Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

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Protocol

1. Title of the project

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis

2. Name of TAR team and 'lead'

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3. Plain English Summary

Juvenile idiopathic arthritis (JIA) is an inflammation of the joints (arthritis) that begins in people under 16 years of age (juvenile) where the cause or trigger is uncertain or unknown (idiopathic). JIA lasts for at least six weeks and causes inflammation, pain, stiffness and swelling of the affected joints. There are several different forms of JIA characterised by the number of affected joints or associated features. Several forms of JIA also cause eye inflammation. This review will include the following forms of JIA: extended oligoarticular JIA (at the start 4 or fewer joints are affected, but after 6 months 5 or more joints become affected); polyarticular JIA (5 or more joints are affected); enthesitis related arthritis (as well as joint inflammation the arthritis is associated with inflammation of the points of insertion of tendons into bones, these insertion points are called entheses); psoriatic arthritis (associated with psoriasis which is a flaky skin condition in the patient or a close relative); undifferentiated arthritis (arthritis that does not fit into any other JIA category, or that fits into more than one). Two forms of JIA are not included in this assessment, oligoarthritis (4 or fewer joints affected) and systemic JIA (arthritis associated with regular fevers and a rash).

The aim of JIA treatment is to achieve complete absence of disease by controlling inflammation and joint pain, reducing the number of affected joints, preventing long term damage and improving quality of life. Treatment typically follows a stepped approach that begins with a non-steroidal anti-inflammatory drug (e.g. ibuprofen) taken to help reduce joint pain and stiffness. Individual joints may be treated by injecting a steroid directly into the joint and steroid tablets may be needed to improve symptoms particularly if the specific type of JIA affects other parts of the body. If these treatments do not provide adequate control then a disease modifying anti-rheumatic drug (DMARD), commonly methotrexate, is used. If an adequate response is not achieved with methotrexate one of several biological therapies may be offered. Biological therapies help to control JIA by modifying the body's inflammatory response.

The aim of this review is to assess the available studies on four different biological therapies (abatacept, adalimumab, etanercept and tocilizumab) to enable the National Institute for Health and Care Excellence (NICE) to make evidence-informed policy recommendations for the treatment of specific subtypes of JIA. In addition, an overall estimate will be made of the benefit to patients in relation to how much each treatment option costs, taking into account any effect on patients' quality of life. This will allow NICE to determine whether each treatment option represents an efficient use of health service money.

4. Decision problem

The aim of this multiple technology appraisal (MTA) is to assess the clinical and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. This will be conducted through systematic review and economic evaluation. An appraisal of etanercept for this condition was conducted in 2002 (NICE TA35).[1] This MTA is a review of that appraisal to incorporate changes to the licence indication for etanercept, and to include three newer licenced drugs.

4.1 Background

Juvenile idiopathic arthritis (JIA) is an umbrella term that encompasses all forms of arthritis with onset before the age of 16 years and symptoms that persist for more than 6 weeks for which the cause is unknown.[2, 3] A recent (2014) systematic review of the prevalence and incidence of JIA in Europe[4] found that rates varied greatly among published studies. Incidence rates ranged from 1.6 to 23 per 100,000 (33 studies) and prevalence rates from 3.8 to 400 per 100,000 (29 studies). The estimated annual incidence of JIA in England 1989-1991 was 11 per 100,000.[5] Prevalence in the UK has not been estimated since 1959 when a

figure of 65 per 100,000 was reported.[5] The Children's Chronic Arthritis Association website states that annual incidence is approximately 1 per 10,000 (i.e. 10 per 100,000) and prevalence is about 1 per 1,000 (i.e. 1000 per 1,000,000),[6] but the sources of these data are not given.

At onset the particular sub-type of JIA will be diagnosed according to the presenting features as either oligoarthritis, polyarthritis, enthesitis-related JIA, psoriatic arthritis, systemic-onset JIA, or undifferentiated arthritis where the type of arthritis does not fit in any of the categories, or fits more than one (Table 1).

Table 1 Sub-types of JIA diagnosed at disease onset

JIA onset type & features[7-12]
Oligoarthritis • The most common type of JIA • Usually starts before 6 years of age and more common in girls than boys • Affects 4 or fewer joints in the first 6 months, most commonly one or both knees and/or ankles, which are swollen and may be painful • Regular checks for chronic anterior uveitis (painless eye inflammation) required
Polyarthritis • The second most common type of JIA affecting about 1 in 4 children with arthritis • Usually starts either before 7 years of age or later in childhood • Causes painful swelling of 5 or more joints in multiple sites. The same joints on both sides of the body will often be affected. • Either rheumatoid factor (RF) positive or negative. RF negative is the most common form. RF positive subtype is more often seen in teenage girls. • Associated with chronic uveitis (painless eye inflammation)
Enthesitis-related JIA • Affects the entheses (sites where tendon attaches to bone) often of lower limb and pelvic joints as well as the joints themselves (spine or peripheral joints). • Can affect girls and boys although teenage onset disease mainly affects boys. • Associated with acute uveitis (red painful eye)
Psoriatic arthritis • Joint pain associated with the skin condition psoriasis (although the typical rash of psoriasis may not occur until many years after the onset of arthritis) or with a family history of psoriasis. Typically affects finger and toe joints. • Usually starts around 6 years of age and about twice as common in girls as in boys.

