South African National Department of Health
Brief Report
Component: Tertiary and Quaternary Hospital Level

TITLE: Rapid Review Report on additional literature search (Health related quality of life and cost-effectiveness) for medicine review on Juvenile Idiopathic Arthritis for children who are refractory or intolerant to standard of care

Date: May 2023

Overview

The medicine reviews for Tumour Necrosis Factor Inhibitors for treatment of patients with Juvenile Idiopathic Arthritis who are refractory or intolerant to standard of care were presented to the NEMLC in March 2023. See accompanying documents for medicine review of TNF-inhibitors for JIA PICO 1 (without uveitis) and PICO 2 (with uveitis). The NEMLC requested that a rapid search of health-related quality of life/utility data from published economic evaluation literature be conducted.

Methods

A rapid search of quality-of-life literature and HTA reports was thus conducted in April 2023 in PubMed, Cochrane, Tuft Registry and the International HTA database (See Appendix A for search strategy). A targeted search of HTA agency websites was also conducted. Articles were screened, selected and extracted by one reviewer (KM). Selected articles and data extraction were reviewed by a second reviewer (JR) and then presented to the TQ ERC for final review.

Results

The search resulted in 95 results, after screening 16 documents remained. After full text review, seven articles were selected (one systematic review, two cost-effectiveness studies, four HTA reports). See Appendix B for list of excluded studies and Tables 1-4 for description of include studies.

Health Related Quality of Life

A systematic review conducted by Gidman *et al.* 2015[1] of health-related quality of life studies for children with JIA reported a paucity of studies. Only one observational study comparing quality of life pre and post an intervention with a TNF-inhibitor was found (See Table 1). The prospective cohort study conducted by Prince *et al.* (2011)[2] evaluated quality of life for participants on etanercept who were on the Dutch Arthritis and Biologicals in Children register. Data on the Health Utilities Index Mark 3 (HUI3) were collected from caregivers of the participants at 3, 15 and 27 months after start of treatment. Mean parent multi-attribute utility increased from 0.53 (S.E.M 0.04) to 0.78 (S.E.M 0.07), P=0.001 over the study period of 27 months.

Table 1 – Systematic review of Health-Related Quality of Life studies

Author, date	**Setting**	**Population**	**Study Type**	**Results & conclusion**	**Limitations**
Gidman *et al.* 2015[1]	Not specific, global	Children with JIA with insufficient response to maximum dose of methotrexate.	Systematic review of articles reporting Health-related quality of life or economic burden of JIA	Only two studies found describing quality of life pre and post pharmaceutical agents and only one study for interventions of interest for this medicine review: 1) Prince *et al*. 2011[2] identified as the only preference based HRQoL study (utilised in the Shepard *et al*. HTA described below). The study was a cohort survey conducted on children with JIA in the Netherlands pre and post intervention with etanercept. The survey was conducted by the parents and the mean parent multi-attribute utility increased from 0.53 (S.E.M 0.04) to 0.78 (S.E.M 0.07) P=0.001 over the study period of 27 months. Response was observed from 3 months and 15 months with an increase to 0.69 (S.E.M 0.05), and 0.74 (S.E.M 0.06) respectively.	For Prince et al. study: - No placebo control as etanercept already authorized in Netherland public sector. - Small sample size - Different types of JIA For the systematic review – dearth of evidence noted especially related to data that can be utilised to compare different interventions or against placebo.

Cost-effectiveness

Two cost-effectiveness studies were included, one conducted by Hughes *et al.* (2019)[3] specifically on JIA related uveitis and another for individuals with JIA in general (Shepard *et al*. 2016[4]), see Table 2 for details.

The study conducted by Shepard *et al.* 2016 explored the cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab with or without methotrexate for individuals aged two years and older. A Markov model with three health states developed from the health payer perspective was utilised. A systematic review was conducted to inform utility parameters. The findings aligned with the systematic review conducted by Gidman *et al.* (See Table 1) with only one appropriate study found to inform quality of life namely Prince *et al.* 2011. The ICERs reported for adalimumab and etanercept were £38 127 and £32 526 per QALY gained respectively. This analysis informed the HTA report conducted by NICE in 2015 and the decision to reimburse adalimumab and etanercept for individuals older than 2 years old who have not responded adequately to one or more DMARDs (See Table 3 and 4 for details). Several limitations were noted including lack of head-to-head data between agents and limited data on health-related quality of life. The model was most sensitive to changes in health-related quality of life estimates.

The study on uveitis conducted by Hughes *et al.* 2019 utilised a Markov model with three health states and sourced utilities from a subset of participants in the SYCAMORE trial[5] (25 participants). The analysis was conducted from the health payer perspective (United Kingdom) and compared adalimumab and methotrexate to methotrexate alone. The analysis found that based on 2016 prices, adalimumab was not cost-effective with an ICER of £129 025 per QALY gained compared to methotrexate alone. A reduction of 84% in the price of adalimumab would have been required in order to reach the £30 000 cost-effectiveness threshold. Price of adalimumab in 2016 was cited to be £352.14 for 40mg prefilled syringe (Humira) thus a price of £56.34 (R1 272) would have been required. Several limitations were noted in the study and by letters to the editor.[6,7,8,9] The main limitations were the small sample size, the method of measuring vision loss (utility calculations) and the lack data for long term complications and sequalae.

