The British Society for Paediatric and Adolescent Rheumatology

Registered Charity # 1132967

Submission to NICE

MTA – Abatacept, Adalimumab, Etanercept and Tocilizumab for the treatment of Juvenile Idiopathic Arthritis

05/03/2014

Summary

We believe that both the published evidence, and the widespread experience of paediatric rheumatologists throughout the world, show clear and significant benefits of all four treatments under review in the treatment of Poly-Articular-course Juvenile Idiopathic Arthritis (Poly-JIA). If these conditions are inadequately treated the results include severe physical and psychological harm for both affected children and their families. Failure to endorse the proposed treatments of children with this condition would be a devastating blow to their and their families' health

'Poly-JIA' is a descriptive, rather than a diagnostic term encompasses several different sub-types of JIA; it refers to any form of JIA in which the patient has clinical or radiological evidence of active synovitis in a cumulative total of five different synovial joints. As such it includes: Extended Oligo-articular JIA, Poly-articular JIA (both Rheumatoid factor positive and negative), Systemic-onset JIA, Psoriatic JIA and Enthesitis-related Arthritis. It is important to recognise that all clinical trials of the treatments under review have included patients with all these subtypes and we do not believe there is sufficient evidence to exclude any of these sub-types from the review and the subsequent recommendation.

BSPAR has recently submitted, and had accepted, an interim statement to NHS England with a comprehensive programme for the use of all the commonly used 'Biologic' treatments currently available in the UK, including both licensed and unlicensed treatments. This has been attached in Appendix A. The statement expands and clarifies the use of these expensive, but highly effective treatments. In particular it defines concepts of disease activity and remission to be assessed by clinicians and attempts to provide a framework for their sequential use in clinical practice.

Response to the Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of NICE, December 2014

3. Plain English Summary –

We would argue that a significant proportion of children with Systemic-onset JIA (SoJIA) follow a poly-articular pattern to their disease. Although Tocilizumab is a licensed treatment specifically used for SoJIA and should therefore be used first-line there are children who do not respond or who are unable to tolerate it. These children need access to alternative biologics and all 3 of the other treatments under review included children with SoJIA in the clinical trials which led to their being granted a licence. Additionally the final treatment option for all children with JIA would be an Allogeneic Bone-Marrow transplant under the NSCAG-funded programme in the UK. In order for a child to be accepted for consideration of this

treatment modality a child must have failed at least 3 different 'Biologics'. Therefore to exclude children with SoJIA may delay their access to treatment and lead inevitably to further illness and suffering for affected children

Although we accept that, in general, children with JIA affecting a cumulative total of less than 5 joints should not be covered by this TA, there is a specific circumstance in which we think it is important to include those with less than 5, namely when a child has bilateral sacroiliitis. This is most commonly seen in older children with Enthesitis-related Arthritis (ERA) in whom recent evidence has shown a high proportion will proceed to develop the adult form of this disease – Ankylosing Spondylitis (AS). Adults with AS are covered by NICE guidance (TA143) which specifically allows for the use of both Etanercept and Adalimumab in adults with AS affecting only the sacro-ileac joints i.e. only 2 active joints. Adalimumab and Etanercept are licensed for the treatment of ERA and we argue that there is no difference clinically between an adolescent and a young adult with this clinical finding. This is in accordance with the BSPAR interim summary in Appendix A

4.3: Place of the Intervention in the treatment pathway

Both Adalimumab and Abatacept have become accepted treatments in JIA and are widely used. Data given to BSPAR by the national registries (BCRD and BECS) show that 113 and 26 patients have been registered as taking Adalimumab and Abatacept respectively. These figures are likely to be a significant underestimate as registration is not mandatory and registration rates vary between centres.

4.4 Comparators

NICE clinical guidance is significantly out of date. No paediatric rheumatologist in the UK would advocate the use of Non-Steroidal Anti-Inflammatory drugs (NSAIDs) as first-line treatment for any form of JIA and none would use Sulphasalazine or Leflunomide as a first-line DMARD. The first-line treatment for poly-JIA should be IV or intra-articular steroids and the immediate use of Methotrexate. Oral steroids are only used as a bridging agent until Methotrexate takes effect and NSAIDs are only used for their analgesic properties.

Methotrexate is also the first-line DMARD used in all ages, including the under-3 age group. There is no alternative DMARD with better safety or efficacy and treatment should not be delayed by arbitrary age limits.

4.5 Population and Relevant sub-groups

We do not accept that a child with SoJIA should be excluded from inclusion in this appraisal for the reasons given above.