• Chronic anterior uveitis is fairly common.
Systemic-onset JIA • The rarest type of JIA affecting fewer than 1 in 10 children with arthritis. • Usually starts before 5 years of age and affects boys and girls about equally • General illness with fever, tiredness, rash, loss of appetite and weight loss as well as joint pain. May also have enlarged glands, spleen and liver. More rarely pericarditis (inflammation of sac surrounding the heart)
Undifferentiated arthritis • JIA that does not fit into any of the above categories or that has features of more than one.

As JIA progresses more joints may become affected. For some whose JIA was classified at onset as oligoarthritis, problems with 5 or more joints develop after 6 months and the JIA type is then described as extended oligoarthritis. Similarly, JIA may be described as having a polyarticular course when after 6 or more months 5 or more joints are affected. The concept of polyarticular course JIA has been used for clinical trials which can typically include RF positive and RF negative polyarthritis, extended oligoarthritis, enthesitis-related JIA, psoriatic arthritis and undifferentiated arthritis. Systemic JIA may also be included providing there have been no active systemic symptoms during the previous 6 months.[13]

The long term outlook for JIA varies by JIA subtype (Table 2). In general outcomes for all types of JIA have improved with recent treatment advances.

Table 2 Long term outcomes for different sub-types of JIA

Long-term outcome[7-12]
Persistent oligoarthritis • Often mild and may resolve with little or no lasting damage to joints, has the best outlook of all the types of JIA. • Approximately half of children will have symptoms for at least 10 years, a third or more of children will have arthritis continuing into adulthood. • Chronic anterior uveitis may cause blindness if not detected and treated early enough.
Extended oligoarthritis • Causes damage to joints so early treatment to minimise this is needed.
Polyarthritis • Approximately half of children will have symptoms for at least 10 years and at least one third of children will have arthritis continuing into adulthood (most likely with the RF

positive type, which is more aggressive and can require more aggressive treatment). • Joints may become damaged if inflammation is not controlled, leading to potential need for joint replacement.
Enthesitis-related JIA • May evolve to ankylosing spondylitis in the adult years and may require long term disease modifying or biologic agents.
Psoriatic arthritis Although there is not much long term data, disease course may be similar to chronic arthritis (either oligoarthritis or polyarthritis) and is likely to continue into adulthood.
Systemic-onset JIA • A third of children will have one or two episodes that settle with treatment, a third will have relapses and need intermittent treatment, a third require ongoing treatment into adulthood and are at risk of joint damage.
Undifferentiated arthritis Although there is not much long term data clinical advisors indicate that the long-term outcome is likely to depend on the predominant features of the arthritis and whether persistent oligoarthritis or polyarticular course arthritis.

The aim of JIA treatment is to achieve clinical remission (complete absence of active disease). Aggressive early treatment aims to control inflammation and thus symptoms (e.g. joint pain); to decrease the number of actively affected joints preventing joint damage, loss of function and disability; and to maintain or improve quality of life. Response to treatment is assessed in clinical trials by a validated core set of variables that were adopted by the American College of Rheumatology (ACR) in 1997 and are now known as the ACR Pediatric 30.[14] The ACR Pediatric 30 core variables are:

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

Response is defined as an improvement in three of any six of the core variables by at least 30%, and no more than one of the remaining variables worsened by more than 30%. In addition to the ACR Pediatric 30, higher levels of response can also be defined - the ACR Pediatric 50, 70, 90 and 100 levels of response require at least 50%, 70%, 90% or 100% improvement respectively in at least three of any six of the core set variables, with no more than one of the remaining variables worsening by more than 30%.[13, 15]

More recently in 2009 the Juvenile Arthritis Disease Activity Score (JADAS) was proposed and validated.[16] The JADAS is a composite score that can be quickly calculated because it is the arithmetic sum of the scores from the following four individual component measures:

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

The component measures are also measures used in the ACR Pediatric 30.[14]

The count of joints with active disease in the JADAS is primarily based on a 27-reduced joint count (JADAS-27, total score range 0-57) although scores based on a full 72 joint count (JADAS-72, total score range 0-101) and a 10 joint count (JADAS-10, total score range 0-40) have also been validated.[16] Further studies have shown that a 3-item JADAS that does not use ESR data is also a robust measure[17, 18] which is of particular benefit for children who do not need to provide a blood sample for routine medication monitoring. As the JADAS has become more widely used further proposals have been made that would define low, medium and high disease activity[18, 19] and define improvement.[20] With these definitions in place the future management goal would be to achieve minimal disease activity (MDA) for all children with JIA.[21]

