption due to lack of other more appropriate evidence. The resulting HRQL values are not outside the range of other utility estimates identified from secondary sources (see 6.4.7).

- HRQL while on treatment is assumed constant. This is assumed due to lack of evidence for a time-dependent assumption. This is a conservative assumption against tocilizumab.

- HRQL while with uncontrolled disease is assumed constant. This is assumed due to lack of evidence for a time-dependent assumption. This is a conservative assumption against tocilizumab.

Assumptions on measurement and valuation of costs:

- Treatment with tocilizumab and adalimumab is assumed to be administered with concomitant MTX (70% of the cohort). This is a necessary assumption to reflect the market authorisation of the two interventions.

- Comparator treatments have a similar administration regimen for systemic JIA patients as for other JIA subtype populations currently indicated. To date, there is no other treatment indicated directly for patients with systemic JIA.

- Nurse visit for administration of injections (adalimumab, anakinra, and etanercept) is assumed to be GP nurse. Sensitivity analysis tests alternative values.

- Nurse visit is assumed to be required per each administration for 20% of children (less than 10 years old) and 10% of older patients. This assumption is validated by clinical experts (see section 6.5.5). Sensitivity analysis tests alternative values.

- IV infusion is assumed to cost £150 per administration. This is inflated from a UK source [Barton et al. 2004].

- Resource use assumptions are based on cost schedule from UK sources [Epps et al. 2005, Thornton et al. 2008a, Thornton et al. 2008b, Barton et al. 2005].

- Assumptions on resource use are conservative and based on expert opinion [PC Westhovens R, Woo P, Wright S, Baildam E].

- To avoid double-counting diagnostics tests were excluded from the proportion of patients who are hospitalised.

- To avoid double-counting monitoring cost of treatment (subcutaneous injections) is excluded and assumed to be performed during routine visits to rheumatologists. This is a conservative assumption against tocilizumab.

Assumptions in exploring uncertainty:

- Due to lack of data, in PSA, distribution parameters are assumed based on expert opinion or a reasonable range around the mean.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The quality of life of patients with sJIA is affected by short and long term consequences of the disease. The short term consequences are a result of the symptoms experienced when a patient is having a disease flare episode. Pain, fever and loss of mobility can be so severe that patients are completely disabled requiring hospitalization. Outside of the disease flare state, pain is a persistent problem affecting the ability of sJIA patients to perform activities of daily living, attend school and partake in any physical exercise.

As a consequence of continuing disease activity and prolonged exposure to the necessary cortiscosteroid treatment over time patients experience growth disturbances and osteoporosis. For many cases the damage from long-term complications is irreversible. These complications are generally a problem for older patients with longer disease duration. Other complications such as uveitis and nutritional impairment are not perceived to be the main problems impacting on the quality of life of sJIA patients.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Clinical expert opinion [PC: Westhovens R 2/3/2011] suggests that as sJIA patients get older their ability to cope with their disease improves and therefore a concomitant improvement in HRQL is also observed. However, it is estimated that for about 60% of patients who have chronic illness, definite destruction of joints and bones will develop as they age. This bone destruction would have a more profound negative effect on their HRQL such that any benefit potentially acquired from their psychosocial and physical coping mechanism would not be noticed. There is no robust evidence on changes of patients HRQL over time and therefore the analysis will not apply any adjustment.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HUI, the preferred instrument for measuring HRQL in children, was not included in the clinical trial. The TENDER study included the Child Health Questionnaire (CHQ) as an instrument eliciting patient HRQL. The CHQ assesses a child's physical, emotional, and social well-being from the perspective of a parent or guardian (CHQ-PF50). Areas measured include: general health, family cohesion,

physical functioning, change in health, limitations in schoolwork and activities with friends, bodily pain or discomfort, behaviour, self-esteem, mental health limitations in family activities, emotional or time impact on the parent .

The questionnaire is completed twice during the randomised period of the study: at baseline (visit 1) and at week 12 (visit 7).

During the design of the economic evaluation a number of methods were attempted to translate CHQ scores to QALYs for the model. However, due to lack of robust data and many other limitations that are briefly described below, an alternative method to provide QALYs was selected.

The limitations of the use of CHQ are:

- Missing data; when evaluating the CHQ scores of patients in the dataset a number of missing values were identified: 23 (21%) at baseline and 29 (26%) at week 12. This data is not missing at random. Given that CHQ is not validated for children under the age of 5 years most young patients did not provide CHQ at baseline or at week12 of the study. It was also observed that for some of the older patients (>5 years) values were not missing at random, however, the proportion of these values was very small: 2 (2%) at baseline and 8 (8%) at week 12. The cause of this data missing was mainly early withdrawal or escape to active treatment (placebo arm). Overall the proportion of missing CHQ was around 27%. Since missing values were not at random, none of the established methods of value imputation were deemed appropriate here. Moreover, using a method of available cases only was deemed weak as an assumption given the large proportion of missing values (>5%).

- Lack of mapping formula in the literature; a literature review did not identify any method that could provide mapping of CHQ to QALY. A number of studies provided evidence on the HUI of healthy and arthritis affected

children [Mittmann et al. 1999] or the CHQ and CHAQ scores of healthy and systemic JIA affected children [Oliveira et al. 2007]. However, the available evidence is not sufficient to derive a mapping formula for CHQ and QALYs.

- Lack of mapping formula from the trial; in previous cases in adult RA data from the trial was used to derive a mapping formula between EQ-5D and HAQ scores. The TENDER trial does not include any data on HUI or EQ-5D to perform a similar analysis for sJIA affected patients.

- Separate physiological and psychosocial scores; A large study (N=6,639) on CHQ concluded that although both physiological (CHQ-PhS) and psychosocial (CHQ-PsS) summary measures discriminate well among patients with JIA with different levels of disability, the discriminative ability of the PhS was superior to that of the PsS because patients with JIA had less impairment in psychosocial well being than in physical well-being [Oliveira et al. 2007]. Therefore, given the above and in the absence of any method of combining the two scores, the inclusion of CHQ in the database would need to differentiate between physiological and psychosocial data.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

The economic evaluation uses a non-linear model to map CHAQ to QALY. The use of non-linear models to translate functional status to HRQL is previously

endorsed by NICE as a reasonable assumption [NICE TA195 2010]. This mapping formula is derived from an adult RA population, and therefore, the use of this formula implies the following assumptions;

- CHAQ of child is equal to HAQ score of adult
- Adult EQ-5D is equal to the HRQL of a child

Roche acknowledges that the above assumptions have no evidence basis. It is solely due to lack of other available data that this mapping method is preferred for the analysis in order to derive QALYs for the economic model.

The mapping formula for the base case analysis is using data from a pool of two tocilizumab trials of adult RA patients (OPTION and LITHE, N=1800). The method is briefly described below:

HAQ scores were regressed on EQ-5D utility data using a linear mixed model. The significance of coefficients for HAQ and the square of HAQ were tested and the fit of strictly linear and non-linear models were compared.

Results showed that a linear model generated coefficient estimates similar to those reported by Boggs and colleagues [2002]:

EQ5D =0.89 – 0.28*HAQ

($p<.0001$)

Consistent with Boggs and colleagues [2002], inclusion of a model term for the square of the HAQ score resulted in an improved fit and a significant coefficient for the non-linear term.

Table 57: HAQ / EQ-5D mapping formula

Coefficient	Estimate	Standard Error	Pr>t
Intercept	0.8229	0.008621	<0.0001
HAQ	-0.1125	0.01360	<0.0001
HAQ_SQ	-0.06874	0.005200	<0.0001

HAQ: Health assessment questionnaire

From the mixed model output report the log likelihood chi square for the model with the linear and squared term is 2462.0 (non-linear) while the chi square for the bivariate model (linear) is 2141.9. This yields a difference of 320.1. The p value for chi square distributed variable with 1 degree of freedom [chidist (320.1,1)] is 1.38*e-71. This strongly suggests that the model with the squared term model has a better 'fit' and hence was selected to inform the basecase model.

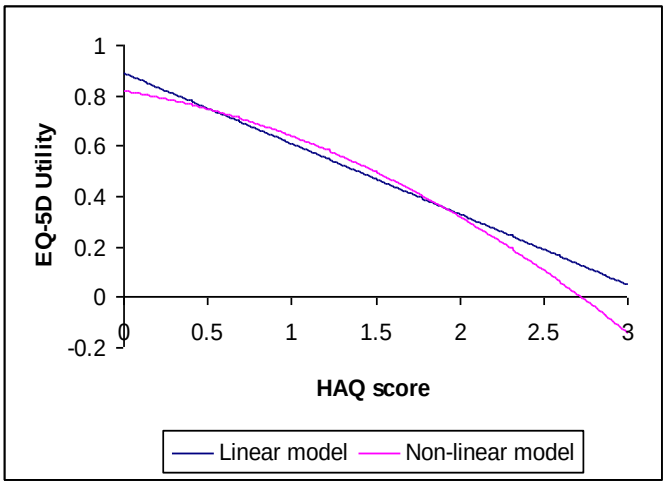
An additional analysis that included age as a covariate in the non-linear model was performed. The coefficient estimates were found to be essentially unchanged. This suggests that there is little correlation between the variables. Assuming that age is entered into the model as years, the coefficient for age is 0.0008 which means that 1 year increase in age is projected to change the HAQ by 8/10,000. Therefore, the model used in the base-case model does not include age as covariate.

The base-case analysis uses the non-linear formula reflecting the assumption that decreases in CHAQ level are more valuable (as measured by change in utility) for severely disabled patients than for patients who are less disabled. Sensitivity analysis tested alternative utility mapping scenarios assuming linear relationship between the two model parameters (see Figure below):

1. Roche quadratic (base case): HRQL=0.82-0.11*CHAQ-0.07*(CHAQ^2)

2. NICE quadratic [NICE 2010 Addendum to TA195]: HRQL=0.804-0.203*CHAQ-0.045*(CHAQ^2)
3. Roche linear: HRQL=0.89 – 0.28*CHAQ
4. Boggs et al. 2002 linear: HRQL= 0.76 - 0.28*CHAQ+0.05*Female

Figure 11: HAQ score and EQ-5D mapping



Application of utility scores to the model health states:

As discussed in 6.2.4, health states reflect the condition of patients dependent on ACR response after a 12 week period on treatment. The utility of the health state is characterised by the resulting CHAQ triggered by the ACR response.

By assuming a starting CHAQ of 1.702 the QoL for each health state is presented in Table 60.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used.

The search strategy used should be provided in section 9.12, appendix 12.

The search strategy for HRQL evidence was conducted as described in section 6.1.1 and formed part of the economic evidence search. This ensured that during our economic literature search as well as retrieving economic evaluations, all studies reporting costs and/or valuation of health benefits including HRQL related were also captured.

A separate review was performed for HRQL studies where the focus of the review was to segregate studies reporting any HRQL information and extract any transferable data. The review process as described in section 6.1.1 retrieved 949 citations, 34 of which were studies reporting on quality of life.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.

- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Of the 34 studies identified in the review reporting on quality of life, none reported any utility values that were used in the economic evaluation presented here.

A summary of the study characteristics of all 34 studies is presented in the Table below.

Table 58: Review of HRQL evidence from the literature

Study	Population	Recruitment info	Interventions assessment tools	Sample size	Response rates	Method of elicitation and valuation	Appropriateness for CE analysis
Amine 2009	JIA	Patients were enrolled between 2006 and 2007. Participants included children and adolescents with diagnosis of JIA aged less than 18yrs.	JAQQ,	80	100	Questionnaire	JAQQ scores provided but cannot be converted to utility values.
Angeles_Han 2010	JIA (uveitis)	Patients were enrolled between 2007 to 2008 with JIA or uveitis, age 8-18 at time of study and age <16 at time of JIA diagnosis, at least a 3rd grade reading and comprehension level, presence of parent/guardian to complete demographic questionnaire, visit with opthalmologist and rheumatologist within last 3 months	PedsQL 4.0	27	100	Questionnaire by interview	No utility scores provided and focusing on impact of uveitis on QoL
April_2006	JIA	Participants included JIA patients 9-18 years. Patients and parents were approached to participate if sufficient comprehension either English or French.	JAQQ	72	76.4	Questionnaires guided by interviewer for patients, parents without interviewer	The objective of the study is to compare scores from patients and parents. No utility scores provided.
Arkela 2005	JIA	JIA patient of RFH	Rand36	181	67.9558011	Questionnaire by interview	Rand 36 scores given. No utilities given. Study of patients in early adulthood. Not relevant for CE analysis
Arkela 2006	JIA	JIA patient of RFH	Functioning: Fin-MDHAQ, Fin-AIMS2	187	65.77540107	Questionnaire during rheumatology visit	Patient responses evaluated for each category. No combined utility scores provided
Brunner 2003	Musculoskeletal disorder patients	Patients were included aged between 1-18 yrs, diagnosis of JRA, dermatomyositis, systemic lupus, erythematosus, fibromyalgia, hemophilia or other chronic joint disease	SG, rating scales, HUI (no high response)	80	100 for all except HUI	Interview	Small sample of JRA patients. No utility values for specific health state and pooling data across wide population. Not appropriate for CE analysis
Brunner 2005	Juvenile rheumatoid arthritis	Children with JRA requiring second-line agents and one of their parents were recruited during routine visits to the rheumatology clinic over an 8-month period	GISSK, PedsQL	77 families	Alll parents and only 52 children aged 8 yrs or older were asked to complete questionnaires. Assume all asked	Interview	Investigating GI symptoms and HRQoL of JRA patients. No utility values provided.

					responded.		
Brunner 2004	Chronic arthritis	Families of children with arthritis were recruited during routine clinic visits within a 3 month period. Eligible patients were aged 1-18 yrs with chronic arthritis irrespective of diagnosis. To be included in study arthritis had to be present for at least 3 months continuously.	JAQQ, PedsQL	119		Interview	Investigating strength of association between different measures of QoL. No utility values provided.
Cavallo 2010	Parents of JIA child	Parents of JIA child attending Canadian clinic	JAQQ, Coping Health Inventory for Parents (CHIP), Symptom checklist 90-Revised (SCL-90-R)	235	77.4	Questionnaire by mail	Investigating whether patients QoL is related to parents ability to cope. Scores provided but no utilities.
Cespedez 2008	JIA patients	Patients were extracted from PRINTO database	CHQ	521	79	Self administered questionnaire	Utility scores not provided
Duarte 2007	Polyarticular arthritis and ankylosing spondylitis	All patients were included between May 2003 - May 2004, cohort of 60 out patients with JIA > 18yrs. 32 patients were included in the study	SF36, EQ 5D	32		Questionnaire	Correlations among GFS, HAQ DI, BASFI with SF36 provided but no utility scores. Population for JIA is small and only of the polyarticular subtype. Adult patients only
Feldman 2000	Rheumatology care patients	Convenience sample of all consecutively seen new referrals. 122 patients studied over 18 months. Median age was 11.7 years range 10 months to 18 years	Quality of My Life Questionnaire (QOML)	122	0.901639344	Questionnaire at time of clinic visit	Various diagnosis groups (systemic subtype representing only ~ 9%). No utility values provided
Foster 2003	JIA patients	Adult rheumatology department database used to identify patients under umbrella term juvenile arthritis. Patients had mean age 30 range 17-68, median disease duration 21 years (range 3-61 years)	SF36	101	0.811881188	Elicitation: Questionnaire, Valuation: VAS	Includes adult patients not children
Grootenhuis 2007	Children with chronic disease (congenital heart disease, coeliac disease, asthma, cancer, juvenile chronic arthritis, capillary haemangiomas,	Data on 8-11 year old patients with a chronic condition were obtained from several ongoing studies at different hospitals (Netherlands)	Netherlands instrument: TACQoL which assesses 7 domains of HRQoL	318	less than 2% missing in all groups	Questionnaire during rheumatology visit	Netherlands instrument scores given but no utility values provided. (very small proportion of juvenile arthritis patients)

	severe meningococcal disease						
Gutierrez-Suarez 2007	JIA	PRINTO multinational cohort study, enrolled by PRINTO members between April 1998 to March 2000 with diagnosis of JIA and healthy children <18 yrs	CHQ	3167		Questionnaire (81% completed by mother, 19% father or guardian)	Summary CHQ scores provided, no utility values reported.
Jolles 2008	Severe juvenile rheumatoid arthritis	Retrospectively reviewed 14 adult patients with severe JRA treated with primary total knee arthroplasty between 1989 and 2001	EQ5D, SF36, WOMAQ	14	100	Questionnaires at follow up visit	Mean outcome scores provided from different measures. Population JIA patients with knee arthroplasty and older in age. The cost effectiveness analysis is not considering knee arthroplasty.
Laas 2009	Common rheumatic diseases (of 295 respondents, 9 adults with JIA not necessarily systemic subtype)	Data collected prospectively from May 2002-April 2003. All adult patients with new referral to the Dept of Rheumatology were included.	15D (generic instrument 15 dimensions)	676	57%	Questionnaires by mail	Population largely different to that in analysis (various rheumatic disease) and much older (average 53 years). Assessment tools used also differ. Mean scores given but no utilities for health states.
McDonagh 2007	JIA (adolescents)	Patients and parents recruited from 10 paediatric rheumatology centres represented in the British Society of Paediatric and Adolescent Rheumatology (BSPAR). Eligibility criteria including 1) diagnosis of JIA, 2) expected to remain in paediatric careof consultanat of BSPAR for at least 6 months 3) aged 11,14 or 17 years - reflecting stages of adolescent development.	JAQQ	359	308 (85.79% adolescents, 84.4% parents)	Questionnaires self completed or with support form local programme co ordinator where necessary	Investigating effect of transitional care programme on HRQL of adolescents with JIA. JAQQ scores reported for parent and patients at 6 and 12 months but no utility values.
Norrby 2006	4 diagnostic groups 1) asthma, 2) diabetes, 3) short stature, 4) juvenile chronic arthritis	Swedish children between 9-16 yrs and parents. Children were registered as consecutive outpatients and scheduled for check up at Queen Silvia Children's Hospital	CHQ	199		Questionnaire with nurse or investigator present to answer questions.	Purpose of study was to assess the reliability and validity of swedish version of CHQ, determine correlation between childrens and parents responses to CHQ and describe and compare responses to CHQ on 4 diagnostic groups (1. asthma, 2. diabetes, 3. short stature, 4. juvenile chronic arthritis). Correlations between parent and patient scores given. No utility values provided.

