NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Tocilizumab for the treatment of systemic juvenile idiopathic arthritis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
British Society for Paediatric and Adolescent Rheumatology	1.1 We note that the European Commission and FDA have recently approved tocilizumab for the treatment of active sJIA in patients two years of age and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs and systemic corticosteroids, can information be gained from their processes that may help the NICE review process 1.2 There are difficulties associated with the objective health states requested as the basis of cost analysis.	Comments noted. In response to the 'minded no' in the appraisal consultation document (ACD) the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations have been amended in the final appraisal determination (FAD), see section 1.
British Society for Paediatric and Adolescent Rheumatology	Most systemic JIA presents before 5 years and it is likely that the median age when sJIA patients will be identified as resistant to NSAIDs, corticosteroids and methotrexate is likely to be under 5 years. As already mentioned impact of corticosteroid load is large and so ability to reduce corticosteroid dose is important when comparing different treatments.	Comment noted. See section 4.14 of the FAD for the Committee's consideration of this issue.
British Society for Paediatric and Adolescent Rheumatology	There is variation in current UK treatment of systemic JIA resistant to NSAIDs, corticosteroids and methotrexate. The majority of UK centres prefer tocilizumab, second choice usually anakinra and third anti-TNF alpha inhibitors (with etanercept or infliximab used most widely). Prior to the availability of tocilizumab many centres would treat sJIA with infliximab (possibly requiring doses greater than that required for polyarticular JIA) over etanercept. It should be noted again that some children with systemic JIA meet criteria from the NICE Technology Appraisal Guidance no.35 (March 2002, but not reviewed) but we highlight there is an extremely limited	Comments noted. See sections 4.2 and 4.4 of the FAD for the Committee's considerations of these issues.

Consultee	Comment	Response
	evidence base for the use of any anti TNF agent in sJIA, and no RCT data. The evidence of benefit of resistant sJIA is much clearer to tocilizumab than to anakinra or any anti-TNF alpha agent.	
British Society for Paediatric and Adolescent Rheumatology	1.3 Data on radiographic evidence of progression of joint damage would be interesting, but I doubt this data is available and certainly not available from alternative agents on a scale that would allow comparison. We think it is fair to assume that reduced sJIA activity translates to reduced joint damage.	Comment noted. See section 4.9 of the FAD for the Committee's considerations of this issue.
British Society for Paediatric and Adolescent Rheumatology	3.11 The main studies looking at etanercept for all subtypes of JIA (including sJIA patients) do not seem to be covered Eg -Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Giannini EH et al Arthritis & Rheumatism. Volume 60, Issue 9, pages 2794–2804, September 2009 - Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Lovell DJ et al. Arthritis Rheum. 2008 May;58(5):1496-504.	Comments noted. The Committee considered the evidence presented by the manufacturer for the clinical and cost effectiveness of tocilizumab.
British Society for Paediatric and Adolescent Rheumatology	3.14 We are not sure that an adjustment factor in one study is translatable to other studied populations, althought accept it is a crude way to derive to gain some 'ballpark' information where studies are limited	Comment noted.
British Society for Paediatric and Adolescent Rheumatology	3.16 I don't really understand the Markov modelling, but as discussed at the meeting in July we believe children can move between ACR response lines. 3.20 and 3.30	Comment noted.
British Society for Paediatric and Adolescent	Assumptions of cost of managing disease at different levels of CHAQ score will be very different between patients and are very subjective estimates. More accurate information may be available from the UK biologics registry.	Comment noted. See section 4.13 of the FAD for the Committee's considerations of this issue.

Consultee	Comment	Response
Rheumatology	Uncontrolled sJIA with a significant 'systemic features' can require frequent infusions of IV high dose methylprednisolone (30+ per year is not unheard of) and lengthy inpatient stays.	
British Society for Paediatric and Adolescent Rheumatology	4.2 Many UK Paediatric Rheumatology centres currently use tocilizumab if sJIA does not respond to NSAIDs, corticosteroids and methotrexate. If tocilizumab was unavailable most would use anakinra. Etanercept, adalimumab or infliximab are options, particularly for arthritis symptoms and most centres have experience of these being effective, but less commonly than anakinra or tocilizumab. Tocilizumab has largely superceded anti TNF agents in sJIA.	Comments noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.2 and 4.4 of the FAD for the Committee's considerations of these issues.
British Society for Paediatric and Adolescent Rheumatology	4.4 Increasing the interval between tocilizumab infusions when remission is sustained does not yet have an evidence base, but experience suggests that this can be done without deterioration much sooner than 18 months, perhaps at 6 months, thus reducing the cost of tocilizumab.	Comment noted. See section 4.18 of the FAD for the Committee's consideration of this issue.
British Society for Paediatric and Adolescent Rheumatology	<u>In response to the specific questions:</u> <u>Has all of the relevant evidence been taken into account?</u> Etanercept trials as above. Data from UK registry re costings may be helpful.	Comment noted. The Committee considered the evidence presented by the manufacturer.
British Society for Paediatric and Adolescent Rheumatology	<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u> We are convinced that there is clinical and cost effectiveness. Concerns with desire for estimated costs associated with absolute CHAQ levels and ignoring the improvement of core outcome variables as reflecting improvement of sJIA activity which is the hallmark of trials in this area.	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
British Society for Paediatric and Adolescent	<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and