Preliminary criteria to define clinical remission in oligoarticular (persistent and extended), RF positive and RF negative polyarticular, and systemic JIA have also been developed.[22] Two levels of clinical remission have been proposed, clinical remission on medication and clinical medication off medication. The criteria for both types of clinical remission are based on achieving inactive disease, which is defined as:

- no joints with active arthritis
- no fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA

- no active uveitis
- normal ESR or CRP (or both normal if both tested)
- physician's global assessment of disease activity indicates no disease activity

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

Since the original publication of the preliminary criteria to define clinical remission,[22] validation of the criteria for defining clinical inactive disease in oligoarticular (persistent and extended), polyarticular (RF positive and RF negative) and systemic JIA has been undertaken. This has led to three changes: the addition of a definition for no active uveitis [as defined by the Standardization of Uveitis Nomenclature (SUN) Working Group]; clarification that the ESR or CRP level should be within the normal limits in the laboratory where tested or, if elevated, not attributable to JIA; and one additional criterion (duration of morning stiffness of 15 minutes or less).[23]

In addition to definitions of response to treatment and clinical remission some publications also report on the outcome of disease flare (periods when symptoms worsen). A preliminary definition based on the ACR Pediatric 30 core response variables was obtained from single small study (n=51).[24] This preliminary definition was worsening in any 2/6 core response variables by 40% or more without concomitant improvement of more than one of the remaining core response variables by 30% or more. However, other studies have used different flare definitions e.g. a worsening of ≥30% in 3 of 6 ACR Pediatric 30 variables.[25]

4.2 Definition of the intervention

Four biologic disease modifying anti-rheumatic drugs (DMARDs) for the treatment of JIA are being considered in this MTA: abatacept, adalimumab, etanercept and tocilizumab.

Abatacept

Abatacept (trade name Orencia®; Bristol-Myers Squibb) is a fusion protein produced by recombinant DNA technology in Chinese hamster ovary cells. It inhibits T-cell activation by specifically binding to CD80 and CD86 thereby selectively inhibiting a costimulatory pathway that is required for full activation of T lymphocytes.[26, 27] Through this mechanism,

abatacept modulates the downstream T lymphocyte-dependent antibody responses and inflammation that cause the symptoms of JIA.

Product information[27] states that abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular JIA in paediatric patients 6 years of age and older, who have had an insufficient response to other disease modifying anti-rheumatic drugs (DMARDs) including at least one tumour necrosis factor (TNF) inhibitor. (The European Marketing Authorisation (EMA) therapeutic indication for abatacept was extended in 2010).

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA. The recommended dose of abatacept for patients 6 to 17 years of age with JIA who weigh less than 75kg is 10mg/kg calculated based on the patient's body weight at each administration. Dosing for paediatric patients weighing 75kg or more follows that of adults (body weight ≥ 60 kg to ≤ 100 kg c750mg, body weight > 100kg 1,000mg, dose not to exceed a maximum of 1,000mg). Abatacept is administered as an intravenous infusion given during a period of 30 minutes. The second and third infusions should be given at 2 and 4 weeks after the first infusion with subsequent infusions every 4 weeks thereafter.

Abatacept product information states that if a response to abatacept is not present within 6 months of treatment, the continuation of the treatment should be reconsidered. Abatacept is not recommended in combination with TNF-inhibitors.[27]

Adalimumab

Adalimumab (trade name Humira®; AbbVie) is a fully human monoclonal antibody drug initially tested as a treatment for rheumatoid arthritis (hence the trade name Humira - **HU**man **M**onoclonal antibody **I**n **R**heumatoid **A**rthritis). It binds specifically to the inflammatory cytokine TNF thereby neutralising its biological function[28] and modifying the inflammatory disease process. The EMA therapeutic indication for adalimumab was extended to the treatment of JIA in July 2008.

Product information[28] states that adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular JIA in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Adalimumab can be given as monotherapy in the case of intolerance to methotrexate or when continued methotrexate treatment is inappropriate. Adalimumab is also indicated for the treatment of active enthesitis-related

arthritis in patients 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of JIA and patients treated with adalimumab should be given the special alert card. The recommended dose of adalimumab for patients 2 to 12 years of age with polyarticular JIA is 24mg/m^2 body surface area up to a maximum single dose of 20mg adalimumab (for patients aged 2 to <4 years) and up to a maximum single dose of 40mg adalimumab (for patients 4 to 12 years). Adalimumab is administered as a subcutaneous injection given every other week (volume for injection is selected from a chart based on patient height and weight). The dose of adalimumab for patients from 13 years of age is 40mg administered every other week regardless of body surface area.

Adalimumab product information states that a clinical response is usually achieved within 12 weeks of treatment and that continued therapy should be carefully reconsidered in a patient not responding within this time period.

