

WHO EML Application

Tocilizumab

Condition Juvenile Idiopathic Arthritis

1	<p>Summary statement of the proposal for inclusion.</p> <p>The application proposes the inclusion of Tocilizumab on the complementary list of the EML/EMLc/both for the treatment of Systemic Onset Juvenile Idiopathic Arthritis (SOJIA).</p> <p>The rationale for the complementary list is that the use of this drug requires specialised care. The proposed listing on both the EML and EMLc reflects the fact that JIA affects children through adolescence and into adulthood. This rationale is consistent with the listing for the anti-TNF biologics currently listed for JIA.</p> <p>Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood, affecting approximately one per 1000 children (1, 2). JIA is characterised by joint inflammation of more than 6 weeks' duration, with onset before age sixteen years and where no other cause is found (2).</p> <p>JIA is an autoimmune, non-infective, inflammatory joint disease, the cause of which remains poorly understood with both genetic and environmental contributions (3). It is a distinct entity from rheumatoid arthritis, differing in clinical presentations, prognosis, disease outcomes and treatment approaches. The age of onset in JIA is typically young, with a peak incidence between 1-3 years of age, although the disease persists into adulthood in approximately 50% of cases (4). Even in patients in whom the inflammatory disease resolves, joint or extra-articular damage – with associated disability – are common and if not treated then can result in irreversible sequelae and impact on quality of life (5).</p> <p>Current treatment approaches for children with JIA aim for normal physical and psychosocial functioning, and with access to modern treatments, good outcomes are a realistic and achievable goal for many children with this condition (6) .</p> <p>A noteworthy complication of JIA is inflammatory uveitis. This affects up to 30% of children with JIA and – if untreated – may cause irreversible loss of vision (7). There is considerable overlap between the medications used to treat JIA-arthritis and JIA-uveitis, namely immunosuppressive agents.</p> <p>Over recent decades the outcomes for children with JIA have improved substantially. In order to prevent joint destruction, chronic pain and disability, as well as extra-articular complications such as blindness from uveitis, the treatment paradigm for JIA has shifted: earlier, more aggressive therapy with early introduction of disease modifying anti-rheumatic drugs (DMARDs) therapy, and in many cases biological agents, is now the standard of care (8).</p>
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	<p>Notably, treatment with NSAID alone is no longer recommended (9). Furthermore, corticosteroids play a role in the early management of most forms of JIA, but their use in long term health conditions is limited by side their extensive side effect profile (9).</p> <p>The International League of Associations for Rheumatology (ILAR) recognizes 7 distinct subtypes of JIA; this classification is based primarily on the disease phenotype as well as demographic and serological factors (10). The term JIA replaces Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA) – there are differences in the terminology based on disease presentation and classifications (10). This is important to bear in mind when reviewing the literature and clinical studies when different classifications were used. Across the different classifications however the definitions for Systemic Onset disease are essentially the same (2).</p> <p>Systemic Onset JIA (SOJIA) subtype - characterised by arthritis, fever, rash and systemic inflammation – warrants particular attention as unlike other JIA subtypes, SOJIA is now recognised as an autoinflammatory syndrome (11). The proportion of children JIA who have SOJIA ranges from approximately 10% to 50% depending on the population with higher rates being reported in less resourced regions such as India (12). SOJIA can be complicated by the serious and often fatal Macrophage Activation Syndrome (MAS) with an uncontrolled ‘cytokine storm’ that has a fatality rate up to 23% in SOJIA (13). Early recognition and treatment of SOJIA is essential to improve outcomes and reduce the risk of MAS.</p> <p>At present, the WHO Essential Medicines List (EML) for JIA does not include the recommended medicines used to manage SOJIA - namely interleukin 6 inhibitor Tocilizumab and interleukin-1 inhibitors: Anakinra and Canakinumab. This application focuses on Tocilizumab and an additional application has been submitted for Anakinra which has particular advantages in the context of treating MAS. Canakinumab is a long acting form of interleukin-1 inhibitor and also used to treat SOJIA; we have not submitted an application for Canakinumab as this medicine is very expensive.</p>
2	<p>Relevant WHO technical department and focal point.</p> <p>We have been advised that the Non-Communicable Diseases Department is likely the most relevant technical department.</p>
3	<p>Name of organization(s) consulted and/or supporting the application.</p> <p>Please see the attachments in the Appendix; Letter of introduction from the Paediatric Global Musculoskeletal Task Force and Letters of Support from many institutions and organisations from around the world.</p> <p><u>International / National / Regional Organisations</u></p> <ul style="list-style-type: none"> • Paediatric Task Force for Global Musculoskeletal Health (members of the Task Force have worked together to submit this application) • Paediatric Rheumatology European Society

	<ul style="list-style-type: none"> • Australian and New Zealand Paediatric Rheumatology Group • South African Rheumatism and Arthritis Association • Paediatric Association for African League of Associations for Rheumatology • American College of Rheumatology • Childhood Arthritis and Rheumatology Research Alliance • Asia Pacific League of Associations for Rheumatology Paediatric Rheumatology Interest Group <p><u>Patient Organisations:</u></p> <ul style="list-style-type: none"> • Arthritis Kids South Africa • European Network for Children with Arthritis • Juvenile Arthritis Foundation Australia • Versus Arthritis (UK) <p>A recent online survey by the Paediatric Global Task Force for Musculoskeletal Health resulted in 97 responses from key opinion leaders in 42 countries (mostly Africa and Asia) to determine the key medicines to treat JIA in their country and health care settings (Scott et al in press PROJ and added as an Appendix); >80% respondents deemed the inclusion of Tocilizumab in the WHO EML to be 'ideal'.</p>
4	<p>International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.</p> <p>INN: Tocilizumab</p> <p>ATC: L04AC07</p>
5	<p>Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).</p> <p>Tocilizumab is available as both an intravenous infusion and a subcutaneous injection.</p> <p>The subcutaneous injection offers significant benefits with the ease of availability for patients and their families (as the medicine can be administered at home) and decreased associated costs (such as day case admission for infusion, staffing requirements).</p> <p>Tocilizumab is supplied in the following forms and dose strengths.</p> <p>Injection (Subcutaneous): 162mg/0.9mL</p> <p>Injection (Intravenous): 80mg/4mL in 4mL vial, 200mg/10mL in 10mL vial, 400mg/20mL in 20mL vial</p>