Consultee	Comment	Response
Rheumatology	We cannot support the guidance not to recommend tocilizumab for specific situations of children with resistant sJIA, being fully aware of the health and cost implications of this situation.	additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
British Society for Rheumatology	The British Society for Rheumatology fully support the comments on the ACD for Tocilizumab for Juvenile Idiopathic Arthritis submitted by the British Society for Paediatric and Adolescent Rheumatology.	Comment noted.
National Rheumatoid Arthritis Society	**Tocilizumab for SJIA – NICE Minded negative decision** Following Ailsa's submission of 24th March and the recent minded "no" decision by NICE I wish to make a further submission in regard to the STA in respect of Tocilizumab for the treatment of juvenile idiopathic arthritis. We at NRAS are very concerned of the impact that denial of such an effective treatment for children with Systemic JIA will have on not just the child themselves but on their parents and siblings.	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
National Rheumatoid Arthritis Society	**The scale of the problem** As previously stated in my submission in March the number of children that may be eligible for treatment with Tocilizumab is very small indeed. The number of children with Systemic JIA is approximately 1,200 and Tocilizumab would not necessarily be considered necessary or appropriate treatment for all of them therefore the number of children possibly being denied this life changing drug are in fact very few .Taking this into account if the "minded no" that the appraisal committee has given is based on cost grounds then I would draw their attention to the fact that the actual cost implications for the NHS would be relatively minimal. Clinicians that NRAS work with feel very strongly that there is a very strong evidence base to support the use of tocilizumab in sJIA and they will continue to try and access it for patients but this will be much more complex without NICE approval and will almost certainly mean some children do not access a drug that has potentially massive benefit.	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
National Rheumatoid	**The Impact to Children and their Families** I have heard and seen, having met families who are affected by JIA, the far	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the

Consultee	Comment	Response
Arthritis Society	reaching impact that having a child with such a long term condition. The impact on the child themselves can be not being able to fully participate in all aspects of family life such as family holidays, sports and fun activities to the impact on their education. School absences result in missed classes and can naturally impact on state examination results leading to reduced third level education and career prospects. The impact on the family as a whole the worry of a parent for their child's future, devastation of watching your child in pain and feeling of helplessness when unable to access treatments that have been proven to be effective. Siblings' family life can also be damaged if first consideration has to always be to the child with limited mobility and the requirement to always adapt family outings; holidays; day to day life around the JIA.	Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See section 4.3 of the FAD for the Committee's considerations of these issues.
National Rheumatoid Arthritis Society	**The Need for Tocilizumab** TNF blockade has been disappointing in its effects in methotrexate resistant children and adolescents, therefore given the severity of disease in Systemic JIA and a higher mortality rate, having access to a biologic with a different mode of action, i.e. Tocilizumab, is vital. Clinical Trials in Japan have demonstrated that many of the symptoms of SJIA can be controlled with periodic infusions of Tocilizumab and we await the publication of current UK trials for this agent in SJIA (TENDER) and in polyarticular JIA (CHERISH).	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
National Rheumatoid Arthritis Society	**Potential Economic Benefits of using Tocilizumab vs standard (failing) treatment** The cost to individuals and their families of SJIA is high and should not be measured in monitory terms only. Giving a child with S JIA access to a drug that could open up a world of possibilities and potential will not only benefit the individual but also those who care for them as well as society and the economy. The societal costs and savings if SJIA enters remission before causing damage allowing children to become adults better able to enter the workplace are considerable. There is the probability of being able to reduce other medication, importantly steroids, which are extremely damaging taken long term.	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.2, 4.3, 4.4 and 4.13 of the FAD for the Committee's considerations of these issues.