For patients with enthesitis-related arthritis aged 6 years older the recommended dose of adalimumab is 24mg/m^2 body surface area up to a maximum single dose of 40mg administered as a subcutaneous injection given every other week (volume for injection is selected from a chart based on patient height and weight).[28]

The concomitant administration of Adalimumab with other biologic DMARDs (e.g. anakinra and abatacept) or other TNF-antagonists is not recommended.[28]

Etanercept

Etanercept (trade name Enbrel®; Pfizer) is a fully humanised soluble TNF receptor, a dimeric fusion protein with two copies of the extracellular domain of TNF receptor (p75) linked with the Fc component of human IgG1, binding to TNFa.[29] The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g. cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.[30]

The EMA therapeutic indication for etanercept in the treatment of JIA was extended in July 2012. Product information[30] states that etanercept is used for certain forms of JIA: patients aged from 2 years who have polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis and have not responded adequately to or cannot take methotrexate;

adolescents aged from 12 years who have psoriatic arthritis and have not responded adequately to or cannot take methotrexate; and adolescents aged from 12 years who have enthesitis-related arthritis and have not responded adequately to or cannot take standard treatment.

Etanercept is supplied as a single-use prefilled syringe (25 and 50 mg), single-use auto-injector (50 mg) or a lyophilized powder (10 and 25 mg) for reconstitution and absorbed slowly reaching peak concentrations 2 or 3 days after administration.[29] The recommended dose for JIA is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.[30] Discontinuation of treatment should be considered in patients who show no response after 4 months. No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating etanercept therapy.[30]

Limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older when dosed every week with 0.8 mg/kg subcutaneously, but no formal clinical trials have been conducted in children of this age.[30] There is generally no applicable use of etanercept in children aged below 2 years in the indication for JIA.

Treatment with etanercept may result in the formation of autoimmune antibodies.[30] Due to the risk of sepsis, treatment with etanercept should not be initiated in patients with active infections, including chronic or localised infections.

The combined use of etanercept and anakinra or etanercept and abatacept is not recommended. The long-term safety of etanercept in combination with other DMARDs has not been established but clinical advice indicates that, where possible, methotrexate is given with etanercept as data from adults indicates that the combination is more effective than using the anti-TNF alone. Caution should be used when considering combining etanercept therapy with sulfasalazine.

Tocilizumab

Tocilizumab (trade name RoActemra®; Roche) is a humanised, monoclonal, antihuman Interleukin-6 receptor (IL-6R) antibody that binds to membrane and soluble IL-6R, inhibiting IL-6–mediated signalling - a key cytokine in rheumatoid arthritis pathogenesis.[31] This messenger is involved in causing inflammation and is found at high levels in patients with rheumatoid arthritis, systemic JIA and polyarticular JIA. By preventing IL-6 attaching to its receptors, tocilizumab reduces the inflammation and other symptoms of these diseases.[32] The EMA was granted for tocilizumab in the treatment of JIA in May 2011.

Product information[32] states that in children from two years of age, tocilizumab is used to treat two childhood arthritis conditions, active systemic JIA and JIP (rheumatoid factor positive or negative, and extended oligoarthritis). It is given by infusion in patients who have not responded to other treatments (NSAIDs and corticosteroids) and used in combination with methotrexate, but can be used on its own in patients for whom methotrexate is inappropriate. Tocilizumab is available as a concentrate that is made up into a solution for infusion to be given intravenously, and as a solution for injection to be given subcutaneously in a pre-filled syringe. In JIP, tocilizumab is given as a 1-hour intravenous infusion once every four weeks at a dose of 8 mg per kilogram body weight in children weighing 30 kg or more, or 10 mg per kilogram body weight in children weighing less than 30 kg. If no improvement is seen after twelve weeks it may be appropriate to discontinue treatment.

The dose of tocilizumab or methotrexate may need to be adjusted or treatment interrupted in patients who develop liver or blood problems. Doctors should monitor kidney function carefully in patients with moderately or severely reduced kidney function. Patients who receive tocilizumab should be given a special alert card that summarises the safety information about the medicine and the company must supply all doctors expected to prescribe the medicine with an educational pack containing important information tailored to the needs of doctors, nurses and patients on the safety and correct use of tocilizumab.

The Summary of Product Characteristics (SPCs) for each of the four biologic DMARDs included in the review do not explicitly specify licenced upper age limits for treatment. Clinical advisors have indicated that if adolescents are responding to treatment then this should be continued into adulthood. Furthermore, some JIA patients may need to re-start a biologic DMARD in adulthood and some JIA patients may require a biologic DMARD for the first time in adulthood.

