National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Etanercept, abatacept, adalimumab and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	AbbVie	The background information is accurate. However, there are a couple of points that need some additional clarification. The background info discusses the percentages of patients with oligoarthritis, polyarthritis and systemic JIA. The scope states that "*polyarthritis accounts for 25% of new diagnoses and is diagnosed when 5 or more joints are affected in the first 6 months of disease. Polyarthritis can be further divided into rheumatoid factor positive arthritis, rheumatoid factor negative arthritis, and extended oligoarthritis (where more than 4 joints are affected after 6 months)*." However, the definition of polyarthritis depends on whether it is polyarticular ONSET disease (the disease classification according to the ILAR criteria based on arthritis presentation and evolution over the first 6 months from diagnosis) or polyarticular COURSE (5 or more affected joints whatever the JIA classification) that is referred to. While the prevalence of polyarticular onset JIA according to the ILAR criteria is ~25%, the prevalence of polyarticular course JIA is higher. For example in the adalimumab clinical trial programme, adalimumab was assessed in two studies in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended	The distinction between polyarticular onset disease and polyarticular course disease has been clarified in the scope. The broad term of extra-articular manifestations has been added to the scope.

Section	Consultee/ Commentator	Comments	Action
		oligoarthritis). As such, children with an initial diagnosis of oligoarthritis or psoriatic arthritis, who go on to have 5 or more joints affected would have polyarthritis and be eligible for an anti-TNF. In the previous NICE appraisal of etanercept, the percentage of patients with polyarthritis was estimated to be approximately 40% which was a mixture of onset and course JIA patients. In addition, AbbVie would suggest adding the broad term of extra-articular manifestations to the description of the disease. For example eye problems (uveitis) are mentioned but not inflammatory bowel disease or psoriasis, which also present in a number of children and adolescents with JIA.	
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Oligoarthritis can progress to polyarticular disease (called extended oligoarthritis). Oligoarthritis is the subgroup most commonly affected by uveitis, which is often resistant to DMARDs and can have devastating effects. This MTA should include management of chronic uveitis resistant to DMARDs, or at least a clear plan of how it will be considered by NICE please. Considering the management solely of joint disease in JIA is a little like considering the management of large bowel disease in Crohn's, ignoring disease of the small bowel: they need to be considered together in guidance. As well as children missing schooling, parents / carers need to miss work to care for children and attend appointments. This should be factored in when considering infusions which require regular hospital attendance and as a consequence of uncontrolled JIA. Enthesitis related arthritis is predominantly HLA B-27 associated and a significant proportion develop spondyloarthropathy in adult life.	A definition of extended oligoarthritis has been added to the scope. The management of chronic uveitis is outside the remit of this appraisal. Additional text has been added to the scope to emphasise that parents and carers will also be affected by looking after children with JIA.

Section	Consultee/ Commentator	Comments	Action
	Pfizer	No comment.	Noted.
	Roche	No comment.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	The scope does not mention the concept of disease flares, which was a primary outcome in a number of clinical trials (generally defined in the clinical trials 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 – as defined by the American College of Rheumatology). The ACR also define treatment response in terms of improvement in these criteria (also measured in some of the trials).	A description of disease flares has been added to the background section of the scope and as an outcome.
The technology/ intervention	AbbVie	Yes, however see regulatory section below for extension to licence of adalimumab to include paediatric enthesitis-related arthritis.	The licensing information for adalimumab for paediatric enthesitic-related arthritis has been added to the scope.
	Bristol-Myers Squibb	Yes, the description of abatacept is accurate.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	A fair summary is given, however time should be spent clarifiying the exact wording of UK market authorisation. I do not have internet access at present to allow checking, but some do not specify the Polyarthritis subgroup, but instead specify polyarthritis (ie 5 or more affected joints). This is a confusing, but important distinction because all subtypes (except persistent oligoarthritis) can be affected by polyarthritis (5 or more joints), not just the 2 Polyarthritis subgroups (RF pos and RF neg).	The wording of the marketing authorisations has been checked and the relevant amendments have been made to the