5.2 and 5.3 Inclusion and Exclusion criteria / Screening and Data extraction

We do not believe that 'Best supportive care, if DMARDs are not tolerated' is a valid comparator. The efficacy of Methotrexate over placebo has been well established and no child who is unable to tolerate Methotrexate should be denied access to 'biologics'

Data given to BSPAR from the BCRD and BECS registries should be included in this section, even though it is as yet unpublished. These registries provide 'real-world' data for children with Poly-JIA for all four treatments in the UK over several years. These show sustained improvement in many of the outcome parameters of 806 registered patients. The figures in the table below are the mean for each parameter:

	Start	6 months	12 months	24 months	36 months	48 months	60 months
CHAQ	1.1	0.8	0.7	0.7	0.6	0.6	0.5
Active joint count	8.2	1.9	2.3	1.7	2.0	2.6	2.3
Limited Joint Count	7.2	3.5	3.6	4	4.2	4.3	5
Pain VAS	5.8	3	3.1	3.0	2.5	3.2	2.1
Parental VAS	5.7	2.8	2.8	2.6	2.2	2.6	2.0
Physicians Global assessment	5.1	1.7	1.9	1.5	1.4	1.3	1.4

Figures for each individual drug in 'Poly JIA' patients are smaller but give a similar picture

Etanercept, n=708	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.1	0.7	0.6	0.7	0.6	0.6	0.5
Active joint count	8.4	1.9	2.1	1.7	2.0	2.6	2.3
Limited Joint Count	7.5	3.4	3.3	4.1	4.4	4.3	5.0
Pain VAS	5.9	2.8	2.9	3.0	2.5	3.2	2.1
Parental VAS	5.8	2.7	2.7	2.5	2.2	2.6	2.0
Physicians Global assessment	5.2	1.6	1.9	1.4	1.5	1.3	1.4
Adalimumab, n=64	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.1	0.8	0.9	0.6	0.2		
Active joint count	5.8	1.9	1.3	0.9	0.9		
Limited Joint Count	4.2	2.2	2.1	2.0	1.4		
Pain VAS	4.8	3.9	3.7	2.6	1.8		
Parental VAS	5.0	3.5	3.0	2.6	1.5		
Physicians Global assessment	4.2	1.4	1.4	1.2	1.0		
Abatacept, n=15	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.1	1.1	1.2				
Active joint count	8.9	2.5	2.4				
Limited Joint Count	9.1	6.2	2.				
Pain VAS	3.7	3.3	5.0				
Parental VAS	4.3	3.3	5.3				
Physicians Global assessment	5.7	3.4	2.4				
Tocilizumab, n=19	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.3	13	1.0	11	1.1		
Active joint count	8.9	3.9	9.5	3.1			
Limited Joint Count	7.6	6.5	10.2	7.0			
Pain VAS	5.5	4.0	4.5	4.0	1.8		
Parental VAS	5.2	3.9	4.4	4.9			
Physicians Global assessment	4.2	3.2	3.7	3.4			

The same patient cohort has been analysed by disease subtype and provides further proof of efficacy across all JIA subtypes included in 'Poly-JIA'

