South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Tumor Necrosis Factor inhibitor (TNFi) therapy for the use in children & adolescents with Polyarticular Juvenile Idiopathic Arthritis (JIA) *without JIA related uveitis* (PICO 1) who are refractory to conventional disease modifying anti-rheumatic drugs (DMARDs). *Please see accompanying document for evidence related to PICO 2 - *JIA with JIA related uveitis*

Date: March 2023

Key findings

- There are medicine treatment options for patients with Polyarticular Juvenile Idiopathic Arthritis (JIA) at Paediatric Adult Hospital Level (NSAIDS, oral and intra-articular glucocorticoids and methotrexate). However, there are some patients who are intolerant or refractory and may benefit from Tumor Necrosis Factor Inhibitor (TNFi) therapy.
- We conducted a rapid review of systematic reviews, meta-analyses and clinical trials reporting on the efficacy and safety of TNFi therapy for polyarticular JIA without uveitis (PICO 1) and with uveitis (**PICO 2 – see accompanying document for evidence and findings**).
- On NEMLC request, a rapid review of quality-of-life, economic literature and HTA agency decisions was also conducted (See accompanying document for details).
- We identified 4 trials for inclusion for PICO 1. A Cochrane risk-of-bias assessment (version 2) of the main outcomes (disease flare and JIA ACR Pedi 30% response) per trial resulted in an evaluation of 'some concerns' or 'low risk' for trials, with no trial identified as 'high risk' for any of the outcomes.
- ***PICO 1 – patients with polyarticular JIA without uveitis – (1 RCT, 3 randomised withdrawal trials, n = 535)***

  TNF inhibitors (pooled effect of golimumab, adalimumab, etanercept, infliximab) compared to placebo
  - Number of participants who developed a JIA disease flare
    TNF inhibitors are likely to reduce JIA disease flares, **NNT=3** 95% CI [2 to 50]; **P=0.04**, i^2=67%, 3 trials, n=263, moderate certainty). At subgroup level, both adalimumab and etanercept trials alone showed superiority compared to placebo. No difference observed in the golimumab trial alone.
  - Number of participants with a JIA ACR Pedi 30% response
    TNF inhibitors may increase response to treatment, (RR 1.4 (95% 95% CI [0.97 to 2.02], **P=0.07** - not significant), i^2=67%, 4 trials, n=380, low certainty**.** At subgroup level, both adalimumab and etanercept trials showed superiority compared to placebo; No difference observed in the golimumab trial alone. Results in the infliximab study were in favour of infliximab over placebo, however not statistically significant.
  - Safety
    More adverse events were reported in the adalimumab group compared the placebo group (n=405 vs n=308, statistical significance not reported). No statistically significant difference was found in adverse events between etanercept and placebo groups.
- A high-quality clinical practice guideline (AGREE II score of 82% overall and 85% for rigour and methodology) published by American College of Rheumatology and the Arthritis Foundation in 2019 conditionally recommends for moderate/high disease activity, adding a biologic to DMARD monotherapy over changing to a second DMARD and conditionally recommends adding a biologic over changing to triple DMARD therapy (low quality evidence).
- A rapid review of quality-of-life, economic literature and HTA agency decisions found only one study on quality-of-life however many positive recommendations from HTA agencies for this indication (JIA patients with inadequate response to traditional DMARDs). Further quality-of-life evidence is unlikely to emerge.

- TNF-inhibitors (etanercept and adalimumab) are safe and effective in this population (low certainty for treatment response and moderate certainty for disease flare). These agents are recommended in good quality clinical practice guidelines and reimbursed by several HTA agencies. Due to price and efficacy estimates across both PICOs, adalimumab is the preferred agent.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Rationale: The Tertiary and Quaternary Hospital Level Committee suggests adalimumab for children and adolescents with Polyarticular Juvenile Idiopathic Arthritis (JIA) without JIA related uveitis (PICO 1) and with uveitis (PICO 2) who are refractory to conventional disease modifying anti-rheumatic drugs (DMARDs).
PICO 1: TNF inhibitors likely decrease JIA disease flares and may increase treatment response. The individual trials show that adalimumab and etanercept were both superior to placebo for the two outcomes.
PICO 2: TNF inhibitors may improve treatment response and reduce treatment failure for uveitis. Evidence appeared more favourable for adalimumab compared to placebo than etanercept compared to placebo.

Adalimumab and etanercept are recommended in good quality clinical practice guidelines and reimbursed by several HTA agencies. Both agents are administered subcutaneously which is feasible in terms of administration however adalimumab is less resource intensive. Adalimumab is more resource intensive than current standard of care.

Level of Evidence: Disease flare – moderate certainty, JIA ACR Pedi 30% response – low certainty, treatment success and failure for uveitis – low to moderate certainty.

(Refer to appendix 1 for the evidence to decision framework)

Summary of findings tables

PICO 1 - JIA without uveitis (combined TNFi compared to placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with TNFi				
Disease flares Assessed with: Worsening of 30% or more in at least three of the six core criteria for JIA and an improvement of 30% or more in no more than one of the criteria Follow-up: range 12 weeks to 32 weeks	592 per 1,000	**355 per 1,000** (219 to 580)	**RR 0.60** (0.37 to 0.98)	263 (3 RCTs)	⊕⊕⊕◯ Moderate[a,b]	TNF inhibitors likely reduce disease flares
ACR Pedi 30 Assessed with: Improvement of 30% or more in at least three of the six core criteria for JIA and a worsening of 30% or more in no more than one of the criteria. Follow-up: range 12 weeks to 32 weeks	471 per 1,000	**659 per 1,000** (457 to 951)	**RR 1.40** (0.97 to 2.02)	380 (4 RCTs)	⊕⊕◯◯ Low[a,c]	TNF inhibitors may increase response to treatment/ACR Pedi 30.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by 1 level due to inconsistency: substantial heterogeneity present, (I2=67%) potentially due to differences in agents, dosing regimens and follow-up periods
b. Not downgraded due to imprecision: Sample size meets OIS criterion to detect at 40% difference in flares between the groups (n=60) and 95% CI does not cross the line of no effect
c. Downgraded by 1 level due to imprecision: wide confidence intervals that crosses the line of no effect and includes important benefit

BACKGROUND

Juvenile Idiopathic Arthritis (JIA) is a group of chronic heterogenous disorders characterized by relapsing and remitting episodes of inflammation of the synovial membrane of the joints (synovitis) in patients aged <16 years which, unless treated, leads to damage and deformity of the affected joints and subsequent disability. JIA is not the same as rheumatoid arthritis or other forms of inflammatory arthritis and, although there are similarities with adult forms of arthritis. JIA should be considered separately in both children and young adults.[1,2,3]

According to the International League of Associations for Rheumatology (ILAR), seven different subtypes are recognized to classify patients: oligoarticular, rheumatoid factor (RF) positive polyarticular, RF negative polyarticular, enthesitis related arthritis (ERA), systemic onset, psoriatic arthritis, and undifferentiated arthritis.[4] Although onset and disease course differ, the subtypes of JIA share the occurrence of chronic inflammation of the joints, with infiltrations of immunocompetent cells that secrete inflammatory mediators. The disease is characterized by a disproportionate activation of the immune system, due to cytokine production by different types of cells. Tumor necrosis factor (TNF) is one of these cytokines.[5]

The global prevalence of JIA has been estimated to range from 3.8 to 400/100,000 with an incidence of 1.6 to 23/100,000.[6] The prevalence of JIA in Africa and Middle East was observed to be towards the lower range of the global estimate in a systematic review done by Al-Mayouf *et al*. [7]and it was highlighted that a huge unmet medical need in the region exists for reliable epidemiological data[8].

The current standard of care for treatment of polyarticular JIA includes NSAIDS, oral and intra-articular glucocorticoids, and methotrexate. However, approximately 20% of patients do not achieve adequate disease control and potentially require further treatment such as biological DMARDs [9, 10, 11]. A motivation was received for inclusion of Tumour Necrosis Factor Inhibitors (TNF inhibitors) onto the National Essential Medicines List for patients with inadequate response to DMARDS[12].

RESEARCH QUESTION:

During the research question and PICO development, two different PICOS were identified due to variation in outcomes and manner in which evidence was reported in studies; PICO 1 described below for individuals without uveitis and PICO 2 for individuals with uveitis. For ease of reading, efficacy and safety results for PICO 2 have been reported in an accompanying document. Although the findings are reported separately, the other elements (evidence to decision framework, costing, recommendation) reported in the document pertain to PICO 1 and PICO 2.

PICO 1: Is it safe and effective to add a tumor necrosis factor inhibitor (TNFi) to conventional synthetic DMARDs in patients with JIA *without JIA related uveitis* (PICO 1) having an inadequate response or being intolerant to NSAIDs, intra-articular glucocorticoids, and methotrexate? See accompanying document for PICO 2.

Eligibility criteria for review

PICO 1: Tumor necrosis factor inhibitors for individuals with JIA **without** uveitis (*see accompanying document for PICO 2) PICO 2: See accompanying document	
Population	Children, Adolescents & young adults with Juvenile Idiopathic Arthritis **without** uveitis refractory or intolerant to NSAIDs, intra-articular glucocorticoids and methotrexate.
Intervention	• Addition of a TNF-i to current standard of care • TNFi: Adalimumab, Etanercept, Golimumab, Infliximab
Comparator/s	• Current standard of care (NSAIDS, intra-articular glucocorticoids, methotrexate) AND / OR • Placebo
Outcome/s	*Efficacy* Primary outcomes • Number of participants with a disease flare • Number of participants with a JIA ACR 30% response Secondary outcomes • Number of participants with a JIA ACR 50% response • Number of participants with a JIA ACR 70% response • Number of participants with a JIA ACR 90% response *Safety* • *Serious adverse events, adverse events*
Study design/s	• Randomized Controlled Trials/systematic reviews/meta-analyses • International Treatment Guidelines.