Section	Consultee/ Commentator	Comments	Action
		Previous NICE guidance for etanercept (and the licensing) allowed its use for polyarthritis, regardless of the subgroup eg etanercept was sanctioned by previous (current) NICE guidance for polyarthritis in the any subgroup including eg psoriatic or systemic subgroups. This was appropriate from the trial evidence and clinically appropriate.	text.
	Pfizer	No comment.	Noted.
	Roche	No comment.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	The licence for tocilizumab specifies that it should be used in combination with methotrexate (except where inappropriate), though the scope doesn't explicitly include combination treatment (adding 'within their licensed indication' would accommodate this). Some of the RCTs of etanercept, abatacept and adalimumab include methotrexate as background therapy. The scope as currently written does not explicitly acknowledge/permit the inclusion of background or combination therapy.	'Within their licensed indications' has been added to the Interventions and Comparators parts of the table in the scope.
Population	AbbVie	Not quite. The scope proposes to exclude systemic JIA as it will be covered by a review of TA238 as tocilizumab is the only drug licensed for use in systemic JIA. However, a proportion of systemic JIA patients may have ≥5 joints affected 6+ months after diagnosis and would therefore have polyarticular disease and be eligible for adalimumab, etanercept or abatacept. It is important to note the meaning of polyarthritis can depend on whether it is polyarticular 'onset' arthritis (estimated as 25% as the scope states), which is ≥5 joints affected in the first 6 months; or polyarticular course arthritis, which is characterised by the involvement of 5 or more joints after the initial 6 months since diagnosis, irrespective of JIA onset type. Such that patients may have a diagnosis of PsA, enthesitis-related arthritis, extended	The population section of the scope has been updated to clarify that people with polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course), enthesitis related arthritis and psoriatic

Section	Consultee/ Commentator	Comments	Action
		oligoarthritis, systemic JIA or undifferentiated JIA and be eligible for treatment with adalimumab if they have 5 or more joints affected and have failed conventional DMARDs. In contrast, no biologic therapy is licensed for patients with persistent oligoarthritis i.e. the involvement of 4 or fewer joints, so this group would not be appropriate for inclusion in this review. While the prevalence of polyarticular onset JIA according to the ILAR criteria is ~25%, the prevalence of polyarticular course JIA is higher. Patients with JIA associated uveitis are an important subgroup of JIA patients. Despite current screening and conventional DMARD therapy 10% to 15% of children with JIA-associated uveitis may develop bilateral visual impairment and be certified legally blind. The value of adalimumab in the treatment of JIA-associated uveitis is currently being assessed in the SYCAMORE trial (Ramanan AV, et al SYCAMORE Trial Management Group. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials. 2014 Jan 9;15:14.).	arthritis are included in this appraisal. 'Patients with JIA associated with extra-articular manifestations, such as uveitis' has been added as a potential subgroup in the Other considerations section of the scope.
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Trials of medications for JIA are mainly limited to children, but the same disease continues in a significant proportion into adult life. It is the same disease, with no biologically plausible rationale to think adults with JIA do not respond in the same way to treatment as children with JIA. Adults with JIA should be included in this review. They are often incorrectly included with Rheumatoid Arthritis.	The Population in the scope is not limited to children, it states 'People with …'. However, NICE can only make recommendations that are in line with the

Section	Consultee/ Commentator	Comments	Action
			marketing authorisation of each product.
	Pfizer	Pfizer request that the various JIA sub-groups be included in the population. The draft scope states: *"People with juvenile idiopathic arthritis (excluding systemic juvenile idiopathic arthritis)"* Pfizer suggest that the draft scope population should be more explicit and changed to: People with juvenile idiopathic arthritis and the following sub-group diagnoses: • polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis); • enthesitis related arthritis; and • psoriatic arthritis	The Population in the scope has been amended for clarity.
	Roche	Systemic juvenile idiopathic arthritis (sJIA) should be included within the MTA. The current guidance in TA238 is due for review in December 2014, therefore this MTA provides a well-timed opportunity to ensure a review of all subsets of JIA. A separate review of sJIA at a later date may also not be a good use of resources, considering the rarity of the condition. A combined review of this proposed MTA along with a review of TA238 (tocilizumab in sJIA) may, therefore, represent an approach which better suits all concerned stakeholders.	Thank you for your comment.
	Southampton	The licensed indications for the drugs specifies treatment in patients with an	'Within their licensed