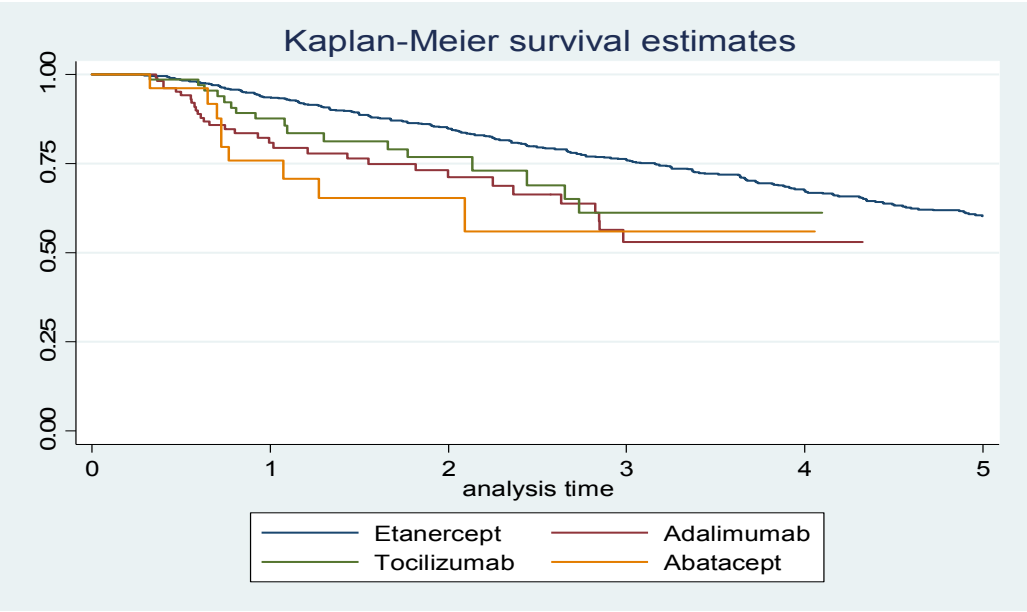
Extended oligo, n=149	Start	6 months	12 months	24 months	36 months	48 months	60 months
CHAQ	1.0	0.6	0.7	0.6	0.3	0.6	0.1
Active joint count	9.9	1.1	1.6	0.8	1.3	1.3	1.2
Limited Joint Count	8.3	2.4	2.5	2.4	2.5	1.6	1.2
Pain VAS	6.4	2.6	2.8	4.0	1.6	6.0	1.6
Parental VAS	6.6	2.2	2.7	2.1	1.3	2.2	1.4
Physicians Global assessment	5.9	1.1	1.3	1.5	0.7	1.4	1.2
Poly (RhF –ve), n=301	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.2	0.8	0.8	0.7	0.7	0.7	0.8
Active joint count	9.9	2.5	2.5	1.6	2.0	2.0	2.7
Limited Joint Count	8.3	4.4	4.0	5.1	5.4	5.1	6.9
Pain VAS	6.4	2.9	3.3	2.9	2.5	2.3	2.5
Parental VAS	6.6	2.8	3.0	2.9	2.2	2.4	2.6
Physicians Global assessment	5.9	2.0	2.2	1.5	1.5	1.3	1.5
Poly (RhF +ve), n=101	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.1	0.7	0.7	0.7	0.9	0.6	
Active joint count	10	2.5	3.2	2.7	3.2	12.3	2.2
Limited Joint Count	8.7	3.7	4.2	4.7	4.7	9.3	8.2
Pain VAS	5.4	2.8	3.1	2.6	4.1	3.6	
Parental VAS	4.9	2.1	2.6	2.5	3.4	4.3	
Physicians Global assessment	5.0	1.9	2.6	1.4	2.7	2.5	
Psoriatic JIA, n=61	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.1	0.8	0.6	0.5	0.6	0.4	
Active joint count	8.0	1.8	5.3	1.5	3.6	4.3	
Limited Joint Count	6.5	3.0	6.9	2.7	5.0	9.4	
Pain VAS	7.4	2.5	3.0	2.3	3.9	2.5	
Parental VAS	6.4	3.9	4.1	1.9	4.0	2.2	
Physicians Global assessment	7.1	1.5	3.0	1.2	2.8	1.2	
ERA, n=75	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.0	0.7	0.5	0.4	0.2	0.2	
Active joint count	5.8	1.6	1.4	2.0	1.3	0.8	
Limited Joint Count	4.0	2.1	1.4	2.6	1.1	0.8	
Pain VAS	5.3	4.8	3.1	2.6	2.9	1.6	
Parental VAS	5.1	4.0	2.5	2.2	2.5	1.3	
Physicians Global assessment	4.4	1.3	1.3	1.4	0.8	0.04	
Undifferentiated JIA, n=45	**Start**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
CHAQ	1.4	1.2	0.6	0.8	0.5	0.6	
Active joint count	10.1	2.2	0.8	1.9	1.5	0.8	2.0
Limited Joint Count	11.6	5.7	5.1	4.0	5.2	2.8	2.9
Pain VAS	4.1	2.6	2.7	2.3	1.9	2.1	
Parental VAS	5.2	2.0	2.1	2.7	1.5	2.9	
Physicians Global assessment	4.6	2.0	1.9	1.8	0.9	0.7	0.8

In addition, there is evidence from the registries to support the use of these biologics in the treatment of SoJIA. There are 88 patients recorded as having been treated with Etanercept, 2 each with Adalimumab and Abatacept, and 44 with Tocilizumab. The overall figures are given below.