METHODS

A rapid search of evidence was conducted in PubMed and the Cochrane Library in November 2022 for both PICOs. Studies included with the submitted motivation were also assessed for inclusion. The search strategy is outlined in Appendix 2 (same for both PICOs). Screening and selection of articles were conducted independently by two reviewers (JR and KM). Data extraction was conducted by two reviewers (JR and KM) and reviewed by the ERC. Selected RCTs for PICO 1 were assessed for risk of bias by two reviewers (SD & TL) using the Risk of Bias 2 Assessment Tool[13]. Individual agent comparisons compared to placebo were reported narratively and meta-analysis was undertaken to determine the pool efficacy for TNF-inhibitors compared to placebo (SD & TL) and a GRADE Assessment[14] was conducted by two reviewers (SD and TL). Guidelines were assessed with the AGREE II tool by two reviewers (KM & JR or KM & LD).

RESULTS

Results of the search

The search produced 353 results (both PICO 1 and 2) and 16 duplicates were removed. After title and abstract screening, full text review was carried out on 43 articles (18 trials, 16 SRs or MAs, 9 guidelines – both PICO 1 and 2). For PICO 1 four trials (6 articles) and 3 guidelines were included for data extraction (See Appendix 3 – Characteristics of included studies and Table 2 under the Guidelines section). A summary of the excluded studies can be found in Appendix 4 (PICO 1 and 2).

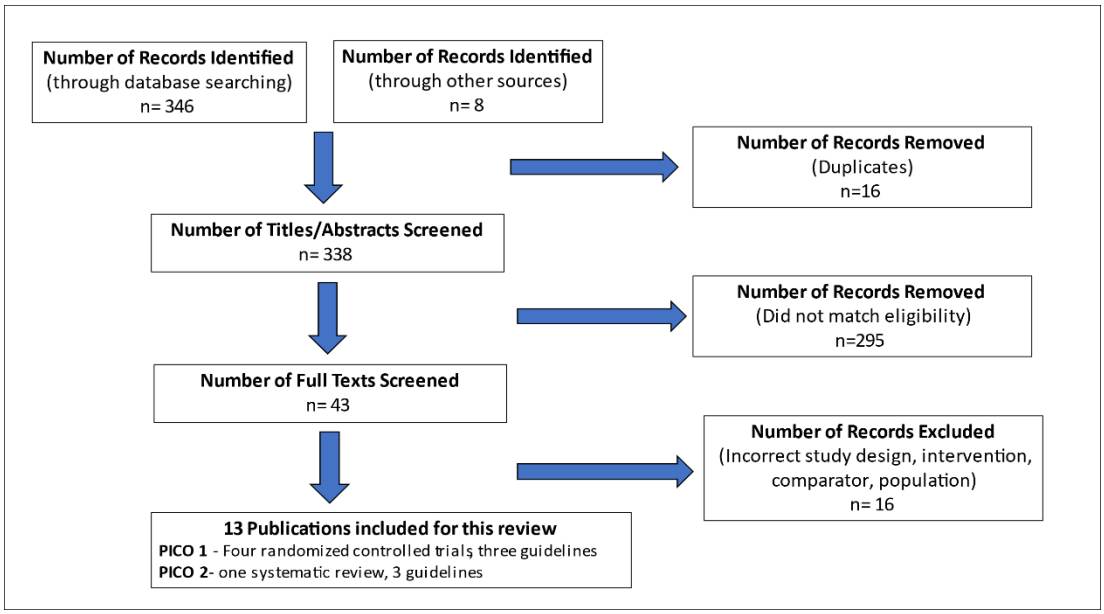


Figure 1 - Prisma Diagram

Description of studies included

PICO 1 – Tumor necrosis factor inhibitors for individuals with JIA **without uveitis** (PICO 2 - see accompanying document)

- Brunner *et al*. 2018[15] conducted a withdrawal trial on individuals aged 2-17 years with active JIA of six months or more despite treatment with methotrexate of at least three months (n=154 for randomised component). The trial comprised a 16-week open-label lead-in. Thereafter there was a 32-week randomised double-blinded placebo-controlled component for individuals who achieved a JIA American College of Rheumatology (ACR) Pediatric (Pedi) 30% response during the open-label component. The study explored the safety and efficacy of subcutaneous golimumab dosed at 30 mg/m2 of body surface area (maximum dose: 50 mg) every 4 weeks in addition to standard care compared to placebo and standard of care. The primary outcome of the randomised control component was JIA flares. Secondary outcomes included JIA ACR 50%, 70%, 90% responses, clinical remission, and safety
- Lovell *et al*. 2008[16] & 2020[17] (NCT00048542) reported on the results of withdrawal trial and long-term follow up respectively on individuals aged 4-17 years with JIA previously treated with NSAIDs (n=171). The trial comprised an initial 16-week, open-label lead-in (randomised by concomitant use of methotrexate) of adalimumab followed by a 32-week, randomised, placebo-controlled trial for ACR Pedi 30 responders (stratified by methotrexate concurrent use). The safety and efficacy of adalimumab 24mg/m2 of BSA subcutaneously every other week with or without methotrexate compared to placebo with or without methotrexate was explored. Thereafter there was 360-week, open-label extension. The primary outcome for the double-blind component was number of individuals with disease flares. Secondary outcomes were number achieving JIA ACR Pedi 30%, 50%, 70% and 90% responses at week 16 and adverse events. The primary outcome of the long-term open label extension was adverse events and secondary outcomes were JIA ACR 30%, 50%, 70% or 90% responses and the proportions of patients achieving 27-joint Juvenile Arthritis Disease Activity Score (JADAS27), low disease activity (LDA, ≤3.8) and inactive disease (ID, ≤1).

- Lovell *et al*. 2000[18] conducted a withdrawal trial on individuals ages 4-17 years with polyarticular JIA resistant or intolerant to methotrexate (n=69). The trial comprised a 3-month lead-in component followed by a 4-month, randomised double-blinded, placebo-controlled component for individuals who achieved the pre-specified response criteria. The study examined the safety and efficacy of 0.4 mg/kg etanercept subcutaneously twice weekly with subcutaneous placebo. The primary outcome was number of individuals who had a JIA disease flare by the end of the study. Secondary outcomes included JIA ACR Pedi 30%, 50%, 70% and 90% responses and adverse events.
- Ruperto *et al*. 2007[19] & 2010[20] (NCT00036374) reported on a multi-part randomised double blind trial on individuals aged older than 4 but younger than 18 years with JIA, and suboptimal response to methotrexate after 3 months or more of treatment, 5 or more active joints, and no active systemic symptoms (n=122). The trial comprised an initial 14-week, double-blind, placebo-controlled trial comparing infliximab 3 mg/kg infusion and methotrexate to placebo and methotrexate. Thereafter the individuals in the 3mg/kg infliximab group continued to receive treatment and the placebo group received 6mg/kg infliximab for 30 weeks. Lastly an open label extension of 146 weeks was conducted. The primary outcome for the placebo-controlled component was number achieving JIA ACR Pedi 30 response at week 14. Secondary outcomes included JIA ACR Pedi 30%, 50%, 70% and 90% responses and adverse events. Safety was the primary outcome for the open-label extension.

Risk of bias 2 assessment

A risk of bias 2 assessment was conducted for each study for the primary outcomes, see Figure 2 below for summary.

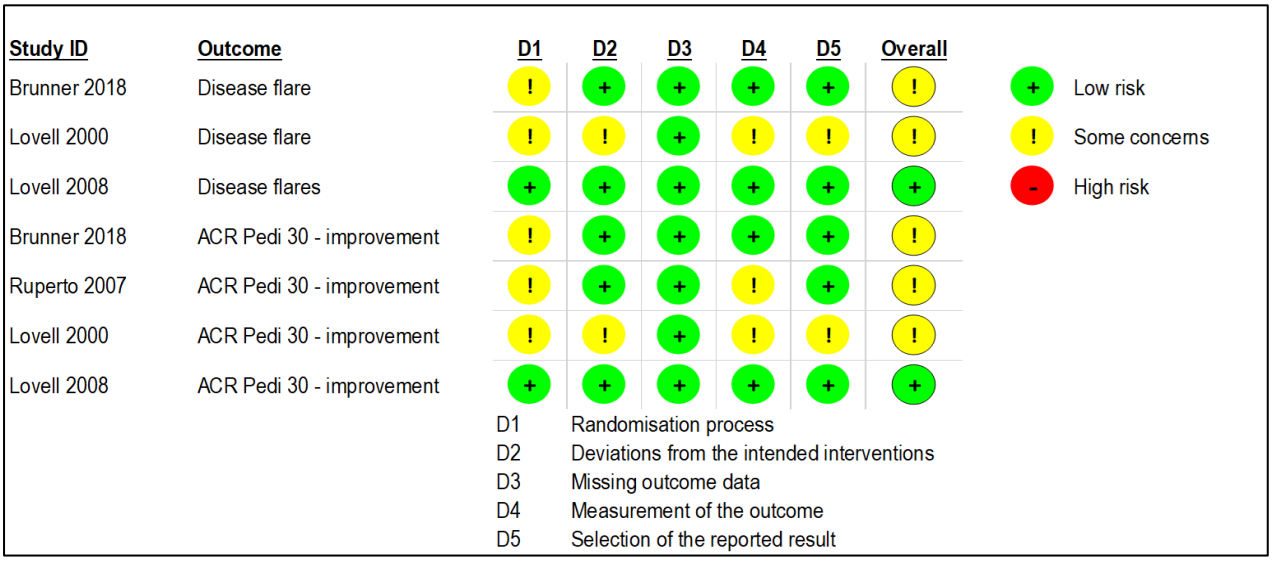


Figure 2: Cochrane risk-of-bias assessment version 2 results (Outcomes – developing a disease flare and achieving an ACR Pedi 30% response)

The study on golimumab (Brunner *et al*. 2018[15]) and the study on etanercept (Lovell *et al*. 2000[18]) both were evaluated to have some concerns for the outcome of JIA disease flare and the study in adalimumab (Lovell *et al.* 2008[17]) was considered 'low risk'. Results were the same for the ACR Pedi 30% response with the addition of the study on infliximab (Ruperto *et al*. 2007[19]) which was assessed to have 'some concerns' – See Appendix 5 for full assessment and domain results.