Section	Consultee/ Commentator	Comments	Action
	Health Technology Assessments Centre (SHTAC)	inadequate response/intolerance to various treatments including DMARDs, NSAIDs, corticosteroids, anti-TNFs. The population in the scope does not reflect this, though this could be accommodated by adding 'within their licensed indication' to the intervention section.	indications' has been added to the Interventions section.
Comparators	AbbVie	Similarly to ankylosing spondylitis in adults, the efficacy of DMARDs has not been established for enthesitis or axial involvement, so DMARDs would be less likely to be used in these patients unless there is active synovitis.	Comment noted.
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Currently there is widespread agreement that methotrexate (oral or sc) is the standard long-term first line steroid sparing treatment of polyarthritis, with the possible exception of the ERA subgroup, when some would use sulfasalazine first. Intra-articular or systemic corticosteroids are used to induce remission, but polyarthritis nearly always warrants a medium term medication to maintain remission. It is interesting to note that oral methotrexate (very cheap) is not licensed for JIA, but frequently used in view of tolerability. Subcutaneous preparation(s) of methotrexate are licensed for JIA. There is evidence that psychology interventions can significantly reduce the rate of needing to stop methotrexate due to intolerance, and so prevent the need in some children to progress to a biologic agent. Consideration of whether these psychological interventions are cost effective would seem wise, due to the high cost of the biologic medications.	Comment noted. Psychological interventions to prevent progression to biologic medications would occur earlier in the treatment pathway than the interventions in this scope, therefore psychological interventions are not relevant comparators for this appraisal.
	Cardiff and Vale University Local	Infliximab and the other monoclonal anti-TNF inhibitors (Golilumab, Certolizumab) are used in clinical practice. They are primarily used in patients	Comment noted. NICE can only make

Section	Consultee/ Commentator	Comments	Action
	Health Board	with uveitis who have underlying oligo or enthesitis related arthritis who are intolerant or lose response to adalimumab. AS uveitis is a relatively common extra articular manifestation the use of alternative monoclonal anti TNF inhibitors should be assessed.	recommendations that are in line with the marketing authorisation of each product, and the remit does not cover these other TNF inhibitors.
	Pfizer	Pfizer agree that etanercept, abatacept, adalimumab and tocilizumab are the standard treatments licenced to treat persons affected by JIA in England and Wales who are intolerant to, or have inadequately responded to methotrexate (MTX) or other DMARD. However, we would like to take this opportunity to highlight the differences in the respective marketing authorisations due to variations in age and JIA subgroups. The draft scope states that: *"Etanercept, abatacept, adalimumab and tocilizumab should be compared with each other where appropriate"* Pfizer would like to highlight that etanercept is licenced to treat: • Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. • Psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. • Enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		Therefore, the only two appropriate comparisons between etanercept and other bDMARDs (abatacept, adalimumab, and tocilizumab) that reflect market authorisations are: 1. tocilizumab and adalimumab in patients diagnosed with polyarticular JIA; and 2. tocilizumab alone in extended oligoarthritis. In the remaining indications etanercept is licenced (enthesitis related arthritis and psoriatic arthritis) comparative data is only available versus a historical placebo arm. Pfizer considers that medicines regulation has been developed in Europe to assess how medicines should be authorised for use and there is clearly a need to ensure that the special position of the regulatory bodies is recognised. We are concerned to ensure that NICE guidance that is inconsistent with the marketing authorisation cannot be seen to undermine the regulatory framework by inappropriately influencing clinicians' professional obligation to act in the best interests of their patients. This is relevant whether the unlicensed medicine is being selected as a technology for appraisal, a comparator in the appraisal, or where NICE recommendations are outside of a marketing authorisation. Where comparisons can be made between etanercept and other bDMARDs, it is likely that heterogeneity between the available data will lead to considerable uncertainty in an economic evaluation. Published research has concluded that comparing etanercept with adlimumab in JIA is challenging and inconclusive. Differences between bDMARDs in pivotal study populations (e.g., patient characteristics, age, disease sub-group and treatment history), trial design and evolution of licence	The remit of the EMA differs from the remit of NICE. EMA gives advice on quality, efficacy and safety, whereas NICE makes recommendations on the use of a technology in routine clinical practice, based on clinical and cost effectiveness. NICE can only make recommendations within any licensed indications, unless otherwise instructed by the Department of Health.