Oen 2009	JIA	Research in Arthritis in Canadian children emphasizing outcomes (ReACCh Out) study is ongoing multicentre prospective inception cohort study of JIA conducted at 16 paediatric rheumatology centres in Canada. Subset of participants selected for study were enrolled in ReACCh-Out within 6 months after diagnosis between Jan 2005-Dec 2007	JAQQ	356	300 patients completed JAQQ at 6 months	Questionnaire	JAQQ scores given for active and inactive disease but no mapping method.
Oliveira 2007	JIA	A total of 6639 participants were enrolled from 32 countries. Patients and healthy children enrolled by PRINTO members from April 1998-March 2000. Inclusion criteria for patients were a diagnosis of JIA by ILAR criteria and < 18 yrs at time of evaluation	CHQ	3324 JIA 3315 healthy		CHQ completed by mother or father	Both CHQ and CHAQ reported matching tocilizumab trial measurements. Potentially useful for to evaluate utility estimates in the de-novo cost effectiveness analysis.
Prince 2010	JIA	53 JIA patients with etanercept treatment	CHQ, HUI3	53		Questionnaires validated in Dutch	CHQ, CHAQ and HUI3 are reported. However, evidence are not stratified by level of response related to a specific health state.
Riddle 2006	JIA	Inclusion 1) diagnosis of JIA, 2) beginning new medication treatment (NSAIDs, MTX or steroids) 3) range in age from 1-18 years	PedsQL v4	63 parent/child pairs	57 pairs completed study	Questionnaire aided by research assistant if required	Study investigating effectsof JIA treatment on HRQOL, effects of NSAIDs, MTX and steroid treatment were compared within and across treatment groups as were frequency and severity of their side effects. PedsQL data reported but not comparable to tools applied in TENDER.
Ringold 2009	JIA (polyarticular)	Eligible families were identified through a search of the billing database of patients at Seattle Childrens Hospital (SCH) associated with diagnosis for polyarticular and JRA not otherwise specified. Children identified by this search diagnosed and treated at clinic between Jan 2000-Dec 2006.	PedsQL	104	79%	Questionnaire aided by research assistant if required	Study comparing child self report and parent/proxy report of HRQOL in children with the polyarticular JIA subtype. Scores provided but not comparable to tools used in tocilizumab trial. Not appropriate for CE analysis.
Robinson 2003	JRA (Polyarticular & systemic)	All patients receiving etanercept via s/c injection twice each week over a 14 month period were included in the study	PedsQL, JAFAR	21	100%	Questionnaire	The study aims were to assess functional status, emotional well being & QoL in patients with polyarticular and systemic JIA treated with etanercept. Not appropriate for use in the cost effectiveness analysis as measuremet tools differ.
Ruperto 1997	JRA	1) 1st examined in Rheumatology units between 1958 & 1990 within 6 months of onset of symptoms, 2) diagnosis of JRA by	QOLS	227		Self administered questionnaire	Not relevant for cost effectiveness analysis: no comparable measurements and

		ACR criteria, 3) disease duration at least 5 years at the time of assessment of outcome.				by mail	no information on age of participants.
Sawyer 2004	JIA	Children aged 8-18 yrs diagnosed with JIA at least 6 months prior to the study and attending the rheumatology clinic at the Womens and childrens hospital in South Australia and their parents were approached to participate in the study.	PedsQL,	81	64 (79%)	Questionnaire aided by research assistant if required	Study was investigating relationship between HRQL, experience of pain and pain coping strategies in children with JIA.
Sawyer 2005	extension of 2004 study	As Sawyer 2004 above	PedsQL	81	79%	Questionnaires completed at home aided by research assistant if required	Study was investigating relationship between HRQL, experience of pain and pain coping strategies in children with JIA and to investigate extent to which this changes over 12 month period.
Seid 2009	JIA	Study based on clinical database prospectively collected by clinical protocol in the paediatric rheumatology clinic at Cincinnati Childrens Hospital Medical centre between 2003-2007. all children aged 2-18 yrs old who presented for evaluation and treatment of JIA and completed PedsQL were included.	PedsQL	524			Study examining variability in HRQL in children with JIA experiencing no or minimal clinical symptoms and in a subgroup with polyarticular JIA treated with biologic agents for 12 months.
Shaaban 2006	JRA	Case control study comprising 52 children and adolescents suffering from JRA and attending the Rheumatology and Rehabilitation clinic of Kaser El-Aini and AbuElrich hospitals during the period from December 2004 to August 2005. Ages ranging from 5 to 18 years.	CHQ	52		Questionnaire completed by primary caretaker and children aged 12 years and older.	Study assessing HRQL in children and adolescents suffering from JRA. Correlations between Disability index and CHQ provided as well as effect of disease activity on disabilty index and CHQ.
Shaw 2006	JIA	Participants were part of a national clinical trial to evaluate a program of transitional care. Three age cohorts (11, 14 or 17 years, +/- 1 month) corresponding to early, middle and late phases of adolescence were recruited from 10 pediatric rheumatology centres represented in BSPAR).	JAQQ,	359	85.79% (308)	Questionnaires for self completion with support from local program coordinators where necessary.	JAQQ summary scores provided but no relationship to HRQL.
Solari 2008	JIA	Cross sectional study where all consecutive patients were included if they were seen as inpatients or outpatients between Sept 2002 and Dec 2006 at the pediatric rheumatology units of the Istituto G Gaslini of Genoa Italy and meeting the following criteria: 1) diagnosis of JIA, 2) disease duration of > 5 years 3)	CHQ	310			Investigating different outcomes of JIA but no clear link to disease severity and quality of life.

		informed consent to participate inthe study					
Toupin 2009	JIA	Study population consisted of parents of children with JIA aged between 2-18 years who attended the arthritis outpatient clinics in Montreal and Vancouver.	JAQQ,	235	76.43% (Montreal, 63.92% Vancouver)		This study was investigating the association between complementary and alternative healthcare (CAHC) and subsequent health outcomes. No utility scores provided.
Zebracki 2004	Primary Immunodeficiency, JIA, healthy	A comparison study comparing parental reports of HRQoL of children with PI disease with those of JIA children and healthy children. Families invitied to participate if had child belonging to one of these groups.	CHQ	108 (36 Pi, 36 JIA, 36 healthy)			Comparison study reporting CHQ scores of different groups. No utility values provided..

CE: cost-effectiveness, CHQ: Child Health Questionnaire, GISSK: Gastrointestinal Symptom Scale for Kids, HUI: The *Health* Utilities Index, JAQQ: Juvenile Arthritis Quality of Life Questionnaire, JIA: Juvenile idiopathic arthritis, JRA: Juvenile rheumatoid arthritis, PedsQL: Pediatric Quality of Life Inventory, QOML: Quality of my Life, RFH: Rheumatism Foundation hospital, SG: standard gamble

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

A comparison between the utility scores estimated by the mapping mechanism and the ones retrieved from the literature is presented below.

Prince et al. [2010] provides HRQL scores based on HUI3. The study suggests that after 3 months patients with etanercept have a HRQL of around 0.64 (SE ±0.05). This is similar to the evidence calculated in this submission for patients in categories ACR 50 and ACR 70 response.

Arkela et al. [2005] provide HRQL scores based on Rand 36 for JIA patients in early adulthood. Patients with active disease had poorer HRQL in the physical health components than those with inactive disease. Physical health summary: inactive disease 0.539 (SD 4.9), active 0.476 (SD 9.3). These scores are slightly higher than the uncontrolled disease category 0.4152, which may be a consequence of the different populations investigated. This study includes patients with a mean age of 23 and the subtype is predominantly the oligoarthritis subtype.

Riddle et al [2006] assessed HRQL by using the Pediatric Quality of Life Inventory (PedsQL^{TM}), Version 4.0, Generic Core Scales, and Version 3.0, Rheumatology Module. Their findings are presented in the Table below.

Table 59: PedsQL from Riddle et al [2006]

	Generic PedsQL	Rheumatology PedsQL
Pre MTX	0.713 (15.2)	0.684 (13.7)
Post MTX	0.765 (16.5)	0.735 (17.2)
Pre steroids	0.487 (13.5)	0.557 (19.9)
Post steroids	0.709 (18.7)	0.780 (14.0)
Pre NSAIDs	0.801 (18.2)	0.820 (17.7)
Post NSAIDs	0.852 (13.5)	0.869 (13.0)

MTX:Methotrexate, NSAIDs: Nonsteroidal Antiinflammatory Drugs

The scores for the pre and post steroid treatment from the Generic PedsQL are consistent with the mapped values for no-ACR30-response or uncontrolled disease (0.4152) and in the ACR 90 category following treatment (0.7150).

Ringold et al. [2009] measured HRQL using the PedsQL instrument in polyarticular JIA patients with active and inactive disease. Scores reported in this study are higher: active disease 0.8098 (16.83), inactive disease 0.8562 (11.84). Given that the mean CHAQ of the cohort of this study is 0.321, the disease severity is not comparable to those in the TENDER study [WA18221 - Roche Clinical Study Report 1035146, 2010] who had a score at baseline above 1.5 and so as expected their uncontrolled score would be much lower.

Angeles Han et al [2010] also measured HRQL using the PedsQL instrument in JIA patients comparing quality of life in those patients with and without uveitis. The scores were not very different between those having uveitis (0.79) and those without (0.80). These reported scores are slightly higher than the mapped value of the ACR 90 category (0.7150), which may be a consequence of the predominantly polyarthritis subtype and no systemic patients.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

In the first comparison (tocilizumab vs. MTX), patients in the tocilizumab arm receive also MTX in line with the market authorisation and license of the intervention. Observed evidence from the TENDER trial did not identify any significant differences between the active and control arms of the study (see section 5.9). Therefore, it is assumed the two model arms have the same safety profile in this comparison.

In the second comparison (tocilizumab vs. biologics), as discussed in section 5.9, a review of comparator safety did not identify any notable differences in serious adverse events with high incidence (over 5%). The identified adverse events are of minor severity, lasting a short duration, and it can be assumed that they do not have a considerable bearing on the HRQL of patients [PC: Wright S. 16/03/2011].

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 60: Summary of quality-of-life values for cost-effectiveness analysis

Health state name	CHAQ	Assumed QoL	Assumed SE	Adult RA values (for reference)
No response or uncontrolled disease	1.7442	0.4152	30% of the mean	0.4651
ACR 30	1.2699	0.5674		0.5660*
ACR 50	1.1351	0.6050		0.6084
ACR 70	0.8601	0.6736		0.6289
ACR 90	0.6692	0.7150		N/A

*refers to ACR 20 and not ACR 30 in adult RA

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please refer to section 6.3.5

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

As discussed in 6.4.2 patient HRQL is affected by short-term and long-term disability. With regards to the short-term complications, HRQL could vary depending on the individual experiencing a flare or being in a state of quasi-disease-remission. When patients experience disease flare HRQL is considered very low, with substantial disability for the patient (see details in 6.4.2). When patients do not experience a disease flare their HRQL could be considered as high as that of a healthy person. On the other hand, when considering long-term disability of patients affected with sJIA, the condition shares characteristics with other chronic diseases (such as RA) (see details in 6.4.2), implying a continuously lowering HRQL.

The applied utility in the model for each health state is based on patient observations of change in CHAQ score depending on ACR response. There is not evidence to adjust the derived utility for variance in HRQL either due to short-term changes in patients' condition or due to long-term complications.

The above assumption is supported by clinical trial data. An analysis of observed patient CHAQ over the extension of the clinical trial demonstrated that until week 72 responders sustain a level of CHAQ similar to that achieved at week 12 (see Figure below). Moreover, data from the literature support a non-worsening utility while on treatment (see Table below) [Prince et al. 2010].

Figure 12: Long-term sustainability of CHAQ score by ACR category

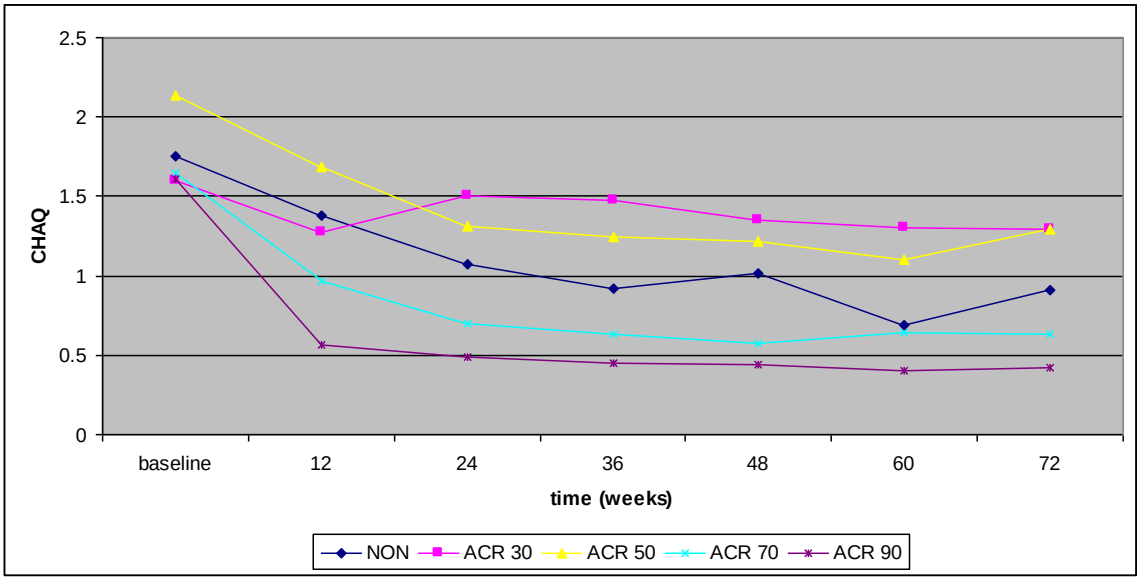


Table 61: HUI3 scores in JIA patients with etanercept treatment

Time	Mean HUI3	±SE
Start	0.51	0.04
3 months	0.64	0.05
15 months	0.70	0.06
27 months	0.77	0.08
p-Value	0.001	

Source: Prince et al. 2010

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

It is assumed that through the mapping mechanism, changes in CHAQ include all relevant HRQL impairment for patients with sJIA. Health decrements due to adverse events were excluded due to reasons presented in 6.4.8.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The HRQL assumptions do not include a baseline quality of life (such as that of a healthy individual) and decrements from this for each disease health state.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Due to reasons presented in 6.4.11 HRQL is assumed to be constant over time.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No other adjustment of the derived utility values from the mapping formula is applied to the analysis

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

There is no single HRG or PbR code that describes the clinical management of the condition. A synthesis of HRG from the NHS reference costs and data from

secondary sources is used for costing in the economic evaluation. Details are presented in section 6.5.6.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Roche considered either PbR tariffs or NHS reference costs for the costing in the economic evaluation. The NHS reference costs provided a more comprehensive and relevant to the disease area range of values. For consistency the analysis uses NHS reference costs where available. Data from secondary sources were retrieved where values were not available or appropriate from the NHS reference cost schedule. Details are presented in section 6.5.6.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The search strategy for resource data was conducted as described in section 6.1.1 and formed part of the economic evidence search. This ensured that during our economic literature search as well as retrieving economic evaluations,

all studies reporting costs, resource use and/or valuation of health benefits including HRQL related were also captured.

A separate review was performed for economic studies where the focus of the review was to segregate studies reporting any cost information and resource use data in order to extract any transferable data. The review process as described in section 6.1.1 retrieved 949 citations, 9 of which were studies reporting on resource use and associated costs.

Of the 9 studies identified 2 were conducted in the UK [Thornton et al. 2008a, Thornton et al. 2008b], 2 in Germany [Minden et al. 2004 and 2009], 1 in Canada [Bernatsky et al. 2007], 1 in Sweden [Bjelle et al. 1983], 1 in Finland [Haapasaari et al. 2004] and 2 in the USA [Shawns et al. 2008 and Allaire et al. 1992]. All studies collected costs associated with JIA except 2 which focused on various rheumatic disorders [Bjelle et al. 1983 and Shawns et al. 2008]. The Table below presents a summary of the identified evidence.

Table 62: Economic evidence review: cost studies

Study	Population	Treatment considered	Country	Form of analysis	Time-horizon	Main results	Relevance to the Decision Problem
Allaire 1992	JRA (juvenile rheumatoid arthritis)	No specific treatment	USA	Cost/economic impact	Annual	The mean annualized direct cost per child was $7905 (inpatient costs $1717, outpatient costs $5700 and nonmedical costs $488). Family costs were $1524 per year representing 5% of the mean family income. The mean extra school cost was $1449 per 9 months.	Cost data and utilisation is specific to USA. Not applicable for UK analysis
Bernatsky 2007	JIA	No specific treatment	Canada	Economic impact	Annual	The total difference in annualized average direct medical costs for children with JIA versus controls was $1,686 (95% confidence interval $875, $2,500).	Cost data and utilisation is specific to Canada. Not applicable for UK analysis
Bjelle 1983	Rheumatic disorders	No specific treatment	Sweden 1978	Utilisation study	1 year (1978)	Shows distribution of rheumatic patients per hospital department.	Not very relevant, data is valid for Sweden and 1978. Not applicable for UK analysis
Haapasaari 2004	JIA	Etanercept	Finland	Cost of treatment	Annual	When the costs due to etanercept are excluded, the change in the median direct costs was –54% (approximately –$10,000 per patient on an annual basis)	Cost data and utilisation is specific to Finland. Not applicable for UK analysis
Minden 2004	JIA	No specific treatment	Germany	Burden and cost of illness	Annual	The mean total cost of late JIA was estimated to be €3,500 per patient and year, of which the direct cost	This is a retrospective study conducted from a societal

						contributed more than half	and patient's perspective in Berlin. Not applicable for UK analysis
Minden 2009	JIA	DMARDs, biologics	Germany	Cost	Annual	The mean total cost of JIA was estimated to be €4,663per patient per year. The highest costs were calculated for patients with seropositive polyarthritis and systemic arthritis (€7,876), and the lowest costs were seen for patients with persistent oligoarthritis (€2,904)	Cost data and utilisation is specific to Germany. Not applicable for UK analysis
Thornton 2008a (id11)	JIA	NSAIDs, DMARDs	UK	SR on strategies to reduce fracture risk. Contains Cost of JIA management	Annual	Mean (SD) cost for systemic subtype £1929 (925)	Resource use and cost according to CAPS (Childhood arthritis prospective study). UK relevant
Thornton 2008b (id281)	JIA	No specific treatment	UK	Cost study	Annual	The mean annual total cost per child was £1649 (S.D. £1093, range £401-£6,967). The highest cost component was for appointments with paediatric rheumatologists.	Cost data UK specific and includes utilisation by JIA subtypes.
Shawns 2008	Various arthritis, Crohns disease and spondyloarthropathies	Biologic response modifiers	US	Not obvious	Monthly	Approximate costs in dollars for the following therapies (not JIA specific): adalimumab, alefacept, anakinra, efalizumab,	Reports on therapy costs per annum rather than for specific population, pools

						etanercept, infliximab	all populations using particular therapy. US study. Not applicable for UK analysis.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please refer to section 6.3.5.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The Table below summarises the unit cost of the intervention and its comparator treatments.

Table 63: Unit costs associated with the technology in the economic model

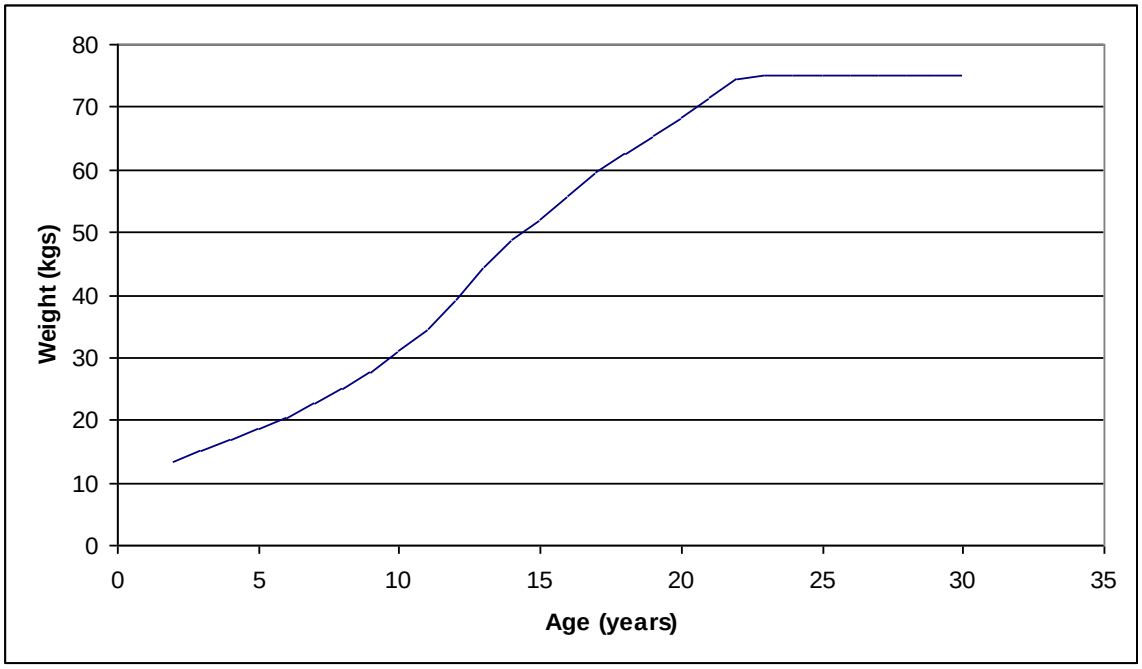
Treatment	Abatacept	Adalimumab	Anakinra	Etanercept	Methotrexate	Tocilizumab
Technology unit cost	£242.17 per 250mg	£357.50 per 40mg	£26.23 per 100mg	£83.38 per 25mg	£0.5649 per 10mg	£102.40 per 80mg, £256 per 200mg, and £512 per 400mg
Reference	BNF61	BNF61	BNF61	BNF61	BNF61	BNF61
Number of administrations per year	13	26	364	104	52	26
Administration cost	£124 per infusion (inflated to 2010) = £150 (assume SE 30% of mean)	Assume patients can self-administer injection. 20% (assume SE 30% of mean) of children require a nurse visit. Over 10 years of age only 10% (assume SE 30% of mean) require nurse visit. Nurse unit cost: £13 per home visit (GP nurse); £20 with qualifications assume range £6-£20.			Assume no cost (oral administration)	£124 per infusion (inflated to 2010) = £150 (assume SE 30% of mean)
Reference	Barton et al. 2004; inflation indices by Curtis et al. 2010	Assumption; Nurse visit cost by Curtis et al. 2010			Assumption	Barton et al. 2004; inflation indices by Curtis et al. 2010
Maintenance dose	10 mg/kg when less than 75 kg and 6-17 years; 750mg over 75kgs and <100kgs if over 17 years via IV infusion every 4 weeks	40 mg every other week via subcutaneous injection	2mg/kg daily via subcutaneous injection	0.4mg/kg twice a week (max 25mg) via subcutaneous injection	Assume 10mg administered orally	12 mg/kg for patients < 30 kg; 8 mg/kg for patients ≥ 30 kg) and administered intravenously (IV) every two weeks
Reference in submission	See maintenance schedule described in 6.2.7					

Cost is adjusted for technologies that require dose based on patient weight. The analysis uses and extrapolates data from a previous NICE rapid review of etanercept for the weight of a typical patient [NICE 2001]. It is assumed that patient weight does not change after 75kgs. Data on patient weight used in the model are presented in table Bxxxbelowxxx and figure Bxxxbelowxxx.