Effects of Interventions

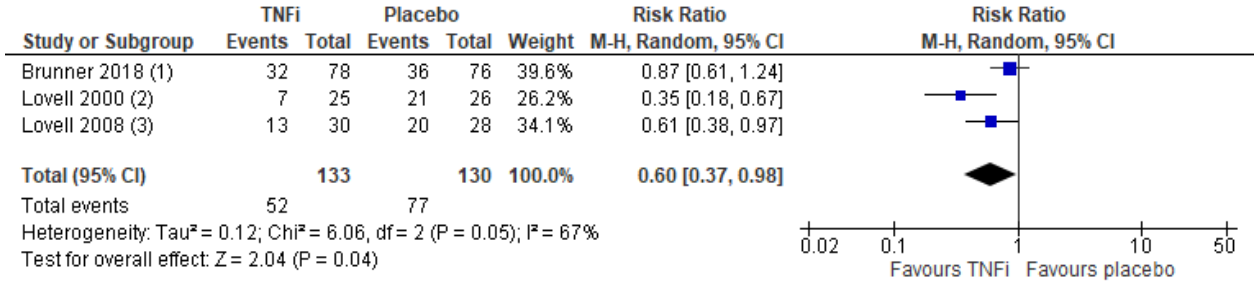
PICO 1 – Tumor necrosis factor inhibitors for individuals with JIA without uveitis (PICO 2 – see accompanying document)

Efficacy

Comparison 1: TNF-inhibitors versus placebo (4 trials, n=380[15,16,18,19])

Outcome 1.1 Number of participants with a JIA disease flare:

TNF inhibitors likely reduce disease flares compared to placebo (RR 0.60, 95% CI 95% [0.37 to 0.98], NNT 3, 95% CI [2 to 50]; P=0.04, i^2=67% (moderate heterogeneity), 3 trials, 263 participants, moderate certainty evidence). See Figure 3 below.



Footnotes

(1) Golimumab 30 mg/m2 of body surface area (maximum dose: 50 mg) every 4 weeks. Follow-up: 32 weeks

(2) Etanercept subcutaneous 0.4 mg/kg twice weekly. Follow-up: 12 weeks

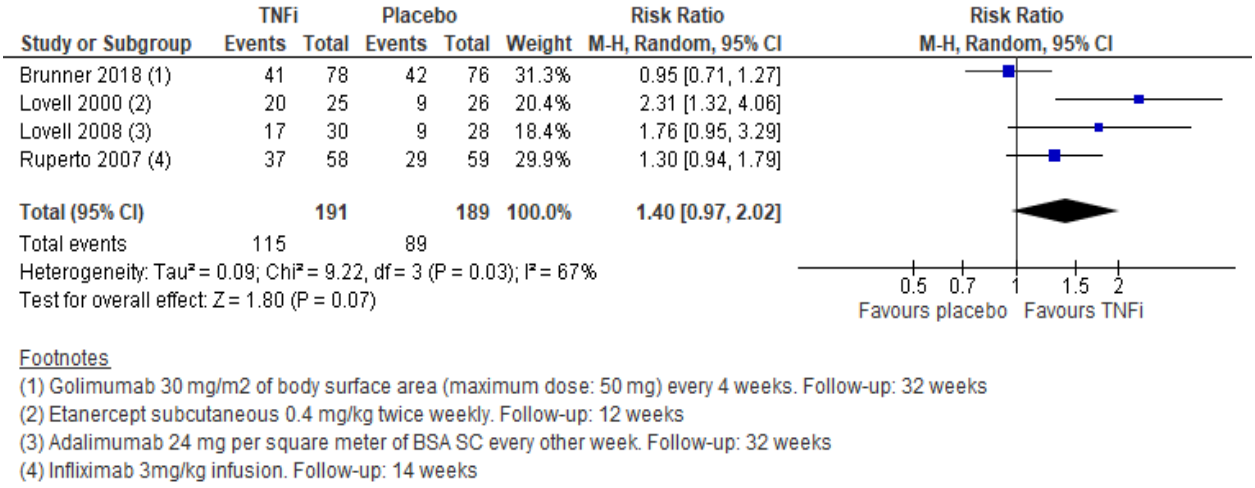
(3) Adalimumab 24 mg per square meter of BSA SC every other week. Follow-up: 32 weeks

Figure 3: Forest plot for meta-analysis conducted for Outcome 1. 1 - Number of participants with a JIA disease flare

- The trial on golimumab reported that the proportion of participants who developed a JIA flare was similar in each group (RR=0.87 in favour of placebo, CI 95% [0.85 to 1.49]; P = 0.41 – not significant).
- The trial on adalimumab trial reported that the proportion of participants who developed a JIA flare was higher in the placebo groups than the adalimumab groups (Without methotrexate group comparison - RR=0.61 in favour of adalimumab, CI 95% [0.38 to 0.97], NNT=4 95% CI [2 to 28]; P = 0.03 – significant; With methotrexate group comparison – RR=0.57 in favour of adalimumab, CI 95% [0.35 to 0.92], NNT=4 95% CI [2 to 16]; P=0.02 – significant).
- The trial on etanercept reported that the proportion of participants who developed a JIA flare was higher in the placebo group than the etanercept group (RR=0.35 in favour of etanercept, CI 95% [0.18 to 0.67], NNT=2 95% CI [2 to 4]; P = 0.0003 – significant.

Outcome 1.2 Number of participants with a JIA ACR Pedi 30% response:

TNF inhibitors may increase ACR Pedi 30 response (RR 1.4 (95% CI [0.97 to 2.02], P=0.07 (not significant), i^2=67% (moderate heterogeneity), 4 trials, 380 participants, low certainty evidence) – See Figure 4 below.



Footnotes
(1) Golimumab 30 mg/m2 of body surface area (maximum dose: 50 mg) every 4 weeks. Follow-up: 32 weeks
(2) Etanercept subcutaneous 0.4 mg/kg twice weekly. Follow-up: 12 weeks
(3) Adalimumab 24 mg per square meter of BSA SC every other week. Follow-up: 32 weeks
(4) Infliximab 3mg/kg infusion. Follow-up: 14 weeks

Figure 4: Forest plot for meta-analysis conducted for Outcome 1. 2 - Number of participants with a JIA ACR Pedi 30% response

- The trial on golimumab shows that less patients in the golimumab group (n=47, 69.1%) had a JIA ACR 30% response by week 96 than the placebo (n=45, 73.8%) group (RR: 0.94, 95% CI [0.75 to 1.17]; P = 0.56 – not significant).
- The trial on adalimumab trial reported that there was a higher percentage of participants who achieved a JIA ACR Pedi 30% response in the adalimumab groups compared to the placebo groups (Without methotrexate group comparison - RR=1.76 in favour of adalimumab, CI 95% [0.95 to 3.29], P = 0.06 – not significant; With methotrexate group comparison – RR=1.67 in favour of adalimumab, CI 95% [1.03 to 2.70], NNT 4, 95% CI [3-30], P=0.03 – significant).
- The trial on etanercept reported that there were more patients in the etanercept (n=20; 80%) group with an ACR JIA 30 response at the end of the study than the placebo (n=9, 35%) group (RR 2.13, 95% CI [1.23 to 3.71]; NNT 3, 95% CI [2 to 5]; P<0.01 - significant).
- The trial on infliximab reported that there was a higher percentage of participants who achieved a JIA ACR Pedi 30% response in the infliximab group compared to the placebo group (RR=1.32 in favour of infliximab, CI 95% [0.95 to 1.84], P=0.12 – not significant).

*Comparison 2: **Adalimumab** 24 mg per square meter of BSA SC every other week versus placebo (1 randomised controlled withdrawal trial, n=171[16])*

Outcome 2.1 Number of participants with a JIA ACR Pedi 50% response:
There was a higher percentage of participants who achieved a JIA ACR Pedi 50% response in the adalimumab groups compared to the placebo groups (Without methotrexate group comparison - RR=1.66 in favour of adalimumab, CI 95% [0.88 to 3.13], P = 0.10 – *not significant*; With methotrexate group comparison – RR=1.67 in favour of adalimumab, CI 95% [1.03 to 2.70], NNT 4, 95% CI [3-30], P=0.03 – *significant*).
Outcome 2.2 Number of participants with a JIA ACR Pedi 70% response:
There was a higher percentage of participants who achieved a JIA ACR Pedi 70% response in the adalimumab groups compared to the placebo groups (Without methotrexate group comparison - RR=1.63 in favour of adalimumab, CI 95% [0.81 to 3.29], P = 0.16 – *not significant*; With methotrexate group comparison – RR=2.34 in favour of adalimumab, CI 95% [1.31 to 4.18], NNT 3, 95% CI [2-7], P=0.0002 – *significant*).
Outcome 2.3 Number of participants with a JIA ACR Pedi 90% response:
There was a higher percentage of participants who achieved a JIA ACR Pedi 90% response in the adalimumab groups compared to the placebo groups (Without methotrexate group comparison - RR=1.68 in favour of adalimumab, CI 95% [0.64 to 4.41], P = 0.28 – *not significant*; With methotrexate group comparison – RR=1.58 in favour of adalimumab, CI 95% [0.82 to 2.98], P=0.17 – *not significant*).