	Start	6 months	12 months	24 months	36 months	48 months	60 months
CHAQ	1.1	0.9	0.8	0.8	1.3	0.5	0.8
Active joint count	10.5	2.5	1.5	2	2	0.5	1.5
Limited Joint Count	7.5	6.5	2.9	7.8	3.7	1.3	1.7
Pain VAS	3.4	3.1	2.0	1.8	3.0	2.7	2.5
Parental VAS	3.7	2.8	1.9	3.1	3.3	1.5	2.9
Physicians Global assessment	4.2	2.0	1.3	1.8	2.4	1.0	1.5

The registries have also been analysed to show drug survival data for Poly JIA, however it is important to note that these data cannot be used to compare treatment effects, since they do not take into account patient differences between treatment groups at outset:

	Total	1 Year	2 Years	3 Years	4 Years	5 Years
Etanercept						
Total Patients	674	606	383	286	200	140
Survival (95% CI)		0.99 (0.98, 0.99)	0.86 (0.83, 0.89)	0.77 (0.73, 0.81)	0.68 (0.64, 0.73)	0.60 (0.55, 0.65)
Adalimumab						
Total Patients	55	48	12	6	1	1
Survival (95% CI)		0.92 (0.81, 0.97)	0.70 (0.54, 0.82)	0.51 (0.25, 0.73)	..)	..
Abatacept						
Total Patients	14	14	4	3	2	1
Survival (95% CI)		0.93 (0.59, 0.99)	0.63 (0.27, 0.85)	0.63 (0.27, 0.85)	0.63 (0.27, 0.85)	..
Tocilizumab						
Total Patients	20	19	8	4	2	1
Survival (95% CI)		0.95 (0.68, 0.99)	0.67 (0.38, 0.85)	0.67 (0.38, 0.85)	0.67 (0.38, 0.85)	..



Report compiled by [redacted] and [redacted] on behalf of BSPAR

A similar pattern can again be seen with those patients treated for SoJIA:

	Total	1 Year	2 Years	3 Years	4 Years	5 Years
Etanercept						
Total Patients	88	88	72	60	50	39
Survival (95% CI)		0.97 (0.90, 0.99)	0.79 (0.69, 0.86	0.71 (0.60, 0.79)	0.6 (0.48, 0.69)	0.54 (0.43, 0.64)
Adalimumab						
Total Patients	1	1	1	0	0	0
Survival (95% CI)						
Abatacept						
Total Patients	2	2	2	1	1	1
Survival (95% CI)						
Tocilizumab						
Total Patients	38	33	18	9	3	1
Survival (95% CI)		0.94 (0.78, 0.99)	0.87 (0.68, 0.95)	0.66 (0.39, 0.83)	0.66 (0.39 (0.83)	

Conclusion

We believe the data given from these national registries, and the emerging cohort data international endorse the clinical experience we have, namely that these biologics are essential in the management of polyarticular course JIA. Without them the quality of life of children and young people suffering from these diseases would be significantly diminished and their engagement in education and subsequent social and economic contribution in adult life severely curtailed.

Acknowledgements
BSPAR would like to acknowledge, with grateful thanks, the data supplied from the BCRD and BECS registries by [redacted] and xxxxxxxxxxxx
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Appendix B and C (sent as separate e-mail attachments) are papers that have been submitted for publication from the registries which contain further valuable data analysis of use to this MTA. The authors have given permission to share these in confidence.

Appendix A

NHS England

Interim Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA)

July 2014

Reference: NHS ENGLAND E03/PS/a

Report compiled by [redacted] and [redacted] on behalf of BSPAR

NHS England

Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis

First published: July 2014

Prepared by NHS England Clinical Reference Group for Paediatric Medicine

First published July 2014

Report compiled by [redacted] and [redacted] on behalf of BSPAR

Published by NHS England, in electronic format only.

POLICY STATEMENT: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis	**Policy Ref:** **NHS England** E03/PS/a

Background:	Juvenile Idiopathic Arthritis (JIA) is the commonest rheumatic disease of childhood. It is characterised by relapsing and remitting episodes of inflammation of the synovial membrane of the joints (synovitis) which, unless treated, leads to damage and deformity of the affected joints and subsequent disability. It has an annual incidence of 1:10,000 children and an overall prevalence in childhood of 1:1000. The term Juvenile refers to the *age at onset* and historical data suggests that around half of children with JIA continue to have active arthritis as adults [(1)]. • Estimated 12,000,000 children <18yrs in England and Wales • At any one time there are >12,000 children with JIA • Estimated half of these will go on to have arthritis in adulthood • Estimated 1 in 3 will not have arthritis in adulthood but will have sustained permanent damage to one or more joints JIA is not the same as rheumatoid arthritis or other forms of inflammatory arthritis and, although there are similarities with adult forms of arthritis, JIA should be considered separately in both children and adults. JIA is an 'umbrella' term which covers a number of different sub-types listed here: • Oligo-articular JIA • Extended Oligo-articular JIA • Poly-Articular JIA (RF –ve) • Poly-Articular JIA (RF +ve) • Systemic-Onset JIA • Psoriatic JIA • Enthesitis-Related Arthritis In addition there are forms of inflammatory arthritis indistinguishable from JIA, but not listed under the umbrella term 'JIA'. These include: • Arthritis associated with Inflammatory Bowel Diseases (Crohn's and Ulcerative Colitis), • Arthritis found commonly in Downs Syndrome and other similar chromosome disorders. The treatment of these is effectively identical to that of JIA and