4.3 Place of the intervention in the treatment pathway(s)

The 4 intervention drugs within the scope of this MTA are classified as biological DMARDs, as they target pro-inflammatory cytokines that are involved in joint destruction, in particular TNF-alpha and Interlukin-1.[33, 34] Biological DMARDs are generally only used when standard treatment with NSAIDs, corticosteroids and methotrexate has not worked.[35]

There is currently no NICE guidance on the use of abatacept or adalimumab for the treatment of JIA. Single technology appraisals for both of these drugs were discontinued in 2010 and 2011 respectively following discussions with the Department of Health. In both cases the STAs were discontinued because the marketing authorisations suggested there would be limited use of each drug in a small population of those with JIA.

NICE guidance (TA35, published in 2002)[1] recommends etanercept for children aged 4 to 17 years with active polyarticular-course JIA in cases where the condition has not responded adequately to, or who have proved intolerant of, methotrexate. Treatment should be withdrawn in the event of severe drug-related toxicity or because of lack of response at 6 months. The guidance stated that there was no evidence to support treatment beyond 2 years, with continuation of therapy being contingent upon ongoing monitoring of disease activity and clinical effectiveness in individual cases.[1] The licensed therapeutic indication for etanercept has since changed and is now broader than that covered this guidance. In addition to active polyarticular JIA, etanercept is now licensed for extended oligoarthritis (from the age of 2 years), psoriatic arthritis (from the age of 12 years) and enthesitis-related arthritis (from the age of 12 years). The lower age range for treating polyarticular disease has been reduced from 4 to 2 years and the marketing authorisation no longer specify an upper age limit of 17 in the therapeutic indications section of the SPC.[30]

NICE guidance (TA238) recommends tocilizumab for the treatment of systemic JIA in children and young people ≥2 years, whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate. Tocilizumab is not recommended in cases where the disease continues to respond to methotrexate or in cases not previously treated with methotrexate.[36]

4.4 Comparator(s)

NICE clinical guidance recommends that drug treatment for JIA involves, sequentially, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular, intravenous or oral corticosteroids for the management of systemic complications, and DMARDs.[1] However,

such a sequential stepwise approach may no longer be followed. Current practice aims to address the underlying inflammation with use of corticosteroids (route dependent on clinical scenario), early or concomitant commencement of a non-biologic DMARD (typically methotrexate), and early (e.g. after 3 months) step-up to a biologic DMARD. NSAIDs approved for children such as tolmetin, naproxen, meloxicam and ibuprofen can help to reduce pain, stiffness and swelling. Oral corticosteroids such as prednisolone are used and the non-biological (or synthetic[33]) DMARDs[35] that is almost exclusively used is methotrexate. Alternative non-biological DMARDs include sulphasalazine or leflunomide.

DMARDs dampen down inflammation and slow or stop disease progression, reducing the risk of permanent structural joint damage.[37] They act by different mechanisms against inflammation[38] and have different side-effect profiles that can complicate treatment. These drugs are slow to take effect and benefits may not be noticed for several months.[39] Methotrexate, a non-biological DMARD, is commonly used in the treatment of children with JIA and is often started in conjunction with NSAIDs or corticosteroids which are used as a bridging therapy until the methotrexate takes effect and then they are usually stopped. Clinical advisors have indicated that methotrexate can be and is often used long-term (for 2-3 years) if tolerated for that length of time. A trial withdrawal of methotrexate would then be undertaken with methotrexate being restarted as soon as possible if a disease flare occurs. No upper limit has been put on the length of methotrexate so in some cases patients can be on treatment for many years although there are concerns regarding the long term risk of malignancy in comparison to no treatment or treatment with biologic DMARDs.

Although methotrexate is widely used in the treatment of JIA oral and intravenous methotrexate are not licensed for JIA in the UK.[40] 'Metoject' methotrexate pre-filled syringes (50mg/ml - 1 pre-filled syringe of 0.15 ml contains 7.5 mg methotrexate) were licensed in August 2013 for the treatment of polyarthritic forms of severe, active JIA when the response to NSAIDs has been inadequate. Dosage in children and adolescents below 16 years with polyarthritic forms of JIA is 10 - 15 mg/m² body surface area (BSA)/once weekly. Product information[41] states that in therapy-refractory cases, the weekly dosage may be increased up to 20 mg/m^2 body surface area/once weekly, but an increased monitoring frequency is indicated if the dose is increased. Due to limited data availability about intravenous use in children and adolescents, parenteral administration may be commonly by subcutaneous injection.[41] Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population. Side-effects of nausea with methotrexate is common and often treatment limiting but serious side effects are rare. Monitoring with regular blood tests is needed.