Comparison 3: Infliximab 3 mg/kg infusion and methotrexate versus placebo and methotrexate (1 randomised controlled withdrawal trial, n=122[19])

Outcome 3.1 Number of participants with a JIA ACR Pedi 50% response:

There was a higher percentage of participants who achieved a JIA ACR Pedi 50% response in the infliximab group compared to the placebo group (RR=1.50 in favour of infliximab, CI 95% [0.96 to 2.34], P=0.078 – *not significant*).

Outcome 3.2 Number of participants with a JIA ACR Pedi 70% response:

There was a higher percentage of participants who achieved a JIA ACR Pedi 70% response in the infliximab group compared to the placebo group (RR=1.49 in favour of infliximab, CI 95% [0.69 to 3.23], P=0.130 – *not significant*).

Safety

The trial on golimumab[15] reported no significant difference between the golimumab and placebo groups in participants with more than one adverse event (78.2% vs 82.9%, RR 0.94, 95% [CI 0.81 to 1.1], n=154 - not significant) or more than one serious adverse event (n=8 vs n=10, RR 0.78 95% CI [0.33 to 1.87], not significant) during the double-blind randomised component. After 160 weeks of open label golimumab 92.5% of participants had a one or more adverse event and upper respiratory tract infections was the most common adverse event. Thirty-nine participants (22.5%) had a serious adverse event (12 of which were potentially linked to the treatment).

In the adalimumab trial[16,17] There were more adverse events reported in the adalimumab groups (without methotrexate n=171, with methotrexate n=234) compared the placebo groups (without methotrexate n=153, with methotrexate 155) and the most common adverse event was injection site reaction during the double-blind component. Only one serious adverse event occurred which was in the placebo group. Infections (n=880, 148.4/100 patient years) and injection site reactions (n=912, 153.8/100 patient years) were the most common adverse event reported during the long-term extension. Incidence of severe adverse events potentially linked to adalimumab was 19 (3.2/100 patient years).

The trial on etanercept[18] found no significant difference between the etanercept and placebo groups in frequency of adverse events during the double-blind component. During the open label component, the most common adverse events recorded were injection site reaction (39%) and upper respiratory tract infections (35%).

In the infliximab[19,20] study difference in adverse events between placebo and infliximab groups during the double-blind component were not reported. During the long-term follow-up by week 204, ninety-one percent of participants had an adverse event and the most common event recorded was upper respiratory tract infection (39.7%). Twenty-two percent had a serious adverse event of which worsening of arthritis was the most common (8%).

Quality of the Evidence

The certainty of evidence for TNFi therapy compared to placebo for number of participants who developed a JIA disease flare was considered **moderate certainty** (See Summary of Findings Table). The certainty of evidence was not downgraded for risk-of-bias (See Figure 2). The certainty of evidence was not downgraded due to imprecision, indirectness or publication bias. There was however moderate heterogeneity (i^2=67%)

potentially due to differences in agents, dosing regimens and follow-up periods thus the certainty of evidence was downgraded by 1.

The certainty of evidence for TNFi therapy compared to placebo for number of participants with a JIA ACR Pedi 30% response was categorised as **low certainty** (See Summary of Findings Table). The certainty of evidence was not downgraded for risk-of-bias (See Figure 2). The certainty of evidence was not downgraded due to indirectness or publication bias. Likewise with the disease flare outcome, there was moderate heterogeneity (i^2=67%) potentially due to differences in agents, dosing regimens and follow-up periods and the certainty of evidence was downgraded by 1. The certainty of evidence was downgraded further by 1 for imprecision due a wide confidence interval, crossing the line of no effect and important benefit.

Guidelines

Three relevant guidelines on the treatment of JIA without uveitis (PICO 1) were found (See accompanying document for PICO 2). These guidelines were produced by American College of Rheumatology (ACR) in collaboration with Arthritis Foundation 2019[21], the National Institute of Health and Care Excellence (NICE) 2015[22], and the German Society of Pediatric and Juvenile Rheumatic Diseases (GKJR) 2022[23]. The clinical guidelines were appraised using the AGREE II tool (see Appendix 6) and were found to vary in quality from lower quality (GKJR 2022) to higher quality (NICE 2015, ACR 2019). The relevant recommendations from each guideline and selected items from the AGREE II appraisal outcome are presented in Table 2.

Table 2. Clinical guideline quality assessments and recommendations – PICO 1: JIA without uveitis

Guideline	Recommendations	Strength of evidence	AGREE II*
American College of Rheumatology (ACR) 2019 & Arthritis Foundation (AF) Error! Bookmark not defined.	<u>In children and adolescents with JIA and active polyarthritis:</u> **Subsequent therapy: Low disease activity (cJADAS-10 ≤2.5 and ≥1 active joint)** For children receiving a DMARD and/or biologic: - Escalating therapy is conditionally recommended over no escalation of therapy. Escalation of therapy may include: Intraarticular glucocorticoid injection(s), optimization of DMARD dose, trial of methotrexate if not done, and adding or changing biologic. **Subsequent therapy: Moderate/high disease activity (cJADAS-10 >2.5)** *If patient is receiving DMARD monotherapy:* - *Adding a biologic to original DMARD is conditionally recommended over changing to a second DMARD* - *Adding a biologic is conditionally recommended over changing to triple DMARD therapy* <u>Biologic DMARDs</u> • *In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (<u>etanercept, adalimumab, golimumab</u>, abatacept, or tocilizumab) combination therapy with a DMARD is conditionally recommended over biologic monotherapy.* *Subsequent therapy: Moderate/high disease activity (cJADAS-10 >2.5)*	Very low quality Low quality Low quality Very low quality (etanercept, golimumab); moderate quality (adalimumab), Low, quality	**Rigour of development:** 85% **Overall score:** 82%

	Combination therapy with a DMARD is strongly recommended for infliximab		
Guideline	**Recommendations**	**Strength of evidence**	**AGREE II***
National Institute of Care and Excellence Technology Appraisal 2015[22]	• Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorisations, as options for treating polyarticular juvenile idiopathic arthritis (JIA), including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is: - *for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD* - *for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, methotrexate* • When more than 1 technology is suitable (taking into account extra-articular manifestations) treatment should be started with the least expensive technology, taking into account administration costs, the dose needed and the product cost per dose.	Consensus, quality results not reported	**Rigour of development:** 69% **Overall score:** 76%
German Society of Pediatric and Juvenile Rheumatic Diseases (GKJR)[23]	Recommendation 6: We suggest using TNF-alpha inhibition in case of inadequate response or intolerance to conventional synthetic DMARD therapy (e.g., MTX) in non-systemic JIA	100% consensus by group – no quality result reported	**Rigour of development:** 60% Overall score: 49%

COSTING AND BUDGET IMPACT (PICO 1 and 2)

Table 1: Costing per patient (est. 40kg) per month (Incremental to standard of care)

Agent	Regimen	Pack size	Price per unit		Cost p/ dose	Cost p/ month	Cost per annum
Adalimumab SC	20mg *every second* week if < 30kg, and 40mg *every second week* if > 30kg	40mg per syringe x2 (80mg/pack)	Quote	R1 688.86[A]	R1 688.86	R3 377.71	R40 532.52
			SEP	R2 412.65*	R2 412.65	R4 825.29	R57 903.48
Etanercept SC	0.8mg/kg (max 50mg) SC *weekly*	25mg vial (4s)	Quote	R632.50[B]	R1 265.00	R5 060.00	R60 720.00
			SEP	R1 050.41~	R2 100.82	R8 403.28	R100 839.36
Infliximab IV	6kg/mg at week 0, 2, and 6 weeks thereafter 6kg/mg *every 6-8 weeks*	100mg vial	Quote	R2 269.00[C]	R6 807.00	R6 807.00	R81 684.00
			SEP	R3 241.68^	R9 725.04	R9 725.04	R116 700.48

A. State quote as of January 2023 (Amgen – Amgevita) ; * SEP as of March 2022 Amgevita
B. State quote as of December 2022 (Enbrel PFP – Pfizer); ~ SEP as of January 2023 Enbrel
C. State quote as of December 2022 (Cipla – Remiflex)

Table 2: Budget Impact Per Annum

Agent	Cost per annum per patient		Number of patients	Incremental budget / annum	
	Quote	SEP		Quote	SEP
Adalimumab	R40 532.52	R57 903.48	80*	R3 242 601.60	R4 632 278.40
Etanercept	R60 720.00	R100 839.36		R4 857 600.00	R8 067 148.80
Infliximab**	R81 684.00	R116 700.48		R7 079 280.00	R10 114 041.60

* Estimate based on expert opinion in the field - Estimated 600-700 patients with JIA in the country with access to paediatric rheumatology services, 10-15% estimated require biologics, mid-way estimate 80 patients.
**Based on initial year (induction and maintenance).

CONCLUSION

The current standard of care for treatment of polyarticular JIA includes NSAIDS, oral and intra-articular glucocorticoids, and methotrexate however some individuals are refractory or intolerant to these agents and may require additional treatment with TNF inhibitors. A meta-analysis was undertaken on four trials conducted on four different agents (golimumab, adalimumab, infliximab and etanercept exploring two main outcomes (development of a JIA disease flare and response to treatment – JIA ACR Pedi 30% response). Outcomes across the trials were classified as having 'some concerns' or 'low risk'.

Evidence for JIA disease flares rated as moderate certainty - TNF inhibitors are likely to reduce JIA disease flares. Evidence for treatment responses rated as low certainty – TNF inhibitors may increase response to treatment. International guidelines (evaluated to be of good quality) highlighted evidence as low to moderate quality but recommended TNF inhibitors in this population group. Evidence for PICO 2 was aligned with PICO 1 (see accompanying document for details). A rapid review of quality of life, economic literature and HTA agency decisions found that despite the small evidence base of quality of life data in this population group, several HTA agencies recommended inclusion of TNF inhibitors (NICE, CADTH, PBAC) for the indication.