Table 64: Patient weight in the model

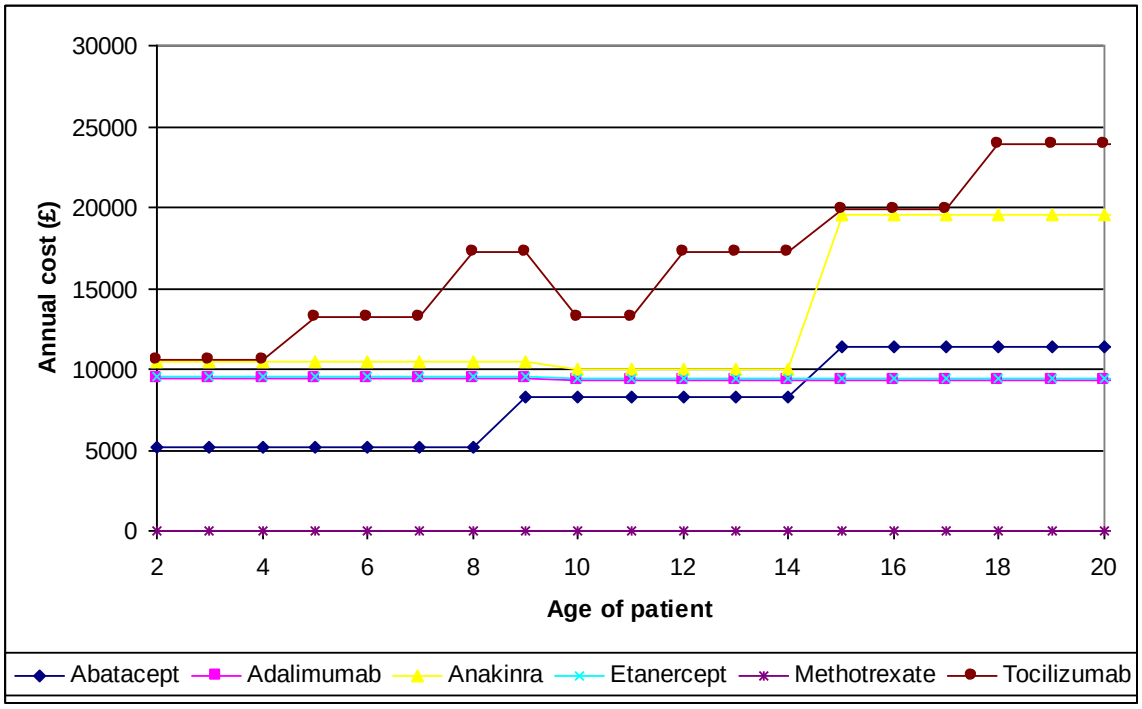
Age (years)	Assumed weight (kgs)	Source
2	13.25	Extrapolation
3	15	Extrapolation
4	16.75	NICE Etanercept rapid review 2002
5	18.5	NICE Etanercept rapid review 2002
6	20.25	NICE Etanercept rapid review 2002
7	22.75	NICE Etanercept rapid review 2002
8	25	NICE Etanercept rapid review 2002
9	27.5	NICE Etanercept rapid review 2002
10	31	NICE Etanercept rapid review 2002
11	34.75	NICE Etanercept rapid review 2002
12	39.25	NICE Etanercept rapid review 2002
13	44.5	NICE Etanercept rapid review 2002
14	49	NICE Etanercept rapid review 2002
15	52	NICE Etanercept rapid review 2002
16	55.75	NICE Etanercept rapid review 2002
17	59.5	NICE Etanercept rapid review 2002
18	62.5	NICE Etanercept rapid review 2002
19	65.5	Extrapolation
20	68.5	Extrapolation
21	71.5	Extrapolation
22	74.5	Extrapolation
23	75	Extrapolation

Figure 13: Patient weight in the model



Based on the above, the estimated average cost per year for the duration of the model is shown in the Figure below. Wastage is included in treatment cost calculations.

Figure 14: Annual cost of treatment in the model by patient age



Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

A resource use schedule for a JIA patient was identified by Epps et al. [2005] and modified here for the economic analysis. The list of resources was augmented by a similar schedule by Thornton et al. [2008a and 2008b] and Barton et al. [2004]. Evidence from Thornton and colleagues [2008a and 2008b] was reviewed.

Thornton et al. [2008a and 2008b] provide evidence on cost of JIA with no differentiation for response / no response to treatment. Roche considered that in the development of the economic model clinical expert opinion on resource use

for ACR 30 responders / ACR 30 non-responders would be more relevant for the analysis.

In order to establish the differences between the resource use for each health state, items from the combined cost schedule were presented to clinical experts in structured interviews to determine (section 6.3.5):

- the proportion of patients that make use of a resource item
- the frequency of use.

Several items were excluded from the Epps et al. [2005] and Thornton et al. [2008a and 2008b] list. An outpatient visit for ear, nose and throat check, as well as a visit to an ophthalmologist were excluded as not relevant for systemic patients based on clinical opinion [PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Woo P 21/03/2011, Baildam E 28/03/2011]. A visit to orthopaedic surgeon was excluded because it was considered very rare (once in a lifetime for ACR 30 responders and every 2-3 years for patients with uncontrolled disease). The cost of a nephrology visit was suggested that should be included only as urinalysis tests and no outpatient visit [PC: Baildam E 28/03/2011]. The social worker cost was deemed to be outside the perspective of the NHS, as patients in the UK might more often receive disability living allowance rather than employ a social worker. Diagnostic tests were limited to full blood count, liver function, erythrocyte sedimentation rate, C-reactive protein, urea, electrolytes and creatinine, assuming that the remaining tests would be included in relevant HRGs for paediatric arthritis visits or inpatient stay. To avoid double-counting diagnostics tests were excluded from the proportion of patients who are hospitalised. All the above assumptions and exclusions are conservative against tocilizumab as cost-effectiveness results would improve with inclusion of these items.

The Table below presents the unit cost and resource use for each health state.

Table 65: List of health states and associated costs in the economic model

Health states	Items	Value	Precision measures	Reference
ACR response	Cost of inpatient stay (per day)	£310 inflated to 2010 = £428.32	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of days in hospital (per year)	7.5	Assume range 5-10	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Proportion of patients requiring inpatient stay –ACR 30	22.5%	Assume range 20%-25%	PC: Wright S 16/03/2011
	Proportion of patients requiring inpatient stay –ACR 50	15%	N/A	Assume linear reduction from 25% (ACR 30) to 0% (ACR 90)
	Proportion of patients requiring inpatient stay –ACR 70	7%	N/A	Assume linear reduction from 25% (ACR 30) to 0% (ACR 90)
	Proportion of patients requiring inpatient stay –ACR 90	0%	N/A	Assume linear reduction from 25% (ACR 30) to 0% (ACR 90)
	Cost of GP visit	£32	N/A	Curtis et al. 2010
	Number of GP visits (per year)	3.5	Assume range 3-4	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Haematological (per visit)	£91	N/A	NHS reference cost 2010: Code 253 Consultant Led: Follow up Attendance Non-Admitted Face to Face
	Number of haematological visits (per year)	2	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Radiological (per visit)	£101 inflated to 2010 = £139.55	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of radiological visits (per year)	2	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Proportion of patients requiring radiological visit	20%	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Podiatrist / foot problem management (per visit)	£11	N/A	Curtis et al. 2010

	Number of podiatrist visits (per year)	1	Assume SE 30% of mean	PC: Wright S 16/03/2011
	Proportion of patients that require podiatrist visit	2.5%	Assume range 2-3	PC Wright S 16/03/2011
	Opthalmologist (per visit)	£51 inflated to 2010 = £70.47	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of ophthalmologist visits (per year)	2	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Rheumatology paediatric (per visit)	£193 inflated to 2010 = £266.66	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of rheumatology paediatric visits (per year)	3	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Psychologist paediatric (per visit)	£89.00	N/A	Curtis et al. 2010 p.181 (assume 1 hour visit)
	Number of psychologist paediatric visits (per year)	1	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients that require psychologist paediatric visit	20%	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Orthodontist (per visit)	£101.00	N/A	NHS reference cost Code 143 Consultant Led: Follow up Attendance Non-Admitted Face to Face
	Number of orthodontist visits (per year)	1	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients that require orthodontist visit	20%	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Occupational therapist /hand problem management (per visit)	£15.00	N/A	Curtis et al. 2010 p.152
	Number of occupational therapist visits (per year)	1	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients that require occupational therapist visit	20%	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Social worker (per visit)	£49.00	N/A	Curtis et al. 2010 p.173 (assume 20mins visit)
	Diagnostic test: Full blood count	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010

	Diagnostic test: Liver function test	£6.19 inflated to 2010 = £8.55	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: Erythrocyte sedimentation rate	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: C-reactive protein	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: Urea, electrolytes and creatinine	£0.08 inflated to 2010 = £0.11	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Number of diagnostic tests a year	3	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011; assume 3 weeks of flare and tests performed once a week
	Total: Response ACR 30	£545.60		
	Total: Response ACR 50	£486.55		
	Total: Response ACR 70	£428.64		
	Total: Response ACR 90	£374.16		
Uncontrolled disease or no-ACR30-response	Cost of inpatient stay (per day)	£310 inflated to 2010 = £428.32	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of days in hospital (per year)	24.5	Assume range 3-4 weeks	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients requiring inpatient stay	90%	Assume range 85%-95%	PC: Wright S 16/03/2011
	Cost of GP visit	£32	N/A	Curtis et al. 2010
	Number of GP visits (per year)	20.8	Assume range every 2-3 weeks	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Haematological (per visit)	£91	N/A	NHS reference cost 2010: Code 253 Consultant Led: Follow up Attendance Non-Admitted Face to Face
	Number of haematological visits (per year)	12	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Radiological (per visit)	£101 inflated to 2010 = £139.55	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010

	Number of radiological visits (per year)	2	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients requiring radiological visit	90%	Assume range 85% - 95%	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Podiatrist/ foot problem management (per visit)	£11	N/A	Curtis et al. 2010
	Number of podiatrist visits (per year)	1	Assume SE 30% of mean	PC: Wright S 16/03/2011
	Proportion of patients that require podiatrist visit	10%	Assume SE 30% of mean	PC: Wright S 16/03/2011
	Opthalmologist (per visit)	£51 inflated to 2010 = £70.47	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of ophthalmologist visits (per year)	2	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Rheumatology paediatric (per visit)	£193 inflated to 2010 = £266.66	N/A	Epps et al. 2005; inflation indices by Curtis et al. 2010
	Number of rheumatology paediatric visits (per year)	10	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Baildam E 28/03/2011
	Psychologist paediatric (per visit)	£89.00	N/A	Curtis et al. 2010 p.181 (assume 1 hour visit)
	Number of psychologist paediatric visits (per year)	1.5	Assume range 1-2	PC: Wright S 16/03/2011
	Proportion of patients that require psychologist paediatric visits	0.85	Assume range 75%-95%	PC: Baildam E 28/03/2011
	Orthodontist (per visit)	£101.00	N/A	NHS reference cost Code 143 Consultant Led: Follow up Attendance Non-Admitted Face to Face
	Number of orthodontist visits (per year)	1	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Proportion of patients that require orthodontist visit	35%	Assume SE 30% of mean	PC: Westhovens R 02/03/2011, Wright S 16/03/2011
	Occupational therapist /hand problem management (per visit)	£15.00	N/A	Curtis et al. 2010 p.152
	Number of occupational therapist visits	3.5	Assume range 3-4	PC: Wright S 16/03/2011

	(per year)			
	Diagnostic test: Full blood count	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: Liver function test	£6.19 inflated to 2010 = £8.55	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: Erythrocyte sedimentation rate	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: C-reactive protein	£11.15 inflated to 2010 = £15.41	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Diagnostic test: Urea, electrolytes and creatinine	£0.08 inflated to 2010 = £0.11	N/A	Barton et al. 2004; inflation indices by Curtis et al. 2010
	Number of diagnostic tests a year	18	Assume range 12-24	PC: Westhovens R 02/03/2011, Wright S 16/03/2011; assume flare occurs 3 times a year and it takes 4-8 weeks to resolve
	Total: No response	£3,640.51		

Note: when proportion of patients for a resource item is not stated assume 100% [PC: Westhovens R 02/03/2011, Wright S 16/03/2011]

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

In the first comparison (tocilizumab vs. MTX), patients in the tocilizumab arm receive also MTX in line with the market authorisation and license of the intervention. Observed evidence from the TENDER trial did not identify any significant differences between the active and control arms of the study (see section 5.9). Therefore, it is assumed the two model arms have the same safety profile in this comparison.

In the second comparison (tocilizumab vs. biologics), as discussed in section 5.9, a review of comparator safety did not identify any notable differences in serious adverse events with high incidence (over 5%).

In all comparisons the identified adverse events are of minor severity, lasting a short duration, and have a minuscule cost impact for their management. Therefore, it can be assumed that they do not have a considerable bearing on the incremental cost of the two model arms.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

All relevant costs are considered in sections 6.5.5 to 6.5.7.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The following structural assumptions are considered:

- Timeframe: the model is run for different time periods (see section 6.7.9)
- Treatments in sequence: the analysis considers different number of treatments in each sequence (see section 6.7.9)

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The Table below summarises the parameters and the rationale for sensitivity analysis.

Table 66: Sensitivity analysis changes and rationale

Parameter	Index	Model changes and rationale
ACR response	1	Consider ACR response rates of TNFαs as from Ruperto et al. [2007] without adjustments
	2	Adjust the ANK ACR response rates based on efficacy observed in Quartier et al. 2010 after 2 months; assume response is degraded by 2/3
	3	Use the ANK ACR response rates for all biologics
	4	Use ACR + fever definition
	5	Use ACR response of ITT population for MTX strategy (base case uses PBO+ MTX only patients)*
	6	Do not use ACR 90
Withdrawal risk	7	Consider lower limit of withdrawal risk
	8	Consider higher limit of withdrawal risk
Mortality risk	9	Consider lower limit of mortality risk
	10	Consider higher limit of mortality risk
Starting age	11	Change the age of young person to 7 years
	12	Change the age of young person to 7 years
Utilities formula	13	Consider the NICE quadratic formula [2010] for estimation of QALYs from CHAQ
	14	Consider the Roche linear formula for estimation of QALYs from CHAQ
	15	Consider the Boggs et al. 2002 formula for estimation of QALYs from CHAQ
Starting CHAQ	16	Change baseline CHAQ to 1.73 (all missing data patients excluded) N=89
	17	Change baseline CHAQ to 1.63 (all patients with age <5 years) N=21
	18	Change baseline CHAQ =2
Health-state-related cost	19	Half cost of inpatient stay
	20	Make time on inpatient stay equal across health states (24.5 days)
	21	Increase cost of inpatient stay by 50% for non-responders (given clinical expert opinion on conservative assumptions)
	22	Half all health-state-related costs
	23	Double all health-state-related costs
	24	Consider low limit of resource utilization (visits)
	25	Consider high limit of resource utilization (visits)
	26	Consider low limit of resource utilization (proportion of patients)
	27	Consider high limit of resource utilization (proportion of patients)

Administration cost for IV infusion	28	Half administration cost of IV infusion
	29	Double administration cost of IV infusion
Administration cost for subcutaneous injection	30	Half nurse visit cost (subcutaneous injection)
	31	Double nurse visit cost (subcutaneous injection)
	32	Consider low limit of proportion of patients who require assistance for subcutaneous injection
	33	Consider high limit of proportion of patients who require assistance for subcutaneous injection
Treatment cost	34	Assume no wastage

*Not applicable for second comparison

The Table below summarises the parameters and the rationale for scenario analysis.

Table 67: Scenario analysis changes and rationale

Parameter	Index	Model changes and rationale
Patient life/ model duration	1	Patients 2-32 years
	2	Patients 2-22 years
	3	Patients 5-18 years
	4	Patients 5-32 years
	5	Patients 10-18 years
Number of treatments in the sequence	6	One treatment only
	7	Two treatments
	8	Three treatments
Etanercept	9	Use etanercept as a comparator

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken. All relevant parameters were sampled if appropriate. The Table below presents the parameters that were sampled and the corresponding distributions.

Table 68: PSA parameters and assumptions

Parameter	Summary statistics		Sampling Distribution	Distribution parameters	
	Mean	SE		Beta: alpha	Beta: beta
				Gamma: alpha	Gamma: beta
				Uniform: low limit	Uniform: high limit
ACR response rates	See 6.3.6	N/A	Dirichlet	Dirichlet distribution: assume N=alpha of the one parameter Gamma distribution for each ACR category	
Withdrawal risk of biologics	0.0227	0.0068	Beta	10.8359	466.0480
Withdrawal risk of MTX	0.0674	0.0202	Beta	10.2944	142.3591
Mortality risk	0.0002	0.0001	Beta	4.8308	29892.1554
uACR30	0.5674	N/A	Linked	Probabilistic parameter linked to No ACR response	
uACR50	0.6050	N/A	Linked	Probabilistic parameter linked to No ACR response	
uACR70	0.6736	N/A	Linked	Probabilistic parameter linked to No ACR response	
uACR90	0.7150	N/A	Linked	Probabilistic parameter linked to No ACR response	
uACRNR	0.4152	0.1246	Beta	6.0827	8.5677
Health state cost					
Unit costs					
Inpatient stay (per day)	428.32	N/A	No sampling	Sampling of resource use was undertaken	
GP visit (per visit)	32.00	N/A	No sampling	Sampling of resource use was undertaken	
Haematological (per visit)	91.00	N/A	No sampling	Sampling of resource use was undertaken	
Radiological (per visit)	139.55	N/A	No sampling	Sampling of resource use was undertaken	
Podiatrist (per visit)	11.00	N/A	No sampling	Sampling of resource use was undertaken	
Opthalmologist (per visit)	70.47	N/A	No sampling	Sampling of resource use was undertaken	
Rheumatology paediatric (per visit)	266.66	N/A	No sampling	Sampling of resource use was undertaken	
Psychologist paediatric (per visit)	89.00	N/A	No sampling	Sampling of resource use was undertaken	
Orthodontist (per visit)	101.00	N/A	No sampling	Sampling of resource use was undertaken	
Occupational therapist (per visit)	15.00	N/A	No sampling	Sampling of resource use was undertaken	
Full blood count	15.41	N/A	No sampling	Sampling of resource use was undertaken	
Liver function test	8.55	N/A	No sampling	Sampling of resource use was undertaken	
Erythrocyte sedimentation rate	15.41	N/A	No sampling	Sampling of resource use was undertaken	
C-reactive protein	15.41	N/A	No sampling	Sampling of resource use was undertaken	

Urea, electrolytes and creatinine	0.11	N/A	No sampling	Sampling of resource use was undertaken	
Resource use: response					
Inpatient stay (annual units)					
Number of days	7.500	1.276	Gamma	34.5744	0.2169
Proportion of patients ACR 30	0.225	0.013	Beta	240.9314	829.8750
Proportion of patients ACR 50	0.148	N/A	Linked	Probabilistic parameter linked to ACR 30	
Proportion of patients ACR 70	0.072	N/A	Linked	Probabilistic parameter linked to ACR 30	
Proportion of patients ACR 90	0.000	N/A	Linked	Probabilistic parameter linked to ACR 30	
GP visit (annual units)					
Number of visits	3.500	0.255	Gamma	188.2384	0.0186
Haematological (annual units)					
Number of visits	2.000	0.600	Gamma	11.1111	0.1800
Radiological (annual units)					
Number of visits	2.000	0.600	Gamma	11.1111	0.1800
Proportion of patients	0.200	0.060	Beta	8.6889	34.7556
Podiatrist (annual units)					
Number of visits	1.000	0.300	Gamma	11.1111	0.0900
Proportion of patients	0.025	0.003	Beta	93.6140	3650.9460
Opthalmologist (annual units)					
Number of visits	2.000	0.600	Gamma	11.1111	0.1800
Proportion of patients	1.000		No sampling		
Rheumatology paediatric (annual units)					
Number of visits	3.000	0.900	Gamma	11.1111	0.2700
Proportion of patients	1.000		No sampling		
Psychologist paediatric (annual units)					
Number of visits	1.000	0.300	Gamma	11.1111	0.0900
Proportion of patients	0.200	0.060	Beta	8.6889	34.7556
Orthodontist (annual units)					
Number of visits	1.000	0.300	Gamma	11.1111	0.0900
Proportion of patients	0.200	0.060	Beta	8.6889	34.7556
Occupational therapist (annual units)					