	should be included accordingly. Drug therapy is dependent upon the number and type of joints involved, as well as the presence of any extra-articular manifestations. The commonest extra-articular complication of JIA is inflammation of the eye (uveitis). Uveitis may predate the onset of arthritis and can be severe even if the degree of arthritis is of a milder course. Unless treated properly uveitis can rapidly cause irreversible damage to the eye leading to permanent blindness. The aim of drug therapy in patients with JIA is to induce and maintain a complete remission of all symptoms, and thus to allow a child to achieve normal growth, development, and allow full participation in school, career, sport and all other aspects of normal life. The initial aim is induction of complete disease remission using corticosteroids – either intravenously or intra-articular. Oral corticosteroids are avoided where possible to avoid side effects (can affect growth or increase risk of osteoporosis) but may be needed for short periods of time. In patients with mild disease limited to <5 joints it may be possible to induce remission which lasts for >6months with intra-articular steroids, particularly if using the long-acting corticosteroid Triamcinolone Hexacetonide. Patients with more severe disease may need intravenous steroids to induce remission, although intra-articular steroids are used in some patients as an alternative. To maintain remission, those patients whose arthritis affects a cumulative total of 5 or more joints, or severely affecting crucial joints such as the spine, ankles, hips, and wrists, should initially be treated with Methotrexate (MTX). This accounts for around half of all children who develop JIA – i.e. around 6000 children in the UK at any one time. Methotrexate has been the first line Disease-Modifying Anti-Rheumatic Drug (DMARD) for the treatment of JIA for over 30 years. Whilst effective in reducing the amount and severity of arthritis it only induces complete remission in 30-50% of patients. Those with JIA arthritis that remains active despite optimal dosing, or who are intolerant of Methotrexate need treating with a 'Biologic'. The term 'Biologics' refers to a range of relatively new treatments which utilise either monoclonal antibodies, or soluble cytokine receptors, to specifically target individual components of the immune system. Currently all of them need to be given either intravenously or subcutaneously. Many are given in co-administration with MTX to optimise their effect. It is estimated that up to a third of all children who start treatment with MTX need to progress to a biologic. Current data from the biologics Registries and their databases in the UK includes children from all over the UK who are receiving biologics for JIA. According to these databases, 890 children in England alone, are receiving a biologic for JIA; most, but not all, are receiving NICE approved biologics for JIA. Given

	that registration to the database is recommended but not mandatory, it is likely that this number of 890 is an underestimate. We would suggest 950 children with JIA in England to be currently on a biologic treatment as a pragmatic estimate. The purpose of this interim policy statement is to provide guidance for the use of biologics in patients with JIA until the planned NICE guidance is published.
Commissioning position:	**<u>All types of JIA</u>** Treatment pathways for JIA are detailed in Appendix A. Initiation of treatment with DMARDs and Biologics should only be undertaken at a specialist centre within a clinical network, and should always involve a consultant paediatric rheumatologist and a paediatric-trained Clinical Nurse Specialist (CNS). MTX is the first-line DMARD for children with JIA. Biologics should not be used unless a patient is intolerant to, or has failed optimised treatment with MTX; this is defined as 15mg/m^2 given subcutaneously once-weekly for at least 3 months; higher doses have no evidence to suggest increased efficacy [(2)]. For full details see 'Treatment Failure Definition' below. The only exceptions to this would be: • The 1st-line use of Anti-TNF in patients with Axial disease or sacroiliitis (as in Appendix A). This is accepted and NICE-approved practice in adults with Spondyloarthropathy [(3).] • Patients with Systemic-Onset JIA who show signs of Macrophage Activation Syndrome (MAS). This uncommon, but potentially fatal, complication is usually treated with high-dose steroids. Where MAS is severe or steroid resistant, treatment with Anakinra may be life-saving and should not be delayed [(4)] . The Biologic therapy should be initiated by the consultant paediatric rheumatologist following full discussion with the child, carers, and the specialist multidisciplinary team (MDT). The decision will be based primarily on the JIA subtype and will usually follow the flow diagram in Appendix A. However when choosing between individual Anti-TNF drugs, or between biologics for Systemic-Onset JIA, it may be necessary to consider the mode of administration, required dosing frequency, presence of extra-articular complications such as uveitis, adherence and response to previous medications. In the case of Systemic-Onset JIA, the potentially fatal complication of Macrophage Activation Syndrome (MAS) may necessitate the use of Anakinra [(4)], with evidence of this drug being rapidly effective and life saving. All children who commence treatment with a Biologic should be offered the option of enrolling in the appropriate long-term national Registries. These Registries are designed to provide

long-term safety data for all these drugs and enrolment of data to the Registries is strongly recommended