Consultee	Comment	Response
	The costs of caring for children with JIA can also be considerable, especially when parents have to leave work or reduce their working hours to look after the child and the financial cost of reduced income simply adds to the overall burden of stress on the whole family. It is abundantly clear to see the enormous potential in returning an extremely sick child, requiring significant on-going and expensive NHS services, to 'normal' health as demonstrated in Kieran's story which was submitted with NRAS's March submission. Steroid burden and toxicity can be huge in SJIA, and there is considerable evidence now available that disease control with Tocilizumab will allow steroid reduction potentially to zero. I hope that the Committee will reconsider their "minded no" and NRAS are happy to be re-contacted for any further information as required.	
Roche Products	**Has all of the relevant evidence been taken into account?** We feel that the clinical evidence has not been interpreted fully in light of tocilizumab's license. Please see our comments to specific points on the ACD below.	Comment noted. See responses to specific points below.
Roche Products	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Generally the summary of clinical evidence was sound. However, we have very specific comments regarding the interpretation by the ERG and Appraisal Committee of our economic modeling which we have set below specific comments from the ACD below	Comment noted. See responses to specific points below.
Roche Products	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No, we feel that the provisional recommendations may change upon receipt of our revised base case and patient access scheme.	Comment noted. In response to the 'minded no' in the ACD the manufacturer (Roche Products) provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
Roche Products	**Are there any aspects of the recommendations that need particular**	Comments noted.

Consultee	Comment	Response
	consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? We have not identified any issues which have the potential to lead to unlawful discrimination, but without consulting legal specialists this is a difficult question to answer. We can only emphasise that sJIA does affect a particular age group. Therefore any recommendation which impinges directly on this age group does require particular attention. We are in no doubt that the Institute fully understands these issues and the need for careful consideration, given its extensive experience with appraisals of medicines which are primarily given to elderly patients.	
Roche Products	**Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** We have not identified any such issues.	Comment noted.
Roche Products	3.24 – No justification is given as to why the model health states are not mutually exclusive. In page 55 of the ERG report it is stated that the model assumes a homogenous cohort; which contradicts the above criticism. We feel that our choice of ACR as a model parameter was justified given current clinical practice; ACR is considered by clinicians to be the most meaningful clinical outcome. In fact, we encountered resistance to the notion of establishing CHAQ thresholds, as no clinician would be able to use these thresholds to truly assess a patient's level of illness, much less decide whether to switch or continue treatment. ACR response may explicitly refer to a proportionate improvement level, but it in clinical practice its interpretation appears to be broader, incorporating a certain set of expectations about a patient's likely state once ACR30,50,70 or 90 have been achieved. That is why our original model strove to use ACR response level as an indicator for expected CHAQ score change, rather than as an explicitly linked 'health state' in its own right.	Comment noted. See section 3.33 of the FAD for the ERG's comments on the revised economic model. See section 4.11 of the FAD for the Committee's consideration of the revised economic models' health states.

Consultee	Comment	Response
	We also would like to point out that our model mechanism was based on that used in adult RA to allocate patients to health states. The only difference is that in adult RA a mechanism is built to calculate different CHAQ values over time (improvement/deterioration) based on treatment line. Indeed our original model's health state allocation was identical (NOT just 'similar' as has been assumed) to that used in adult RA.	
Roche Products	3.25 - Roche has evidence that the proportion of "high" responders (ACR 70-90) increases over time following the first 12 weeks. However, this evidence is available only for tocilizumab. Therefore, we have adapted our model to allow some movement over time (albeit based on an arbitrary assumption), but we have taken a conservative approach in not attempting to model this sustained response among "high" responders which was observed in TENDER trial patients after the main experimental phase of the study.	Comment noted. See section 3.33 of the FAD for the ERG's comments on the revised model.
Roche Products	3.30 - The key driver of the quoted difference in cost is hospitalization rate. Patients that do not respond to treatment are predominantly treated in the hospital. Given the severe symptoms associated with uncontrolled, non-responding disease (which may include fever and skin rash), and also considering that all patients are of young age, it seems plausible to suggest that extensive hospitalisation would occur while patients experience a disease flare. It is also expected that non-responders would experience a number of disease flares in a given year. Clinical experts suggested that for non-responders the length of hospitalisation could far exceed three weeks and that the average patient could stay in hospital for as much as three months in a year. Our model took a conservative approach to this estimate and considered the lowest value suggested by clinical experts (equating to 3-4 weeks a year) rather than the highest.	Comment noted. See sections 3.33 and 3.34 of the FAD for the ERG's comments on the revised model. See section 4.13 of the FAD for the Committee's considerations of the costs in the model.
Roche Products	3.33 - We noted these experimental changes by the ERG. We also noted that apart from the change to model starting age, all other modifications essayed had a negligible impact on the model results. We would like to point out that in our original submission, we considered both linear and exponential models for withdrawal risk and did provide a range of possible distribution types and widths for probabilistic sensitivity analysis.	Comments noted.