	<p>All the above listed formulations and strengths are suitable for use in both paediatric and adult populations.</p>
6	<p>Whether listing is requested as an individual medicine or as representative of a pharmacological class.</p> <p>We propose that Tocilizumab is to be listed as an individual medicine as there are currently no other anti-IL6 products approved for use in JIA.</p> <p>We have submitted another application for Anakinra (anti-IL1) as a medicine to treat SOJIA although the focus of that application is for the use of Anakinra in Macrophage Activation Syndrome as a severe life threatening complication of SOJIA.</p> <p>Canakinumab is a long acting form of anti-IL1 and also used to treat SOJIA – we have not submitted an application for this medicine as it is very expensive.</p>
7	<p>Treatment details (requirements for diagnosis, treatment and monitoring).</p> <p>Systemic onset JIA (SOJIA) is the most severe subtype of JIA, with high grade fevers, rashes, organomegaly, lymphadenopathy, and carries the most significant risk of mortality. Arthritis may not be clinically apparent with the initial presentation but commonly an aggressive polyarthritis will develop (2). SOJIA has a highly variable course, with some patients having a monocyclic course of variable length, but the majority will have a chronic course, often with flares and remissions of polyarthritis, with or without systemic features (2). In low resource countries particularly, the concomitant risks of infection can trigger episodes of Macrophage Activation Syndrome (MAS) as a serious life threatening complication of SOJIA with high risk of mortality (8). Historically, patients with SOJIA were treated with high dose and prolonged courses of glucocorticoids, with significant long-term side effects such as obesity, hypertension, cataracts, and osteoporosis.</p> <p>It is thought by many that a ‘window of opportunity’ exists in managing SOJIA and other rheumatic diseases, whereby early treatment is more likely to be efficacious (14-19). This emphasises the urgent need to improve access to specialist paediatric rheumatologists and to these medications, in order to limit long-term damage to joints and associated disability and impact on quality of life; an international Task Force of paediatric rheumatologists has stated that the goals of treatment of JIA are to control signs and symptoms, prevent structural damage; to avoid comorbid conditions and drug toxicities; and to optimise function, growth and development, quality of life and social participation (19). However there are significant issues with access to specialist paediatric rheumatologists, multi-disciplinary teams, and treatments, in many low-resource countries and this further contributes to the burden of disease and long term disability (20).</p>

	<p>JIA disease activity is monitored using standard assessment tools and over the decades various tools have been used in clinical practice (21). Increasingly, clinicians and clinical studies have used the Juvenile Arthritis Disease Activity Score (JADAS), which includes: Active Joint Count, Patient/Parent Visual Analogue Scale (VAS) for health status and a Physician/health care provider VAS for disease activity (21). The JADAS also includes blood markers of inflammation (such as CRP and ESR) and there are well defined 'cut-offs' of the JADAS for low disease activity and remission which are the ultimate aim of therapy.</p> <p>Current treatments of SOJIA include steroids (oral or intravenous) and disease modifying anti-rheumatic agents (DMARDs), such as Methotrexate, Anakinra or Tocilizumab (9). Methotrexate, while known to be efficacious in many forms of JIA, has a limited role to play in SOJIA in isolation, but is often used in combination with a biologic DMARD such as Tocilizumab (19). Management with DMARD agents such as Tocilizumab or Anakinra is now advocated to minimise severe side effects of steroids whilst effectively controlling the underlying disease. Tocilizumab is recommended for the treatment of SOJIA by the American College of Rheumatology (ACR) (22) the National Institute for Clinical Excellence (NICE), UK, the British Society for Rheumatology (23, 24) and is recommended as part of a consensus based treatment strategy in Germany (25).</p> <p>Tocilizumab is available as both an intravenous infusion and a subcutaneous injection. The subcutaneous injection offers significant benefits in the ease of availability for patients and their families and decreased associated costs (such as day case admission for infusion, staffing requirements).</p> <p>Dosing of subcutaneous Tocilizumab for SOJIA is based on a child's weight as follows:</p> <ul style="list-style-type: none"> • Child <30kg: 162mg SC every 2 weeks • Child >30kg: 162mg SC weekly <p>Intravenous Tocilizumab:</p> <ul style="list-style-type: none"> • Child <30kg: 12mg/kg every 2 weeks • Child >30kg: 8mg/kg every 2 weeks <p>Patients (and their parents) who are commencing subcutaneous Tocilizumab require education on the administration of the medication at home, as well as regular monitoring blood tests. For those starting intravenous Tocilizumab, more specialised equipment and staff are required, such as the availability of a regular day case/inpatient bed in a hospital or clinic with cannulation equipment and staff with appropriate expertise. Some patients receiving Tocilizumab require pre-medication to minimise the risk of an infusion reaction, such as intravenous hydrocortisone and/or an antihistamine, which also needs to be taken into consideration. It has been shown that those who are younger, with short stature, lighter weight and high disease activity in the early stages of Tocilizumab administration are more likely to react to the medication (26). The distance that the family travels to the hospital and the availability of transport may be a limiting factor in their ability to attend every fortnight for a few hours, and in addition this impacts on the child's school attendance.</p> <p>All patients should be tested for tuberculosis prior to commencing Tocilizumab. The ACR recommend that for children at low risk of tuberculosis with negative initial screening test, screening should be repeated at any point if their risk of tuberculosis changes to moderate or</p>
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	<p>high, as determined by regional infectious diseases guidelines (22). Awareness of tuberculosis risk in patients treated with Tocilizumab and other biologic DMARD medications is of particular importance in low resource settings with high rates of tuberculosis. This is emphasised in a paper of consensus statements on JIA care in low resource settings as level 3b evidence, strength A statement with 100% consensus (20). It is also recommended that JIA patients with a positive PPD or QuantiFERON test should receive appropriate prophylaxis for tuberculosis (as per their current national/international guidelines) at the start of biologic therapy, when on biologic therapy and a previously negative PPD converts to positive at the mandatory annual tuberculosis screening, and if they have a new exposure to tuberculosis (20).</p>
8	<p>Information supporting the public health relevance.</p> <p>The incidence of JIA is 1.6-23 per 100,000 (27); the range of incidence may reflect true differences across different racial and ethnic groups but may also reflect ascertainment and selection bias in the clinical studies (28). SOJIA is the most rare subtype of JIA, accounting for approximately 4-9% of cases in European nations, with population study in Norway recording an incidence of 0.6 per 100,000 per year (29). However, it is more common in certain ethnic groups, representing up to 25% and 50% of JIA in India and Japan (30); this corresponds to 312,000 patients with SOJIA in India alone (31). SOJIA is typically a chronic illness affecting young children - the age of onset is typically 1-5 years (32) - with significant burden of disease as patients usually require treatment for months to years after the onset of symptoms, as well as close monitoring for complications or flares of disease including the potentially fatal Macrophage Activation Syndrome (MAS).</p> <p>Most epidemiological studies of JIA are from high resource income settings (28). There are an estimated more than 2 million children with JIA around the world, most of whom are in Africa and Asia (33) – these estimates have been derived from known prevalence rates of JIA and modelling using population data for each country. It is acknowledged that the many children with JIA in Asia and Africa are likely to have little or no access to specialist care or medicines (34) and that many children with JIA, have essentially no treatment and this is borne out with worse clinical outcomes in low resource income countries (35). A study describing children with SOJIA treated in Mumbai, India, described high rates of long term complications and damage (36). Children who had a longer duration of time from onset of disease to definitive diagnosis and treatment were more likely to have a chronic/persistent course of disease. In reviewing the treatments offered to these children, 50 of 53 were treated with methotrexate, and 5 had received biologics (3 receiving Tocilizumab and 2 Etanercept), though significantly, none could sustain these treatments for longer than 2 months due to cost considerations. Additionally, 52 of 53 were treated with oral corticosteroids, and 34 were also given pulses of intravenous methylprednisolone. This is in stark contrast to well-resourced countries, where recent trials have focused on commencing DMARDs in steroid-naïve patients, to gain early control of disease and minimise side effects (16).</p> <p>The consequences of untreated JIA are known from historical studies that predate current approaches to treatment; essentially untreated arthritis results in pain, joint damage, functional disability and impact on quality of life (5, 8, 37) and uncontrolled inflammation carries significant risk of high morbidity and potential mortality from Macrophage Activation Syndrome (36). Chronic use of glucocorticoids results in complications (including growth failure,</p>