Clinical Trials

It is a fundamental principle that children should have access to participate in clinical trials. The evidence for many of the treatments used in paediatric rheumatology is incomplete and further evidence base to inform clinical practice is needed.

- The suggested pathways in Appendix A should be taken as a guide. Clinical trials may be available in the future, at any of the decision points in those pathways.
- Children and young people from all clinical networks in England should be offered the opportunity to participate in any trial for which they are eligible.
- Ineligibility or inability to participate in clinical trials must not impede a child's access to appropriate care along those pathways.
- At the end of any trial there should be no delay in deciding appropriate future treatment, if ongoing access to the trial drug is not available a suitable alternative must be offered.

Definitions

1. **Definition of 'Response':** Response to therapy should be assessed after 3 months of therapy and re-assessed every 3 months whilst treatment continues. It should document the current status of every synovial joint as either:

    - Active synovitis
    - No active synovitis but decreased range of movement
    - No synovitis and full range of movement

    In addition the presence of absence of extra-articular complications including Psoriasis, Inflammatory Bowel Disease, Uveitis, Fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributed to JIA should be noted.
2. **Definition of 'clinical inactive disease'** [5] (all must be met)

    - No joints with active arthritis
    - No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributed to JIA
    - No active uveitis
    - ESR or CRP level (both if both tested) within normal limits for the laboratory where tested or, if elevated, not attributable to JIA
    - Physician's global assessment of disease activity score as lowest possible on whichever scale is used
    - Duration of morning stiffness ≤15 min

	3. Definition of 'clinical remission on medication' [5] Satisfaction of the definition of clinical inactive disease for at least 6 continuous months while on therapy for JIA. **4. Definition of 'clinical remission off medication'** [5] Satisfaction of the definition of clinical inactive disease for at least 12 continuous months while off all therapy for JIA **5. Treatment failure definition:** • Persistent synovitis in 2 or more joints • Within 12 months; 2 or more separate episodes of corticosteroid use to control flares of disease • Development/worsening of erosive disease due to ongoing synovitis • Intolerance of therapy – including inability to tolerate the injections • Ongoing evidence of active uveitis, even in the presence of quiescent joint disease. **6. Biologic 'Switching'** Patients who do not achieve, or who fail to maintain, good control of their disease will need to switch to an alternative 'Biologic' from the list above. The decision will be based primarily on the JIA subtype and will usually follow the flow diagram in Appendix A. Evidence to support the sequential use of biologics is based on reported use in international Registries [18]; there are no RCTs for sequential use of therapies. The choice between the different anti-TNF agents for JIA is based on clinical factors (presence of, or history of JIA related uveitis), patient factors (history of poor adherence or intolerance of subcutaneous injections, geographical location and distance from day unit centres. The use of Infliximab (given as an intravenous infusion usually on a monthly basis) is often recommended by paediatric rheumatologists if there has been a history of poor adherence or intolerance to subcutaneous injections and there is a history of JIA uveitis. The use of Adalimumab is is often recommended by paediatric rheumatologists if there has been a history of JIA uveitis. Children with ongoing arthritis and who fail anti-TNF agents may be recommended to receive other biologics – Tocilizumab, Abatacept (rheumatoid factor negative (RF-ve) polyarticular JIA, or Rituximab (rheumatoid factor positive (RF+ve) polyarticular JIA). Tocilizumab is NICE approved for Systemic Onset JIA. Anakinra may be recommended by paediatric rheumatologists in children with Systemic Onset JIA and with potentially life threatening Macrophage Activation Syndrome.