Consultee	Comment	Response
Roche Products	3.35 - There is no evidence that a patient's condition improves (by 10% or other probability) across all treatments. There is some evidence that this occurs under tocilizumab, however if this improvement was assumed to apply only to tocilizumab only the analysis would "unfairly" favour treatment sequences involving Roche's product. We also noted that the ERG assumed both improvement and deterioration would occur between ACR categories. It is unclear to us whether it was the overall improvement or overall deterioration caused by these adjustments which impacted the results. Our diagnostic analysis of the ACR responses predicted when 'deterioration' or 'improvement' is introduced to the model suggests that this approach will generate unpredictable and difficult-to-interpret model results.	Comments noted.
Roche Products	4.4 - We are surprised to read this summary of the discussions at the Appraisal Committee meeting. Our notes suggest that clinicians named etanercept as a commonly-used first line option, with tocilizumab sometimes given after it in case of inadequate response. We noted that infliximab and anakinra were both also mentioned as treatment options, with anakinra considered less efficacious. We agree that the discussions on the day reflected the great variation in clinical use of tocilizumab in sJIA, but cannot agree with the statement that tocilizumab is 'in general' used in patients who have already received anakinra or infliximab. We would urge the Committee to seek further clarification ahead of the next meeting. We would also point out that the infliximab Summary of Product Characteristics (SPC) does not include an indication for sJIA, and specifically states that evidence for use in children is not available. A similar SPC is found for anakinra; this product is not recommended for use in children or adolescents under 18 years of age with sJIA.	Comments noted. See sections 4.2 and 4.4 of the FAD for the Committee's considerations of this issue.
Roche Products	4.6 - The TENDER study addresses Populations 1 and 2, as stated on page 39 of the manufacturer submission (MS): "As such, by viewing only the inclusion criteria, the TENDER population matches population 1: children and young people 2 years and	Comments noted. See sections 4.6 and 4.7 of the FAD for the Committee's considerations of the populations in the TENDER trial.

Consultee	Comment	Response
	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 was also clarified in Roche's Response to Clarification Questions (A2, p2).	
Roche Products	4.10 - Please see comments on 3.24.	Comment noted.
Roche Products	4.12 - We would like to emphasise the clinicans' consensus that the health state costs we had used were reasonable, as this conclusion addresses the ERG's concern at the disparity observed in costs between 'ACR non-responder' and 'responding' ACR categories. Due to a lack of evidence, the cost savings from reductions in orthopaedic surgery for future joint damage and in bone marrow transplant and stem cell procedures are not taken into account in the model	Comments noted. See section 4.13 of the FAD for the Committee's considerations of these issues. .
Roche Products	4.13 - In our original model, we preferentially used the ACR-No fever outcome for comparison with other biologics, in cases where only this outcome was available from the clinical trials.	Comment noted.
Roche Products	4.14 - We are somewhat surprised to read that the Committee considers that infliximab is 'often' used, if this consideration is based only on the discussions held at the Appraisal Committee Meeting. Our notes suggest that whilst infliximab was named as a treatment option with benefits as stated in 4.14, it was not by any means regarded as a standard of care.	Comments noted. See sections 4.2, 4.4 and 4.16 of the FAD for the Committee's considerations of this issue.

Consultee	Comment	Response
	Infliximab was not included our original model's choices because it is not recommended for the treatment of children or adolescents with JIA due to insufficient evidence [Infliximab Summary of Product Characteristics accessed 20/03/2011]. Only one TNF study could be used in the comparison with TENDER for ACR response. This was NCT00036374 (infliximab study). Our original model used the response rates from NCT00036374 to inform a "class effect" estimate for all anti-TNF medicines rather than for infliximab only. The single infliximab trial was selected from the available evidence because it was the only trial with a comparable trial design to TENDER. From the infliximab SPC: The safety and efficacy of Remicade in children and adolescents younger than 18 years in the indications juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis have not been established. No data are available.	
Roche Products	4.15 - This concern has been noted and we have responded by providing a revised economic model.	Comment noted.
Roche Products	4.16 - We feel that the Appraisal Committee has made an unfair decision regarding the population of patients who have responded inadequately to DMARDs and systemic corticosteroids. The TENDER trial's comparison with methotrexate reflects clinical reality, in which methotrexate use is endemic and the clinical question of interest is whether methotrexate can be dispensed with in future and tocilizumab given without the need for methotrexate. The European regulatory authority accepted this approach and considered the safety and efficacy data from TENDER sufficient for the granting of a license in this spirit. By contrast, the ERG's emphasis on obtaining a comparison of tocilizumab with methotrexate in 'methotrexate-naive' patients reflects a misunderstanding of clinical practice. The decision about treating with methotrexate does not represent an important clinical juncture at which a doctor will choose to either prescribe a biologic or methotrexate, bearing in mind cost-effectiveness at this time. We believe that the ERG and Appraisal Committee have been too quick to reject	Comment noted. See section 4.7 of the FAD for the Committee's full consideration of the population of patients whose systemic JIA had failed to respond to NSAIDs and systemic corticosteroids.