Due to lack of efficacy, golimumab was not costed. All agents are more resource intensive than current standards of care. Adalimumab is less resource intensive than etanercept or infliximab based on state quote prices and SEP. It is suggested that adalimumab be recommended for use in JIA refractory to conventional therapy.

Reviewers: Kim MacQuilkan, Jane Riddin, Liezl du Plessis, Solange Durao, Sumayyah Ebrahim, Trudy Leong

Declaration of interests:

- Kim MacQuilkan (EDP, NDoH supported by Right to Care) has no interests to declare.
- Jane Riddin (EDP, NDoH) has no interests to declare.
- Liezl du Plessis (Department of Health, Northern Cape, Robert Sobukwe Hospital)
- Solange Durao (SAMRC, Cochrane)*
- Sumayyah Ebrahim (SAMRC, Cochrane)*
- Trudy Leong (SAMRC, Cochrane)*

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Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: X Low: ☐ Very low: ☐	PICO 1 • Outcome: JIA disease flare – GRADE assessment was moderate, downgraded by 1 for heterogeneity (See Quality of Evidence section).
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: X Very low: ☐	PICO 1 • Outcome: JIA ACR Pedi 30% response – GRADE assessment was low, downgraded by 1 for heterogeneity and 1 for imprecision (See Quality of Evidence section).
	What is the certainty/quality of evidence? High: ☐ Moderate: X Low: ☐ Very low: ☐	PICO 2 (see accompanying document for more detail): • Outcome: Treatment success and failure as defined by individual study – considered moderate quality based on AMSTAR 2 assessment (See Quality of the Evidence section in accompanying document).
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: X Very low: ☐	PICO 2 (see accompanying document for more detail): • Outcome: Treatment success and failure as defined by increase or decrease in SUN AC grading – GRADED as low within the systematic review, downgraded by 2 for imprecision (See Quality of the Evidence section in accompanying document.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: X Small: ☐ None: ☐	*PICO 1* *Outcome: JIA disease flare* • *TNFi pooled vs placebo* – RR 0.60, CI 95% [0.37 to 0.98], **NNT 3**, 95% CI [2 to 50]; P=0.04. • *Adalimumab (with methotrexate) vs placebo* – RR 0.57 CI 95% [0.35 to 0.92), **NNT=4** 95% CI [2 to 16], P=0.02 • *Etanercept vs placebo* – RR 0.35 95% CI [0.18 to 0.67], **NNT=2** 95% CI [2 to 4]; P=0.0003
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☐ Small: X None: ☐	*PICO 1:* Outcome: *JIA ACR Pedi 30% response* • *TNFi pooled vs placebo* – RR 1.4 (95% CI [0.97 to 2.02], P=0.07 • *Adalimumab (with methotrexate) vs placebo* – RR 1.67 CI 95% [1.03 to 2.70], **NNT 4**, 95% CI [3-30], P=0.03. • *Etanercept vs placebo* – RR 2.13 95% CI [1.23 to 3.71], **NNT 3** 95% CI [2 to 5], P < 0.01. • *Infliximab vs placebo* – RR 1.32 95% CI [0.95 to 1.84], P=0.12.

	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ X Small ☐ None ☐	*PICO 2* (see accompanying document for more detail)*:* *Outcome:* Treatment success as defined by individual study • *TNFi pooled vs placebo* – RR 2.6 95% CI [1.30 to 5.20], **NNT 4** 95% CI [3 to 13]; P=0.007] • *Adalimumab vs placebo* – RR 3.11 95% CI [1.40 to 6.90], **NNT 4** 95% [3 to 10]; P=0.005. • *Etanercept vs placebo* – RR 0.27 95% CI [0.27 to 4.23], P=0.92.
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☐ None ☒ X	*PICO 2* (see accompanying document for more detail)*:* Outcome: Treatment success as defined by increase or decrease in SUN AC grading • *TNFi pooled vs placebo* – RR=0.66, 95% CI [0.21 to 2.10]; P=0.49. • *Adalimumab vs placebo* – RR=0.63, 95% CI [0.12 to 3.24], P = 0.58. • *Etanercept vs placebo* – RR=0.71, 95% CI [0.15 to 3.50], P = 0.68.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ X Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*PICO 1 and PICO 2: Not GRADED but considered low – individual reports per study*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ X None ☐	*Small – individual reports per study*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ x Favours control ☐ Intervention = Control *or* Uncertain ☐	*Yes*
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ X No ☐ Uncertain ☐	*TNFi initiation / monitoring:* *TNFis will be initiated & monitored by a pediatric rheumatologist & ophthalmologist.* *Mode of delivery:* *Etanercept: s/c injection q weekly* *Adalimumab: s/c injection q2 weekly* *Golimumab: s/c injection q4weekly* *Infliximab: IV infusions – less feasible*

<table>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td>
<td>Cost of medicines/ month:
<table><tr><th rowspan="2">Medicine</th><th colspan="2">Cost (ZAR)</th></tr><tr><th>State quote</th><th>SEP</th></tr><tr><td>Adalimumab SC</td><td>R3 377.71</td><td>R4 825.29</td></tr><tr><td>Etanercept SC</td><td>R5 060.00</td><td>R8 403.28</td></tr><tr><td>Infliximab IV</td><td>R6 807.00</td><td>R9 725.04</td></tr></table>Additional resources: administration costs would be additional costs for infliximab</td>
</tr>
<tr>
<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor: X
Major:
Uncertain:

Is the option acceptable to key stakeholders?
Yes: X
No:
Uncertain:</td>
<td>JIA influences all aspects of a child's life and those of the family. The goal of JIA treatment aims to achieve inactive disease state, preventing disability and damage and age-appropriate development of these children and adolescents.

Motivation received from clinicians

Guidelines recommend TNF inhibitors

The WHO-Essential Medicine List (complimentary) – for priority diseases, includes adalimumab (and other therapeutic alternatives, such as etanercept / infliximab) for the treatment of JIA.</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes:
No:
Uncertain: X</td>
<td>Affects a potentially marginalised group (rare disease and disability)

Some remote provinces do not have readily access to these specialists. With newer technology such as telemedicine the hope would be that all patients with JIA and refractory disease could be evaluated and assessed by a pediatric rheumatologist to determine safety & suitability of a TNFi.</td>
</tr>
</table>

Appendix 2: Search strategy

PUBMED

#	Query	Search Details	Results
6	Search: **#1 AND #2** Filters: **Meta-Analysis, Systematic Review, randomized controlled trials**	Search: ((((((((((((tumor necrosis factor inhibitor[MeSH Terms])) OR (tumor necrosis factor inhibitor[Title/Abstract])) OR (tumor necrosis factor alpha inhibitor[Title/Abstract])) OR (tumour necrosis factor inhibitor[Title/Abstract])) OR (tumour necrosis factor alpha inhibitor[Title/Abstract])) OR (adalimumab[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (golimumab[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (etanercept[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract]) AND (juvenile idiopathic arthritis[MeSH Terms]) OR (Juvenile idiopathic arthritis[Title/Abstract]) Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review	**345**
5	#3 AND #4	((((((((((((tumor necrosis factor inhibitor[MeSH Terms])) OR (tumor necrosis factor inhibitor[Title/Abstract])) OR (tumor necrosis factor alpha inhibitor[Title/Abstract])) OR (tumour necrosis factor inhibitor[Title/Abstract])) OR (tumour necrosis factor alpha inhibitor[Title/Abstract])) OR (adalimumab[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (golimumab[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (etanercept[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract]) AND (juvenile idiopathic arthritis[MeSH Terms]) OR (Juvenile idiopathic arthritis[Title/Abstract]) AND (((((((randomized controlled trial[Publication Type]) OR (Systematic Review[Publication Type])) OR (Meta-analysis[Publication Type])) OR (Controlled Clinical Trial[Publication Type])) OR (randomized[Title/Abstract])) OR (systematic review[Title/Abstract])) OR (meta-analysis[Title/Abstract])) NOT (animals[Title/Abstract])	508
4	#1AND #2	((((((((((((tumor necrosis factor inhibitor[MeSH Terms])) OR (tumor necrosis factor inhibitor[Title/Abstract])) OR (tumor necrosis factor alpha inhibitor[Title/Abstract])) OR (tumour necrosis factor inhibitor[Title/Abstract])) OR (tumour necrosis factor alpha inhibitor[Title/Abstract])) OR (adalimumab[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (golimumab[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (etanercept[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract]) AND (juvenile idiopathic arthritis[MeSH Terms]) OR (Juvenile idiopathic arthritis[Title/Abstract])	6631
3		(((((((randomized controlled trial[Publication Type]) OR (Systematic Review[Publication Type])) OR (Meta-analysis[Publication Type])) OR (Controlled Clinical Trial[Publication Type])) OR (randomized[Title/Abstract])) OR (systematic review[Title/Abstract])) OR (meta-analysis[Title/Abstract])) NOT (animals[Title/Abstract])	305 247
2	TNF-inhibitors	((((((((((((tumor necrosis factor inhibitor[MeSH Terms])) OR (tumor necrosis factor inhibitor[Title/Abstract])) OR (tumor necrosis factor alpha inhibitor[Title/Abstract])) OR (tumour necrosis factor inhibitor[Title/Abstract])) OR (tumour necrosis factor alpha inhibitor[Title/Abstract])) OR (adalimumab[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (golimumab[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (etanercept[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract])	28627
1	JIA	(juvenile idiopathic arthritis[MeSH Terms]) OR (Juvenile idiopathic arthritis[Title/Abstract])	13 213

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search	Query	Results
#1	MeSH descriptor: [Arthritis, Juvenile] explode all trees	343
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	97
#3	#1 AND #2	1

Appendix 3: Characteristics of included studies

Table 1 – PICO 1 (JIA without uveitis)