cataracts, osteoporosis) (37). Arthritis involving lower limb joints results in difficulty walking, transferring, getting up from sitting or a squat position and for arthritis involving upper limb joints there are problems with writing, dressing and eating. Untreated JIA results in children missing school, social and peer interactions with long term psychosocial impact, mental ill health and higher unemployment compared to healthy peers (5, 37). The mortality rates in SOJIA are higher than for children with other forms of JIA in the UK (Standardised Mortality Ratio 8.3, 95% CI 2.7 to 19.4 vs 1.7, 95% CI 0.5 to 4.0) (38).

A recent multinational survey of 61 patients and caregivers with SOJIA revealed that even in the biologic era and in well-resourced countries, the burden of disease is significant (39). Although these children were treated with biologics relatively early - mean time from diagnosis to biologic 1.3 years - 54% required at least 1 assistive device, and 20% required home or care alterations. A recent multinational epidemiological study included less resourced countries affiliated with the Paediatric Rheumatology International Trials Organisation (PRINTO) indicated that children with JIA in less resourced countries have higher rates of active disease, more joint damage and worse clinical outcomes than their counterparts in high resource countries (21). The social implications are also important, with 36% of caregivers reporting that they had reduced their hours of work or stopped working due to their child's SOJIA, and they lost on average 25 days of work per year.

The use of Tocilizumab for children with SOJIA improves the short and long term outcomes for these patients with the evidence summarised further in section 9. Short term, it allows control of disease with less use of corticosteroids thereby minimising disease morbidity and reducing side effects (of steroids). Early control of disease is important to minimise irreversible damage and in the longer term, control of arthritis leads to an improved functional outcome, with lower rates of deformity, disability and chronic pain. In SOJIA the risk of uncontrolled inflammation and subsequent Macrophage Activation Syndrome, which has a high mortality rate, is a particular concern.

There are multiple potential outcomes to consider in assessing the impact of any treatment on a disease such as SOJIA, which include rates of disease flare, rates of Macrophage Activation Syndrome and mortality, clinical assessment scores such as Childhood Health Assessment Questionnaire (CHAQ) and long-term joint health. Historically, 40% of patients reported at least moderate functional disability (40). In a study of SOJIA patients treated with biologics, mean (\pm SD) Child Health Questionnaire Parent-Form 50 (CHQ-PF50) physical and psychosocial summary scores were significantly lower in SOJIA patients than a normative population (Physical 40.0 ± 18.2 vs 53.0 ± 8.8 ; psychosocial 46.6 ± 11.3 vs 51.2 ± 9.1) (39).

A small Japanese study (9 patients) investigating the radiological outcomes in patients with SOJIA reported that radiologic improvement was seen in 47 joints (52%), with worsening of disease in 10 joints (11%) following treatment with intravenous Tocilizumab (41). In particular, evidence of joint-space narrowing, subchondral bone cysts, and erosions improved after treatment, from 44.3, 13.1 and 22.5 to 29.7, 1.3 and 0% respectively ($p < 0.05$ for joint space narrowing, $p < 0.01$ for subchondral bone cyst and erosion). Patients in this study also had improved CHAQ scores, from 2.1 prior to treatment to 0.4 afterwards. A similar study reported marked radiographic improvement of damaged large joints in SOJIA treated with Tocilizumab (42). Radiographic findings of joint destruction all diminished after Tocilizumab treatment, and