Consultee	Comment	Response
	evidence in this setting, potentially driving a needless and clinically unrealistic limitation to patient access. This potential limitation is underscored by the apparently strong clinical and cost-effectiveness case for tocilizumab compared to methotrexate alone.	
Roche Products	**IV) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None	Comment noted.
Royal College of Nursing	There are no further comments to submit at this stage on behalf of the Royal College of Nursing.	Comment noted.
Commentator		
Arthritis Research UK	1. **Appropriate use of paediatric outcome measures and assessments of quality of life.** It is important, indeed critical, that NICE recognises that outcomes traditionally used for different diseases such as rheumatoid arthritis (RA) are inappropriate to be used as measures of outcome for juvenile idiopathic arthritis (JIA), and especially sJIA. sJIA has a debilitating systemic inflammatory component that has contributed to fatalities including from myocarditis and from secondary haemophagocytic lymphohistiocytosis in the children and young people, as well as longer term fatalities due to amyloidosis from uncontrolled disease as in the 1960s and 1970s. This is unlike adult RA. JIA is a spectrum of disorders and the vast majority (over 90%) of children do not have rheumatoid factor positive polyarthritis, CCP positive antibodies nor are they HLADR4 positive. Children with sJIA are both clinically and genetically different from RA. Therefore, it is imperative that NICE does not use the CHAQ alone, or out of context, simply because of the use of the adult "HAQ" (which has a very different utility and validation) in assessing clinical improvement or to define severity appropriate for the use of a therapeutic agent. CHAQ is a poor indicator of paediatric quality of life and there are separate	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.11, 4.12, 4.13 and 4.16 of the FAD for the Committee's considerations of these issues.

Consultee	Comment	Response
	tools for paediatric patients. Indeed, there is international consensus on the most appropriate way of assessing disease activity in JIA as stated below. The CHAQ is only used as one of six core set criteria which together inform the calculation of internationally approved and recognised measure of clinical improvement and disease activity for arthritis in children, but it is well documented that this does not fully reflect sJIA disease activity. The internationally approved American College of Rheumatology JIA paediatric outcome criteria that have been used in the TENDER trial and all current JIA trials are robustly validated. Both the FDA and the European Medicines Agency accept these as criteria for clinical effectiveness in JIA clinical trials. For sJIA, there are in addition clinical manifestations of systemic inflammation that are recognised and measured in all clinical trials of agents for this subtype, such as high quotidian fevers, serositis and macrophage activation, all of which necessitate hospitalisation. Therefore to use only the CHAQ in an economic model is entirely insufficient and inappropriate. Absence of systemic features, normal growth velocity and the ability to reduce corticosteroid use, are also important measures of outcome in sJIA.	
Arthritis Research UK	2. **The challenge of treating children with sJIA cannot be understated.** The number of repeated hospital attendances and inpatient admissions due to systemic features in sJIA such as uncontrollable high fevers alone is costly to the health service in addition to loss of the ability to work fulltime for the carer. Developmental delay, growth retardation, osteoporosis and missed educational and employment opportunities all lead to poor quality adult life. Long term uncontrolled inflammation of the joints may lead to joint replacements in young teenagers after 10+ years of damage, and more subsequent operative procedures. Amyloidosis as a complication has already been mentioned. A drug that would prevent these problems, so costly to the individual, the family and the state, must suppress significantly disease activity using these appropriate outcome measures. Tocilizumab is the first therapeutic agent that is close to achieving this goal for sJIA.	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.3, 4.4, 4.13 and 4.16 of the FAD for the Committee's considerations of these issues.
Arthritis Research UK	**3. Cost comparisons to ineffective / partially effective alternatives** Using a costing model that compares Tocilizumab against ineffective/partially effective treatments with NSAIDs, corticosteroids and	Comments noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and