Citation	Study design	Population (n)	Treatment	Main findings
Brunner *et al*. 2018[15]	Randomised double-blinded placebo-controlled **withdrawal trial** (open-label 16-week lead in followed by 32-week randomised double-blinded component)	Open label, Patients aged 2–17 years diagnosed with rheumatoid factor (RF)-positive or RF-negative polyarticular, extended oligoarticular JIA, systemic JIA without systemic features or juvenile psoriatic arthritis and disease duration of ≥6 months and active JIA despite ≥ months of methotrexate treatment, n = 173 Double-blind, Patients from open label with JIA American College of Rheumatology (ACR) 30 response after 16 weeks, n=154	Open label Subcutaneous **golimumab** dosed at 30 mg/m2 of body surface area (maximum dose: 50 mg) every 4 weeks and standard of care (methotrexate, NSAIDs, corticosteroids at stable dosing), THEN double-blind Subcutaneous **golimumab** plus standard care (n=76) OR Placebo plus standard care (n=78)	**Efficacy** Open label: • One hundred and fifty-four of the 173 patients (89%) were JIA ACR30 responders. One hundred and thirty-seven (79.2%), 114 (65.9%) and 63 (36.4%) patients were JIA ACR50/70/90 responders respectively. Fifty-nine (34.1%) reached clinically inactive disease. Double-blind: *Primary outcome* • Proportion with JIA flare in each group was similar, 40 out 76 patients (53%) in the placebo group vs 46 out 78 patients (59%) in the golimumab group (RR=1.12 CI 95% [0.85 to 1.49], P = 0.41, – *not significant*). *Secondary Outcomes* • No difference observed in clinical remission between placebo and golimumab groups (placebo =11.8% vs golimumab=12.8%, P = 0.848). • Less patients in the golimumab group (n=47, 69.1%) had a JIA ACR 30% response by week 96 than the placebo (n=45, 73.8%) group (RR: 0.94, 95% CI [0.75 to 1.17]; P = 0.56 – *not significant).* **Safety** Open label: • During the open label run in period 118 patients (68.2%) had one or more adverse event with infections or infestations the most common adverse event (68 patients, 38.7%). Eight patients had one or more severe adverse event (4.6%). Double-blind: • Number of patients with more than 1 adverse event during the double-blind component was similar in placebo (n=63, 82.9%) and golimumab (n=61, 78.2%) groups (RR 0.94 CI 95% [0.81 to 1.1], P=0.46). There was no difference found in patients with one or more severe adverse events between groups (golimumab n=8 vs placebo n=10, RR 0.78 Ci 95% [0.33 to 1.87], P = 0.58). Long-term follow-up Safety was monitored for 160 weeks for patients who continued or switched to golimumab (n=173). One hundred and sixty patients (92.5%) had one or more adverse event and 39 patients (22.5%) had one or more serious adverse event.

Citation	Study design	Population (n)	Treatment	Main findings
Lovell et.al. 2008[16] & 2020[17]	Randomised double-blinded placebo-controlled **withdrawal trial** (open-label 16-week lead in followed by 32-week randomised double-blinded component) Followed by a 360-week open-label long-term extension	Open-label, children (age 4-17) with juvenile rheumatoid arthritis, previously treated with NSAIDs, N=171 Double-blind, children from the open label with an ACR Pedi 30 response, n=133	Open label randomised **Adalimumab** 24 mg per square meter of BSA SC every other week for 16 weeks AND methotrexate OR adalimumab only THEN double-blind **Adalimumab** AND methotrexate (n=38) OR Placebo AND methotrexate (n=37) OR **Adalimumab** only (n=30) OR Placebo only (n=28) (Stratified based on methotrexate use) THEN open label **Adalimumab**	**Efficacy** Open label: • Eighty of the 85 patients (94%) taking methotrexate and 64 of the 86 patients not administered methotrexate were JIA ACR30 responders at week 16. Double-blind: *Primary outcome* • Among patients not receiving methotrexate, disease flares occurred in 43% (n=13) of those receiving adalimumab and 71% (n=20) of those receiving placebo (RR 0.60 CI 95% [0.38 to 0.97], NNT=4 95% CI [2 to 28]; P = 0.03). *Secondary outcomes* • Among patients receiving methotrexate, flares occurred in 37% (n=14) of those receiving adalimumab and 65% (n=24) of those receiving placebo (RR 0.57 95% CI [0.35 to 0.92], NNT=4 95% CI [2 to 16]; P = 0.02). • At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70 responses were significantly greater (P=0.03, P=0.03, P=0.002) for those receiving adalimumab (63%, 63%, 63%) than for those receiving placebo (38%, 38%, 27%). The percentage achieving ACR Pedi 90 was not significant (P=0.17). • At 48 weeks, the percentages of patients treated without methotrexate who had ACR Pedi 30, 50, 70, 90 responses were greater but not significantly (P=0.06, P=0.10, P=0.16, P=0.28) for those receiving adalimumab (57%, 53%, 47%, 30%) than for those receiving placebo (32%, 32%, 29%, 18%). Open label extension: • By week 104, most patients had achieved ACR Pedi 30 (n=90, 96%), 50 (n=88, 94%) 70 (n=84, 89%) and 90 (n=62, 66%) – based on observational analysis (observed without imputation). Non-responder imputation analysis ranged from 36%-53%. • Similarly, majority of patients achieved JADAS27 Low disease activity (observed analysis: 73%, NRI analysis: 44%) at week 104. JADAS27 Inactive disease was achieved by 43% of patients in the observed analysis and 26% in the non-responder imputation analysis at week 104. • The response rates were generally maintained through week 312 – only figures provided. **Safety** Open label: • There was a total of 869 adverse events reported (422 in methotrexate group – 15.5 per patient year and 447 in the no methotrexate group – 15.3 per patient year). The most common adverse event was injection-site reactions. There were three serious adverse events (0.1 patient years) in the methotrexate group and seven (0.1 patient years) in the no methotrexate group. Double-blind: • There was a total of 405 adverse events reported in the adalimumab groups (234 in methotrexate group – 12.8 per patient year and 171 in the no methotrexate group – 11.9 per patient year) and a total of 308 in the placebo groups (155 in methotrexate group – 10.3 per patient year and 153 in the no methotrexate group – 14.4 per patient year. The most common adverse events were injection-site reactions. There was only one serious adverse event across the groups (placebo and methotrexate group).

				Open-label extension: • A total of 3605 (608.1/100 patient years) adverse events and 75 (12.7/100 patient years) serious adverse events were reported (592.8 patient years adalimumab). Incidence of adverse events and serious adverse events possibly related to the study drug were 1394 (235.2/100 patient years) and 19 (3.2/100 patient years). Injection site reactions (n=912, 153.8/100 patient years) and infections (n=880, 148.4/100 patient years were the most common).

Citation		Study design	Population (n)	Treatment	Main findings
Lovell et.al. 2000[18]		Randomised double-blinded placebo-controlled **withdrawal trial** (open-label 3 months lead in followed by 4-month randomised double-blinded component)	Open-label, children aged 4-17 years with polyarticular juvenile rheumatoid arthritis, not tolerating methotrexate or with an inadequate response, n=69 Double blind placebo controlled, with a response to etanercept, n= 51	**Etanercept** subcutaneous 0.4 mg/kg SC twice weekly (up to 3 months). THEN **Etanercept** subcutaneous OR Placebo subcutaneous	**Efficacy** Open label: • 51 of the 69 patients (74%) had responses to etanercept (ACR Pedi 30), Forty-four (64%) achieved ACR Pedi 50 and 25 achieved ACR Pedi 70). Double-blind: • 21 out of 26 patients in the placebo group (81%) had a JIA disease flare, compared to 7 of the 25 patients in the etanercept (28%) group (RR 0.35 CI 95% [0.18 to 0.67], P=0.003). • The median time to disease flare with placebo was 28 days, as compared with > than 116 days with etanercept (P<0.001). • More patients in the etanercept (n=20; 80%) group had an ACR JIA 30 response at the end of the study than the placebo (n=9, 35%) group (RR 2.13, 95% CI [1.23 to 3.71]; P<0.01). **Safety** Open label: • Most common adverse event reported in the study was injection site reaction (39% of patients) followed by upper respiratory tract infections (35%). • In the double-blind study, there were no significant differences between the two treatment groups in the frequency of adverse events

Citation		Study design	Population (n)	Treatment	Main findings
Ruperto et al. 2007[19] & 2010[20]		Randomized, Double-Blind, Placebo-Controlled, 14 weeks	Double blind trial Children age > or 4 years but < 18 years with JIA, and suboptimal	Double-blind, placebo component Infliximab 3 mg/kg infusion and methotrexate (n=60)	**Efficacy** Double-blind Placebo *Primary outcome* • A higher number of patients in the infliximab group (n=37, 61.67%) achieved an ACR Pedi 30 response at week 14 than the placebo (n=29, 46.77%) group (RR 1.32 CI 95% [0.95 to 1.84], P = 0.12). *Secondary Outcomes*

		Followed by double-blind all active treatment extension 30 weeks (different doses) Followed by 146-week open-label component	response to methotrexate after 3 months or more of treatment, 5 or more active joints, and no active systemic symptoms, n=122 Double-blind active – n=117 Open-label extension – n=78	OR Placebo and methotrexate(n=62) <u>Double-blind active component</u> Infliximab 3 mg/kg infusion and methotrexate (n=59) OR Infliximab 6 mg/kg infusion and methotrexate (n=58) <u>Open-label</u> Infliximab 3mg-6mg/kg and methotrexate and standard care (n=78)	• More patients in the infliximab group achieved an ACR Pedi 50 response (n=29, 48.33%) than the placebo (n=20, 32.26%) group (RR 1.50 95% CI [0.96 to 2.34], P = 0.078). • A larger number of patients in infliximab group also met the ACR Pedi 70 response criteria (n=13, 21.67%) than the placebo (n=9, 14.52%) group (RR 1.49 95% CI [0.69 to 3.23], P = 0.130). • The mean number of joints with active arthritis at week 14 was lower in the infliximab group compared to placebo (P =0.016). No significant difference was found for other response assessments. <u>Double-blind active – different doses</u> • The number of patients with 0 active joints at week 52 was similar in each infliximab group (3mg/kg group – n=26, 44.1%; 6mg/kg group – n=25, 43.1%). • No significant difference was found in the number of patients achieving ACR Pedi responses between infliximab groups and across all patients 73.2%, 69.6%, and 51.8% achieved ACR Pedi 30, 50, and 70 response criteria. **Safety** <u>Double-blind Placebo</u> • Adverse events were not reported separately for the active group at 14 weeks, in the placebo group 49 patients (81.7%) had an adverse event. Three patients had a serious adverse event (5%). <u>Double-blind active – different doses</u> • Number of patients with adverse events were similar between infliximab groups (3mg/kg group – n=58, 96.7%; 6mg/kg group – n=54, 94.7%). • There were more patients in the 3mg/kg group (n=19, 31.7%) with a serious adverse event than in the 6mg/kg – n=5, 8.8%). <u>Open label one arm</u> • Seventy-one patients had an adverse event by week 204 (91%) with the most common adverse event reported upper respiratory tract infection (n=31, 39.7%). • Seventeen patients had a serious adverse event (22%).