Number of visits	1.000	0.300	Gamma	11.1111	0.0900
Proportion of patients	0.200	0.060	Beta	8.6889	34.7556
Outpatient diagnostic tests (annual units)					
Number of tests	3.000	0.900	Gamma	11.1111	0.2700
Resource use: no-response, uncontrolled disease					
Inpatient stay (annual units)					
Number of days	24.500	1.786	Gamma	188.2384	0.1302
Proportion of patients	0.900	0.026	Beta	123.5678	13.7298
GP visit (annual units)					
Number of visits	20.800	2.211	Gamma	88.5105	0.2350
Haematological (annual units)					
Number of visits	12.000	3.600	Gamma	11.1111	1.0800
Radiological (annual units)					
Number of visits	2.000		Linked	Parameter not sampled independent of health state	
Proportion of patients	0.900	0.026	Beta	123.5678	13.7298
Podiatrist (annual units)					
Number of visits	1.000		Linked	Parameter not linked independent of health state	
Proportion of patients	0.100	0.030	Beta	9.9000	89.1000
Opthalmologist (annual units)					
Number of visits	2.000		Linked	Parameter not linked independent of health state	
Proportion of patients	1.000		No sampling	Not appropriate distribution available	
Rheumatology paediatric (annual units)					
Number of visits	10.000	3.000	Gamma	11.1111	0.9000
Proportion of patients	1.000		No sampling	Not appropriate distribution available	
Psychologist paediatric (annual units)					
Number of visits	1.500	0.255	Gamma	34.5744	0.0434
Proportion of patients	0.850	0.051	Beta	40.7833	7.1971
Orthodontist (annual units)					
Number of visits	1.000	0.300	Gamma	11.1111	0.0900
Proportion of patients	0.350	0.105	Beta	6.8722	12.7627
Occupational therapist (annual units)					

Number of visits	3.500	0.255	Gamma	188.2384	0.0186
Proportion of patients	1.000		No sampling	Not appropriate distribution available	
Outpatient diagnostic tests (annual units)					
Number of tests	18.000	3.061	Gamma	34.5744	0.5206
Treatment cost					
Administration cost of infusion (per admin)	149.760	44.928	Gamma	11.1111	13.4784
Nurse visit cost (per visit)	13.000	3.571	Gamma	13.2496	0.9812
Children requiring assistance	0.200	0.060	Beta	8.6889	34.7556
Young persons requiring assistance	0.100	0.030	Beta	9.9000	89.1000
Young person age	10.000		Uniform	7.0000	13.0000
Starting age	2.000		No sampling	Sampling not appropriate: 1st order variability	
Patient weight	Age-dependent		No sampling	Sampling not appropriate: 1st order variability	

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

This is not relevant to the model results. The economic uses the trial data and extrapolates beyond the clinical trial (12 week duration).

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The information requested here is too large to be presented. Please see rows 284 to 347 in MarkovChain spreadsheet in the workbook provided with the submission.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The information requested here is too large to be presented. Please see rows 1270 to 1334 in MarkovChain spreadsheet in the workbook provided with the submission.

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Not relevant

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 69: Summary of QALY gain by health state: comparison with MTX

Health state	QALYs Strategy TCZ	QALYs Strategy MTX	Incremental	Absolute increment	% absolute increment
Line1_NR	0.1038	0.1038	0.0000	0.0000	0.0000
Line1_ACR30	0.2578	0.1597	0.0981	0.0981	0.0774
Line1_ACR50	0.7430	0.0000	0.7430	0.7430	0.5866
Line1_ACR70	1.8926	0.0960	1.7966	1.7966	1.4185
Line1_ACR90	2.2436	0.0993	2.1443	2.1443	1.6930
Line2_NR	0.0811	0.1035	-0.0224	0.0224	0.0177
Line2_ACR30	0.0635	0.1055	-0.0420	0.0420	0.0331
Line2_ACR50	0.1830	0.3040	-0.1210	0.1210	0.0956
Line2_ACR70	0.4661	0.7744	-0.3083	0.3083	0.2434
Line2_ACR90	0.5526	0.9180	-0.3655	0.3655	0.2885
Line3_NR	0.0672	0.0931	-0.0259	0.0259	0.0205
Line3_ACR30	0.2884	0.5086	-0.2201	0.2201	0.1738
Line3_ACR50	0.0485	0.0855	-0.0370	0.0370	0.0292
Line3_ACR70	0.0929	0.1638	-0.0709	0.0709	0.0560
Line3_ACR90	0.1212	0.2136	-0.0925	0.0925	0.0730
Line4_NR	0.0590	0.0855	-0.0265	0.0265	0.0209
Line4_ACR30	0.2421	0.4416	-0.1995	0.1995	0.1575
Line4_ACR50	0.0407	0.0742	-0.0335	0.0335	0.0265
Line4_ACR70	0.0780	0.1423	-0.0643	0.0643	0.0508
Line4_ACR90	0.1017	0.1855	-0.0838	0.0838	0.0662
Line4_UCD	1.7175	3.5196	-1.8021	1.8021	1.4228
Death	0.0000	0.0000	0.0000	0.0000	0.0000
ResultUndiscounted	9.4441	8.1776	1.2665	1.2665	1.0000
ResultDiscounted	5.4465	4.7161	0.7304	0.7304	N/A

Table 70:Summary of QALY gain by health state: comparison with ANK

Health state	QALYs Strategy TCZ	QALYs Strategy ANK	Incremental	Absolute increment	% absolute increment
Line1_NR	0.1038	0.1038	0.0000	0.0000	0.0000
Line1_ACR30	0.2578	0.1088	0.1490	0.1490	0.1706
Line1_ACR50	0.7430	0.3135	0.4295	0.4295	0.4917
Line1_ACR70	1.8926	0.7986	1.0940	1.0940	1.2524
Line1_ACR90	2.2436	0.9467	1.2969	1.2969	1.4846
Line2_NR	0.0811	0.0942	-0.0131	0.0131	0.0150
Line2_ACR30	0.3766	0.5292	-0.1526	0.1526	0.1747
Line2_ACR50	0.0633	0.0889	-0.0256	0.0256	0.0294
Line2_ACR70	0.1213	0.1705	-0.0492	0.0492	0.0563
Line2_ACR90	0.1582	0.2223	-0.0641	0.0641	0.0734
Line3_NR	0.0722	0.0869	-0.0147	0.0147	0.0168
Line3_ACR30	0.3193	0.4620	-0.1427	0.1427	0.1633
Line3_ACR50	0.0537	0.0776	-0.0240	0.0240	0.0274
Line3_ACR70	0.1029	0.1488	-0.0460	0.0460	0.0526
Line3_ACR90	0.1341	0.1941	-0.0599	0.0599	0.0686
Line4_NR	0.0637	0.0793	-0.0156	0.0156	0.0179
Line4_ACR30	0.2689	0.4001	-0.1311	0.1311	0.1501
Line4_ACR50	0.0452	0.0672	-0.0220	0.0220	0.0252
Line4_ACR70	0.0866	0.1289	-0.0422	0.0422	0.0484
Line4_ACR90	0.1130	0.1681	-0.0551	0.0551	0.0631
Line4_UCD	1.9278	3.1657	-1.2379	1.2379	1.4171
Death	0.0000	0.0000	0.0000	0.0000	0.0000
ResultUndiscounted	9.2287	8.3552	0.8736	0.8736	1.0000
ResultDiscounted	5.3223	4.8185	0.5038	0.5038	N/A

Table 71: Summary of treatment costs by health state: comparison with MTX

Health state	Tx cost Strategy TCZ	Tx cost Strategy MTX	Incremental	Absolute increment	% absolute increment
Line1_NR	£2,642.58	£7.34	£2,635.24	£2,635.24	0.031
Line1_ACR30	£6,472.92	£8.27	£6,464.66	£6,464.66	0.076
Line1_ACR50	£17,500.87	£0.00	£17,500.87	£17,500.87	0.206
Line1_ACR70	£40,036.23	£4.19	£40,032.04	£40,032.04	0.471
Line1_ACR90	£44,711.12	£4.08	£44,707.04	£44,707.04	0.526
Line2_NR	£2,199.12	£2,621.84	-£422.72	£422.72	0.005
Line2_ACR30	£1,388.69	£2,125.53	-£736.84	£736.84	0.009
Line2_ACR50	£3,754.61	£5,746.82	-£1,992.20	£1,992.20	0.023
Line2_ACR70	£8,589.32	£13,146.82	-£4,557.51	£4,557.51	0.054
Line2_ACR90	£9,592.26	£14,681.93	-£5,089.67	£5,089.67	0.060
Line3_NR	£1,538.89	£2,141.21	-£602.32	£602.32	0.007
Line3_ACR30	£4,817.75	£8,518.08	-£3,700.32	£3,700.32	0.044
Line3_ACR50	£759.46	£1,342.77	-£583.31	£583.31	0.007
Line3_ACR70	£1,307.30	£2,311.39	-£1,004.09	£1,004.09	0.012
Line3_ACR90	£1,606.04	£2,839.58	-£1,233.54	£1,233.54	0.015
Line4_NR	£1,330.33	£1,930.10	-£599.77	£599.77	0.007
Line4_ACR30	£3,993.58	£7,289.78	-£3,296.21	£3,296.21	0.039
Line4_ACR50	£629.54	£1,149.14	-£519.61	£519.61	0.006
Line4_ACR70	£1,083.66	£1,978.09	-£894.43	£894.43	0.011
Line4_ACR90	£1,331.30	£2,430.12	-£1,098.82	£1,098.82	0.013
Line4_UCD	£0.00	£0.00	£0.00	£0.00	0.000
Death	£0.00	£0.00	£0.00	£0.00	0.000
ResultUndiscounted	£155,285.56	£70,277.08	£85,008.48	£85,008.48	1.000
ResultDiscounted	£89,554.10	£40,529.21	£49,024.89	£49,024.89	N/A

Table 72: Summary of treatment costs by health state: comparison with ANK

Health state	Tx cost Strategy TCZ	Tx cost Strategy ANK	Incremental	Absolute increment	% absolute increment
Line1_NR	£2,642.58	£2,623.53	£19.05	£19.05	0.000
Line1_ACR30	£6,472.92	£2,172.22	£4,300.70	£4,300.70	0.071
Line1_ACR50	£17,500.87	£5,873.05	£11,627.82	£11,627.82	0.193
Line1_ACR70	£40,036.23	£13,435.61	£26,600.62	£26,600.62	0.441
Line1_ACR90	£44,711.12	£15,004.43	£29,706.68	£29,706.68	0.492
Line2_NR	£1,860.70	£2,167.30	-£306.60	£306.60	0.005
Line2_ACR30	£6,295.16	£8,868.28	-£2,573.12	£2,573.12	0.043
Line2_ACR50	£992.35	£1,397.97	-£405.62	£405.62	0.007
Line2_ACR70	£1,708.20	£2,406.42	-£698.22	£698.22	0.012
Line2_ACR90	£2,098.55	£2,956.33	-£857.77	£857.77	0.014
Line3_NR	£1,630.34	£1,963.63	-£333.29	£333.29	0.006
Line3_ACR30	£5,267.80	£7,626.28	-£2,358.48	£2,358.48	0.039
Line3_ACR50	£830.40	£1,202.19	-£371.79	£371.79	0.006
Line3_ACR70	£1,429.42	£2,069.40	-£639.98	£639.98	0.011
Line3_ACR90	£1,756.07	£2,542.29	-£786.22	£786.22	0.013
Line4_NR	£1,085.93	£1,184.87	-£98.94	£98.94	0.002
Line4_ACR30	£3,939.67	£5,336.57	-£1,396.91	£1,396.91	0.023
Line4_ACR50	£621.04	£841.24	-£220.20	£220.20	0.004
Line4_ACR70	£1,069.03	£1,448.08	-£379.05	£379.05	0.006
Line4_ACR90	£1,313.33	£1,779.00	-£465.67	£465.67	0.008
Line4_UCD	£0.00	£0.00	£0.00	£0.00	0.000
Death	£0.00	£0.00	£0.00	£0.00	0.000
ResultUndiscounted	£143,261.71	£82,898.69	£60,363.01	£60,363.01	1.000
ResultDiscounted	£82,619.87	£47,808.17	£34,811.71	£34,811.71	N/A

Table 73: Summary of health state costs by health state: comparison with MTX

Health state	Tx cost Strategy TCZ	Tx cost Strategy MTX	Incremental	Absolute increment	% absolute increment
Line1_NR	£3,640.51	£3,640.51	£0.00	£0.00	0.000
Line1_ACR30	£991.36	£614.18	£377.18	£377.18	0.006
Line1_ACR50	£2,390.26	£0.00	£2,390.26	£2,390.26	0.041
Line1_ACR70	£4,817.33	£244.39	£4,572.94	£4,572.94	0.078
Line1_ACR90	£4,696.08	£207.86	£4,488.22	£4,488.22	0.077
Line2_NR	£2,845.02	£3,631.53	-£786.51	£786.51	0.013
Line2_ACR30	£244.16	£405.64	-£161.48	£161.48	0.003
Line2_ACR50	£588.68	£978.03	-£389.35	£389.35	0.007
Line2_ACR70	£1,186.43	£1,971.12	-£784.69	£784.69	0.013
Line2_ACR90	£1,156.57	£1,921.50	-£764.94	£764.94	0.013
Line3_NR	£2,355.86	£3,265.76	-£909.90	£909.90	0.016
Line3_ACR30	£1,109.43	£1,956.08	-£846.66	£846.66	0.014
Line3_ACR50	£155.96	£274.98	-£119.02	£119.02	0.002
Line3_ACR70	£236.51	£417.00	-£180.49	£180.49	0.003
Line3_ACR90	£253.63	£447.19	-£193.56	£193.56	0.003
Line4_NR	£2,067.88	£2,997.51	-£929.62	£929.62	0.016
Line4_ACR30	£931.15	£1,698.60	-£767.45	£767.45	0.013
Line4_ACR50	£130.90	£238.78	-£107.89	£107.89	0.002
Line4_ACR70	£198.51	£362.11	-£163.61	£163.61	0.003
Line4_ACR90	£212.87	£388.32	-£175.45	£175.45	0.003
Line4_UCD	£60,239.07	£123,443.49	-£63,204.43	£63,204.43	1.078
Death	£0.00	£0.00	£0.00	£0.00	0.000
ResultUndiscounted	£90,448.17	£149,104.59	-£58,656.43	£58,656.43	1.000
ResultDiscounted	£52,161.99	£85,989.50	-£33,827.51	£33,827.51	N/A

Table 74: Summary of health state costs by health state: comparison with ANK

Health state	Tx cost Strategy TCZ	Tx cost Strategy ANK	Incremental	Absolute increment	% absolute increment
Line1_NR	£3,640.51	£3,640.51	£0.00	£0.00	0.000
Line1_ACR30	£991.36	£418.30	£573.07	£573.07	0.014
Line1_ACR50	£2,390.26	£1,008.55	£1,381.71	£1,381.71	0.034
Line1_ACR70	£4,817.33	£2,032.63	£2,784.70	£2,784.70	0.069
Line1_ACR90	£4,696.08	£1,981.47	£2,714.61	£2,714.61	0.068
Line2_NR	£2,845.02	£3,304.52	-£459.50	£459.50	0.011
Line2_ACR30	£1,448.60	£2,035.58	-£586.98	£586.98	0.015
Line2_ACR50	£203.64	£286.15	-£82.52	£82.52	0.002
Line2_ACR70	£308.82	£433.95	-£125.13	£125.13	0.003
Line2_ACR90	£331.17	£465.36	-£134.19	£134.19	0.003
Line3_NR	£2,533.51	£3,049.32	-£515.81	£515.81	0.013
Line3_ACR30	£1,228.05	£1,776.82	-£548.77	£548.77	0.014
Line3_ACR50	£172.63	£249.78	-£77.14	£77.14	0.002
Line3_ACR70	£261.80	£378.79	-£116.99	£116.99	0.003
Line3_ACR90	£280.75	£406.20	-£125.46	£125.46	0.003
Line4_NR	£2,235.67	£2,782.65	-£546.98	£546.98	0.014
Line4_ACR30	£1,034.34	£1,538.72	-£504.38	£504.38	0.013
Line4_ACR50	£145.40	£216.31	-£70.90	£70.90	0.002
Line4_ACR70	£220.50	£328.03	-£107.52	£107.52	0.003
Line4_ACR90	£236.46	£351.77	-£115.31	£115.31	0.003
Line4_UCD	£67,614.22	£111,030.58	-£43,416.35	£43,416.35	1.083
Death	£0.00	£0.00	£0.00	£0.00	0.000
ResultUndiscounted	£97,636.13	£137,715.97	-£40,079.84	£40,079.84	1.000
ResultDiscounted	£56,307.34	£79,421.62	-£23,114.28	£23,114.28	N/A

Table 75: Summary of costs by strategy: comparison vs. MTX

	Strategy TCZ	Strategy MTX	Incremental
Treatment cost	£89,554.10	£40,529.21	£49,024.89
Health state cost	£52,161.99	£85,989.50	-£33,827.51
Total cost	£141,716.09	£126,518.71	£15,197.38

Table 76: Summary of costs by strategy: comparison vs. ANK

	Strategy TCZ	Strategy ANK	Incremental
Treatment cost	£82,619.87	£47,808.17	£34,811.71
Health state cost	£56,307.34	£79,421.62	-£23,114.28
Total cost	£138,927.21	£127,229.78	£11,697.43

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 77: Base-case results: comparison versus MTX

Technologies	Total costs (£)	Total LYG in response	Total QALYs	Incremental costs (£)	Incremental LYG in response	Incremental QALYs	ICER (£) incremental (QALYs)
Strategy TCZ	£141,716.09	6.4341	5.4465	£15,197.38	2.6071	0.7304	£20,806.31
Strategy MTX	£126,518.71	3.8270	4.7161				

Table 78: Base-case results: comparison versus anakinra

Technologies	Total costs (£)	Total LYG in response	Total QALYs	Incremental costs (£)	Incremental LYG in response	Incremental QALYs	ICER (£) incremental (QALYs)
Strategy TCZ	£138,927.21	6.1284	5.3223	£11,697.43	1.7797	0.5038	£23,219.02
Strategy ANK	£127,229.78	4.3486	4.8185				

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table 79: Sensitivity analysis: comparison vs. MTX