	<p>osteoporosis showed marked amelioration. Damaged joints were remodelled and improvement of radiographic findings was maintained for 5 years.</p> <p>Other key outcomes include linear growth, which can be affected by chronic inflammation, ill health and by medications such as chronic use of glucocorticosteroids. 'Catch-up growth' was reported by de Benedetti <i>et al</i> in a post hoc analysis of 83 patients treated with Tocilizumab (43); patients having significant catch up growth (above normal height velocities of 6.6cm/year $p<0.0001$), normalisation of IGF-1 levels and bone balance improvement favouring bone formation. In another study of 45 patients treated with Tocilizumab, 38 (84%) had a clinical response with improved growth by week 144 (44); Mean SD height was -2.7 and inversely correlated with disease duration. Mean disease duration was 4.1 +/- 3.2 years. A significant improvement was seen from 1 year prior to 1 year after baseline (-6.0 +/- 4.0 to -2.5 +/- 3.9, $p = 0.0064$). Reduction in corticosteroid exposure was significantly associated with improvement in height velocity. Eight patients (17.8%) reduced their corticosteroid dose by 50% and 26 (57.8%) reduced their steroid dose by 70%.</p> <p>Current treatment approaches for children with SOJIA aim for normal physical and psychosocial functioning, and with access to modern treatments, this is now an achievable goal for many children and joint damage, chronic pain and subsequent disability can be prevented with considerable improvement in quality of life (8). This paradigm shift to earlier, more aggressive therapy with early introduction of disease modifying therapy, is now the standard of care in high resource settings (45, 46). It is therefore more important than ever that the inequity in access to right care is addressed and this is a priority for the paediatric rheumatology community (47); raising awareness, models of care and training to enable the existing workforce to make a diagnosis of JIA and deliver care are the focus of many collaborative initiatives (47). The growth of paediatric rheumatology around the world is gaining momentum; having necessary medicines available through the WHO Essential Medicines List (EML) will be an important step to address inequity and enable many children with JIA to be treated to avoid disability and have a better quality of life.</p> <p>At present, the medicines included on the WHO EML for JIA do not include the standard DMARDs used to manage SOJIA - namely interleukin 6 inhibitor Tocilizumab and interleukin-1 inhibitors: Anakinra and Canakinumab. This application focuses on Tocilizumab and an additional application focuses on Anakinra as this agent has particular advantages in the context of treating MAS. Canakinumab is a long acting form of interleukin-1 inhibitor and also used to treat SOJIA and MAS – we have not submitted an application for Canakinumab as this medicine is very expensive.</p>
9	<p>Review of benefits: summary of evidence of comparative effectiveness.</p> <p>Search strategy: PubMed search of Tocilizumab, paediatric, systemic, juvenile idiopathic arthritis.</p> <p>There are a paucity of large trials and systematic reviews for Tocilizumab in SOJIA. The trials for intravenous Tocilizumab are described below, as well as a number of systematic reviews and registry studies detailing safety and efficacy data (17, 48-55). There are also a small</p>

number of studies describing the use of subcutaneous Tocilizumab, and reviewing patient and family opinions regarding this switch (56, 57). Due to the small numbers of trials, and small numbers of patients involved, the systematic reviews and meta-analyses review these same individual trials, however all these reviews outline in detail the difficulty of drawing clear conclusions due to variations in outcome measures and datasets. However, despite these limitations, it is worth noting that Tocilizumab is a recommended therapeutic choice for children with SOJIA in most well-resourced countries (22, 24, 25).

Yokota *et al*/ reported a randomised, double-blind, placebo-controlled, withdrawal phase III trial, (56 children aged 2-19 years refractory to DMARDs and biologics) (48). The study incorporated the American College of Rheumatology (ACR) Pedi response criteria (58) based on the core outcome variables for juvenile arthritis (namely, physician global assessment of disease activity (10-cm VAS), parent/patient assessment of overall well-being (10-cm VAS), functional ability, number of joints with active arthritis (defined as joint effusion or limitation of motion accompanied by heat, pain, or tenderness), number of joints with limited range of movement and ESR.) An ACR (Pedi) 30 response is defined as at least a 30 % improvement from baseline in three of six variables, with no more than one remaining variable worsening by >30 %. Similarly, the ACR Pedi 50, 70, 90, and 100 response definitions require 50 %, 70 %, 90 %, and 100 % improvement, respectively, in at least three core set variables without worsening of more than one variable by >30 %. Conversely, flare is defined as worsening of two variables by at least 40 % without improvement in more than one variable by 30 %. These criteria are the gold standard for the assessment of response to therapy in JIA. The ACR Pedi 30 was adapted for use in clinical trials in SOJIA by adding, besides the six core set variables, the demonstration of the absence of spiking fever (>38 °C) during the week preceding the evaluation (59).

In the initial phase, ACR Pedi 30, 50, 70 responses were achieved by 51 (91%), 48 (86%), 38 (68%) of patients respectively. By week 48 of the open-label extension phase, ACR Pedi 30, 50, 70 responses were achieved by 47 (98%), 45 (94%), 43 (90%) of 48 patients.

De Benedetti *et al*/ described a randomised placebo controlled trial for 112 children (age 2-17, persistent disease for >6 months and inadequate response to NSAIDs and glucocorticoids) of intravenous Tocilizumab (50). After 12 weeks, the primary end point of ACR Pedi 30 response and absence of fever was met by 85% (64/75) in the treatment group and 24% (9/37) in the placebo group $p < 0.001$. At week 52, 80% in the Tocilizumab group had at least 70% improvement, 48% had no active arthritis and 52% had ceased oral glucocorticoids. In this study, 84% of patients in the treatment group had previously been treated with a biologic agent, including 55% with and interleukin-1 inhibitor and 73% with an anti-TNF agent.

Yokota *et al*/ reported that in SOJIA patients refractory to conventional therapy, ACR Ped 30,50,70 responses were achieved by 51 (91%), 48 (86%), and 38 (68%) of those treated with Tocilizumab (49). Patients who remained on Tocilizumab in the double-blind phase had sustained improvement in clinical measures of effectiveness and wellbeing, whereas most of those in the placebo group (18/23 patients) needed rescue treatment. This is Category 1B evidence. Patients on Tocilizumab reported a decreased in mean corticosteroid dosage from 0.9mg/kg/day at enrolment to 0.2mg/kg/day at 52 week. 12.3% (19 patients) discontinued steroids.