	Children who fail to achieve good control with 3 or more different 'Biologics,' consideration should be given to referral to a specialist centre to discuss the options for Bone-Marrow transplantation or Autologous Stem cell rescue.
Effective from:	July 2014
Evidence summary:	**Clinical Efficacy and Safety** Current 'Biologics' and the references detailing their efficacy and safety are listed below: • Tumour Necrosis Factor (TNF) Inhibitors: Etanercept [6, 7], Adalimumab [8] [14], Infliximab [9, 15], Golimumab, Certolizumab. (All types of JIA) • Interleukin-1 Inhibitors: Anakinra [4,10], Rilonacept [4, 11], Canakinumab [4,12] (Systemic-Onset JIA only) • Interleukin-6 Inhibitors: Tocilizumab [4,13, 14, 15] (All types of JIA) • T-cell co-stimulation inhibitors: Abatacept [16] [18] (All types of JIA) • B-cell inhibitors: Rituximab [17] (Poly-Articular RF+ve JIA only) **Poly-articular-course JIA**: High quality randomised, placebo-controlled, double blind trials demonstrate efficacy and safety of Etanercept, Infliximab, Adalimumab, Tocilizumab, and Abatacept. These are summarised in a recent systematic review [18]. The review identified seven RCTs , one each for Etanercept, Infliximab, Adalimumab, Abatacept, and Anakinra, and one each looking at Etanercept or Infliximab as first-line therapies. It found that there was strong evidence to support the efficacy and safety of biologics over the short-term. Long-term data is available for Etanercept, for other treatments it is sparse [18]. • There are no data from comparative trials between different agents or for sequential use of biologics, therefore the suggested treatment pathway in Appendix A is based on the consensus of the British Society for Paediatric and Adolescent Rheumatology Clinical Affairs Committee pending further NICE guidance which is planned. These recommendations are consistent with the recent systematic review [18] **Systemic-Onset JIA:** • High-quality randomised placebo-controlled, double-blind trials demonstrate efficacy and safety of Tocilizumab, Anakinra, and Canakinumab in Systemic-onset JIA. There is no data from comparative studies, but the use

	of all these agents is covered in the recent update by the American College of Rheumatology [4] The following biologics are currently licensed and/or NICE approved: In children: • Licensed and/or NICE approved for - o JIA: Etanercept and Tocilizumab are licensed and approved by NICE for use in children with JIA; o Poly-articular JIA: Etanercept is approved by NICE o Systemic-Onset JIA: Tocilizumab is approved by NICE for Systemic-Onset JIA • Licensed but not NICE approved for- o JIA: Adalimumab, Abatacept, and Canakinumab. In adults: • Licensed and NICE approved o Rituximab, Infliximab, Adalimumab, Certolizumab and Abatacept are licensed and NICE-approved in adults with inflammatory arthritis. • Licensed but not NICE approved o Golimumab is licensed but not currently NICE-approved in adults with inflammatory arthritis o Anakinra is licensed but currently not NICE approved for children with some autoinflammatory syndromes (Cryopinopathies) – Systemic Onset JIA is now regarded as an autoinflammatory syndrome. o Anakinra is licensed but not NICE approved
Equality impact:	Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.
Responsible CRG:	Paediatric Medicine
Mechanism for	Funded in some centres through existing contracts and submitted as part of cost and volume or high cost drugs

Funding:	payments, or through IFRs. The patients on biologic treatments currently (figures from UK registries) suggests 890 children with JIA currently on biologics and not all are NICE approved).
Date Approved by Clinical Priorities Advisory Group	XXXX
Policy review date:	During 2016 or sooner once further guidance from NICE is received.