Section	Consultee/ Commentator	Comments	Action
		amendments suggests that an indirect treatment comparison (ITC) is inappropriate (Otten et al. 2013).	
	Roche	No comment.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	Including DMARDs as a comparator implies that etanercept, abatacept, adalimumab and tocilizumab could replace DMARDs as treatment. However, the licensed indication for etanercept, abatacept, adalimumab specifies that patients should be treated if there is an insufficient response to DMARDs. Retaining DMARDs as a comparator might be appropriate if DMARDs are used in combination with the intervention drugs as background therapy.	The marketing authorisations for abatacept, adalimumab and tocilizumab state that treatment is to be given in combination with methotrexate where appropriate and so DMARDs are an appropriate comparator for this scope for situations where DMARDs are tolerated.
Outcomes	AbbVie	The impact of treatments on important extra-articular manifestations such as uveitis and Crohn's disease should also be considered. A working group has proposed outcome measures for assessing JIA-associated uveitis (Heiligenhaus A et al; Multinational Interdisciplinary Working Group for Uveitis in Childhood. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis Care Res (Hoboken). 2012 Sep;64(9):1365-72.). Growth retardation is an important outcome for treatment of JIA that should be added to the scope. (Giannini C, Mohn A, Chiarelli F. Growth	'Extra-articular manifestations (such as uveitis)' and 'growth' have been added to the scope.

Section	Consultee/ Commentator	Comments	Action
		abnormalities in children with type 1 diabetes, juvenile chronic arthritis, and asthma. Int J Endocrinol. 2014:2659540). It will be important to consider the impact of JIA on the long term physical, emotional and educational development of children and adolescents. A Dutch study highlighted that young females with JIA who have to apply for disability benefits are at risk for impaired HRQOL and a delay in their psychosocial developmental trajectory. The authors note that parents, physicians and other health-care providers should pay systematic attention to the development of social and independent functioning of children with JIA (Haverman L et al. Health-related quality of life and psychosocial developmental trajectory in young female beneficiaries with JIA. Rheumatology (Oxford). 2012 Feb;51(2):368-74. Children and adolescents with JIA can exhibit emotional difficulties and a delay of psychological development leading to low self-esteem, a distorted self-image, more anxiety and depression traits, and a worse quality of life, when compared to healthy subjects (Bomba M et al. Body experiences, emotional competence, and psychosocial functioning in juvenile idiopathic arthritis. Rheumatol Int. 2013 Aug;33(8):2045-52.). As noted below it will be important that the physical, social, psychological development of children and adolescents with JIA is captured as these domains would not be necessarily reflected in CHAQ or EQ-5D scores. Although possibly outside NICE's reference case it may be useful to consider the benefits of successful treatment on the health related quality of life of parents in terms of factors such as anxiety.	The EQ5D has a mental health domain. All health effects can be considered in an appraisal, not only the health effects on the

Section	Consultee/ Commentator	Comments	Action
			patients.
	Bristol-Myers Squibb	Flare of arthritis and/or time to flare are also relevant outcomes for consideration.	These have been added to the scope.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	The outcomes described are reasonable. Other important ones include school attendance and parent / carer time off work caring for affected child. May not find all outcomes described in some very useful published trials.	Such benefits are outside the NICE reference case, but any evidence on these outcomes can be provided during the appraisal.
	Cardiff and Vale University Local Health Board	Employment in adulthood is an important outcome measure for the efficacy of treatments for JIA and should be included as a health related benefit.	Such benefits are outside the NICE reference case, but any evidence on these outcomes can be provided during the appraisal.
	Pfizer	No comment	Noted.
	Roche	Growth is a relevant outcome within JIA.	This has been added to the scope as body weight and height.
	Southampton Health Technology Assessments	The outcomes appear to cover the ACR core criteria for a flare/response, except for erythrocyte sedimentation rate (or other laboratory assessment of inflammation). It may be necessary to mention flare and treatment response	'Disease flares' has been added to the scope.