A German registry study reported that over a 5 year period, 46 of 200 patients with SOJIA were treated with Tocilizumab (51). A clinical response rate (defined as no symptoms and normal inflammatory markers) of 35% was reported in the first 12 weeks of treatment, and inactive disease/remission on medication (as defined in the Wallace criteria (21)) was reported in 75% after 1 year.

Initial trials and approval for Tocilizumab were for the intravenous formulation, and the first studies showing efficacy in SOJIA were in 2005. Approval for the subcutaneous formulation was given after the JIGSAW trial, a 52-week, open-label, multicentre phase 1b trial evaluating pharmacokinetic and pharmacodynamic data to determine appropriate dosing (56). A trial comparing clinical outcomes and patient satisfaction with switching from intravenous to subcutaneous formulation for SOJIA and polyarticular JIA revealed no difference in active joint counts, physician or patient VAS and JADAS71, and 8/9 patients were satisfied with subcutaneous administration in terms of life quality, school success, and reduced school absenteeism (57).

Comparative effectiveness

SOJIA can also be effectively treated with agents such as Anakinra and Canakinumab, which are interleukin 1 inhibitors (16, 60, 61). While they are efficacious in managing the disease, there are practical and financial challenges - Anakinra requires a daily subcutaneous injection, which is a challenge in the paediatric population and Canakinumab is prohibitively expensive, although it is administered 4 weekly which is more convenient. Further detail on comparative costs is given in section 11. A study is currently ongoing to compare clinical effectiveness and safety of the four consensus treatment plans published by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) which include the biologic DMARDS (62).

A systematic review and meta-analysis of trials reported that Canakinumab and Tocilizumab are more effective than Rilonacept which is another interleukin 1 inhibitor (53). However, this review identified only 5 eligible trials albeit with heterogeneous eligibility criteria and study designs raising concern about the applicability of the results. Quality assessment was performed with Risk of Bias tool (Cochrane collaboration). Those treated with Rilonacept were less likely to respond than those treated with Canakinumab (Odds ratio (OR) 0.10 95% CI 0.02-0.08 $p=0.0001$) or Tocilizumab (OR 0.12 95% CI 0.03-0.44 $p=0.0001$), however the evidence was low-quality, with indirect comparisons and inconsistency. In particular, some of the trials described ACR responses without including systemic features, though both patients with and without systemic features were enrolled. In addition, modified JIA ACR30 responses were used as a measure of response, with serious adverse events used as a proxy for harm, (detailed in section 10 below). It was recommended by this trial that two categories of SOJIA be considered in future trials, the first, with mainly systemic features and minimal joint disease, likely to be more responsive to IL-1 therapy, and the second with systemic features and severe arthritis, which are more likely to be amenable to IL-6 therapy.

While anti-tumour necrosis factor alpha agents, (such as Etanercept and Adalimumab, which are already on the WHO Essential Medicines List to treat JIA) have proven efficacy in many other subtypes of JIA, they are not effective for patients with SOJIA (54, 63). A systematic review including 25 studies with over 4000 patients with JIA, including 1185 with SOJIA, concluded SOJIA appeared to be less responsive to Etanercept when compared to Tocilizumab over 12 weeks (Etanercept: ACR30 58-78% and Tocilizumab: ACR30 85%) (64).

	<p>A German study comparing the efficacy of Tocilizumab with interleukin 1 inhibitors and Etanercept described that the JIA-ACR 30/50/70/90 response was achieved more often over 24 months in those treated with Tocilizumab or Interleukin 1 inhibitors (17). It was also noted that those treated with Tocilizumab were less often treated with systemic glucocorticosteroids than those treated with Etanercept when starting the medication (44% vs 83% p<0.001).</p> <p>A recently published meta-analysis on the benefit-risk balance for biological DMARD agents in JIA (1458 patients, 19 RCTs) demonstrated that those with SOJIA had higher rates of therapeutic success without serious adverse events, compared to patients with non-systemic JIA patients (65). In this meta-analysis, patients with SOJIA were treated with agents such as rilonacept, canakinumab or tocilizumab. This meta-analysis includes studies described elsewhere in this document (48, 50, 66).</p>														
10	<p>Review of harms and toxicity: summary of evidence of safety</p> <p>Adverse events reported in the double-blind phase of de Benedetti's trial included infections (60, 2 serious) in the tocilizumab group compared to 15 in the placebo group (50). In the double-blind and extension period combined, there were 39 serious adverse events (25 per 100 patient years), including 18 serious infections (11 per 100 patient years). Adverse events led to the discontinuation of Tocilizumab in 6 patients, including 2 due to elevated aminotransferase levels. Three episodes of MAS were reported, all of which resolved. Three deaths occurred during treatment, 1 in a 17 year old with long standing disease and severe growth retardation, who had a JIA ACR 90 response, who died suddenly from a tension pneumothorax; another patient who died from injuries sustained in a traffic accident, and a third from probable streptococcal sepsis (50).</p> <p>Table 1: Overall Estimates of frequency of adverse events</p> <table> <tr> <th>Event</th><th>Study</th></tr> <tr> <td> Serious Infections/Infestations <ul style="list-style-type: none"> 11/100 PY (Patient Years) 18.2/100 PY </td><td> (50) (49) </td></tr> <tr> <td> Neutropenia <ul style="list-style-type: none"> 19/112 patients (16.9%), 17 patients with grade 3 and 2 patients grade 4 </td><td>(50)</td></tr> <tr> <td> Lymphopenia <ul style="list-style-type: none"> 15/18 patients </td><td>(52)</td></tr> <tr> <td> Leukopenia <ul style="list-style-type: none"> 4/46 patients 4.2/100PY </td><td> (51) (49) </td></tr> <tr> <td> Elevated aminotransferases <ul style="list-style-type: none"> 21/112 patients 2/46 patients </td><td> (50) (51) </td></tr> <tr> <td> Macrophage Activation Syndrome <ul style="list-style-type: none"> 3/112 </td><td>(50)</td></tr> </table>	Event	Study	Serious Infections/Infestations <ul style="list-style-type: none"> 11/100 PY (Patient Years) 18.2/100 PY 	(50) (49)	Neutropenia <ul style="list-style-type: none"> 19/112 patients (16.9%), 17 patients with grade 3 and 2 patients grade 4 	(50)	Lymphopenia <ul style="list-style-type: none"> 15/18 patients 	(52)	Leukopenia <ul style="list-style-type: none"> 4/46 patients 4.2/100PY 	(51) (49)	Elevated aminotransferases <ul style="list-style-type: none"> 21/112 patients 2/46 patients 	(50) (51)	Macrophage Activation Syndrome <ul style="list-style-type: none"> 3/112 	(50)
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<ul style="list-style-type: none"> • 6.4/100 PY • No events • 2.5/100PY • No events (0/48 patients) 	(49) (51) (55) (48)
Tuberculosis <ul style="list-style-type: none"> • No cases • No cases 	(50) (49)