Table 3 Summary of recommendations for medication safety monitoring by the American College of Rheumatology[42]

Non-steroidal anti-inflammatory drugs (NSAIDs)	Complete blood cell count, liver enzymes, serum creatinine • Prior to or soon after initiation of routine use • Repeat approximately twice yearly for chronic daily use • Repeat approximately once yearly for routine use (3-4 days per week)
Methotrexate	Complete blood cell count, liver enzymes, serum creatinine • Prior to initiation • Approximately 1 month after initiation • Approximately 1–2 months after increase in dose • Repeat approximately every 3–4 months if prior results normal and dose stable
Tumour Necrosis Factor α Inhibitors	Complete blood cell count, liver enzymes, serum creatinine • Prior to initiation • Repeat approximately every 3–6 months Tuberculosis screening • Prior to initiation

Non-biologic DMARDs can be prescribed in a continuous approach (≥2 DMARDs combined for prolonged use) or a step-up approach (starting with a single DMARD and if found inadequate, additional DMARDs are included). In the step-down approach, several DMARDs are included at the early stage, followed by removal of either the most toxic or most expensive agent once the treatment goal is reached.[38, 43] However, up-to-date guidelines are currently lacking and treatment is changing rapidly.[15] Evidence now suggests a more aggressive approach to control the disease, with earlier introduction of DMARDs to prevent or minimise long term sequelae of the disease, but existing guidelines have not been revised to include such advice.[15] The prompt use of DMARDs and biologics may reduce the need to use steroids.

As noted above the most commonly non-biological DMARD used in practice is methotrexate. Other biological DMARDs that may be used in the UK for the patient groups under consideration in this review include infliximab and rituximab. Infliximab is particularly used (as a 1st, 2nd or 3rd line therapy) for those with compliance issues (because it is given intravenously in hospital) or who are unable to tolerate subcutaneous injections. It is also

used for children with uveitis. Rituximab is used second line for refractory polyarticular JIA, those with RF+ve disease or refractory uveitis.

4.5 Population and relevant subgroups

The population of patients included within this assessment are people with juvenile arthritis diagnosed either at onset as polyarthritis (RF positive and RF negative) or those with extended oligoarthritis, and those with other forms of polyarticular course arthritis e.g. enthesitis-related JIA, psoriatic arthritis or undifferentiated arthritis. Included drug interventions will be considered only within their licenced indications and therefore the age of the people included in this assessment may vary by intervention because of differences in the licenced indications. People with active systemic arthritis are excluded from the assessment. However, as described above (Section 4.1), providing there have been no active systemic symptoms during the previous 6 months, some people diagnosed initially with systemic JIA may be included within the definition of polyarticular course arthritis. People with JIA and uveitis are also relevant.

4.6 Key factors to be addressed

As specified in the NICE scope, the following outcome measures are included in the decision problem:

- disease activity
- disease flares
- physical function
- joint damage
- pain
- corticosteroid reducing regimens
- extra-articular manifestations (e.g. uveitis)
- body weight and height
- mortality
- adverse effects of treatment
- health-related quality of life
- cost-effectiveness

Biosimilars have not been included as comparators in the NICE scope because it was not expected that they would be in established NHS practice at the time of the appraisal.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify all relevant clinical effectiveness studies of etanercept, abatacept, adalimumab and tocilizumab for juvenile idiopathic arthritis. Separate searches will be conducted for the economic evaluation section of the MTA as described below (Section 6.1).

A draft search strategy for Medline is shown in Appendix 10.2. This will be adapted for other databases. The following databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); Medline In-Process and Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); Zetoc (Mimas); NIHR-Clinical Research Network Portfolio; Clinical Trials.gov, Current Controlled Trials and WHO ICTRP (international clinical trials research platform).

Bibliographies of related papers will be assessed for relevant studies where possible. The company's submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Members of our advisory group will be contacted to identify additional published and unpublished evidence. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager software.

All databases will be searched from inception to the present. Searches will be restricted to the English language. All searches will be updated when the draft report is under review, prior to submission of the final report to NICE.

5.2 Inclusion and exclusion criteria

Interventions	• etanercept • abatacept (with or without methotrexate) • adalimumab (with or without methotrexate) • tocilizumab (with or without methotrexate)

	Only data for the drugs evaluated within their licensed indication will be included. Studies of treatment without methotrexate are permitted where patients are intolerant to methotrexate or for whom treatment with methotrexate is inappropriate.
Participants	People with juvenile idiopathic arthritis: • polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course) • enthesitis related arthritis • psoriatic arthritis. Studies of patients with systemic JIA will not be included as this is the subject of a separate NICE appraisal
Comparator	• Disease modifying anti-rheumatic drugs (DMARDs) (such as methotrexate which is the most common conventional treatment in the UK), if DMARDs can be tolerated • Best supportive care, if DMARDs are not tolerated • Etanercept, abatacept, adalimumab and tocilizumab will be compared with each other within their licensed indications where appropriate and where data allow.
Outcomes	Studies reporting one or more of the following outcomes will be included: • Disease activity • Disease flares • Physical function • Joint damage • Pain • Corticosteroid reducing regimens • Extra-articular manifestations (such as uveitis) • Body weight and height • Mortality • Adverse effects of treatment • Health-related quality of life
Design	Randomised Controlled Trials will be prioritised for inclusion. Where data for outcomes are not available from RCTs (e.g. long term adverse events; height and growth) then non-randomised studies will be considered for inclusion.