Section	Consultee/ Commentator	Comments	Action
	Centre (SHTAC)	as composite outcomes.	
Economic analysis	AbbVie	This review is evaluating children and adolescents with JIA. However it is likely that the condition will continue into adulthood in a proportion of patients, therefore both the time horizon and the modelling of transitional care needs to reflect the fact that some children will continue treatment beyond 18 years of age. Whilst AbbVie understands that the NICE reference case stipulates costs and benefits must be calculated from an NHS and social services perspective, given the age of those suffering the condition it will be important to also consider the costs and outcomes of treatment from a societal perspective in sensitivity analyses. In particular, major elements may be the impact of successful treatment in minimising disruption to education and productivity costs for patients, parents and carers.	Comment noted.
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Methotrexate is usually given for 4 months (if tolerated) before deciding if effective. When to stop biologics after they induce remission is less well researched. One common approach is to stop after 2 years of remission of JIA, but a proportion flare and need to return onto the medication. Registry information would be very helpful to inform this important consideration to assess costs involved in practice. Many published trials merely continue the medications longterm, so the actual cost in practice would be overestimated	Comment noted.
	Pfizer	No comment	Noted.
	Roche	Given the acknowledged affect that JIA may have on carers and family	Following consultation on the proposal for

Section	Consultee/ Commentator	Comments	Action
		members, we believe a broader definition of value than that assessed through the existing Methods Guide is warranted. Such an approach may be seen with Value Based Assessment (VBA), although the final details of this approach remain unknown.	value based assessment, NICE will not yet amend its methods but instead carry out further work before making changes to the way it appraises new medicines and other technologies for use by the NHS. This will be done as part of a wider review of the innovation, evaluation and adoption of new treatments. https://www.nice.org.uk/news/press-and-media/nice-calls-for-a-new-approach-to-managing-the-entry-of-drugs-into-the-nhs
	Southampton Health Technology Assessments Centre (SHTAC)	No comments.	Noted.
Equality and	AbbVie	It is of concern that currently there are anecdotal reports of JIA patients having their treatment discontinued at age 18 because the existing NICE	Comment noted.

Section	Consultee/ Commentator	Comments	Action
Diversity		guidance for etanercept only makes recommendations for adolescents up to age 17. It will be important that the guidance does not discriminate solely according to the age of JIA patients.	
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Main issue in this realm would be discrimination against adults with JIA. They have not been considered in previous NICE guidance. I understand that the NICE review of seronegative arthritis does not cover JIA, so unless this review covers adults with JIA (or there is a plan on how this will be assessed), this group will be discriminated against.	Comment noted.
	Pfizer	No comment	Noted.
	Roche	No comment.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	No comments.	Noted.
Other considerations	AbbVie	The scope states: "*Where the evidence allows, subgroups by type of JIA will be considered: oligoarthritis, polyarthritis (rheumatoid factor positive, rheumatoid factor negative, and extended oligoarthritis), enthesitis-related arthritis and psoriatic arthritis*." As mentioned in AbbVie's comments on the background section, because polyarthritis can be characterised as either onset polyarthritis, which is ≥5 joints affected in the first 6 months; or course polyarthritis, which is characterised by the involvement of more than 5 joints 6+ months since diagnosis, irrespective of JIA onset type; there will be a	Comment noted. The Other considerations section has been amended to include patients with JIA and extra-articular manifestations as a