Terminology: Grade 3 neutropenia: 0.5×10^9 to $<1.0 \times 10^9$; Grade 4 neutropenia: $<0.5 \times 10^9$, elevated aminotransferases: greater than 2.5 times the upper limit of normal;

Yokota *et al* followed patients in the ‘real world’ setting for 52 weeks, and reported an overall rate of adverse events and serious adverse events of 224.3/100 patient years (PY) and 54.5/100 PYs, which were higher than previously reported in clinical trials (49). Adverse events leading to discontinuation of Tocilizumab occurred in 4.1% of patients (17/417). The most common adverse events were infections and infestations, with a rate of 69.8/100PY. Two deaths occurred in the 52 week period, one due to vasculitis with cardiac failure, and one due to *Pseudomonas* infection, interstitial lung disease and sepsis. In the case of seven episodes of Macrophage Activation Syndrome, infections were thought to contribute, and for 2 events a reduced dose of corticosteroids was thought to contribute.

In a German registry study (51), adverse events were seen in 24% and serious adverse events in 4%. The serious adverse events included a case of Hodgkin’s lymphoma and a gut perforation. No cases of Macrophage Activation Syndrome or death were reported. For 5/46 patients’ adverse events were the reason for stopping Tocilizumab, neutropenia $n = 3$, serious adverse event $n = 2$.

Comparative safety against other agents:

A recently published study on long term surveillance of biologics use in SOJIA (260 patients, 109 who had been treated with Tocilizumab) reported rates of serious adverse events of 21/100 patient years (PY), compared with 21/100 PY for Canakinumab (55). In particular, cytopenia and hepatic events were seen. Rates of MAS were 2.5 per 100 PY for those treated with Tocilizumab, compared with 3.2/100 PY for those treated with Canakinumab, 0.83/100PY for Anakinra and 0.05/100 PY for Etanercept. The mean follow-up in this study was 4.3 years (SD 3.8, median 3.3, 1121 patient years, with total exposure time to biologics of 856 exposure years and 244 exposure years for Tocilizumab specifically. 96 patients had been treated with more than one biologic agent. It was noted by the authors that the preferred choice of biologic agent changed, where after 2013, only 5% of patients were treated with a TNF inhibitor (Etanercept), and almost equal numbers with IL-6 inhibition (Tocilizumab) or IL-1 inhibition (Anakinra, Canakinumab). It was noted that those treated with Tocilizumab and systemic steroids had significantly higher rates of adverse events and serious adverse events (127.5/100 EY vs 79.4/100EY, $p=0.002$, and 28.4/100EY vs 15.6/100EY $p=0.019$) respectively, compared to those treated with Tocilizumab without systemic steroids. The adverse events included 93 infectious events in 37 patients on Tocilizumab (38/100EY; RR= 1.4 95% CI 0.97-2.0). Cytopenia were reported in 22 cases, with higher rates in Tocilizumab patients (6.2/100EY; RR 5.37, 95% CI 2.19-13.17), although these were not significantly higher after adjustment for presence of systemic signs, concomitant use of Methotrexate and systemic steroids at baseline, disease duration, cJADAS-10, CHAQ, pain and number of prior treatments.

	<p>In a meta-analysis by Tarp <i>et al</i>, adverse events were quite rare, likely related to the short duration of follow-up in the studies analysed (53). There was no difference detected between the medications for serious adverse effects however the quality of evidence was very low. Adverse events were higher with Tocilizumab compared to placebo or Canakinumab. Post hoc analysis of adverse events (evaluated as total number of events per total patient-days) showed that Tocilizumab did not differ from placebo. Tocilizumab (and Canakinumab) gave a statistically significant increase in risk of infections compared to placebo, but not significant when evaluated as events per total patient days.</p> <p>In a pilot study comparing the consensus treatment plans published by CARRA in 30 newly diagnosed patients with SOJIA, 1 grade 4 adverse event infusion reaction occurred with tocilizumab and 1 episode of Macrophage Activation Syndrome occurred also (67). This compares with 2 illnesses requiring hospitalisation for intravenous antimicrobial/antiviral therapy, 1 each in children treated with Canakinumab and Anakinra, and an episode of Macrophage Activation Syndrome in a child treated with Anakinra who responded to treatment with oral prednisolone and did not require hospitalisation. It is noted that this study was observational, allowing choice of medication based on physician and patient/family discretion, and the duration of follow-up, at 9 months, was short.</p> <p>Rates of adverse events were higher in patients treated with Tocilizumab compared to etanercept (Risk ratio (RR) 5.3/patient year; $p<0.0001$), and serious adverse events were seen more frequently in those treated with Tocilizumab (RR 2.9; $p<0.5$) compared to Etanercept, but less than interleukin -1 inhibitors (RR 2.9; $p<0.01$) (17).</p> <p>Any child treated with Tocilizumab (or any biologic DMARD) must have access to urgent paediatric rheumatology review and hospitalisation if needed, should they develop complications such as infection. This is of particular importance in low resource countries where up to 50% of mortality in children age 5-15 is due to infection (68). With this background risk in mind, the importance of monitoring a child who is on immunomodulatory modification in a low resource country cannot be over-emphasised. The trials and studies listed above all occurred in well-resourced countries. It should therefore be noted that local factors (availability of specialist services such as doctors, nurses, urgent review, access to intravenous antibiotics), as well as patient factors (health literacy rates, distance and transport to hospital, co-morbid conditions, poverty, malnutrition) may have significant impacts on the rates of adverse events in low-resource settings.</p>
11	<p>Summary of available data on comparative cost and cost-effectiveness of the medicine.</p> <p>Tocilizumab for intravenous administration costs £102.40 for 80mg vial, £256.00 for a 200mg vial and £512.00 for a 400mg vial in the UK (27). Tocilizumab 162mg/0.9ml prefilled pen/syringes cost £228.28 each via Drug Tariff Part VIIIA Category C (69). Roche (manufacturer of Tocilizumab) have a patient access scheme within the NHS (UK) and provides a discount - the</p>

details of which are confidential (27). A UK review reported the incremental cost-effectiveness ratio (ICER) for tocilizumab for JIA (polyarticular subtype) as £38,656 per QALY gained (27).