Index		Strategy TCZ		Strategy MTX		Incremental results		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER £/QALY
	Base case	£141,716.09	5.4465	£126,518.71	4.7161	£15,197.38	0.7304	£20,806.31
	Clinical parameters							
1	Remove Prince adjustment from ACR response rates (Ruperto et al. 2007)	£140,729.50	5.5191	£124,757.38	4.8480	£15,972.11	0.6711	£23,800.51
2	Adjust the ANK ACR response rates (based on Quartier et al. 2010)	£141,707.77	5.3715	£127,073.28	4.5869	£14,634.48	0.7845	£18,653.40
3	Use the ANK ACR response rates for all biologics	£139,661.03	5.6323	£122,832.93	5.0539	£16,828.11	0.5784	£29,096.29
4	Use ACR+fever definition	£141,314.89	5.3749	£126,928.27	4.6737	£14,386.62	0.7012	£20,517.73
5	Use ACR response of ITT population for MTX arm	£141,716.09	5.4465	£124,374.87	4.7364	£17,341.22	0.7100	£24,423.44
6	Do not use ACR 90	£142,246.71	5.3456	£126,767.67	4.6687	£15,479.04	0.6769	£22,868.15
7	Withdrawal risk low limit	£148,853.27	5.8056	£121,340.96	4.9954	£27,512.31	0.8102	£33,958.33
8	Withdrawal risk high limit	£137,977.87	5.1567	£129,180.84	4.5238	£8,797.04	0.6329	£13,899.77
9	Mortality risk low limit	£142,382.71	5.4706	£127,104.56	4.7370	£15,278.15	0.7335	£20,828.14
10	Mortality risk high limit	£141,077.29	5.4234	£125,957.30	4.6959	£15,119.99	0.7274	£20,785.25
11	Young person age 7	£141,581.37	5.4465	£126,298.59	4.7161	£15,282.78	0.7304	£20,923.23
12	Young person age 13	£141,860.94	5.4465	£126,694.03	4.7161	£15,166.92	0.7304	£20,764.60
	Utilities							
13	NICE formula	£141,716.09	4.6599	£126,518.71	3.8519	£15,197.38	0.8080	£18,808.37
14	Roche linear formula	£141,716.09	5.2648	£126,518.71	4.5484	£15,197.38	0.7164	£21,214.02
15	Boggs et al. 2002 formula	£141,716.09	4.2934	£126,518.71	3.5770	£15,197.38	0.7164	£21,214.02
16	Baseline CHAQ to 1.73 (all missing data patients excluded) N=89	£141,716.09	5.3881	£126,518.71	4.6494	£15,197.38	0.7387	£20,572.43
17	Baseline CHAQ to 1.63 (all patients with age <5 years) N=21	£141,716.09	5.6183	£126,518.71	4.9129	£15,197.38	0.7054	£21,545.15
18	Baseline CHAQ CHAQ =2	£141,716.09	4.6425	£126,518.71	3.8052	£15,197.38	0.8373	£18,151.41
	Costs							

Index		Strategy TCZ		Strategy MTX		Incremental results		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER £/QALY
19	Half cost of inpatient stay	£127,619.33	5.4465	£100,234.61	4.7161	£27,384.73	0.7304	£37,491.66
20	Make time on inpatient stay equal across health states (24.5)	£145,301.30	5.4465	£129,541.62	4.7161	£15,759.68	0.7304	£21,576.14
	Increase duration of stay in hospital by 50% for non-responders	£155,022.00	5.4465	£152,135.99	4.7161	£2,886.01	0.7304	£3,951.15
22	Half all health-state unit costs	£115,635.10	5.4465	£83,523.96	4.7161	£32,111.14	0.7304	£43,962.46
23	Double all health-state unit costs	£193,295.76	5.4465	£211,931.02	4.7161	-£18,635.25	0.7304	TCZ strategy dominating
24	All visits to low limit	£129,560.81	5.4465	£109,394.56	4.7161	£20,166.25	0.7304	£27,609.05
25	All visits to high limit	£153,864.18	5.4465	£143,629.01	4.7161	£10,235.17	0.7304	£14,012.69
26	All proportions of patients to low limit	£141,210.92	5.4465	£126,033.93	4.7161	£15,176.99	0.7304	£20,778.39
27	All proportions of patients to high limit	£143,560.53	5.4465	£129,581.91	4.7161	£13,978.62	0.7304	£19,137.74
28	Half administration cost of infusion	£132,868.88	5.4465	£126,518.71	4.7161	£6,350.17	0.7304	£8,693.84
29	Double administration cost of infusion	£159,410.51	5.4465	£126,518.71	4.7161	£32,891.80	0.7304	£45,031.25
30	Half nurse visit cost	£141,244.66	5.4465	£125,625.43	4.7161	£15,619.23	0.7304	£21,383.85
31	Double nurse visit cost	£142,658.96	5.4465	£128,305.26	4.7161	£14,353.70	0.7304	£19,651.24
32	Proportion of patients who require assistance for S/C injection low limit	£141,161.69	5.4465	£125,468.22	4.7161	£15,693.47	0.7304	£21,485.49
33	Proportion of patients who require assistance for S/C injection high limit	£142,270.50	5.4465	£127,569.20	4.7161	£14,701.30	0.7304	£20,127.13
34	No wastage for costs	£131,114.39	5.4465	£119,482.78	4.7161	£11,631.60	0.7304	£15,924.50

Table 80: Sensitivity analysis: comparison vs. BIO

Index		Strategy TCZ		Strategy Anakinra		Incremental results		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER £/QALY
	Base case	£138,927.21	5.3223	£127,229.78	4.8185	£11,697.43	0.5038	£23,219.02
	Clinical parameters							
1	Remove Prince adjustment from ACR response rates (Ruperto et al. 2007)	£137,224.46	5.4438	£124,677.84	4.9980	£12,546.63	0.4458	£28,142.02
2	Adjust the ANK ACR response rates (based on Quartier et al. 2010)	£138,927.21	5.3223	£127,508.57	4.6959	£11,418.64	0.6264	£18,230.10
3	Use the ANK ACR response rates for all biologics	£135,472.39	5.6323	£122,068.35	5.2766	£13,404.04	0.3557	£37,682.68
4	Use ACR+fever definition	£138,608.08	5.2518	£127,537.89	4.8548	£11,070.19	0.3970	£27,884.31
5	Use ACR response of ITT population for MTX arm	Not applicable						
6	Do not use ACR 90	£139,392.77	5.2338	£127,498.89	4.7673	£11,893.89	0.4664	£25,499.19
7	Withdrawal risk low limit	£146,369.13	5.7122	£125,527.63	5.0938	£20,841.49	0.6183	£33,706.35
8	Withdrawal risk high limit	£135,571.00	5.0316	£128,974.37	4.6185	£6,596.63	0.4131	£15,969.75
9	Mortality risk low limit	£139,574.92	5.3457	£127,811.19	4.8399	£11,763.73	0.5058	£23,258.07
10	Mortality risk high limit	£138,306.50	5.2998	£126,672.63	4.7979	£11,633.87	0.5019	£23,181.32
11	Young person age 7	£138,901.09	5.3223	£127,015.07	4.8185	£11,886.02	0.5038	£23,593.38
12	Young person age 13	£138,954.83	5.3223	£127,395.98	4.8185	£11,558.85	0.5038	£22,943.96
	Utilities							
13	NICE formula	£138,927.21	4.5201	£127,229.78	3.9625	£11,697.43	0.5576	£20,976.37
14	Roche linear formula	£138,927.21	5.1380	£127,229.78	4.6432	£11,697.43	0.4948	£23,638.95
15	Boggs et al. 2002 formula	£138,927.21	4.1434	£127,229.78	3.6486	£11,697.43	0.4948	£23,638.95
16	Baseline CHAQ to 1.73 (all missing data patients excluded) N=89	£138,927.21	5.2624	£127,229.78	4.7529	£11,697.43	0.5095	£22,957.64
17	Baseline CHAQ to 1.63 (all patients with age <5 years) N=21	£138,927.21	5.4985	£127,229.78	5.0120	£11,697.43	0.4865	£24,044.81
18	Baseline CHAQ CHAQ =2	£138,927.21	4.4994	£127,229.78	3.9218	£11,697.43	0.5776	£20,252.42

	Costs							
19	Half cost of inpatient stay	£123,307.28	5.3223	£103,278.56	4.8185	£20,028.72	0.5038	£39,756.37
20	Make time on inpatient stay equal across health states (24.5)	£142,871.87	5.3223	£130,843.63	4.8185	£12,028.24	0.5038	£23,875.67
21	Half all health-state unit costs	£110,773.54	5.3223	£87,518.97	4.8185	£23,254.57	0.5038	£46,159.58
22	Increase duration of patients in hospital by 50% for non-responders	£153,676.99	5.3223	£150,383.83	4.8185	£3,293.16	0.5038	£6,536.82
23	All visits to low limit	£126,187.16	5.3223	£111,096.62	4.8185	£15,090.54	0.5038	£29,954.24
24	All visits to high limit	£151,657.26	5.3223	£143,347.25	4.8185	£8,310.01	0.5038	£16,495.11
25	All proportions of patients to low limit	£138,424.43	5.3223	£126,740.93	4.8185	£11,683.50	d0.5038	£23,191.39
26	All proportions of patients to high limit	£139,429.99	5.3223	£127,718.64	4.8185	£11,711.35	0.5038	£23,246.66
27	Half administration cost of infusion	£129,524.91	5.3223	£126,424.95	4.8185	£3,099.96	0.5038	£6,153.32
28	Double administration cost of infusion	£157,731.81	5.3223	£128,839.44	4.8185	£28,892.37	0.5038	£57,350.44
29	Half nurse visit cost	£138,834.82	5.3223	£126,291.00	4.8185	£12,543.82	0.5038	£24,899.09
30	Double nurse visit cost	£139,111.99	5.3223	£129,107.35	4.8185	£10,004.63	0.5038	£19,858.88
31	Proportion of patients who require assistance for S/C injection low limit	£138,818.56	5.3223	£126,125.77	4.8185	£12,692.79	0.5038	£25,194.78
32	Proportion of patients who require assistance for SC injection high limit	£139,035.86	5.3223	£128,333.79	4.8185	£10,702.07	0.5038	£21,243.26
33	No wastage for costs	£129,098.44	5.3223	£118,881.38	4.8185	£10,217.06	0.5038	£20,280.54

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

In the comparison with MTX, out of 1,000 samples 39% to 72% were below a cost-effectiveness threshold of £20,000 and £30,000 per QALY respectively (See below).

Figure 15: Scatter plot: comparison versus MTX

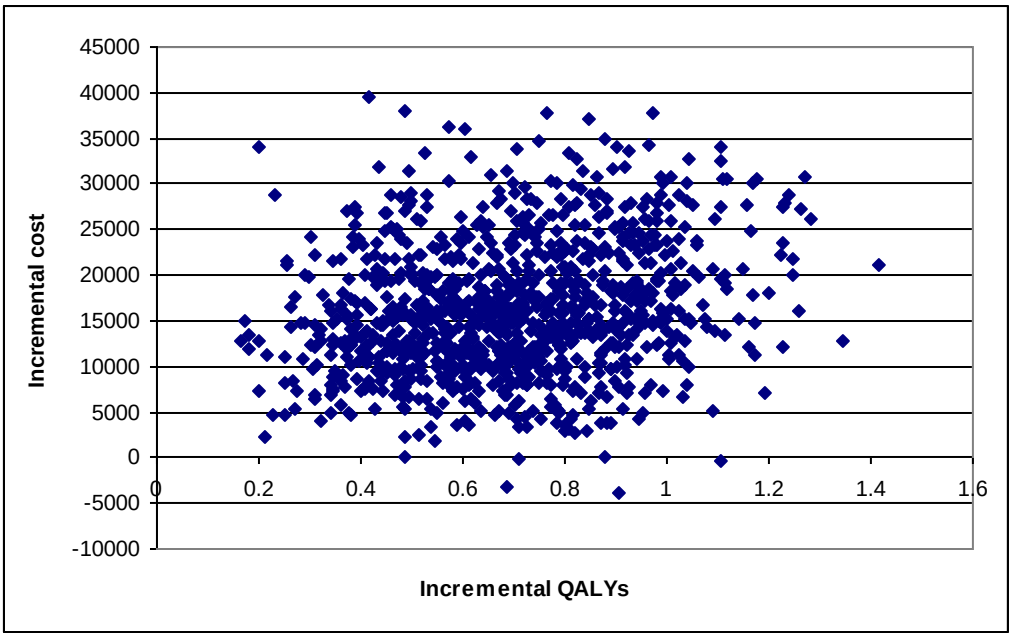
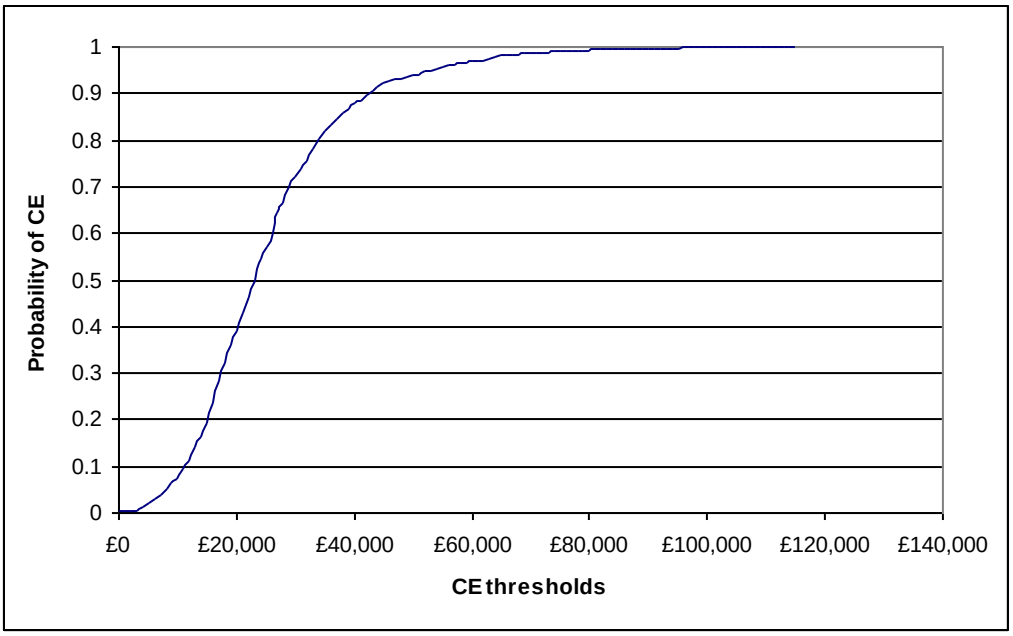


Figure 16: CEAC: comparison versus MTX



In the comparison with anakinra, out of 1,000 samples 38% to 63% were below a cost-effectiveness threshold of £20,000 and £30,000 per QALY respectively (See below).

Figure 17: Scatter plot: comparison versus ANK

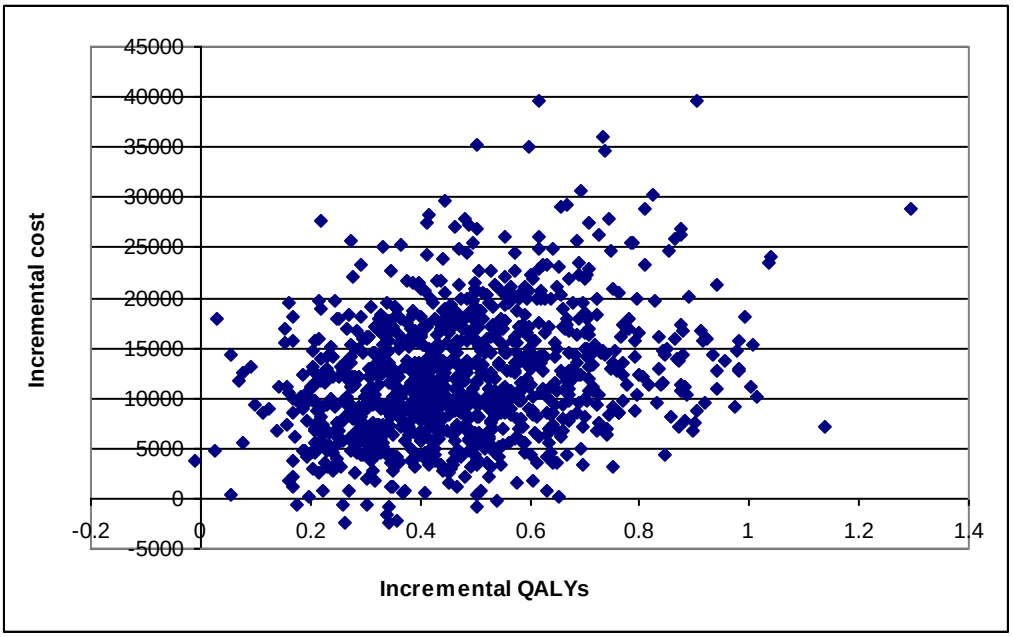
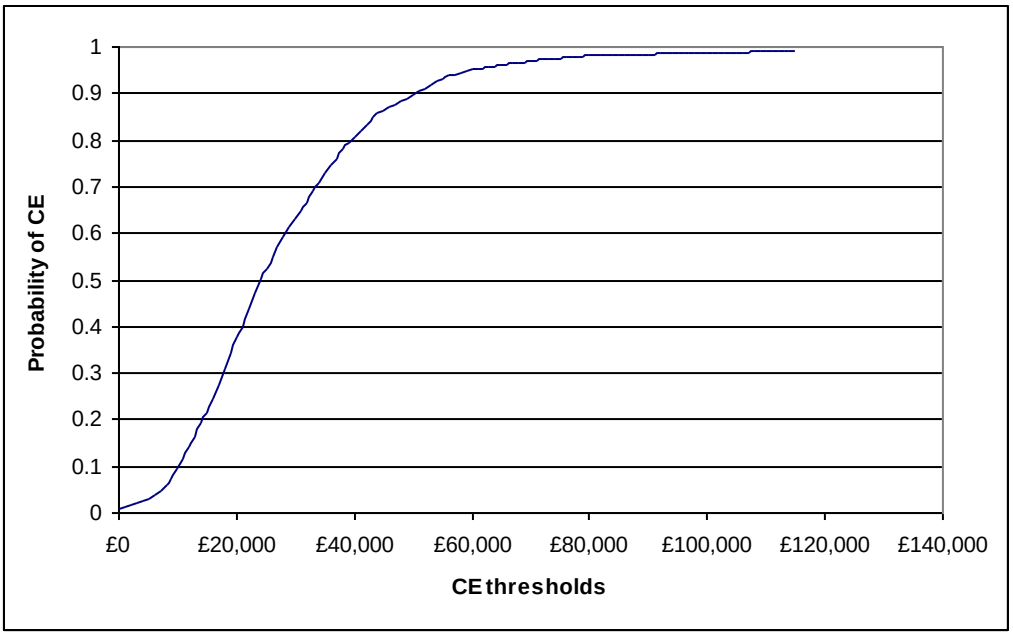


Figure 18: CEAC: comparison versus ANK



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 81: Scenario/structural analysis: comparison MTX

Index		Strategy TCZ		Strategy MTX		Incremental results		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER £/QALY
	Base case	£141,716.09	5.4465	£126,518.71	4.7161	£15,197.38	0.7304	£20,806.31
	Scenarios for age/duration							
1	Patients 2-32	£167,516.58	5.8003	£150,132.27	5.1213	£17,384.31	0.6789	£25,605.11
2	Patients 2-22	£157,426.40	5.7788	£139,534.38	5.0283	£17,892.02	0.7505	£23,838.66
3	Patients 5-18	£137,365.29	5.0100	£114,535.12	4.3252	£22,830.17	0.6848	£33,338.08
4	Patients 5-32	£176,518.87	5.8818	£151,037.65	5.1696	£25,481.22	0.7122	£35,777.73
5	Patients 10-18	£111,227.19	3.7998	£86,346.73	3.2687	£24,880.45	0.5311	£46,844.62
	Scenarios for line of treatments							
6	One treatment only	£142,311.42	4.9769	£130,627.55	3.9112	£11,683.87	1.0656	£10,964.27
7	Two treatments	£143,082.20	5.2565	£129,553.86	4.3759	£13,528.34	0.8807	£15,361.66
8	Three treatments	£142,354.97	5.3598	£127,965.78	4.5580	£14,389.19	0.8019	£17,944.93

Table 82:Scenario/structural analysis: comparison biologic

Index		Strategy TCZ		Strategy Biologic		Incremental results		
		Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER £/QALY
	Base case	£138,927.21	5.3223	£127,229.78	4.8185	£11,697.43	0.5038	£23,219.02
	Scenarios for age/duration							
1	Patients 2-32	£162,133.91	5.6602	£150,340.51	5.2248	£11,793.40	0.4354	£27,088.75
2	Patients 2-22	£153,097.61	5.6404	£140,042.73	5.1368	£13,054.88	0.5036	£25,922.18
3	Patients 5-18	£134,575.21	4.9033	£116,325.91	4.4187	£18,249.29	0.4846	£37,660.44
4	Patients 5-32	£170,056.78	5.7385	£151,870.94	5.2768	£18,185.84	0.4617	£39,390.73
5	Patients 10-18	£108,444.41	3.7351	£90,043.86	3.3383	£18,400.55	0.3968	£46,369.29
	Scenarios for line of treatments							
6	One treatment only	£142,311.42	4.9769	£133,381.86	4.3204	£8,929.56	0.6564	£13,602.96
7	Two treatments	£141,280.73	5.1117	£131,698.19	4.5099	£9,582.55	0.6018	£15,922.92
8	Three treatments	£140,367.44	5.2260	£130,153.42	4.6753	£10,214.02	0.5507	£18,546.26
9	Use Etanercept as comparator	£141,047.12	5.4465	£127,334.73	4.8051	£13,712.39	0.6414	£21,379.41

6.7.10 What were the main findings of each of the sensitivity analyses?

A number of one-way sensitivity analyses were performed to test the model robustness. This approach presents information on the model sensitivity to input changes and explains the driving parameters of the analysis. A number of such analyses were carried out to assess the sensitivity of the model around clinical parameters, utility inputs and cost inputs. The sensitivity analyses were performed for both comparisons (versus MTX and versus anakinra). For both comparisons each of the sensitivity settings applied influenced the model in the same direction; that is, either positively or negatively from the base case.