Section	Consultee/ Commentator	Comments	Action
		great deal of overlap of these subgroups, where patients characterised by an initial sub-group will go on to develop polyarticular disease. It will be imperative to determine the proportion of patients who are diagnosed with e.g. oligoarthritis or enthesitis-related arthritis in the first 6 months who then never develop polyarticular disease in order to carry out analyses in these sub-groups. Particularly as none of the biologic therapies are licensed for persistent oligoarthritis. For clarity, adalimumab can be used for polyarticular onset JIA and polyarticular course JIA regardless of initial onset type as long as ≥5 joints are involved. In addition, subject to the marketing authorisation for adalimumab being approved for the treatment of enthesitis-related arthritis (CHMP positive opinion received in July 2014), this could involve more (and therefore be polyarticular) or less than 5 joints. In addition and if the evidence allows, polyarticular JIA patients with extra-articular manifestations including uveitis, IBD and psoriasis should be included.	subgroup.
	Bristol-Myers Squibb	If evidence allows, subgroup analysis by type of JIA is appropriate.	Comment noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	JIA in adults and uveitis in JIA should be covered, as already described	Patients with JIA and extra-articular manifestations have been added to the Other considerations section of the scope as a potential subgroup. If the evidence and marketing authorisation allows, treatment of

Section	Consultee/ Commentator	Comments	Action
			adults with JIA will be considered. The population is defined as 'People' in the scope to ensure that the appraisal is not limited to children.
	Pfizer	No comment	Noted.
	Roche	No comment.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	In at least one RCT identified so far the patients comprised a mixture of sub-types of JIA, including a proportion (around 20%) with systemic JIA. Although the scope excludes systemic JIA we propose that such studies could still be included in the assessment where the proportion of systemic JIA is relatively low.	The scope sets out the question of the appraisal. The methodology for the inclusion of studies in the evidence base will be considered during the course of the appraisal.
Questions for consultation	AbbVie	Yes. Biologic therapies represent a step-change in the management of JIA which was previously only treatable with DMARDs, such as methotrexate. Anti-TNF therapies have the ability to reduce growth retardation in patients with JIA as well as conferring additional benefits on the extra-articular manifestations associated with JIA e.g. uveitis, IBD, psoriasis etc. The benefits of which mean that children are able to develop emotionally and physically in line with their peers.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		Yes, there are additional health-related benefits that are unlikely to be captured by the QALY. As mentioned above, successful treatment of children with JIA could result in minimal disruption to education and productivity costs, both current (parent/carer) and future (patient). Furthermore, anti-TNFs have been shown to reduce growth retardation allowing catch-up growth resulting in positive social and physical development for the child. These social and behavioural benefits are unlikely to be captured by the QALY. This is particularly true given that EQ-5D data were not collected in any of the JIA trials, in which case it is likely that utilities will be calculated using mapping algorithms from CHAQ or PediACR30/50/70. This means that the QALY will only capture HRQoL improvements limited to symptom and functional improvement, and not any of the aforementioned additional benefits, such as the psychological, social and behavioural benefits of returning a child to school. reducing parental anxiety and reducing growth retardation in JIA. There are some published prospective open label studies and registry data showing impact of JIA on growth, education and employment as these longer term endpoints are not commonly assessed in the clinical trials of biologics for JIA. Q: *Have all relevant comparators for etanercept, abatacept, adalimumab and tocilizumab been included in the scope? Are infliximab, golimumab, rituximab and certolizumab pegol used for treating JIA in clinical practice?* A: All the relevant biologic comparators for etanercept, abatacept, adalimumab and tocilizumab have been included. Infliximab, golimumab, rituximab and certolizumab pegol should not be included as comparators in this appraisal. These agents do not have a licence for use in children with JIA because they have not demonstrated that they are safe and efficacious treatments for this patient population. In addition, there are no RCT data to	