In Australia, Tocilizumab for intravenous administration is available at a cost of \$82 for 80mg/4mL vial, \$203 for 200mg/10mL vial and \$405 for 400mg/20mL vial. It is listed on the Pharmaceutical Benefits Scheme (PBS) therefore this medication is heavily subsidised by the Australian government. In 2020 the maximum cost to the patient for patients with a government issues concession card is \$6.60 per infusion and \$41 per infusion for those without concession. There are strict criteria that must be met to be eligible for subsidy under the PBS including failure to respond or be intolerant to traditional DMARDs (Methotrexate) before commencing this therapy. In some instances the manufacturing drug company Roche provide access to the medication on a compassionate and individual patient basis. The details of this arrangement are confidential.

A submission to the Ontario Committee to Evaluate Drugs (CED) in 2014 determined the annual cost of Tocilizumab to be between \$7000 to \$13000 per year depending on the patient's body weight. It is deemed less expensive than other biologic agents when used in patients' weight 34-75kg. Additional costs are incurred for the intravenous administration such as nursing time and infusion clinic admission.

A Finnish study compared cost effectiveness of Tocilizumab with other common agents (Methotrexate and Anakinra), and reported that Tocilizumab produced 4.47 QALYs (compared to 3.41 and 2.83 QALYs respectively) (70). An additional QALY for treatment with Tocilizumab cost €15181 compared to Methotrexate and €14496 compared to Anakinra. Based on their acceptability frontiers of 20,000euros/QALY gained, Tocilizumab was found to be highly likely to be cost effective. At higher payment thresholds of 27,000euros/QALY or 37,000euros/QALY, probability of cost-effectiveness was 100%. The authors reported that their modelling assumptions were conservative and therefore advise that the results are an underestimate of its cost effectiveness.

A Canadian cost-effectiveness analysis concluded that Tocilizumab with or without Methotrexate had an incremental cost-utility ratio (ICUR) of \$69,787 (Canadian dollars) per additional QALY compared to placebo with Methotrexate, and that it would be a less costly and more effective treatment from a societal perspective (71). Their analysis included a Markov model of ACR responses.

A Thai study reported an ICER of standard treatment plus Tocilizumab was US \$35799 per QALY, using a simulated health state transition model to estimate lifetime costs and health outcomes (72). It is noted that standard treatment for SOJIA in Thailand includes NSAIDs, systemic corticosteroids, and non-biological DMARDs (Sulfasalazine, Methotrexate and Hydroxychloroquine). The data was based on cases of refractory disease in 43 patients treated across 7 tertiary hospitals, and the patients largely had a long duration of disease and greater severity of disease overall. Rates of SOJIA are higher in Thailand than in many well-resourced countries; it represents 33.8% of JIA cases, with 20% of these being refractory to standard treatment. Additionally, this costing only accounted for intravenous Tocilizumab. Given the lack of access to biologic therapies, the longer duration and greater severity of disease, particularly of irreversible damage, the 'window of opportunity' theory, as previously mentioned, would suggest that the treatment of such cases with Tocilizumab earlier in the

	<p>course of disease would be more likely to produce a more cost effective outcome, as well as a better clinical response for the patient.</p> <p>A Russian cost-effectiveness analysis reported that the cost of Tocilizumab is justified by better cost efficiency, reduced social and economic losses in the state budget (73). For example, in patients treated with Tocilizumab, costs of hospitalisation were 12 times less than those treated with standard therapy, and the annual budget losses due to the social burden of disease were substantially lower (226729.10 vs 426144.63RUB).</p> <p>Table 2: Comparative Costs for common agents used to treat SOJIA in the UK (69):</p> <table><tr><th></th><th>Tocilizumab</th><th>Anakinra</th><th>Canakinumab</th></tr><tr><td>Unit cost</td><td>£228.28 For 162mg SC injection</td><td>£183.61 For 100mg SC syringe</td><td>£9927.80 for 150mg vial</td></tr><tr><td>Dosing for 10kg child</td><td>162mg SC every 2 weeks</td><td>1-2mg/kg SC daily, up to 4mg/kg daily</td><td>4mg/kg SC every 4 weeks</td></tr><tr><td>Annual cost 10kg child</td><td>£5935.28</td><td>£67,017.65</td><td>£119,133.60</td></tr><tr><td>Dosing for 50kg child</td><td>162mg SC weekly</td><td>100mg daily, increased if necessary up to 4mg/kg daily (200mg daily)</td><td>4mg/kg every 4 weeks (i.e. 200mg)</td></tr><tr><td>Annual cost 50kg child</td><td>£11,870.56</td><td>£67,017.65-134,035.30*</td><td>£119,133.60-238,267.20*</td></tr></table> <p>*Assuming no vial sharing between patients</p>		Tocilizumab	Anakinra	Canakinumab	Unit cost	£228.28 For 162mg SC injection	£183.61 For 100mg SC syringe	£9927.80 for 150mg vial	Dosing for 10kg child	162mg SC every 2 weeks	1-2mg/kg SC daily, up to 4mg/kg daily	4mg/kg SC every 4 weeks	Annual cost 10kg child	£5935.28	£67,017.65	£119,133.60	Dosing for 50kg child	162mg SC weekly	100mg daily, increased if necessary up to 4mg/kg daily (200mg daily)	4mg/kg every 4 weeks (i.e. 200mg)	Annual cost 50kg child	£11,870.56	£67,017.65-134,035.30*	£119,133.60-238,267.20*
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12	<p>Summary of regulatory status and market availability of the medicine.</p> <p>Tocilizumab has been approved by the FDA for treatment of SOJIA in paediatric patients 2 years of age or older since April 2011, with approval for the subcutaneous form since September 2018 (74).</p> <p>The subcutaneous formulation is approved for use in SOJIA by the European Medicines Agency (EMA) (75) for patients 1 year or older and weighing at least 10kg. The intravenous formulation is approved by the EMA for patients aged 2 years and older.</p> <p>Tocilizumab is licensed for the subcutaneous treatment of SOJIA in patients age 1 year and older and weighing at least 10kg, or for the intravenous treatment of patients age 2 years and older under National Health Service (NHS) England/National Institute for Clinical Excellence (23, 24, 76).</p> <p>Tocilizumab is licensed by the Therapeutic Goods Administration (TGA, Australia) for the treatment of SOJIA in it's subcutaneous form for children aged 1 year and older and weighing 10kg or more, and in the intravenous form for patients 2 years or older.</p> <p>All children receiving Tocilizumab will have regular follow up to assess response to treatment and whether there has been adverse event(s). A database of patients who have received this drug</p>																								