Consultee	Comment	Response
	methotrexate, anti-TNF treatments, and / or Anakinra is clinically inappropriate. As outlined in the response from BSPAR, the very significant clinical data emerging from recent trials of Tocilizumab in sJIA have completely changed the expectation both of the child, family and clinician in what is a reasonable outcome for these children. It is no longer acceptable that children remain on long term cortosteroids, are poorly treated only with NSAIDs or even methotrexate. Although there is encouraging, yet to date very limited data of the probable effectiveness of Anakinra, use of anakinra is not standard practice in sJIA. It is clearly evident from the published literature that the anti-TNF agents are not good in treating sJIA (in contrast to their use in non-systemic, polyarticular-course JIA). In contrast, there is now very strong evidence that Tocilizumab is of significant clinical benefit, far greater than any other agent to emerge in recent times. This must therefore be understood and contextualised in comparing its use within an economic model with traditional ineffective / partially effective treatment pathways.	additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.2, 4.3, 4.4, 4.13 and 4.16 of the FAD for the Committee's considerations of these issues.
Arthritis Research UK	**4. Differences in the biological basis of sJIA, supporting the use of Tocilizumab** It is very important to recognise that the international paediatric rheumatology community consensus, and the published data to date, makes a very strong case that the biological basis of sJIA is distinct from that of the other sub-categories of JIA. This is of particular relevance when it comes to the appropriate use of anti-TNF therapy. Many of the recent trials of biologics in JIA have actually excluded sJIA, or sJIA with systemic features from their inclusion criteria. Thus, the few that were included as polyarticular-course JIA do not constitute statistically significant evidence for its effectiveness in sJIA. Therefore, although there may be some anecdotal evidence of the use of anti-TNF agents in sJIA, it would be very inappropriate for this to be compared in terms of its clinical and therefore cost effectiveness. There is ample peer-reviewed, published evidence focussing on the biological basis of JIA showing that the cytokines IL-6 and IL1beta are key in driving the inflammatory pathway leading to development of sJIA, in contrast to oligo- and polyarticular course JIA . Therefore the rationale for targeting	Comments noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.2 and 4.4 of the FAD for the Committee's considerations of these issues.

Consultee	Comment	Response
	these pathways, supported by the clinical evidence now available for Tocilizimab from the recent TENDER trial data, underline why even in economic models, direct comparison to corticosteroids, methotrexate, or anti-TNF agents gives only a partial, incomplete view of the importance of these recent data.	
Arthritis Research UK	On behalf also of Arthritis Research UK, the NIHR MCRN / Arthritis Research UK Paediatric Rheumatology Clinical Studies Group welcomes the opportunity of discussion and dialogue with NICE as to the challenges of looking at economic models that assess the cost effectiveness, as well as the clinical effectiveness. This is an evolving arena of use of new biologics within the treatment of different sub types of JIA. Biologics will become an ever increasing, important therapeutic opportunity for clinicians within the NHS, both for JIA and other paediatric connective tissue disorders in which biologics are beginning to be used. the NIHR MCRN / Arthritis Research UK Paediatric Rheumatology Clinical Studies Group welcomes the opportunity of discussion and dialogue with NICE as to the challenges of looking at economic models that assess the cost effectiveness	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
Abbott	The manufacturer submission states that: "*Adalimumab, given its indication in polyarticular 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*". In March 2011, the EMEA approved an extension to the existing adalimumab JIA indication, and adalimumab is now licensed to treat patients aged 4 to 12 years as well as those aged 13 to 17[i]. The paediatric vial presentation has been available in the UK since June 2011. Abbott therefore believes that the assumption that adalimumab would be used later in the treatment sequence is no longer valid.	Comment noted. Adalimumab was excluded in the revised analyses considered by the Committee.
iAbbott	**1.2 Adalimumab price** The list price of adalimumab used in the manufacturer's submission is	Comment noted. Adalimumab was excluded in the revised analyses considered by the Committee.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>incorrect. The current list price (as of 1 January 2011) is £352.14 per 40mg[ii], not £357.50 as reported in table 56 of the manufacturer's submission.</td><td></td></tr>
<tr><td>Abbott</td><td>2.1 Use of infliximab in patients with juvenile idiopathic arthritis
Although Abbott understands that infliximab may be used in clinical practice, it is not currently licensed for any form of juvenile arthritis. Therefore, unlike tocilizumab, and the other anti-TNF therapies (adalimumab and etanercept) which currently have a licence for polyarticular JIA, the risk benefit profile of this drug has not been assessed by the regulatory authorities in patients with juvenile arthritis.