Of the clinical parameters, two had most influence on the model, the anakinra response rates and the withdrawal probability. Using the anakinra response rates for all biologics had the effect of inflating the ICER. This has smaller effect in the comparison with methotrexate, since there is no change to the comparator treatment (1st line). When tested an assumed low limit value for the withdrawal risk the ICER is increased. This is anticipated as a greater proportion of patients receive treatment accruing increasing cost. In this case, the increase in costs does not offset the increase in QALYs. The opposite is

observed when applying the higher limit for withdrawal risk; less patients on treatment.

Overall the model results are not sensitive to input changes surrounding utilities. The model results were very sensitive to input changes regarding costs for both comparisons. When assuming double the values for health-state unit costs the TCZ strategy is dominating the alternative. Moreover, given clinical expert opinion, one of the analyses tested the result of increasing the length of stay in hospital for non-responder patients. This results in a lower ICER from the base-case. The infusion administration cost is also found to have a great impact in the model results for both comparisons. The impact is estimated higher on the TCZ strategy as there are no infusion costs for the MTX or biologic comparator strategies.

In the scenario analyses the duration of the model in combination with the starting age of patients has a notable effect to the model results. The model estimates that the older the patient and the longer the analysis the higher the incremental cost and the ICER.

When evaluating different scenarios of treatment sequences (one, two, and three agents) it is estimated that the ICER increases with more treatments in the strategy. This signifies that the base case analysis has taken a conservative approach to evaluate four treatments in the sequence.

6.7.11 What are the key drivers of the cost-effectiveness results?

The main drivers of the economic evaluation results are treatment cost and assumptions around the cost of inpatient stay. Treatment cost, is also influenced by the duration of the model; therefore, assumptions on the starting age of individuals and the model timeframe have an impact on cost-effectiveness results. A description of the variability of these results is presented in sections 6.7.7 to 6.7.10.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model assumptions were validated by clinical experts (PC: Westhovens R 02/03/2011, Wright S 16/03/2011, P Woo 21/3/2011, E Baildam 28/03/2011). An independent analyst verified the model calculations. A report was produced with comments on the model. All comments were acknowledged and considered for the final version of the model.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Not relevant. No subgroup analysis was undertaken.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Not relevant

6.9.3 Please describe how the statistical analysis was undertaken.

Not relevant

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not relevant

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Not relevant.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To date there have been no published abstracts, conference posters or full manuscripts on the cost effectiveness of tocilizumab in the treatment of systemic JIA. Therefore no comparison can be made between the results presented here and published results.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

As discussed in section 6.2.1 the economic evaluation reflects all the relevant groups of patients who could potentially use the technology.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

This is the first cost-utility analysis in patients with sJIA. Moreover, it is the first economic evaluation for tocilizumab versus MTX and versus anti- TNFα treatment or anakinra.

The analysis takes the form of a comparison of two sequences of treatments and reflects a typical clinical pathway. Evidence for the efficacy of the comparators comes from RCT data (MTX) or indirect comparison. In the development of the analysis Roche consulted with clinical experts to ensure all necessary assumptions and methodology are robust and in line with clinical practice. When there was uncertainty about the approach in the methods and the analysis, a conservative assumption was adopted.

The analysis is significantly hampered by the lack of HRQL data. A broad systematic review in JIA did not identify any evidence for the model. Moreover, for reasons described in the relevant sections, data from the clinical trial were not useable. In order to present cost-utility results the analysis resorts in an adult rheumatoid arthritis mapping mechanism. The assumptions on the produced utility scores are described in detail, in the relevant sections, and tested in sensitivity analysis.

Another weakness of the present economic evaluation is lack of efficacy and safety evidence for the comparator biologics. A review did not identify any study for anti-TNFα treatments in this specific population. Moreover, when broadening the review criteria, many pivotal RCTs for other anti-TNFα treatments could not be considered, due to differences in the study design with TENDER. Only one study [Ruperto et al. 2007], provided evidence that could be considered comparable to TENDER, and efficacy data from that study had to be further adjusted for the differences in population subtypes. The assumptions on ACR response rates are tested in sensitivity analysis.

The systematic review on clinical evidence for the comparators identified one recently published study on anakinra [Quartier et al. 2010] in sJIA patients. However, the duration of the study is not comparable to TENDER. Moreover, the study demonstrates that response to treatment is further reduced in the open-label extension phase (2 months). Another factor that reduces the quality of the study is its small sample size. The economic evaluation has taken a conservative approach in not adjusting the results of Quartier et al. [2010] and comparing 1-month evidence on anakinra versus 12-week evidence on tocilizumab.

The TENDER trial demonstrated that tocilizumab and methotrexate have a similar safety profile. Due to lack of evidence for the biologic comparators, Roche resorted in comparing evidence in non-systemic populations. Despite this, the analysis concludes that there not any significant differences in the toxicity of treatments. Moreover, the analysis adopts a conservative approach in considering only adverse events that are observed in TENDER, ignoring any additional side effects for the comparators.

A literature review did not identify any evidence to differentiate in modelling the risk of treatment discontinuation between biologics. The model uses a constant risk of withdrawal and assumes that withdrawal is dependent on exacerbation of patients' sJIA condition –not AE. Although this is a simplifying

assumption it is in line with the model objectives from a parsimony viewpoint and is expected to have little or no influence to the analysis results.

Although, it is known that patients with systemic JIA have an increased mortality risk, in the development of the economic analysis Roche did not find any concrete evidence to support such a claim for responders/non-responders. In practice, treatment of sJIA is expected to have significant influence in patient HRQL but not in patient survival. The analysis takes a conservative view to make no claim over survival benefits based on response to treatment and a constant mortality risk is applied to all health states across the two model arms.

The analysis is largely driven by treatment cost and by the cost of inpatient stay. With regards to the first item, a balanced approach is adopted to estimate total cost of treatments based on patient weight and the available pharmaceutical presentations. Wastage is included in the calculations and assumptions are made for the cost of treatment administration. These assumptions are tested in sensitivity analysis.

With regards to the second item, the analysis adopts a conservative approach against annual frequency of inpatient stay and the accrued cost. Clinical expert opinion [PC: Westhovens R 02/03/2011, Wright S 16/03/2011, Woo P 21/03/2011, Baildam E 28/03/2011] was unanimous in the severity of the condition of active-disease patients. Moreover, they all considered that a month of inpatient stay for uncontrolled disease is an underestimate considering that versus a week for patients responding to treatment. Moreover, the analysis excludes from the cost of inpatient stay any diagnostic tests to avoid double-counting. The cost and assumptions on inpatient stay (frequency of use) are tested in probabilistic and one-way sensitivity analysis.

Starting age has an impact to the model results since it influences treatment cost. Nevertheless, the base-case analysis reflects an appropriate starting age for the cohort. Evidence suggests that the peak age of onset of sJIA is between 18 months and 2 years [Woo et al. 2006]. In a UK cohort the peak

age was 2 years and 61% of patients had an age of onset of 5 years or below [Fishman et al. 1998]. In the CAPS study, another UK prospective study, the median age of onset is reported to be 6.4 years [Adib et al. 2008], indicating that although there is some variability in the age of disease onset, in the UK in most cases disease onset is below 10 years. The scenario analyses performed provide a broad spectrum of the possible ages of disease onset and disease duration, over which associated costs are likely to vary. However, for the purposes of this evaluation the scenarios which are representative of the majority of cases in the UK (age of onset 2-5 yrs) should be given more emphasis.

In exploring uncertainty and variability of model parameters (PSA and one-way sensitivity analysis) Roche had to assume the range of a significant number of values due to lack of data.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Clinical head-to-head evidence on the comparative efficacy and safety of the model comparators would improve the evidence base for many of the analysis parameters. Moreover, trial-based HRQL estimates from the specific patient population would enhance the robustness of the results.

With regards to costs, a resource utilisation study would provide additional detail on the resource requirements and consequent health care costs of sJIA patients. Since treatment cost is an important driver of the model results, a UK-based study on resource utilisation for administering infusible and subcutaneous agents would enhance the robustness of the analysis.

Although all of the above would improve the accuracy of the analysis, they would not have a notable impact on the direction of the overall model results.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Patients eligible for treatment in England and Wales have been estimated using data from various sources as shown in table Cxxxbelowxxx. Evidence from the Office of National statistics provided estimates for the population in England and Wales aged 1-19 years [ONS, 2009]. The prevalence of JIA has been estimated to be around 100 per 100,000 children [Woo et al. 2006]. This is assumed to be the same for England and Wales. The proportion of JIA patients that have the systemic subtype is approximately 6% [Woo et al. 2006]. This figure is similar to the proportion of patients from an ongoing, prospective, UK study (CAPS) (27/507) [Adib et al. 2008]. This results in a total population with sJIA of 790.

For the first and second comparison, the proportion of the population who had inadequate response to NSAID/CS is assumed to be as for MTX non response 68% [Albers et al. 2009].

The evidence described above is used to estimate the number of patients in each of the two populations (See Table below):

Table 83: Data for eligible patient numbers

Parameter	Assumptions	Source
England & Wales population aged 1-19	13,101,013	Office of National statistics [ONS, 2009] (mid 2009-MS09-quinary est)
Prevalence of JIA	100 per 100,000	Woo et al. 2006
Proportion of sJIA	6%	Woo et al. 2006
Proportion of NSAID-IR/CS-IR non responders	68%	Albers et al. 2009 (Assumption)
Proportion of NSAID-IR/CS/MTX-IR non responders	68%	Albers et al. 2009
Assumed growth of population	0.7%	ONS, 2011; assume systemic population will grow as general population
Eligible for treatment population with sJIA (1st population and 2nd population)	542 patients	

The eligible for treatment sJIA population projected for 5 years is assumed to follow a population growth of 0.7% [ONS, 2011].

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Since there is no other biologic with market authorisation in this indication, Roche expects a rapid uptake of tocilizumab by clinicians. The assumed uptake of tocilizumab is 20% in the first year, followed by 30%, 40% and 50% in the second, third and fourth year respectively.

7.3 What assumption(s) were made about market share (when relevant)?

Since there is no other biologic with market authorisation for the indication of sJIA, there is no evidence on market share for comparator treatments. Roche does not have any information of products' market share in this specific subtype. Costs and budget impact are presented separately against each of the comparator treatments.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

When tocilizumab is added to the care pathway it will be administered during hospital outpatient visits. The cost has been determined to be £150 per visit (see section 6.5.5). This cost per administration is added to the total cost estimated in section 7.7.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The cost of treatment is presented in section 6.5.5. No other unit costs are included in this calculation.

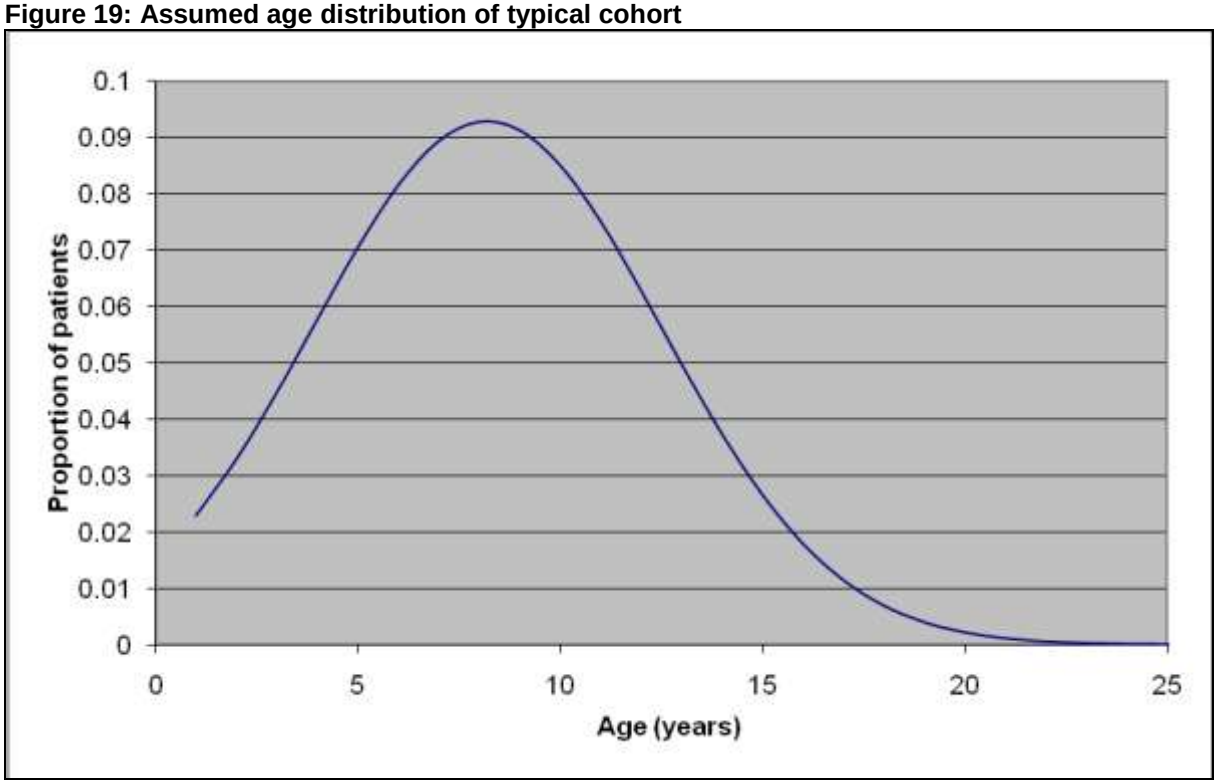
7.6 Were there any estimates of resource savings? If so, what were they?

Although the addition of tocilizumab in the current treatment of sJIA is not associated with any direct, short-term resource savings, its use will generate cost offsets in the long-term. The response rates achieved by sJIA patients treated with tocilizumab are much higher and achieved by a greater proportion of patients which will effectively eradicate the disease for many and with it prevent the need for further treatment and any costs associated with treatment of long term complications.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Evidence from Thornton et al. [2008a], a UK prospective longitudinal study (CAPS), was retrieved for the typical age distribution of sJIA patients. The study includes patients at entry with mean age of 8.2 years (SD 4.3). This distribution is assumed for the typical cohort to estimate the average annual cost per each treatment (See Figure below).

Figure 19: Assumed age distribution of typical cohort



The annual budget impact for the NHS in England and Wales has been calculated separately for each comparator. The budget impact estimates presented in the Table below represent the maximum possible annual costs to the NHS for the use of each of the treatments.

Table 84: Annual Budget Impact for NHS in England and Wales per treatment

	2011	2012	2013	2014	2015
Anakinra	£5,621,187	£5,660,535	£5,700,159	£5,740,060	£5,780,241
Etanercept	£4,850,238	£4,884,190	£4,918,379	£4,952,808	£4,987,477
Methotrexate	£14,980	£15,085	£15,190	£15,297	£15,404
Tocilizumab	£7,564,432	£7,617,383	£7,670,705	£7,724,400	£7,778,470

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Treatment with tocilizumab is not associated with any direct resource savings.

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9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

Draft SPC and EMA submission document supplied (as referenced in Section A).

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

A systematic search was carried out using the DataStar Web platform. Studies were indentified using relevant MeSH and EmTree terms and free text searches. There were no restrictions in place at this stage such as language or publication.

Databases searched include:

- EMBASE – 1993 to date (EMYY)
- EMBASE alert – latest 8 weeks (EMBA)
- MEDLINE – 1993 to date (MEYY)

- MEDLINE in progress – latest 8 weeks (MEIP)
- BIOSIS previews – 1993 to date (BIYY)
- BIOSIS previews – last update (BIOX)

The following searches were also carried out:

- Cochrane library search including: Cochrane reviews, clinical trials, technology assessments and Cochrane groups
- Manual hand search of relevant review and trial reference lists
- Manual screen of internal databases
- Manual screening of relevant publication e-alerts for the period 16.03.2011-submission date
- Conference abstracts including (2005-2010):
    - American College of Rheumatology (ACR)
    - The European League Against Rheumatism (EULAR)

9.2.2 The date on which the search was conducted

The search was carried out on 15.03.2011

9.2.3 The date span of the search

DataStar databases searched: 1993 – last 8 weeks

Conference abstracts searched: 2005 – 2010

Cochrane library: whole back catalogue searched – no date restrictions

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

DataStar search including EMBASE, Medline, BIOSIS, EMBASE in progress, Medline in progress and BIOSIS last update:

No.	Database	Search term	Info added since	Results
1	EMYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	2095
2	EMYY	JUVENILE-RHEUMATOID-ARTHRITIS.MJ.	unrestricted	4094
3	EMYY	tocilizumab	unrestricted	618
4	EMYY	TOCILIZUMAB.W..MJ.	unrestricted	90
5	EMYY	systemic	unrestricted	237607
6	EMYY	1 OR 2	unrestricted	4571
7	EMYY	3 OR 4	unrestricted	618
8	EMYY	6 AND 7	unrestricted	67
9	EMYY	8 AND 5	unrestricted	39
10	MEYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	1823
11	MEYY	ARTHRITIS-JUVENILE-RHEUMATOID.MJ.	unrestricted	3125
12	MEYY	tocilizumab	unrestricted	321
13	MEYY	RECEPTORS-INTERLEUKIN-6.MJ.	unrestricted	718
14	MEYY	systemic	unrestricted	200687
15	MEYY	10 OR 11	unrestricted	3647
16	MEYY	12 OR 13	unrestricted	976
17	MEYY	15 AND 16	unrestricted	43
18	MEYY	17 AND 14	unrestricted	30
19	BIYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	1770
20	BIYY	JUVENILE-RHEUMATOID.DS. OR JUVENILE-IDIOPATHIC-ARTHRITIS.DS.	unrestricted	2499
21	BIYY	tocilizumab	unrestricted	220
22	BIYY	systemic	unrestricted	1045560
23	BIYY	19 OR 20	unrestricted	2767
24	BIYY	23 AND 21	unrestricted	28
25	BIYY	24 AND 22	unrestricted	21
26	MEIP	juvenile ADJ idiopathic ADJ arthritis	unrestricted	123
27	MEIP	tocilizumab	unrestricted	51

29	MEIP	26 AND 27	unrestricted	1
34	EMBA	TOCILIZUMAB.W..KW.	unrestricted	5
39	BIOX	JUVENILE-IDIOPATHIC-ARTHRITIS.DS.	unrestricted	4
41	BIOX BIYY EMBA EMYY MEIP MEYY	combined sets 8, 9, 17, 18, 24, 25, 29, 34, 39	unrestricted	238
43	BIOX BIYY EMBA EMYY MEIP MEYY	unique records from 41	unrestricted	101

Cochrane Search:

No.	Search term	Results
#1	MeSH descriptor Arthritis, Juvenile Rheumatoid	164
#2	Juvenile idiopathic arthritis	86
#3	Juvenile arthritis	262
#4	#1 OR #2	185
#5	#1 OR #3	262
#6	tocilizumab	3
#7	Interleukin 6	13618
#8	#6 OR #7	13620
#9	#4 AND #8	6
#10	#5 AND #8	12
#11	#9 OR #10	12

ACR and EULAR (2005-2010) searches:

35 results → 10 duplicates removed

Total 25 results

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Any internal review of the regulatory submission for RoActemra in sJIA, (attached with Section A) was completed to identify any unpublished data.

[redacted]

9.2.6 The inclusion and exclusion criteria

Inclusion and exclusion criteria for publication selection

	Clinical effectiveness
Inclusion criteria	**Population** Patients with systemic juvenile idiopathic arthritis (sJIA) or systemic juvenile rheumatoid arthritis **Interventions** Tocilizumab, interleukin-6 receptor inhibitor **Outcomes** Disease activity, physical function, joint damage, pain, steroid sparing, mortality, adverse effects of treatment, health-related quality of life **Study design** No restrictions **Language restrictions** No restrictions
Exclusion criteria	No exclusion criteria were used at database level searches. The following exclusions were used during hand screening of results **Population** Patients with JIA subtypes other than systemic ie, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified **Interventions** Any other than tocilizumab **Outcomes** None excluded **Study design** None excluded **Language restrictions** Languages other than English, ie. Japanese

9.2.7 The data abstraction strategy

There were 288 studies identified via searches of the databases outlined in 9.2.1. These were combined and duplicates removed, after which 139 studies remained. A manual review of the paper titles and abstracts excluded 121 studies based on the exclusion criteria above. The main reasons for exclusion were articles in languages other than English, review articles, studies in populations other than sJIA for example polyarticular JIA, and exploratory papers not relevant to the decision problem.