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Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	New template for version 21012014	Cut and pasted into new template	21/03/14	[redacted]
2				
3				
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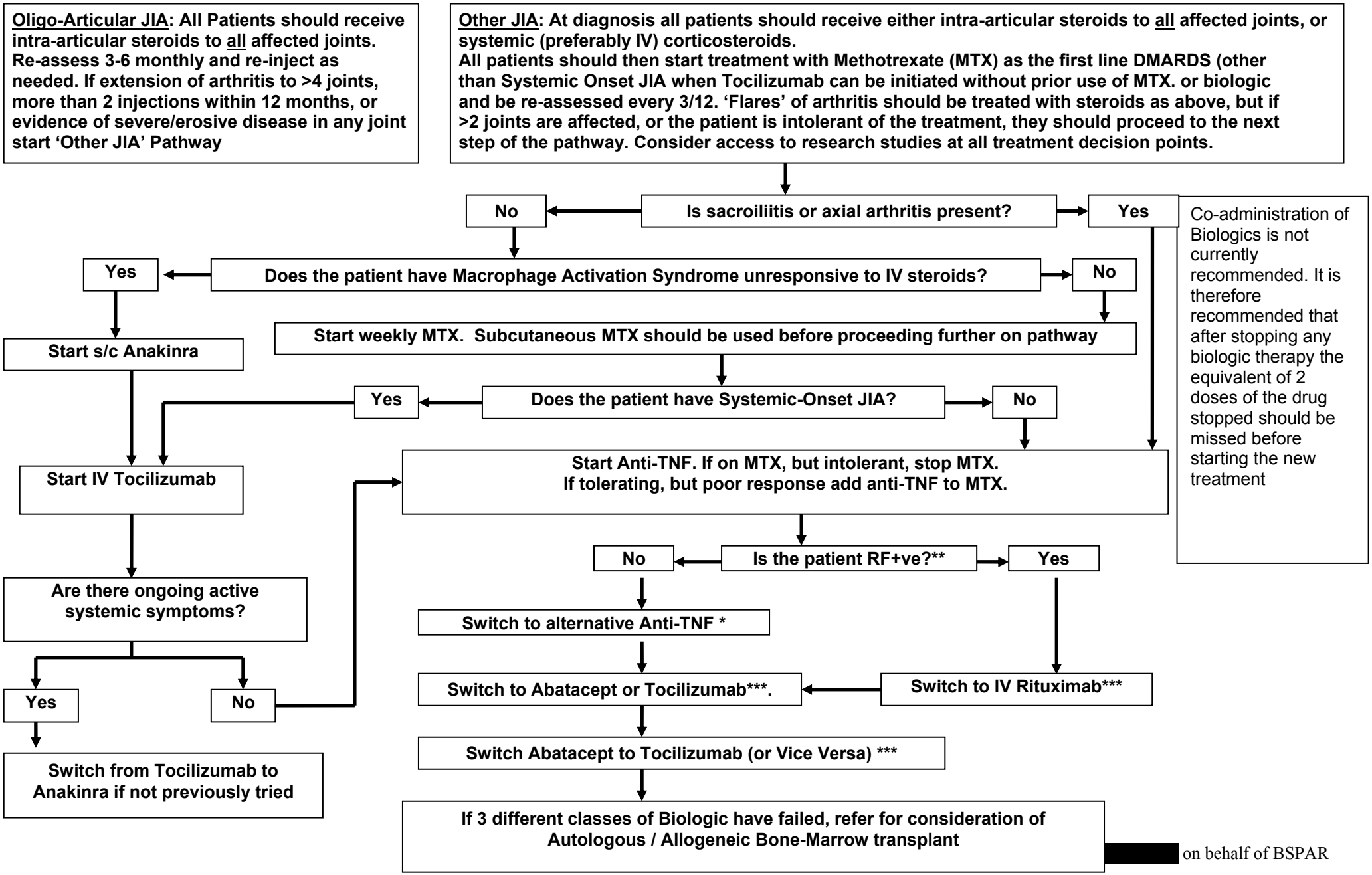
Report compiled by [redacted] and [redacted] on behalf of BSPAR

Appendix A: Suggested Treatment Flow-chart for JIA



Notes on the Pathway:

- *- Etanercept is the usual first choice for JIA. It is licensed and approved by NICE. However there is increasing evidence that it should not be used in children with Chronic Anterior Uveitis as it has been associated with severe, and even sight-threatening worsening of uveitis. In those circumstances Adalimumab would be the usual first-choice as it has the best evidence for efficacy in uveitis as well as JIA and is currently the focus of a multi-centre trial. Infliximab also has some evidence of effectiveness against uveitis, but has a higher risk of infusion-related reactions and is more expensive. It would normally be considered as an alternative to either Etanercept or Adalimumab only when adherence to Etanercept or Adalimumab is suspected to be poor or when treatment with Adalimumab has not proven efficacious in a child with Uveitis and Arthritis

- ** - NICE guidance in adults with Rheumatoid Arthritis, of which RhF +ve Poly-Articular JIA is usually considered to be analogous, suggests Rituximab should be used after failure of any anti-TNF treatment. Usual practice in other forms of JIA would be a trial of an alternative Anti-TNF before proceeding further along the pathway.

- *** - Abatacept and Tocilizumab both have good evidence to back their use in Poly-articular forms of JIA which have failed anti-TNF therapy but there is no head to head comparative trial to assess effectiveness. Tocilizumab appears to have a faster onset of action than Abatacept and therefore may be preferred in cases where arthritis is widespread and erosive. However Tocilizumab has been associated with liver function abnormalities, and appears in clinical practice to have a greater risk of infections being under-recognised by medical staff due to its effect on suppressing both the symptoms of fever and measurement of CRP. The choice of which to use should therefore be at the discretion of the paediatric Rheumatologist. A patient should fail 3 different classes of biologic before being referred for bone-marrow transplantation