Appendix 4: Excluded studies (PICO 1 and PICO 2)

Citation	Article Type	Reason for exclusion
Amarilyo G, Tarp S, Foeldvari I, Cohen N, Pope TD, Woo JM, Christensen R, Furst DE. Biological agents in polyarticular juvenile idiopathic arthritis: A meta-analysis of randomized withdrawal trials. Semin Arthritis Rheum. 2016 Dec;46(3):312-318. doi: 10.1016/j.semarthrit.2016.07.001. Epub 2016 Jul 16. PMID: 27989499.	Systematic review/ meta-analysis	Trials directly matching PICO included
Billiau AD, Loop M, Le PQ, Berthet F, Philippet P, Kasran A, Wouters CH. Etanercept improves linear growth and bone mass acquisition in MTX-resistant polyarticular-course juvenile idiopathic arthritis. Rheumatology (Oxford). 2010 Aug;49(8):1550-8. doi: 10.1093/rheumatology/keq123. Epub 2010 May 5	Trial	Incorrect study design
Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, Unnebrink K, Anderson JK. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res (Hoboken). 2015 Nov;67(11):1503-12. doi: 10.1002/acr.22657.	Trial	Incorrect population
Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013 Apr;72(4):517-24.	Retrospective study	Incorrect study design
Cabrera N, Avila-Pedretti G, Belot A, Larbre JP, Mainbourg S, Duquesne A, Janiaud P, Kassai B, Cucherat M, Lega JC. The benefit-risk balance for biological agents in juvenile idiopathic arthritis: a meta-analysis of randomized clinical trials. Rheumatology (Oxford). 2020 Sep 1;59(9):2226-2236.	Systematic review/ meta-analysis	Incorrect study population, trials directly matching PICO included
Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. Health Technol Assess. 2002;6(17):1-43. doi: 10.3310/hta6170.	Systematic review/ meta-analysis	Trials directly matching PICO included
Davies R, Gaynor D, Hyrich KL, Pain CE. Efficacy of biologic therapy across individual juvenile idiopathic arthritis subtypes: A systematic review. Semin Arthritis Rheum. 2017 Apr;46(5):584-593. doi: 10.1016/j.semarthrit.2016.10.008. Epub 2016 Nov 1.	Systematic review/ meta-analysis	Trials directly matching PICO included
Desai RJ, Thaler KJ, Mahlknecht P, Gartlehner G, McDonagh MS, et al. Comparative Risk of Harm Associated With the Use of Targeted Immunomodulators: A Systematic Review. Arthritis Care Res (Hoboken). 2016 Aug;68(8):1078-88. doi: 10.1002/acr.22815.	Systematic review/ meta-analysis	Incorrect population, incorrect intervention
Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. Clin Rheumatol. 2008 Jan;27(1):67-76. doi: 10.1007/s10067-007-0654-6. Epub 2007 Jun 15.	Systematic review/ meta-analysis	Trials directly matching PICO included
Heiligenhaus A, Horneff G, Greiner K, Mackensen F, Zierhut, M et al. Die Inhibitoren von Tumor Nekrose Faktor alpha zur Behandlung von Arthritis und Uveitis im Kindesalter. Klin Monbl Augenheilkd. 2007 Jun;224(6):526-31. German. doi: 10.1055/s-2007-963174	Trial	Full text not available
Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner JB, et al. HI. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol. 2015 May;67(8):2240-9.	Trial	Incorrect population
Horton S, Jones AP, Guly CM, Hardwick B, Beresford MW, Lee RW, Dick AD, Ramanan AV. Adalimumab in Juvenile Idiopathic Arthritis-Associated Uveitis: 5-Year Follow-up of the Bristol Participants of the SYCAMORE Trial. Am J Ophthalmol. 2019 Nov;207:170-174. doi: 10.1016/j.ajo.2019.06.007. Epub 2019 Jun 13.	Trial	Incorrect study design
Hughes DA, Culeddu G, Plumpton CO, Wood E, Dick AD, et al. Cost-Effectiveness Analysis of Adalimumab for the Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis. Ophthalmology. 2019 Mar;126(3):415-424. doi: 10.1016/j.ophtha.2018.09.043. Epub 2018 Oct 16.	Cost-effectiveness analysis	Cost-effectiveness analysis – based on one trial
Jari M, Shiari R, Salehpour O, Rahmani K. Epidemiological and advanced therapeutic approaches to treatment of uveitis in pediatric rheumatic diseases: a systematic review and meta-analysis. Orphanet J Rare Dis. 2020 Feb 4;15(1):41. doi: 10.1186/s13023-020-1324-x. PMID: 32019589; PMCID: PMC7001204.	Systematic review/ meta-analysis	Most up to date review matching PICO selected – Renton et al.
Kastrati K, Aletaha D, Burmester GR, Chwala E, Dejaco C, et al. A systematic literature review informing the consensus statement on efficacy and safety of pharmacological treatment with interleukin-6 pathway inhibition with biological DMARDs in immune-mediated inflammatory diseases. RMD Open. 2022	Systematic review/ meta-analysis	Incorrect intervention
Kemper AR, Van Mater HA, Coeytaux RR, Williams JW Jr, Sanders GD. Systematic review of disease-modifying antirheumatic drugs for juvenile idiopathic arthritis. BMC Pediatr. 2012 Mar 15;12:29. doi: 10.1186/1471-2431-12-29. PMID: 22420649;	Systematic review/ meta-analysis	Trials directly matching PICO included

Lahdenne P, Vähäsalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis. 2003 Mar;62(3):245-7. doi: 10.1136/ard.62.3.245. PMID: 12594111;	Trial	Incorrect study design
Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014 Mar;121(3):785-96.e3. doi: 10.1016/j.ophtha.2013.09.048. Epub 2013 Dec 17.	Guidelines	More recent guidelines included
Nagy A, Mátrai P, Hegyi P, Alizadeh H, Bajor J, Czopf L, Gyöngyi Z, Kiss Z, Márta K, Simon M, Szilágyi ÁL, Veres G, Mosdósi B. The effects of TNF-alpha inhibitor therapy on the incidence of infection in JIA children: a meta-analysis. Pediatr Rheumatol Online J. 2019 Jan 18;17(1):4. doi: 10.1186/s12969-019-0305-x.	Systematic review/ meta-analysis	Incorrect outcome, trials directly matching PICO included
Otten MH, Anink J, Spronk S, van Suijlekom-Smit LW. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov;72(11):1806-12. doi: 10.1136/annrheumdis-2012-201991. Epub 2012 Nov 21.	Systematic review/ meta-analysis	Most up to date review matching PICO selected – Renton et al.
Pato E, Muñoz-Fernández S, Francisco F, Abad MA, Maese J, Ortiz A, Carmona L; Uveitis Working Group from Spanish Society of Rheumatology. Systematic review on the effectiveness of immunosuppressants and biological therapies in the treatment of autoimmune posterior uveitis. Semin Arthritis Rheum. 2011 Feb;40(4):314-23. doi: 10.1016/j.semarthrit.2010.05.008. Epub 2010 Jul 24.	Systematic review/ meta-analysis	Most up to date review matching PICO selected – Renton et al.
Quartier P, Baptiste A, Despert V, Allain-Launay E, Koné-Paut I, et al.; ADJUVITE Study Group. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Ann Rheum Dis. 2018 Jul;77(7):1003-1011.	Trial	Included in Renton et al. review
Ramanan AV, Dick AD, Benton D, Compeyrot-Lacassagne S, Dawoud D, Hardwick B, et al.; SYCAMORE Trial Management Group. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials. 2014 Jan 9;15:14. doi: 10.1186/1745-6215-15-14.	Trial	Protocol
Ramanan AV, Dick AD, Benton D, Compeyrot-Lacassagne S, Dawoud D, et al.; SYCAMORE Trial Management Group. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials. 2014 Jan 9;15:14. doi: 10.1186/1745-6215-15-14.	Trial	Included in Renton et al. review
Ramanan AV, Dick AD, Jones AP, Hughes DA, McKay A, et al.. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. Health Technol Assess. 2019 Apr;23(15):1-140. doi: 10.3310/hta23150. PMID: 31033434;	Trial	Included in Renton et al. review
Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, et al.. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018 Jun;77(6):819-828. doi: 10.1136/annrheumdis-2018-213030. Epub 2018 Apr 11.	Guidelines	Incorrect outcome
Scott C, Chan M, Slamang W, Okong'o L, Petty R, et al. Juvenile arthritis management in less resourced countries (JAMLess): consensus recommendations from the Cradle of Humankind. Clin Rheumatol. 2019 Feb;38(2):563-575. doi: 10.1007/s10067-018-4304-y. Epub 2018 Sep 28.	Guidelines	Incorrect outcome
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. Health Technol Assess. 2016 Apr;20(34):1-222. doi: 10.3310/hta20340.	Systematic review/ meta-analysis	Relevant trials published since review release – evaluated under guidelines
Smith JA, Thompson DJ, Whitcup SM, Suhler E, Clarke G, Smith S, Robinson M, Kim J, Barron KS. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum. 2005 Feb 15;53(1):18-23. doi: 10.1002/art.20904.	Trial	Included in Renton et al. review
Ungar WJ, Costa V, Burnett HF, Feldman BM, Laxer RM. The use of biologic response modifiers in polyarticular-course juvenile idiopathic arthritis: a systematic review. Semin Arthritis Rheum. 2013 Jun;42(6):597-618. doi: 10.1016/j.semarthrit.2012.10.006. Epub 2013 Jan 18. PMID: 23337074.	Systematic review/ meta-analysis	Trials directly matching PICO included