Infliximab does have a licence for use in patients aged 6-17 with Crohn's Disease. However, section 4.2 of the licence states that:

"Due to insufficient data on safety and efficacy, Remicade is not recommended for use in any other paediatric indication[iii]"

The licence then refers the reader to section 4.8 (undesirable effects) – in particular the section on juvenile rheumatoid arthritis which reports data on infusion reactions, immunogenicity, and infections from the phase III trial of infliximab in patients with active juvenile rheumatoid arthritis. These data are summarised in Table 1 below.

Table 1 Safety findings from infliximab juvenile rheumatoid arthritis phase III trial
<table>
<tr><th></th><th>Infliximab 3mg/kg</th><th>Infliximab 6mg/kg</th></tr>
<tr><td>Infusion reactions</td><td>35%</td><td>17.5%</td></tr>
<tr><td>Serious infusion reaction</td><td>4/60</td><td>2/57</td></tr>
<tr><td>Possible anaphylactic reaction</td><td>3/60</td><td>1/57</td></tr>
<tr><td>Antibodies developed</td><td>38%</td><td>12%</td></tr>
<tr><td>Infections*</td><td>68%</td><td>65%</td></tr>
</table>
*Infection rates for the 3mg/kg dose are over a 52 week period, and over a</td><td>Comments noted.
In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.</td></tr>
</table>

Consultee	Comment	Response
	38 week period for the 6mg/kg dose. Infections were also observed in 47% children receiving placebo for 14 weeks. Further information on the safety findings from this trial are provided by Ruperto et al.(2007), who report that serious adverse events occurred in 31.7% patients receiving 3mg/kg over a 52 week period compared with 8.8% in patients receiving 6mg/kg over a 38 week period and 5% in patients receiving placebo over a 14 week period[iv]. Abbott is concerned that the Committee may choose to not recommend a licensed treatment option in favour of an unlicensed comparator which is specifically not recommended by the regulatory authorities on the grounds of insufficient safety and efficacy data.	
Abbott	**2.2 Uncertainty over the infliximab dose** Although the Committee request that the manufacturer conduct a cost-effectiveness analysis comparing tocilizumab to infliximab, it is unclear what dose of infliximab should be used in this comparison. In the pivotal trial for infliximab in the treatment of patients with juvenile rheumatoid arthritis, patients were randomised to receive either 6 weeks placebo followed by infliximab 6mg/kg plus methotrexate, or infliximab 3mg/kg plus methotrexate. When presenting their findings from the open-label extension (OLE) of this trial, Ruperto et al. reported that: *"Results from the pivotal study suggested that paediatric patients might require higher infliximab doses than adults on a mg/kg basis to maintain adequate serum concentrations and minimise the development of antibodies to infliximab and related infusion reactions[iv]."* Further details of these safety findings are reported in the 2007 publication of the pivotal trial results "the safety profile of infliximab 3 mg/kg appeared less favorable than that of infliximab 6 mg/kg, with more frequent occurrences of serious adverse events, infusion reactions, antibodies to infliximab, and newly induced antinuclear antibodies and antibodies to	Comment noted. The Committee requested the extra scenario analyses involving infliximab to explore the effectiveness of tocilizumab in different positions in a sequence. The Committee noted in section 4.16 of the FAD that only tocilizumab is licensed for systemic JIA.

Consultee	Comment	Response
	double-stranded DNA observed with the 3 mg/kg dose." [v] Following these safety findings, study investigators were offered several options including an increase in the dose of infliximab, or discontinuation of infliximab therapy. It therefore appears that the 6mg/kg dose may be the most appropriate infliximab dose to use in the cost-effectiveness analysis, and those are the costs that should be applied. However, it is worth noting that the effectiveness data used in the manufacturer's mixed treatment comparison were from the 3mg/kg arm of the pivotal trial. Furthermore, since the highest licensed dose for infliximab in any indication (including adult indications) is 5mg/kg, the long-term safety of using a 6mg/kg dose is unknown.	
Abbott	**2.3 Treatment of patients who are intolerant of methotrexate** In the pivotal trial for infliximab in the treatment of patients with juvenile rheumatoid arthritis, all patients were required to receive concomitant methotrexate[iv]. The licence for adult rheumatoid arthritis also requires that infliximab be given concomitantly with methotrexate[iii]. Although infliximab is not licensed for use in a juvenile arthritis population, based on the design of the clinical trial it is likely that the requirement for concomitant methotrexate also applies to its use in this population. If this were the case, infliximab would not be an appropriate treatment option for patients who are intolerant, or contraindicated to methotrexate. In comparison, tocilizumab, adalimumab and etanercept are all licensed as monotherapies for use in a juvenile arthritis population and are therefore suitable for use in patients who are intolerant, or contraindicated to methotrexate.	Comments noted.
Abbott	Abbott understands the Appraisal Committee's conclusion that there was not enough evidence to allow for a comparison of tocilizumab with methotrexate and their consequent decision not to recommend tocilizumab for patients who are methotrexate naïve.	Comments noted.