The remaining 18 articles were manually screened for relevance, which involved a full-text review. At this stage 10 articles were excluded, all of which were conference abstracts either duplicated between the ACR and EULAR congresses, or subsequently fully published.

There were therefore 8 relevant studies included. Six of these studies were not RCTs and were subsequently excluded in the submission. They include early, phase II studies and studies with no comparator, small patient populations, or Japanese patients who are considered less relevant to European populations. The reasons for each study exclusion are included in section 5.2.7. These are relevant to the technology background, but will not be included in the submission for clinical assessment or economic analysis.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

Study ID or acronym TENDER (WA18221):		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	The patient randomization numbers generated by Roche or its designee were given to the investigator over the telephone at the time of individual patient enrollment. The investigator or designee entered a pre-defined patient number in the electronic case report form (eCRF) and entered the corresponding patient randomization number for allocation to the treatment groups in the appropriate place on each patient's eCRF. The patient randomization numbers were allocated sequentially in the order in which the patients were enrolled according to the specification document agreed with the external randomization company for allocation to the treatment groups.	Yes

Was the concealment of treatment allocation adequate?	This was a blinded study, with the sponsor, investigators, and patients/parents unaware of the treatment assignment of each patient at randomization into Part I. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication or independent pharmacological analysis of biological samples was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment. Unblinding was performed by means of the interactive voice response system (IVRS). Written documentation followed any verbal request to unblind a patient's treatment. As per regulatory reporting requirement, Roche unblinded the identity of the study medication for all suspected unexpected SAEs that were considered by the investigator to be related to study drug as per safety reference documents; Investigators Brochure, Core Data Sheet, and Summary of Product Characteristics (SmPC). Any unblinding for independent pharmacological analysis of biological samples including any PK, PD data, or ongoing safety monitoring by a DSMB	Yes

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes, the demographic characteristics at baseline in the placebo group and the all tocilizumab group were similar. In each treatment group, patients were evenly split between male and female patients and they were predominately Caucasian. As expected as a result of the two different doses < or ≥ BW 30 kgs, the mean age, BW, height, and body surface area (BSA) were higher in the tocilizumab 8 mg/kg group in comparison to the tocilizumab 12 mg/kg group. However, these characteristics were similar between the all tocilizumab group and the placebo group. Overall the disease characteristics between the placebo and the tocilizumab group were comparable. The six components of the JIA ACR core set at Baseline were similar but with a slightly higher disease burden in the tocilizumab patients. There were higher proportions of patients with fever (within 7 and 14 days prior to Baseline) and sJIA rash (within 14 days prior to Baseline) in the placebo group compared with the all tocilizumab group. The mean and median CRP was lower in the placebo group compared with the all tocilizumab group but three patients in the tocilizumab groups had very high CRPs that distorted the mean/median values. In addition, this acute phase reactant is not used in the JIA ACR core set. As expected as a result of the two different tocilizumab dosing groups, the number of previous biologics and DMARDs were higher in the tocilizumab 8 mg/kg group compared to the tocilizumab 12 mg/kg group. The stratification factors used in randomization; BW, disease duration, background corticosteroids dose, and background methotrexate use had	

	approximately 50% of patients in each of the binary categories for both the placebo and all tocilizumab group. There were however a high proportion of patients with background methotrexate use at Baseline.	

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was a blinded study, with the sponsor, investigators, and patients/parents or care providers unaware of the treatment assignment of each patient at randomization into Part I. A patient's treatment assignment was only to be unblinded in cases where knowledge of the identity of the test medication or independent pharmacological analysis of biological samples was essential for further patient management. Patients whose treatment assignments were unblinded did not receive any further study treatment, therefore would have been unlikely to bias the results.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were a small number of withdrawals which are discussed in detail in section 5.3.8	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The outcomes reported here are taken directly from the clinical study report. All intended outcomes are discussed in detail in the methods section. Not all of these outcomes have necessarily been reported at the end of 12 week randomised stage (Part I) however, more analyses will be conducted during the later open label stages.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. the TENDER study was analysed using the intent-to-treat (ITT) population. This was an appropriate population to use in analysing the study, and the results of the primary endpoint were confirmed by a second analysis using the per-protocol population, and only including completers of therapy for both of the arms. No patients were excluded from the study at the end of week 12 (the randomized phase). Missing data was handled using the last observation carried forwards method.	Yes

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Databases searched were accessed from the datastar platform for Medline, Embase and Medline (R) In-Process. The Cochrane Library was accessed directly from the Cochrane collaboration via the internet http://www.cochrane.org/.

9.4.2 The date on which the search was conducted.

Searches were performed on 28/03/2011.

9.4.3 The date span of the search.

MEDLINE; 1949 – 28/03/2011

EMBASE; 1974 – 28/03/2011

Medline (R) In Process; (latest 8 weeks) ~ 28/01/2011 – 28/03/2011
Cochrane Library date span – 28/03/2011

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Please see the search strategies below for EMBASE (EMZZ), MEDLINE (MEZZ) and Medline in Process (MEIP), respectively:

Search strategy for EMBASE (EMZZ).

No.	Database	Search term	Info added since	Results
1	EMZZ	(JUVENILE ADJ ARTHRITIS).TI. OR (JUVENILE ADJ ARTHRITIS ADJ C ADJ '12').AB.	unrestricted	350
2	EMZZ	JUVENILE−RHEUMATOID− ARTHRITIS#.DE.	unrestricted	9986
3	EMZZ	CHILD$.TI. OR CHILD$.AB.	unrestricted	222682
4	EMZZ	(RHEUMATOID ADJ ARTHRITIS).TI. OR (RHEUMATOID ADJ ARTHRITIS).AB.	unrestricted	73434
5	EMZZ	3 AND 4	unrestricted	347
6	EMZZ	PAEDIATRIC NEAR ARTHRITIS.TI. OR PAEDIATRIC NEAR ARTHRITIS.AB.	unrestricted	36
7	EMZZ	JUVENILE NEAR ARTHRITIS.TI. OR JUVENILE NEAR ARTHRITIS.AB.	unrestricted	7219
8	EMZZ	CHILD NEAR ARTHRITIS.TI. OR CHILD NEAR ARTHRITIS.AB.	unrestricted	2804
9	EMZZ	IDIOPATHIC NEAR ARTHRITIS.TI. OR IDIOPATHIC NEAR ARTHRITIS.AB.	unrestricted	2369
10	EMZZ	SYSTEMIC NEAR ARTHRITIS.TI. OR SYSTEMIC NEAR ARTHRITIS.AB.	unrestricted	5118
11	EMZZ	1 OR 2 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	unrestricted	16286
12	EMZZ	(RANDOM$ OR PLACEBO$ OR SINGLE ADJ BLIND$ OR DOUBLE ADJ BLIND$ OR TRIPLE ADJ BLIND$).TI,AB.	unrestricted	561680
13	EMZZ	RETRACTED ADJ ARTICLE	unrestricted	4973
14	EMZZ	12 OR 13	unrestricted	566557
15	EMZZ	(BOOK OR CONFERENCE ADJ PAPER OR EDITORIAL OR LETTER OR REVIEW).PT. NOT (EXP ADJ RANDOMISED OR RANDOMIZED) ADJ CONTROLLED ADJ TRIAL	unrestricted	3411371
16	EMZZ	(RANDOM ADJ SAMPL$ OR	unrestricted	23149
		RANDOM ADJ DIGIT$ OR RANDOM ADJ EFFECT$ OR RANDOM ADJ SURVEY OR RANDOM ADJ REGRESSION).TI,AB. NOT (EXP ADJ RANDOMISED OR RANDOMIZED) ADJ CONTROLLED ADJ TRIAL		
17	EMZZ	14 NOT (15 OR 16)	unrestricted	489442
18	EMZZ	ETANERCEPT OR ENBREL.TI,AB.	unrestricted	11683
19	EMZZ	ANAKINRA OR KINERET.TI,AB.	unrestricted	867
20	EMZZ	HUMIRA OR ADALIMUMAB.TI,AB.	unrestricted	2991
21	EMZZ	INFLIXIMAB OR REMICADE.TI,AB.	unrestricted	17510

22	EMZZ	18 OR 19 OR 20 OR 21	unrestricted	22669
23	EMZZ	11 AND 17 AND 22	unrestricted	69
24	EMZZ	23 AND HUMANS	unrestricted	68

Search strategy for Medline (MEZZ)

No.	Database	Search term	Info added since	Results
1	MEZZ	ARTHRITIS−JUVENILE− RHEUMATOID#.DE.	unrestricted	7457
2	MEZZ	(JUVENILE ADJ ARTHRITIS).TI. OR (JUVENILE ADJ ARTHRITIS).AB.	unrestricted	550
3	MEZZ	JUVENILE NEAR ARTHRITIS.TI. OR JUVENILE NEAR ARTHRITIS.AB.	unrestricted	6264
4	MEZZ	CHILD NEAR ARTHRITIS.TI. OR CHILD NEAR ARTHRITIS.AB.	unrestricted	2473
5	MEZZ	PAEDIATRIC NEAR ARTHRITIS.TI. OR PAEDIATRIC NEAR ARTHRITIS.AB.	unrestricted	30
6	MEZZ	(RHEUMATOID ADJ ARTHRITIS).TI. OR (RHEUMATOID ADJ ARTHRITIS).AB.	unrestricted	66183
7	MEZZ	CHILD$.TI. OR CHILD.AB.	unrestricted	585395
8	MEZZ	6 AND 7	unrestricted	1493
9	MEZZ	(IDIOPATHIC ADJ ARTHRITIS).TI. OR (IDIOPATHIC ADJ ARTHRITIS).AB.	unrestricted	1855
10	MEZZ	(SYSTEMIC ADJ ARTHRITIS).TI. OR (SYSTEMIC ADJ ARTHRITIS).AB.	unrestricted	70
11	MEZZ	1 OR 2 OR 3 OR 4 OR 5 OR 8 OR 9 OR 10	unrestricted	9925
12	MEZZ	RANDOMIZED OR (RANDOMISED ADJ CONTROLLED ADJ TRIAL).PT.	unrestricted	439603
13	MEZZ	(RANDOM$ OR PLACEBO$ OR SINGLE ADJ BLIND$ OR DOUBLE ADJ BLIND$ OR TRIPLE ADJ BLIND$).TI,AB.	unrestricted	614622
14	MEZZ	(RETRACTION ADJ OF ADJ PUBLICATION OR RETRACTED ADJ PUBLICATION).PT.	unrestricted	3469
15	MEZZ	12 OR 13 OR 14	unrestricted	715320
16	MEZZ	ANIMALS.SH. NOT HUMANS.SH.	unrestricted	3330067
17	MEZZ		unrestricted	2980919
		(COMMENT OR EDITORIAL OR META−ANALYSIS OR PRACTICE− GUIDELINE OR REVIEW OR LETTER OR JOURNAL ADJ CORRESPONDENCE).PT. NOT RANDOMISED.PT. OR (RANDOMIZED ADJ CONTROLLED ADJ TRIAL).PT.		
18	MEZZ	(RANDOM ADJ SAMPL$ OR RANDOM ADJ DIGIT$ OR RANDOM ADJ EFFECT$ OR RANDOM ADJ SURVEY OR RANDOM ADJ REGRESSION).TI,AB. NOT RANDOMISED OR (RANDOMIZED ADJ CONTROLLED ADJ TRIAL).PT.	unrestricted	335074
19	MEZZ	15 NOT (16 OR 17 OR 18)	unrestricted	232704
20	MEZZ	ETANERCEPT OR ENBREL.TI,AB.	unrestricted	2994
21	MEZZ	ANAKINRA OR KINERET.TI,AB.	unrestricted	529

22	MEZZ	HUMIRA OR ADALIMUMAB.TI,AB.	unrestricted	1598
23	MEZZ	INFLIXIMAB OR REMICADE.TI,AB.	unrestricted	6425
24	MEZZ	20 OR 21 OR 22 OR 23	unrestricted	9173
25	MEZZ	11 AND 19 AND 24	unrestricted	17

Search strategy for Medline in Process (MEIP)

26	MEIP	ARTHRITIS−JUVENILE− RHEUMATOID#.DE.	unrestricted	0
27	MEIP	(JUVENILE ADJ ARTHRITIS).TI. OR (JUVENILE ADJ ARTHRITIS).AB.	unrestricted	9
28	MEIP	JUVENILE NEAR ARTHRITIS.TI. OR JUVENILE NEAR ARTHRITIS.AB.	unrestricted	148
29	MEIP	CHILD NEAR ARTHRITIS.TI. OR CHILD NEAR ARTHRITIS.AB.	unrestricted	45
30	MEIP	PAEDIATRIC NEAR ARTHRITIS.TI. OR PAEDIATRIC NEAR ARTHRITIS.AB.	unrestricted	2
31	MEIP	(RHEUMATOID ADJ ARTHRITIS).TI. OR (RHEUMATOID ADJ ARTHRITIS).AB.	unrestricted	1355
32	MEIP	CHILD$.TI. OR CHILD.AB.	unrestricted	15519
33	MEIP	31 AND 32	unrestricted	14
34	MEIP	(IDIOPATHIC ADJ ARTHRITIS).TI. OR	unrestricted	126
		(IDIOPATHIC ADJ ARTHRITIS).AB.		
35	MEIP	(SYSTEMIC ADJ ARTHRITIS).TI. OR (SYSTEMIC ADJ ARTHRITIS).AB.	unrestricted	4
36	MEIP	26 OR 27 OR 28 OR 29 OR 30 OR 33 OR 34 OR 35	unrestricted	170
37	MEIP	RANDOMIZED OR (RANDOMISED ADJ CONTROLLED ADJ TRIAL).PT.	unrestricted	8111
38	MEIP	(RANDOM$ OR PLACEBO$ OR SINGLE ADJ BLIND$ OR DOUBLE ADJ BLIND$ OR TRIPLE ADJ BLIND$).TI,AB.	unrestricted	18187
39	MEIP	(RETRACTION ADJ OF ADJ PUBLICATION OR RETRACTED ADJ PUBLICATION).PT.	unrestricted	69
40	MEIP	37 OR 38 OR 39	unrestricted	18270
41	MEIP	ANIMALS.SH. NOT HUMANS.SH.	unrestricted	12424
42	MEIP	(COMMENT OR EDITORIAL OR META−ANALYSIS OR PRACTICE−GUIDELINE OR REVIEW OR LETTER OR JOURNAL ADJ CORRESPONDENCE).PT. NOT RANDOMISED.PT. OR (RANDOMIZED ADJ CONTROLLED ADJ TRIAL).PT.	unrestricted	16712
43	MEIP	(RANDOM ADJ SAMPL$ OR RANDOM ADJ DIGIT$ OR RANDOM ADJ EFFECT$ OR RANDOM ADJ SURVEY OR RANDOM ADJ REGRESSION).TI,AB. NOT RANDOMISED OR (RANDOMIZED ADJ CONTROLLED ADJ TRIAL).PT.	unrestricted	1297
44	MEIP	40 NOT (41 OR 42 OR 43)	unrestricted	15944
45	MEIP	ETANERCEPT OR ENBREL.TI,AB.	unrestricted	176
46	MEIP	ANAKINRA OR KINERET.TI,AB.	unrestricted	49

47	**MEIP**	**HUMIRA OR ADALIMUMAB.TI,AB.**	**unrestricted**	**143**
48	**MEIP**	**INFLIXIMAB OR REMICADE.TI,AB.**	**unrestricted**	**256**
49	**MEIP**	**45 OR 46 OR 47 OR 48**	**unrestricted**	**473**
50	**MEIP**	**36 AND 44 AND 49**	**unrestricted**	**2**

The same strategy was used for the Cochrane Library retrieving a total of 194 hits from the following databases as follows:

Cochrane Reviews: 60

Other Reviews: 6

Clinical Trials: 126

Technology Assessments: 1

Economic Evaluations: 1

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional database searches were performed.

9.4.6 The inclusion and exclusion criteria.

Inclusion Criteria:

- **Study design** to include RCTs
- **Disease area** to include all sJIA.
- **Population** (no restrictions by age or disease severity)
- **Treatments** to include adalimumab, anakinra, etanercept and infliximab

Exclusion Criteria:

- **Study design** to exclude all studies except RCTs

- **Disease area** to exclude all other disease areas except JIA related
- **Population** to exclude all other Juvenile idiopathic arthritis subtypes except systemic subtype
- **Treatments** to exclude all treatments other than adalimumab, anakinra, etanercept and infliximab
- **Not English** to exclude all non English citations
- **Outcome** to exclude studies not reporting ACR outcomes

9.4.7 The data abstraction strategy.

A protocol was developed based on the inclusion and exclusion criteria. An analyst assessed each study to determine whether it meets the inclusion criteria of the review. A log of ineligible studies was maintained with the rationale for exclusion. Details are described in the main text of the submission (section 5.7.2).

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

See before.

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Non-RCT evidence was searched for in parallel with the randomised clinical trial evidence outline in appendix 9.2. Details of this search can be found in appendix 9.2

9.6.2 The date on which the search was conducted.

See section 9.2

9.6.3 The date span of the search.

See section 9.2

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 9.2

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 9.2

9.6.6 The inclusion and exclusion criteria.

See section 9.2

9.6.7 The data abstraction strategy.

See section 9.2

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

The Non-RCT data used in this submission is an extension phase of the Phase III randomised TENDER study. A quality assessment of the TENDER study is within section 9.3.

The Non-RCT phase of TENDER the study was open-label extension, therefore not conducted to investigate efficacy in a blinded or randomised fashion.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

A systematic search was carried out using the DataStar Web platform. Studies were indentified using relevant MeSH and EmTree terms and free text searches. There were no restrictions in place at this stage such as language or publication.