Appendix 5: Risk of Bias 2 Assessment

Unique ID	1	Study ID	Brunner 2018	Assessor	TDL
Ref or Label	Brunner 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Golimumab	**Comparator**	Placebo	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Disease flare	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNF-α therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Characteristics for patients randomised to placebo or golimumab in Part 2 were comparable (table 1)".
	Risk of bias judgement	**Some concerns**	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNFα therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided. Characteristics for patients randomised to placebo or golimumab in Part 2 were comparable (table 1)".
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	2.1 and 2.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16".
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	ITT analysis
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	ITT analysis performed
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	ITT analysis performed
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints
Overall bias	**Risk of bias judgement**	**Some concerns**	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNFα therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided. characteristics for patients randomised to placebo or golimumab in Part 2 were comparable (table 1)". ITT analysis ITT analysis performed The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints

Unique ID	2	**Study ID**	Lovell 2000	**Assessor**	TDL
Ref or Label	Lovell 2000	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Etanercept	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	Disease flare	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results
	Risk of bias judgement	**Some concerns**	The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm. It is not clear wether staff providing care were aware of the participant's allocations or not; this is not clearly reported.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	Deviations from protocol not clearly reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	All were analysed according to original randomisation. Last observed values brought forward.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm. It is not clear wether staff providing care were aware of the participant's allocations or not; this is not clearly reported. Deviations from protocol not clearly reported All were analysed according to original randomisation. Last observed values brought forward.

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not clear whether outcome assessors were blinded or not
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Some of the variables measured to ascertain the outcome involve subjective assessments that could be influenced by knowledge of intervention received
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	Not clear whether outcome assessors were blinded or not Some of the variables measured to ascertain the outcome involve subjective assessments that could be influenced by knowledge of intervention received
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple eligible analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm. It is not clear wether staff providing care were aware of the participant's allocations or not; this is not clearly reported. Deviations from protocol not clearly reported All were analysed according to original randomisation. Last observed values brought forward. Not clear whether outcome assessors were blinded or not

			Some of the variables measured to ascertain the outcome involve subjective assessments that could be influenced by knowledge of intervention received

Unique ID	3	**Study ID**	Lovello 2008	**Assessor**	TDL
Ref or Label	Lovello 2008	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Adalimumab + MTX/no MTX	**Comparator**	Placebo + MTX/no MTX	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	Disease flares	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group
	Risk of bias judgement	**Low**	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	ITT analysis
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group

Unique ID	1a	Study ID	Brunner 2018	Assessor	TDL
Ref or Label	Brunner 2018	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Golimumab	Comparator	Placebo	Source	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	ACR Pedi 30 - improvement	Results	ACR Pedi 30 - improvement	Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNFα therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	**Some concerns**	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNFα therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	ITT analysis
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	ITT analysis
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints
Overall bias	**Risk of bias judgement**	**Some concerns**	1.1 "Randomisation, using an algorithm, was done via an interactive voice response system with stratification by geographic region (Europe, North America, Latin America), JIA disease type (psoriatic subtype vs other subtypes), prior anti-TNFα therapy and age at enrolment". 1.2 "Site investigative personnel and patients were blinded to study allocation starting at week 16". Method not provided. ITT analysis The study protocol is available and all pre-specified outcomes have been reported Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints

Unique ID	5a	**Study ID**	Ruperto 2007	**Assessor**	TDL
Ref or Label	Ruperto 2007	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Infliximab+MTX	**Comparator**	Placebo+MTX	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

Outcome	ACR Pedi 30 - improvement	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	Per-protocol analysis 3 loss to FU in placebo- vs 2 in infliximab group
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	3 loss to FU in placebo- vs 2 in infliximab group (4% only)
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	3 loss to FU in placebo- vs 2 in infliximab group Per-protocol analysis was done, and no sensitivity analyses
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Response to therapy was acertained based on a combination of factors i.e. JRA core set parameters, VAS, CHAQ, laboratory measurements of inflammation using ESR - subjective measurements noted
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints Response to therapy was acertained based on a combination of factors i.e. JRA core set parameters, VAS, CHAQ, laboratory measurements of inflammation using ESR - subjective measurements noted
Overall bias	**Risk of bias judgement**	**Some concerns**	Per-protocol analysis 3 loss to FU in placebo- vs 2 in infliximab group 3 loss to FU in placebo- vs 2 in infliximab group Per-protocol analysis was done, and no sensitivity analyses Sponsor terminated trial earlier as failed to meet primary - and major secondary endpoints

Unique ID	2a	**Study ID**	Lovell 2000	**Assessor**	TDL
Ref or Label	Lovell 2000	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Etanercept	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	ACR Pedi 30 - improvement	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Included random element. No information reported regarding allocation sequence concealment.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results
	Risk of bias judgement	**Some concerns**	Included random element. No information reported regarding allocation sequence concealment.

			The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	Deviations from protocol not clearly reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	All were analysed according to original randomisation. Last observed values brought forward.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm. Deviations from protocol not clearly reported All were analysed according to original randomisation. Last observed values brought forward.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	Assessment that could be influenced by knowledge of treatment received
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	Assessment that could be influenced by knowledge of treatment received

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI	
	5.3 ... multiple eligible analyses of the data?	NI	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	No information reported regarding allocation sequence concealment. The groups were well balanced in the double-blind study, except for age group and race (P<0.02) and corticosteroid use at base line (P=0.05). The unequal randomization did not affect the study results Trial described as double-blind. Treatment delivered via subcutaneous injection by site study staff not involved in patient assessments so unlikely patients could identify their treatment arm. Deviations from protocol not clearly reported All were analysed according to original randomisation. Last observed values brought forward. Assessment that could be influenced by knowledge of treatment received.

Unique ID	3a	**Study ID**	Lovello 2008	**Assessor**	TDL
Ref or Label	Lovello 2008	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Adalimumab + MTX/no MTX	**Comparator**	Placebo + MTX/no MTX	**Source**	Journal article(s); Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
Outcome	ACR Pedi 30 - improvement	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study. A separate randomization schedule for each stratum was generated by the study sponsor before the start of the study
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group

	Risk of bias judgement	**Low**	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the studyA separate randomization schedule for each stratum was generated by the study sponsor before the start of the study Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	ITT analysis
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	ITT analysis
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase A separate randomization schedule for each stratum was generated by the study sponsor before the start of the studyA separate randomization schedule for each stratum was generated by the study sponsor before the start of the study Intervention and compartor groups relatively comparable, except more younger patients in the placebo+MTX vs adalimumab+MTX group ITT analysis

Appendix 6: AGREE II ASSESSMENT SUMMARIES

AGREE II assessment scores

ACR JIA TNF-I without uveitis

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	7	7	7	6	7	6	7	6	6	2	7	7	7	6	5	1	4	6	7	139
Appraiser 2	7	7	7	7	7	7	7	7	7	7	7	7	7	2	7	7	7	4	4	1	3	0	7	133
Item Total	14	14	14	14	14	14	14	13	14	13	14	13	13	4	14	14	14	10	9	2	7	6	14	272
Domain Total	42			42			98								42			28				20		272
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	100%			100%			**85%**								100%			42%				67%		**82%**

Overall assessment: Guidelines are recommened for use in this context

Score: (e.g. domain 1)

Maximum possible score = 7 (highest score) x no. of items x no. of appraisers

Minumum possible score = 1 (lowest score) x no. of items x no. of appraisers

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

AGREE II assessment scores

NICE 2015 JIA TNF-i

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	5	7	7	6	6	6	7	6	4	6	6	5	4	7	7	6	6	6	5	7	5	7	7	138
Appraiser 2	6	6	6	6	4	6	7	7	6	6	4	1	1	5	5	5	6	2	4	6	1	5	5	110
Item Total	11	13	13	12	10	12	14	13	10	12	10	6	5	12	12	11	12	8	9	13	6	12	12	248
Domain Total	37			34			82								35			36				24		248
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	86%			78%			**69%**								81%			58%				83%		**76%**

Overall assessment: Guidelines are recommened for use in this context

AGREE II assessment scores																							
GKJR JIA TNF-i																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	5	2	2	5	1	2	5	4	2	6	3	3	5	3	5	5	6	3	4	1	2	3	3	80
Appraiser 2	7	6	6	3	1	5	6	5	5	6	7	7	6	1	5	7	7	1	1	1	1	5	5	104
Item Total	12	8	8	8	2	7	11	9	7	12	10	10	11	4	10	12	13	4	5	2	3	8	8	184
Domain Total	28			17			74								35			14				16		184
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	61%			31%			**60%**								81%			13%				50%		**49%**
Overall assessment:	Guidelines are not recommened for use in this context																							

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