	Studies detailed in abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken, and if published between 2012 and the present. Systematic reviews will be used as a source of references only. Non-English language studies will be excluded.

5.3 Screening and data extraction process

Reference screening

Studies will be selected for inclusion through a two-stage process. The titles and abstracts of studies identified by the search strategy will be screened independently by two reviewers to identify all citations that potentially meet the inclusion/exclusion criteria detailed above. Full manuscripts of studies which appear potentially relevant will be obtained. These will be screened by one reviewer and checked by a second and a final decision regarding inclusion will be agreed. At each stage any disagreements will be resolved by discussion, with the involvement of a third reviewer when necessary.

Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 10.2) and will be checked for accuracy by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.4 Quality assessment strategy

Studies will be critically appraised using the Cochrane Risk of Bias criteria (e.g. selection bias, detection bias, performance bias, attrition bias, and selective reporting bias).[44] Aspects of study quality including statistical procedures, outcome measurement and generalisability will also be assessed. Critical appraisal of the individual studies will be assessed by one reviewer and checked by a second reviewer with any disagreements resolved by consensus and involvement of a third reviewer where necessary. The quality assessment strategy for cost-effectiveness studies is provided in section 6.1

5.5 Methods of data analysis/synthesis of clinical effectiveness data

Clinical effectiveness data will be synthesised through narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity the results from individual studies will be synthesised through meta-analysis to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate it will be performed

using specialised software such as Cochrane Review Manager 5 (RevMan) and presented using forest plots and tabular forms. Potential sub-group analyses will be conducted according to type of JIA, age of patients, presence or absence of uveitis, and co-treatment with steroids, where data are available. If direct evidence comparing the biologic DMARDS is lacking, we will consider appropriate methods of indirect comparisons where appropriate and where data are available.[45]

6. Report methods for synthesising evidence of cost-effectiveness

The cost-effectiveness of biologic agents for the treatment of JIA will be assessed through two stages: a systematic review of cost effectiveness studies and the development of a decision analytic economic model.

6.1 Review of published cost-effectiveness studies

The sources detailed in section 5.1 will be used to identify studies of the cost effectiveness of biologic DMARDs for the treatment of JIA. Studies will be included in the systematic review of cost-effectiveness if they are full economic evaluations (cost effectiveness, cost utility, cost benefit or cost consequence analyses) that report both measures of costs and consequences. The methodological quality of included studies will be assessed using accepted criteria for appraising economic evaluations.[46, 47] Studies will be synthesised through a narrative review that includes a detailed critical appraisal of study methods, data and assumptions used in any economic models and tabulation of the results of included studies. Published studies conducted in the UK and adopting an NHS and Personal Social Services (PSS) perspective will be examined in more detail. Stand alone cost analyses based in the UK NHS will also be searched for and will be retained as sources of information on resource use and cost associated with JIA treatment.

Scoping searches have identified two published studies for biological DMARDs for treating JIA[48, 49]. Ungar and colleauges.[49] developed a decision model for etanercept, infliximab, adalimumab and abatacept compared to methotrexate for polyarticular-course JIA patients in Canada. The 1-year model consisted of two 6-month intervals and incorporated the probabilities that patients would either continue with their treatment or switch to another treatment, based on their response at 6 months. The model estimated the cost per additional responder. Prince and colleauges[48] presented the costs and benefits of etanercept in JIA patients in the Netherlands, by comparing results from the Dutch Arthritis and Biologicals in Children register in the 12 months before the start of etanercept treatment and in the 27 months thereafter.

6.2 Evaluation of costs and cost-effectiveness

A *de novo* decision analytic model will be developed to assess the cost effectiveness of biologic DMARDs for JIA. The structure of the model will be designed to reflect important clinical events over the course of the disease and will be informed by existing economic models, identified in the systematic review of economic evaluations, such as that developed by Ungar and colleagues,[49] evidence from our systematic review of clinical effectiveness and through discussion with expert advisors. Modelling will be conducted according to accepted methodology for economic evaluations.[46, 50] The perspective will be the NHS and Personal Social Services (PSS). Costs and benefits will be discounted using standard rates (3.5%).[50] The model will be developed using standard software such as Microsoft Excel. The model will contain a hypothetical cohort of individuals and will estimate the proportion that respond to treatment over time, and the consequent impact on patient quality of life. Key assumptions of this study will be discussed with our clinical and methodological advisors for their appropriateness.

The parameters of the model for the clinical effectiveness of the biologic DMARDs will be informed primarily by the systematic review of clinical effectiveness studies (section 5). Additional targeted searches will be undertaken to identify specific data to populate the model. These will include searches for data on the epidemiology and natural history of JIA; the health related quality of life impacts of disease stages and the adverse effects of treatment; the cost of treatment and health care costs. Where these data cannot be identified through searches, estimates will be based on information supplied by our expert advisory group and others.