Databases searched include:

- EMBASE – 1993 to date (EMYY)
- EMBASE alert – latest 8 weeks (EMBA)
- MEDLINE – 1993 to date (MEYY)
- MEDLINE in progress – latest 8 weeks (MEIP)
- BIOSIS previews – 1993 to date (BIYY)
- BIOSIS previews – last update (BIOX)

The following searches were also carried out:

- Cochrane library search including: Cochrane reviews, clinical trials, technology assessments and Cochrane groups
- Manual screening of relevant publication e-alerts for the period 21.03.2011-submission date
- Manual screen of internal databases
- Conference abstracts including (2010):
    - American College of Rheumatology (ACR)
    - The European League Against Rheumatism (EULAR)

9.8.2 The date on which the search was conducted.

The search was conducted on 21.03.2011

9.8.3 The date span of the search.

Datastar databases searched: 1993-date

Cochrane library: whole back catalogue searched – no date restrictions

Conference abstracts searched: 2010

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy is as follows:

No.	Database	Search term	Info added since	Results
1	EMYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	2097
2	EMYY	JUVENILE-RHEUMATOID-ARTHRITIS.MJ.	unrestricted	4095
3	EMYY	1 OR 2	unrestricted	4573
4	EMYY	adverse ADJ event	unrestricted	59517
5	EMYY	toxicity	unrestricted	465598
6	EMYY	drug ADJ reaction	unrestricted	713553
7	EMYY	harm	unrestricted	24824
8	EMYY	DRUG-SAFETY.MJ.	unrestricted	5038
9	EMYY	4 OR 5 OR 6 OR 7 OR 8	unrestricted	1108365
10	EMYY	tocilizumab	unrestricted	625
11	EMYY	TOCILIZUMAB.W..MJ.	unrestricted	91
12	EMYY	etanercept	unrestricted	11636
13	EMYY	ETANERCEPT.W..MJ.	unrestricted	2627
14	EMYY	adalimumab	unrestricted	6844
15	EMYY	ADALIMUMAB.W..MJ.	unrestricted	1460
16	EMYY	infliximab	unrestricted	17447
17	EMYY	INFLIXIMAB.W..MJ.	unrestricted	4535
18	EMYY	anakinra	unrestricted	853
19	EMYY	RECOMBINANT-INTERLEUKIN-1-RECEPTOR-BLOCKING-AGENT.MJ.	unrestricted	488
20	EMYY	methotrexate	unrestricted	72587
21	EMYY	METHOTREXATE.W..MJ.	unrestricted	13432
22	EMYY	systemic	unrestricted	237936
23	EMYY	11 OR 13 OR 15 OR 17 OR 19 OR 21	unrestricted	20176
24	EMYY	2 AND 9 AND 23 AND 22	unrestricted	91
25	MEYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	1822
26	MEYY	ARTHRITIS-JUVENILE-RHEUMATOID.MJ.	unrestricted	3131
27	MEYY	adverse ADJ event	unrestricted	50330

28	MEYY	harm	unrestricted	21672
29	MEYY	drug ADJ reaction	unrestricted	9725
30	MEYY	DRUG-TOXICITY.MJ.	unrestricted	1452
31	MEYY	toxicity	unrestricted	282550
32	MEYY	27 OR 28 OR 29 OR 30 OR 31	unrestricted	355829
33	MEYY	tocilizumab	unrestricted	325
34	MEYY	etanercept	unrestricted	2945
35	MEYY	adalimumab	unrestricted	1990
36	MEYY	infliximab	unrestricted	6392
37	MEYY	anakinra	unrestricted	518
38	MEYY	methotrexate	unrestricted	20651
39	MEYY	METHOTREXATE.W..MJ.	unrestricted	6159
40	MEYY	33 OR 34 OR 35 OR 36 OR 37 OR 39	unrestricted	15324
41	MEYY	26 AND 32 AND 40	unrestricted	68
42	MEYY	systemic	unrestricted	201203
43	MEYY	41 AND 42	unrestricted	28
44	BIYY	juvenile ADJ idiopathic ADJ arthritis	unrestricted	1772
45	BIYY	JUVENILE-IDIOPATHIC-ARTHRITIS.DS.	unrestricted	1431
46	BIYY	adverse ADJ event	unrestricted	32831
47	BIYY	harm	unrestricted	11419
48	BIYY	drug ADJ reaction	unrestricted	5489
49	BIYY	toxicity	unrestricted	335687
50	BIYY	TOXICITY.W..DS.	unrestricted	116039
51	BIYY	46 OR 47 OR 48 OR 49 OR 50	unrestricted	377442
52	BIYY	tocilizumab	unrestricted	224
53	BIYY	etanercept	unrestricted	3439
54	BIYY	adalimumab	unrestricted	2187
55	BIYY	infliximab	unrestricted	6270
56	BIYY	anakinra	unrestricted	548
57	BIYY	methotrexate	unrestricted	22537
58	BIYY	52 OR 53 OR 54 OR 55 OR 56 OR 57	unrestricted	29686
59	BIYY	45 AND 51 AND 58	unrestricted	54

60	BIYY	systemic	unrestricted	1048666
61	BIYY	59 AND 60	unrestricted	12
62	EMBA	juvenile ADJ idiopathic ADJ arthritis	unrestricted	44
63	EMBA	JUVENILE-IDIOPATHIC-ARTHRITIS.KW.	unrestricted	11
64	EMBA	systemic	unrestricted	2569
65	EMBA	63 AND 64	unrestricted	5
66	MEIP	juvenile ADJ idiopathic ADJ arthritis	unrestricted	125
67	MEIP	systemic	unrestricted	6441
68	MEIP	66 AND 67	unrestricted	40
69	MEIP	adverse ADJ event	unrestricted	2476
70	MEIP	harm	unrestricted	1011
71	MEIP	drug ADJ reaction	unrestricted	277
72	MEIP	toxicity	unrestricted	5390
73	MEIP	69 OR 70 OR 71 OR 72	unrestricted	8783
74	MEIP	68 AND 73	unrestricted	2
75	BIOX	juvenile ADJ idiopathic ADJ arthritis	unrestricted	2
76	BIOX	JUVENILE-IDIOPATHIC-ARTHRITIS.DS.	unrestricted	2
77	BIOX BIYY EMBA EMYY MEIP MEYY	combined sets 24, 43, 61, 65, 74, 76	unrestricted	140
78	BIOX BIYY EMBA EMYY MEIP MEYY	dropped duplicates from 77	unrestricted	29
79	BIOX BIYY EMBA EMYY MEIP MEYY	unique records from 77	unrestricted	111

Cochrane search:

No.	Search term	Results
#1	MeSH descriptor Arthritis, Juvenile Rheumatoid	164
#2	Juvenile idiopathic arthritis	86

#3	#1 OR #2	185
#4	MeSH descriptor Drug Toxicity	3
#5	Drug Toxicity	13618
#6	#4 OR #5	13620
#7	#3 AND #6	8

Congress Abstracts (ACR and EULAR):

Free word searches including:

'Juvenile idiopathic arthritis' AND 'adverse' for year 2010

ACR 2010 results: 10

EULAR 2010 results: 11

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

[redacted]

9.8.6 The inclusion and exclusion criteria.

References for the RCT adverse events were taken from the search carried out in section 5.7.1 (Appendix 4) (excluding the RCT for methotrexate, and one of the RCTs for tocilizumab which were highlighted in the above search). As such the following inclusion and exclusion criteria were applied to selection of the non-RCT data included in section 5.9.2.

	Clinical effectiveness
Inclusion criteria	**Population** Patients with systemic juvenile idiopathic arthritis (sJIA) or systemic juvenile rheumatoid arthritis **Interventions** tocilizumab, RoActemra etanercept, Enbrel adalimumab, Humira infliximab, Remicade anakinra, Kineret methotrexate **Outcomes** Adverse events, drug toxicity, drug reactions, harm **Study design** No restrictions **Language restrictions** No restrictions
Exclusion criteria	No exclusion criteria were used at database level searches. The following exclusions were used during hand screening of results **Population** Patients with JIA subtypes other than systemic ie, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified **Interventions** Any other those above **Outcomes** Adverse events not included in outcome measures Adverse event outcomes not stratified by JIA subtype **Study design** None excluded **Language restrictions**

	Languages other than English

9.8.7 The data abstraction strategy.

When presenting adverse event profiles, RCTs with an equivalent study design to the phase III pivotal study TENDER (De Benedetti 2010) were the preferred comparator. RCTs in JIA were available for tocilizumab and all the comparators, however only tocilizumab and anakinra studies were specifically in sJIA. As such the search results were assessed for non-RCT data in the subtype sJIA for each comparator.

sJIA is considered a distinct condition compared to other subtypes. Therefore in studies not exclusively investigating sJIA, we excluded studies in which the safety profile was not stratified for subtype.

Large RCTs were the preferred study type. However where these weren't available, large observational, open-label or retrospective studies were utilised. Case studies of under 10 patients were not considered appropriate as trends in safety outcomes can not be assessed in such a small study population.

In summary the search results were assessed by the following criteria:

1) Study in sJIA or sub analysis of sJIA results

2) Large study population ie. not case series

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Quality assessment of non-RCTs

	What was the study design?	Is there an adequate explanation of how adverse effects were identified?	Was a standardised or validated measurement instrument used?	How was the adverse effect(s) attributed to the intervention?	Are the terms clearly explained?
Russo 2009	Prospective open-label observation	Active surveillance	No	Attributed by non-blinded investigator based on AEs leading to discontinuation	Yes
Southwood 2011	Retrospective / prospective open-label registry	Active surveillance at defined intervals and ad hoc	No	Attributed by non-blinded investigator, based on AEs leading to discontinuation	Yes
Kimura 2005	Retrospective questionnaire based analysis	Active surveillance by questionnaire collection	No	Attributed by non-blinded investigators by temporal relationship	Yes
Nigrovic 2011	Retrospective open-label analysis	Active surveillance by questionnaire collection	No	Attributed by non-blinded investigators by temporal relationship	Yes
Lequerré 2008	Retrospective open-label analysis	Active surveillance	No	Attributed by non-blinded investigators by temporal relationship	Yes
Zeft 2009	Retrospective open-label analysis	Active surveillance	No	Attributed by non-blinded investigators by temporal	Yes

				relationship	
Kocharla 2009	Prospective open-label analysis	Clinical laboratory	Yes	Attributed by non-blinded investigators by temporal relationship	Yes
Al-Sewairy 1998	Retrospective open-label analysis	Active surveillance	No	Non-attributed by non-blinded investigator	Yes

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 **The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Databases searched were accessed from the datastar platform for Medline, Embase and Medline (R) In-Process. NHS EED was accessed via the Cochrane Library.

9.10.2 **The date on which the search was conducted.**

Medline, Embase and Medline (R) In-Process searches were performed on the 18th October 2010 and the NHS EED search was performed on 21/10/2010.

9.10.3 **The date span of the search.**

The date span for each search is indicated below:

MEDLINE; 1949 – 18/10/2010

EMBASE; 1974 – 18/10/2010

Medline (R) In Process; (latest 8 weeks) ~ 18/08/2010 – 18/10/2010

NHS Economic Evaluation Database (NHS EED) via Cochrane; the search was conducted on the 21/10/2010.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategy for EMBASE is shown below together with results of each search.

No.	Database	Search term	Info added since	Results
1	EMZZ	(JUVENILE ADJ ARTHRITIS).TI. OR (JUVENILE ADJ ARTHRITIS).AB.	unrestricted	636
2	EMZZ	JUVENILE−RHEUMATOID− ARTHRITIS#.DE.	unrestricted	9740
3	EMZZ	CHILD$.TI. OR CHILD$.AB.	unrestricted	217424
4	EMZZ	(RHEUMATOID ADJ ARTHRITIS).TI. OR (RHEUMATOID ADJ ARTHRITIS).AB.	unrestricted	71707
5	EMZZ	3 AND 4	unrestricted	343
6	EMZZ	PAEDIATRIC NEAR ARTHRITIS.TI. OR PAEDIATRIC NEAR ARTHRITIS.AB.	unrestricted	35
7	EMZZ	JUVENILE NEAR ARTHRITIS.TI. OR JUVENILE NEAR ARTHRITIS.AB.	unrestricted	7063
8	EMZZ	CHILD NEAR ARTHRITIS.TI. OR CHILD NEAR ARTHRITIS.AB.	unrestricted	2751
9	EMZZ	IDIOPATHIC NEAR ARTHRITIS.TI. OR IDIOPATHIC NEAR ARTHRITIS.AB.	unrestricted	2240
10	EMZZ	SYSTEMIC NEAR ARTHRITIS.TI. OR SYSTEMIC NEAR ARTHRITIS.AB.	unrestricted	4978
11	EMZZ	1 OR 2 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	unrestricted	15879
12	EMZZ	COST.AB. OR COST.TI.	unrestricted	276014
13	EMZZ	(ECONOMIC ADJ EVALUATION).AB. OR (ECONOMIC ADJ EVALUATION).TI.	unrestricted	5579

14	EMZZ	ECONOMIC−EVALUATION#.DE. OR COST−EFFECTIVENESS− ANALYSIS#.DE. OR HEALTH− CARE−COST#.DE. OR QUALITY− OF−LIFE#.DE. OR COST−BENEFIT−ANALYSIS#.DE. OR COST#.W..DE. OR HEALTH−ECONOMICS#.DE. OR BIOMEDICAL−TECHNOLOGY−ASSESSMENT#.DE.	unrestricted	628288
15	EMZZ	PHARMACOECONOMIC.AB. OR PHARMACOECONOMIC.TI.	unrestricted	3787
16	EMZZ	DRUG−COST.DE. OR HEALTH−CARE−UTILIZATION.DE.	unrestricted	71192
17	EMZZ	ECONOMIC.TI. OR ECONOMIC.AB.	unrestricted	108668
18	EMZZ	(COST ADJ MINIMISATION ADJ ANALYSIS).TI. OR (COST ADJ MINIMISATION ADJ ANALYSIS).AB.	unrestricted	136
19	EMZZ	COST−MINIMIZATION− ANALYSIS#.DE.	unrestricted	1712
20	EMZZ	(COST ADJ CONSEQUENCE ADJ ANALYSIS).TI. OR (COST ADJ CONSEQUENCE ADJ ANALYSIS).AB.	unrestricted	80
21	EMZZ	COST−OF−ILLNESS#.DE.	unrestricted	10915
22	EMZZ	BURDEN NEAR (DISEASE OR ILLNESS).TI. OR BURDEN NEAR (DISEASE OR ILLNESS).AB.	unrestricted	12535
23	EMZZ	(COST ADJ UTILITY).TI. OR (COST ADJ UTILITY).AB.	unrestricted	2134
24	EMZZ	COST−UTILITY−ANALYSIS#.DE.	unrestricted	3048
25	EMZZ	SOCIOECONOMICS#.W..DE.	unrestricted	121171
26	EMZZ	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25	unrestricted	926271
27	EMZZ	(COST ADJ EFFECTIVE$ ADJ ANALYSIS).TI.	unrestricted	2340
28	EMZZ	(COST ADJ EFFECTIVE$ ADJ ANALYSIS).AB.	unrestricted	4327
29	EMZZ	(HEALTH ADJ STATUS OR QUALITY ADJ OF ADJ LIFE OR QOL OR WELLBEING OR WELL ADJ BEING).AB.	unrestricted	72466
30	EMZZ	(HEALTH ADJ STATUS OR QUALITY ADJ OF ADJ LIFE OR QOL OR WELLBEING OR WELL ADJ BEING).TI.	unrestricted	13214
31	EMZZ	26 OR 27 OR 28 OR 29 OR 30	unrestricted	969454
32	EMZZ	LETTER.PT.	unrestricted	712350
33	EMZZ	EDITORIAL.PT.	unrestricted	360996
34	EMZZ	NOTE.PT.	unrestricted	424553
35	EMZZ	32 OR 33 OR 34	unrestricted	1497899
36	EMZZ	31 NOT 35	unrestricted	859653
37	EMZZ	11 AND 36	unrestricted	843
38	EMZZ	37 AND HUMANS	unrestricted	825

The complete search strategy for MEDLINE is shown below together with results of each search.

No.	Database	Search term	Info added since	Results
1	MEZZ	ARTHRITIS−JUVENILE− RHEUMATOID#.DE.	unrestricted	7339
2	MEZZ	(JUVENILE ADJ ARTHRITIS).TI. OR (JUVENILE ADJ ARTHRITIS).AB.	unrestricted	541
3	MEZZ	JUVENILE NEAR ARTHRITIS.TI. OR JUVENILE NEAR ARTHRITIS.AB.	unrestricted	6126
4	MEZZ	CHILD NEAR ARTHRITIS.TI. OR CHILD NEAR ARTHRITIS.AB.	unrestricted	2434
5	MEZZ	PAEDIATRIC NEAR ARTHRITIS.TI. OR PAEDIATRIC NEAR ARTHRITIS.AB.	unrestricted	29
6	MEZZ	(RHEUMATOID ADJ ARTHRITIS).TI. OR (RHEUMATOID ADJ ARTHRITIS).AB.	unrestricted	64836
7	MEZZ	CHILD$.TI. OR CHILD.AB.	unrestricted	569202
8	MEZZ	6 AND 7	unrestricted	1483
9	MEZZ	COST.TI. OR COST.AB.	unrestricted	233710
10	MEZZ	COST−OF−ILLNESS#.DE. OR HEALTH−CARE−COSTS#.DE. OR DRUG−COSTS#.DE.	unrestricted	46401
11	MEZZ	(ECONOMIC ADJ EVALUATION).TI. OR (ECONOMIC ADJ EVALUATION).AB.	unrestricted	4637
12	MEZZ	COST−BENEFIT−ANALYSIS#.DE. OR COSTS−AND−COST− ANALYSIS#.DE.	unrestricted	151233
13	MEZZ	PHARMACOECONOMIC.TI. OR PHARMACOECONOMIC.AB.	unrestricted	2266
14	MEZZ	QUALITY−OF−LIFE#.DE. OR HEALTH−STATUS#.DE. OR COST−OF−ILLNESS#.DE.	unrestricted	162323
15	MEZZ	ECONOMIC.TI. OR ECONOMIC.AB.	unrestricted	98735
16	MEZZ	MODELS−ECONOMIC#.DE.	unrestricted	7346
17	MEZZ	SOCIOECONOMIC.TI. OR SOCIOECONOMIC.AB.	unrestricted	37051
18	MEZZ	(COST ADJ EFFECTIVE$ ADJ ANALYSIS).TI. OR (COST ADJ EFFECTIVE$ ADJ ANALYSIS).AB.	unrestricted	5011
19	MEZZ	(HEALTH ADJ CARE ADJ UTILISATION).TI. OR (HEALTH ADJ CARE ADJ UTILISATION).AB.	unrestricted	218
20	MEZZ	(COST ADJ UTILITY ADJ ANALYSIS).TI. OR (COST ADJ UTILITY ADJ ANALYSIS).AB.	unrestricted	1037
21	MEZZ	QUALITY−ADJUSTED−LIFE− YEARS#.DE.	unrestricted	4557
22	MEZZ	COST ADJ MINIMISATION OR (COST ADJ CONSEQUENCE ADJ ANALYSIS).AB.	unrestricted	222
23	MEZZ	COST ADJ MINIMISATION OR (COST ADJ CONSEQUENCE ADJ ANALYSIS).TI.	unrestricted	191
24	MEZZ	(HEALTH ADJ STATUS OR QUALITY ADJ OF ADJ LIFE OR QOL OR WELLBEING OR WELL ADJ BEING).AB.	unrestricted	64054
25	MEZZ	(BURDEN NEAR (DISEASE OR ILLNESS)).AB. OR (BURDEN NEAR	unrestricted	11234

		(DISEASE OR ILLNESS)).TI.		
26	MEZZ	LETTER.PT.	unrestricted	705500
27	MEZZ	EDITORIAL.PT.	unrestricted	271446
28	MEZZ	(HISTORICAL ADJ ARTICLE).PT.	unrestricted	267727
29	MEZZ	26 OR 27 OR 28	unrestricted	1232592
30	MEZZ	(IDIOPATHIC ADJ ARTHRITIS).TI. OR (IDIOPATHIC ADJ ARTHRITIS).AB.	unrestricted	1743
31	MEZZ	(SYSTEMIC ADJ ARTHRITIS).TI. OR (SYSTEMIC ADJ ARTHRITIS).AB.	unrestricted	66
32	MEZZ	1 OR 2 OR 3 OR 4 OR 5 OR 8 OR 30 OR 31	unrestricted	9756
33	MEZZ	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25	unrestricted	583661
34	MEZZ	33 NOT 29	unrestricted	553988
35	MEZZ	32 AND 34	unrestricted	457
36	MEZZ	35 AND HUMANS	unrestricted	440

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were performed.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

	Study name Budapest Etanercept study 2006 Score: 0/35	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	No	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	No	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	

12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	

29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	No	
34. Did conclusions follow from the data reported?	No	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name Ungar et al. 2010 Score: 16/35	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	

5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Not clear	Effectiveness measure was proportion of patients who had reduction in symptoms at 1 year according to ACR Ped 30. Response rates from multiple sources
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Not clear	
12. Were the methods used to value health states and other benefits stated?	Not clear	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Not clear	
29. Were the ranges over which the parameters were varied stated?	Not clear	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Not clear	
34. Did conclusions follow from the data reported?	No	
35. Were conclusions accompanied by the appropriate caveats?	Yes	

36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name Barron et al. 2004 Score: 12/36	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Hypothetical drugs were compared
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	No	This is a WTP study not a cost effectiveness study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Not clear	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	N/A	
17. Were the methods for the estimation of quantities and unit costs described?	N/A	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	N/A	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	N/A	

28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name Beukelman et al. 2008 Score: 11/36	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	N/A	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	N/A	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Not clear	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Not clear	
13. Were the details of the subjects from whom valuations were obtained given?	No	

14. Were productivity changes (if included) reported separately?	Not clear	
15. Was the relevance of productivity changes to the study question discussed?	Not clear	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Not clear	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

	Study name Epps et al. 2005 Score: 25/36	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	

6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	Quantities of resource not provided, costs given only
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No discount applied	Given that the time horizon of the analysis was <1 year, total costs and QALYs remain undiscounted, and QALYs were undiscounted
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

	Study name Cummins et al. 2002 Score:20	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Not clear	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	Quantities of resource not provided, costs given only
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	Costs were discounted at 6% per annum and benefits at 1% per annum.
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	

27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.12 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		

13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.13 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Response

9.13.2 The date on which the search was conducted.

Response

9.13.3 The date span of the search.

Response

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.13.6 The inclusion and exclusion criteria.

Response

9.13.7 The data abstraction strategy.

Response

9.14 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.14.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Response

9.14.2 The date on which the search was conducted.

Response

9.14.3 The date span of the search.

Response

9.14.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

9.14.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

9.14.6 The inclusion and exclusion criteria.

Response

9.14.7 The data abstraction strategy.

Response

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the Decision Problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they

will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider

restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the

evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen Decision Problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).