Consultee	Comment	Response
	For the methotrexate failure population, the Appraisal Committee have requested a substantial amount of additional information and analyses from the manufacturer and are therefore “minded not to recommend” tocilizumab for this population. The ACD therefore contains no firm recommendations for this population. However, Abbott does have some concerns about some of the analyses requested (these are outlined above).	In response to the ‘minded no’ in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1.
Abbott	**Are there any equality related issues that may need special consideration?** None that Abbott is aware of.	Comment noted.

Comments received from members of the public

NHS professional 1	On a general note I am surprised and disappointed that the committee are minded not to approve Tocilizumab for Systemic Onset JIA. The negative approval status from NICE will make it very much more difficult for the small number of severely affected patients with this condition to gain access to what is undoubtedly an effective treatment. I believe setting the treatment age at 5 years for treatment is not clinically justified. The appraisal document recognises that disease onset is as early as 2 years and that children under the age of 5 years are the worst affected. If a child of 2 years develops the condition and then goes on to fail steroids and Methotrexate over the course of the next 12 months the child will then have to wait up to 2 years before they are eligible for the most appropriate treatment. A starting age of 2 or 3 years makes the best clinical sense. The stopping rule for Tocilizumab at 2 years is too rigid, some patients will need treatment for longer and the recommendation that treatment interval is increased to 4 weeks at 6 months may also not be achievable by all patients. These decisions should not be taken by a committee such as NICE but left to the expert treating clinician. I believe that although there is some controversy with regard to how the data in the TENDER trial was analysed the results are unequivocal and the beneficial effect of Tocilizumab is very clear and far superior to any other known treatment. The number of patients with systemic onset JIA in the UK is relatively small but the effect on individuals and their families is often devastating. The burden of care on the treating units is also high when these patients are constantly unwell. These factors should be given more weight when coiming to a conclusion about the cost effectiveness of the treatment	Comments noted. In response to the 'minded no' in the ACD the manufacturer provided the Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See section 4.14 of the FAD for the Committee's consideration of the issue of the age for treatment. See section 4.18 of the FAD for the Committee's considerations of potential stopping rules. See sections 4.2, 4.3, 4.4, 4.13 and 4.16 of the FAD for the Committee's considerations of these issues.
Patient/Carer	As commented by the clinical experts the time between infusions does increase in patients, if the infusion go to every four weeks	Comment noted. In response to the 'minded no' in the ACD the manufacturer provided the

	surely this would be half the price? As the disease becomes more controlled, or could be controlled at an earlier stage, less hospital visits are required, whether this would be for inpatient treatment, physiotherapy/hydrotherapy, admission for joint injections, this alone must reduce the true cost. If other treatments had to tried before hand with very little or no success then this has to be a valuable waste of money that could be used for a drug that has shown to be very successful. If the disease becomes better controlled at an earlier stage this would mean less joint replacements in later life. Another plus factor has to be the steroid sparing, taking into consideration the damage that can be caused by steroids, this must also mean less hospital visits. As from a patient/parent/carer point of view Tocilizumab IS a life changing treatment not only from a physical or pain point of view but also from a psychological point of view. The difference it makes to a patients and their families life is amazing I cannot begin to imagine where our lives would be today without the opportunity for having this treatment, our next option would be bone marrow transplant, what would be the costing of that ! I do realise that there does have to be reasonable point at how much can be spent on treatments, not only for JIA.	Committee with a new economic model and additional information. Based on this new data the recommendations in the FAD have been amended, see section 1. See sections 4.2, 4.3, 4.4, 4.13, 4.16 and 4.18 of the FAD for the Committee's considerations of these issues.

[i] Humira (adalimumab) Summary of Product Characteristics, June 2011. Available at: www.medicines.org.uk
[ii] MIMS, August 2011.
[iii] Remicade (infiximab) Summary of Product Characteristics, June 2011. Available at www.medicines.org.uk
[iv] Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, Silverman ED, Balogh Z, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis. 2010 Apr;69(4):718-22.
[v] Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007 Sep;56(9):3096-106.