	<p>will be kept on secure hospital databases and in many countries around the world there are registries to collate anonymised data as part of ongoing efficacy and safety monitoring.</p> <p>Only clinical personnel appropriately trained and experienced will be involved in the use of this drug to treat SOJIA. In addition, families need to have education and support to know about the drug, potential side effects and safety concerns and know when to seek health care attention. These principles are based on recommendations and standards of care for JIA (77-79). The inclusion of this drug in the Essential Medicines List therefore has consequences for training of the workforce (to appropriately diagnose, prescribe and administer the drug and support families), whether given intravenously or subcutaneously. Furthermore, there are implications for the distribution, storage and handling of the drug. At this present time, Tocilizumab appears to be readily available on the market however reports of supply issues have occurred over the past few months in India due to the use of Tocilizumab as a novel treatment and used in clinical trials for the treatment of Covid-19. No reports of shortages elsewhere are evident at time of review.</p>
13	<p>Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).</p> <p>Tocilizumab is available in Martindale and many other standard medication references. We can find no reference to Tocilizumab in the Pharmacopoeias (The British Pharmacopoeia, The International Pharmacopoeia, The United States Pharmacopoeia, The European Pharmacopoeia).</p>
14	<p>Comprehensive reference list and in-text citations.</p> <ol style="list-style-type: none"> 1. Harris JG, Kessler EA, Verbsky JW. Update on the treatment of juvenile idiopathic arthritis. <i>Curr Allergy Asthma Rep.</i> 2013;13(4):337-46. 2. Ravelli A, Martini A. Juvenile idiopathic arthritis. <i>The Lancet.</i> 2007;369(9563):767-78. 3. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, et al. Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. <i>Nat Genet.</i> 2013;45(6):664-9. 4. Sullivan DB, Cassidy JT, Petty RE. Pathogenic implications of age of onset in juvenile rheumatoid arthritis. <i>Arthritis Rheum.</i> 1975;18(3):251-5. 5. Glerup M, Rypdal V, Arnstad ED, Ekelund M, Peltoniemi S, Aalto K, et al. Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. <i>Arthritis Care Res (Hoboken).</i> 2020;72(4):507-16. 6. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile Idiopathic Arthritis: Diagnosis and Treatment. <i>Rheumatol Ther.</i> 2016;3(2):187-207. 7. Clarke SL, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. <i>Pediatr Rheumatol Online J.</i> 2016;14(1):27.

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	<p>systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. <i>Arthritis Rheum.</i> 2013;65(10):2499-512.</p> <p>23. NHS England. Biologic therapies for the treatment of juvenile idiopathic arthritis 2018 [Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Biologic-therapies-for-the-treatment-of-juvenile-idiopathic-arthritis-Appendix-A.pdf.</p> <p>24. British Society for Rheumatology. Tocilizumab use in paediatric and adolescent rheumatology information for health professionals 2020 [Available from: https://www.rheumatology.org.uk/Portals/0/Documents/Guidelines/Paediatric%20guidelines/Tocilizumab Paediatric Adolescent Rheumatology.pdf?ver=2020-03-19-150244-320.</p> <p>25. Hinze CH, Holzinger D, Lainka E, Haas JP, Speth F, Kallinich T, et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. <i>Pediatr Rheumatol Online J.</i> 2018;16(1):7.</p> <p>26. Yasuoka R, Iwata N, Abe N, Kohagura T, Nakaseko H, Shimizu M, et al. Risk factors for hypersensitivity reactions to tocilizumab introduction in systemic juvenile idiopathic arthritis. <i>Mod Rheumatol.</i> 2019;29(2):324-7.</p> <p>27. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. <i>Health Technol Assess.</i> 2016;20(34):1-222.</p> <p>28. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. <i>Joint Bone Spine.</i> 2014;81(2):112-7.</p> <p>29. Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. <i>J Rheumatol.</i> 2003;30(10):2275-82.</p> <p>30. De Benedetti F, Schneider R. Systemic juvenile idiopathic arthritis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. <i>Textbook of Pediatric Rheumatology</i>. 7th ed. Philadelphia: Elsevier; 2016. p. 205-16.</p> <p>31. Janarthanan M. Getting around barriers in biologic treatment for systemic juvenile idiopathic arthritis patients in resource-poor countries. <i>Indian Journal of Rheumatology.</i> 2018;13(1):2-3.</p> <p>32. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). <i>J Rheumatol.</i> 2008;35(2):343-8.</p> <p>33. Dave M, Rankin J, Pearce M, Foster HE. Global prevalence estimates of three chronic musculoskeletal conditions: club foot, juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. <i>Pediatric Rheumatology.</i> 2020;18(1):1-7.</p> <p>34. Chausset A, Pereira B, Echaubard S, Merlin E, Freychet C. Access to paediatric rheumatology care in juvenile idiopathic arthritis: what do we know? A systematic review. <i>Rheumatology.</i> 2020.</p> <p>35. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. <i>The Lancet Child & adolescent health.</i> 2019;3(4):255-63.</p>
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