Section	Consultee/ Commentator	Comments	Action
		form comparisons with. AbbVie understands that under exceptional circumstances NICE may need to make recommendations for off-licence treatments when there are no licensed treatments available. However, in this case there are four licensed biologic agents available and as such these drugs should not be included as comparators.	NICE can only make technology appraisal recommendations for licensed technologies, unless otherwise instructed by the Department of Health.
	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	These treatments are already used for JIA, but a review to guide there rational use is very appropriate. Management at present involves the need for many individual funding requests, with a post-code lottery in existence still as to whether these IFRs are needed and whether they will be funded. Unfortunately published evidence is not available to answer all the questions eg comparing biologics with other biologics in head to head trials. Registry information (including that which is unpublished, but can be accessed on request) should be used. Experience of the UK paediatric rheumatology community should be used for guidance through the issues. QALY calculation will not cover effect on child's schooling and effect on work of parent / carer.	Comment noted.
	Cardiff and Vale University Local Health Board	The introduction of the 'Biologic' treatments being assessed have been a step-change in the treatment of these conditions. The early use of these treatments will reduce long term disability in children with JIA with knock on positive health and economic benefits.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Pfizer	In response to: "*Have all relevant comparators for etanercept, abatacept, adalimumab and tocilizumab been included in the scope? Are infliximab, golimumab, rituximab and certolizumab pegol used for treating JIA in clinical practice?"* Pfizer considers that medicines regulation has been developed in Europe to assess how medicines should be authorised for use and there is clearly a need to ensure that the special position of the regulatory bodies is recognised. We are concerned to ensure that NICE guidance that is inconsistent with the marketing authorisation cannot be seen to undermine the regulatory framework by inappropriately influencing clinicians' professional obligation to act in the best interests of their patients. This is relevant whether the unlicenced medicine is being selected as a technology for appraisal, a comparator in the appraisal, or where NICE recommendations are outside of a marketing authorisation. Therefore, infliximab, golimumab, rituximab and certolizumab pegol should not be included in this appraisal as they are not licenced for the treatment of JIA and licenced alternatives already exist. In response to: *"Do you consider etanercept, abatacept, adalimumab or tocilizumab to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (are they a 'step-change' in the management of the condition)?"* Pfizer believe that without the availability of bDMARDs, such as etanercept, patients who are intolerant to methotrexate (MTX) or MTX-inadequate response would have extremely limited treatment options to manage active	Comments noted.

Section	Consultee/ Commentator	Comments	Action
		disease. Etanercept is the only fully human TNF-α receptor indicated for patients with JIA, and is the only bDMARD licenced for all JIA subgroups included in the draft scope. Etanercept has been available in the UK for over 10 years and has shown to be effective and safe in children/adolescents with JIA; alternative bDMARDs (abatacept, adalimumab, and tocilizumab) also offer clinicians and patients' additional treatment options with alternative modes of action within their respective licences. In response to: *"NICE intends to appraise this technology through its multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process."* Pfizer believe that the remit of a MTA may fail to capture some of the wider issues faced by patients affected by JIA; for example, there is currently little guidance on general disease management and treatment pathways within the NHS (Coulson et al. 2014), including: • Diagnosis • Disease flares – presentation of which vary considerably by JIA subgroup • Comorbidities – both current and increased risk of, e.g., cardiovascular disease, uveitis, bone health, and orthopaedic intervention. In addition, a lack of guidance in transitional care – defined as "a multifaceted active process that attends to the medical, psychosocial and educational/vocational needs of adolescents as they move from child- to	

Section	Consultee/ Commentator	Comments	Action
		adult-centred care" – is likely to, without appropriate preparation, lead to poor clinical attendance, and reduced adherence, both key to optimal disease control (Coulson et al. 2014). Given this and national variation in models of care, it is likely that there is substantial unmet need in this therapy area. Therefore, due to the aforementioned need for guidance combined with the previously described difficulties in comparatively evaluating the respective interventions licenced in JIA, Pfizer recommend that NICE undertake a wider review of JIA (all subgroups) that includes the entire care pathway from childhood/adolescence through to adulthood by way of a clinical guideline (CG). Given potential similarities in care pathways such a CG could also include systemic JIA, incorporating TA238 (considered for review in December 2014) and evidence summary of new medicine (ESNM) 36.	All of the clinical guideline topics are linked directly to the library of Quality standards. This section of the website indicates 'topic selection' for the guidelines programme: http://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/selecting-and-prioritising-guideline-and-quality-standard-topics JIA isn't in the list of topics within the core library and therefore a potential guideline in this area with not be an option for the foreseeable