The resources necessary for providing the treatments will be estimated from the systematic reviews of clinical and cost effectiveness, and from discussion with expert advisers. Unit costs for these resources will be developed based on data in published sources such as the Unit Costs of Health and Social Care, (PSSRU)[51], British National Formulary[52] and National Reference Costs.[53] Where needed, data on the cost of assessing and treating JIA may be sought from University Hospital Southampton NHS Foundation Trust (UHS), which routinely supplies SHTAC with cost data and clinical expertise. Information on resource use and costs will also be derived from company submissions to NICE, as appropriate.

Health-related quality of life (HRQoL) data, where available, will be extracted from studies identified in our targeted search for quality of life evidence. Studies will be included in the

systematic review if they use a preference-based method, such as EQ-5D in patients with JIA. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources, for example by mapping from a disease-based measure to a utility estimate, such as from PedsQL (Pediatric Quality of Life Inventory) to EQ-5D.[54] The review will assess the quality and relevance of studies identified to the decision problem to select the most appropriate HRQoL study to use in the economic model. Our scoping searches have identified two studies that report HRQoL in patients with JIA using preference-based measures: Prince and colleauges[48] used HUI3 (Health Utilities Index Mark 3) in a Dutch registry study and Hendry and colleauges[54] used EQ-5D in JIA patients with inflammatory joint disease affecting their foot or ankle in a trial of foot care in UK. Clear information on the sources for the utilities will be reported, including detailed information about where patient proxy measures have been used, a justification for the use of the utility source and any potential limitations of the data.

The model will provide a cost-effectiveness analysis, reporting the costs of treatments under consideration in the appraisal and their long term consequences in terms of life years saved and Quality Adjusted Life Years (QALYs) gained and additional costs. Results will be expressed in terms of incremental cost-effectiveness ratios (e.g. incremental costs per QALY gained). Uncertainty in model parameters and structure will be investigated through one way deterministic and probabilistic sensitivity analyses, and scenario analyses where appropriate and feasible. The key variables to be explored will include: treatment effect estimates (i.e. treatment response); treatment costs; health related quality of life. Cost-effectiveness acceptability curves (CEACs) will be generated in any probabilistic sensitivity analysis, to illustrate the probability of the treatment being cost-effective over a range of willingness to pay values.

7. Handling the company submission(s)

All data submitted by the companies will be considered if received by the TAR team no later than 24th March 2015. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data will be highlighted in yellow and underlined.

8. Competing interests of authors

None

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10. Appendices

10.1. Draft search strategy

1 Arthritis, Juvenile/

2 JIA.tw.

3 exp Arthritis/

4 (arthriti* or oligoarthriti* or polyarthriti* or polyarticula*).tw.

5 Rheumatoid Factor/

6 "rheumatoid factor".tw.

7 or/3-6

8 (juvenile* or child* or teen* or adolescen* or youth* or "young person" or "young people" or pediatric* or paediatric*).tw.

9 exp Child/ or Adolescent/

10 7 and (8 or 9)

11 1 or 2 or 10

12 (etanercept or enbrel).mp.

13 (abatacept or orencia).mp.

14 (adalimumab or humira).mp.

15 (tocilizumab or toclizumab or RoActemra).mp.

16 or/12-15

17 11 and 16

18 limit 17 to english language

19 limit 18 to humans

20 (letter or editiorial or comment).pt.

21 19 not 20

10.2. Data extraction form

Reviewer 1: **Date:**	**Reviewer 2:** **Date:**	**Version:**	
Reference and design	**Intervention and Comparator**	**Participants**	**Outcome measures**
Study identifier: *Study acronym:* *Study design:* *Country or countries:* *Number of centres:* *Recruitment dates:* *Funding:*	*Intervention*: *Comparator*: *Other interventions used*:	*Number of randomised participants*: n = *Intervention*, n= *Comparator*, n= *Inclusion criteria*: *Exclusion criteria*:	*Primary outcomes:* *Secondary outcomes:* *Method of assessing outcomes:* *Length of follow-up:*
Baseline characteristics	**Intervention n=**	**Comparator n=**	**Comments**
Results			
Primary Outcome	**Intervention n=**	**Comparator n=**	**p-value**
Comments:			
Secondary Outcomes			
Comments:			
Adverse Events			
Comments:			
Methodological comments • *Allocation to treatment groups*: • *Blinding*: • *Comparability of treatment groups*: • *Method of data analysis*: • *Sample size/power calculation*: • *Attrition/drop-out*:			
General comments • *Generalisability*: • *Outcome measures*: • *Inter-centre variability*: • *Conflict of interests*:			

Quality criteria (Cochrane Collaboration Risk of Bias tool) RCTs[a]

Criteria	Judgement[b]	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other sources of bias		

[a]For other study designs, an appropriate method for assessing study quality will be used instead of the Cochrane Collaboration criteria.

[b] Yes (low risk of bias); No (high risk of bias); Unclear (uncertain risk of bias)