Section	Consultee/ Commentator	Comments	Action
	Roche	The licence of all the biologics within the appraisal does not restrict treatment for JIA to patients under the age of 17. We would therefore question what clinical evidence there is to support restricting treatment to children and adolescents. Are NICE proposing the introduction of stopping rules? There are significant benefits that may not be captured in the QALY for this particular condition, including the loss of schooling for children, and the reduced ability to work for the carers and/or parents of the children. RoActemra represents a step change in the management of sJIA as it remains the only licensed and NICE approved treatment.	If there is relevant evidence, the Committee can make recommendations on stopping rules.
	Royal College of Pathologists	Improved understanding of JIA disease pathology has had a direct impact on the development of biologic therapies to treat JIA (and other immunologically-mediated inflammatory conditions). The treatment paradigm for JIA patients has shifted from managing the symptoms to targeting therapy to achieve disease remission. Although these biologics were approved for disease management, clinicians have learned over time that the biologics can also lead to disease remission. There is growing evidence that a biologic combined with a synthetic DMARD like MTX, leads to better long-term outcomes. In addition to an improved understanding of the value of treatments used in combination, research has also demonstrated the benefits of initiating treatment earlier to better control disease progression and improve long-term outcomes among these patients. Patients achieve superior treatment response and duration of remission when biologic therapy is initiated as early as possible, rather than at the point when a patient fails to respond after a series of treatments with several different DMARD agents. Early intervention is now recognized as the best method for preventing extensive joint damage and halting the progress of the disease.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
	Southampton Health Technology Assessments Centre (SHTAC)	At the current stage we don't have an estimate of the available literature for the efficacy of the drugs in adults (aged over 17 years). In relation to the question as to whether adults who had JIA should be included in the assessment of this appraisal, it is likely that this would necessitate a separate economic model with different input parameters. They may therefore be a patient group that is distinct from people aged under 17 years.	Comment noted. If the evidence and marketing authorisation allows, treatment of adults with JIA will be considered. The population is defined as 'People' in the scope to ensure that the appraisal is not limited to children.
Additional comments on the draft scope	Bristol-Myers Squibb	No further comments.	Noted.
	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	A review of all aspects of the management of JIA (including use of corticosteroids, team support needed incl physio, psychology, OT and CNS) would be very welcome, along the lines of the guidance offered for diabetes and cystic fibrosis. Ideally this should be timetabled, but not delay this MTA.	Comment noted.
	Pfizer	References Abbvie 2014, Humira Pre-filled Pen, Pre-filled Syringe and Vial. Date of revision of text: 25 April 2014. http://www.medicines.org.uk/emc/medicine/ Accessed 19/08/14. BMS 2014, SPC ORENCIA 250 mg powder for concentrate for solution for infusion. Date of revision of text April 2014. http://www.medicines.org.uk/emc/medicine/ Accessed 19/08/14.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		Coulson et al. 2014, Employment issues among young adults with juvenile idiopathic arthritis (JIA): patient perspectives and current clinical practice. Ann Rheum Dis 2013;72:A357. Otten et al. 2013, Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov; 72(11):1806-12. Pfizer 2014, SPC Enbrel 25 mg powder and solvent for solution for injection. Date of revision of text: July 2014. http://www.medicines.org.uk/emc/medicine/ Accessed 19/08/14. Roche 2014, SPC RoActemra 20mg/ml Concentrate for Solution for Infusion. Date of revision of text: 23 January 2014. http://www.medicines.org.uk/emc/medicine/ Accessed 19/08/14.	
	Roche	No.	Noted.
	Southampton Health Technology Assessments Centre (SHTAC)	None	Noted.

The following consultees/commentators indicated that they had no comments on the draft scope

Royal College of Paediatrics and Child Health