Table 2 – Cost-Effectiveness Studies

Author, date	Setting	Population	Intervention & comparator	Evaluation details	Results & conclusion	Limitations
Shepard et al. 2016[4]	United Kingdom	Individuals with JIA (systemic or oligoarticular JIA are excluded) who are 2 years and older.	Abatacept, adalimumab, etanercept and tocilizumab with and without methotrexate compared to methotrexate alone and interventions compared to each other	A cost–utility decision-analytic model was developed to compare the cost-effectiveness estimates of biologic DMARDs versus methotrexate. The model used a Markov approach to estimate the costs and health benefits for patients with JIA. The model consisted of three health states: on treatment (with biologic DMARD), off treatment and death, with a further health state of 'clinical remission off treatment' also included in a scenario analysis. The model cycles were 3 months in length to be consistent with timing between outpatient appointments in clinical practice. Patients discontinued treatment owing to adverse events (AEs), inefficacy of the treatment or remission. The model also included the cost and disutility of disease flares. The perspective of the analysis was that of the NHS and Personal Social Services. The model used a time horizon of 30 years and discount rates of 3.5% for costs and health benefits. The outcome of the economic evaluation is reported as cost per quality-adjusted life-year (QALY) gained.	HQoL: Study determined that results from Prince *et al*. 2011[10] were most appropriate: *The results from the study indicated a statistically significant improvement in the HUI3 utility score from 0.53 at baseline to 0.78 at 27 months' follow-up. Mean utility values were 0.69 at 3 months and 0.74 at 15 months' follow-up. For the cohort with more patients, there was a mean utility improvement of 0.25 during the 27 months of treatment.137 The baseline mean utility value was 0.51, and significant changes were observed in the domains of pain, ambulatory and dexterity.* The independent model developed for this assessment report modelled one line of biological treatment for the comparison of adalimumab, etanercept and tocilizumab versus methotrexate. From this model, the incremental cost-effectiveness ratios (ICERs) for adalimumab, etanercept and tocilizumab versus methotrexate are estimated at £38,127, £32,526 and £38,656 per QALY gained, respectively, using the list price drug acquisition costs. The model results are most sensitive to changes in the HRQoL utility values. The changes to the clinical effectiveness parameters, such as treatment discontinuation and disease flare had minimal effect on the model results. The differences in cost-effectiveness of the biologic DMARDs are primarily the effect of the differences in the drug acquisition cost.	*There was insufficient evidence for all input parameters to permit a cost-effectiveness subgroup analysis for each of the respective types of JIA within the scope of the appraisal. The modelled patient population is people with JIA, although it is primarily relevant to those with polyarticular-course JIA. *Limitations include the lack of head-to-head trial comparisons of biologic DMARDs, necessitating an indirect comparison, and the lack of available data to inform the economic evaluation, particularly HRQoL utility estimates (which were the most influential parameters of cost-effectiveness), long-term discontinuation rates and the long-term impact of treatment on disease progression.

Author, date	Setting	Population	Intervention & comparator	Evaluation details	Results & conclusion	Limitations
Hughes *et al*. 2019[3]	United Kingdom	Children and adolescents 2 to 18 years of age with persistently active uveitis associated with JIA, despite optimized methotrexate treatment for at least 12 weeks.	Adalimumab (20 or 40mg, according to body weight) fortnightly in combination with methotrexate (up to 25mg) weekly COMPARED TO Methotrexate alone (up to 25mg) weekly	Data from the SYCAMORE trial utilised. A Markov model was used to extrapolate the effects of treatment based on visual impairment. MAIN OUTCOME MEASURES: Medical costs to the National Health Service in the United Kingdom, utility of defined health states, quality-adjusted life-years (QALYs), and incremental cost per QALY.	Utility: Baseline utility scores were 0.83 (95% CI, 0.76–0.89) and 0.87 (95% CI, 0.78–0.96) for the adalimumab and placebo groups, respectively. Based on a complete case analysis of 25 participants (42%) randomized to adalimumab and 3 participants (10%) randomized to placebo, the number of QALYs over the 18-month trial period was 1.40 (95% CR, 1.35–1.45) and 1.45 (95% CR, 1.41–1.50), respectively. After imputation, the mean QALY scores were numerically higher for adalimumab at 1.35 (95% CI, 1.30–1.41) compared with the placebo group at 1.28 (95% CI, 1.15–1.41). Adalimumab in combination with methotrexate resulted in additional costs of £39 316, with a **0.30 QALY gain** compared with methotrexate alone, resulting in an incremental cost-effectiveness ratio of £129 025 per QALY gained. The probability of cost effectiveness at a threshold of £30 000 per QALY was less than 1%. Based on a threshold analysis, a price reduction of 84% would be necessary for adalimumab to be cost effective. "In conclusion, and based on the only randomized double-blind, placebo-controlled trial, to date in JIA-associated uveitis, adalimumab is unlikely, at present, to represent a cost-effective treatment option in the United Kingdom. Our findings have important implications for the routine availability of adalimumab for this indication across the NHS in the United Kingdom".	• Incomplete data on health utilities (QALYs could be calculated only for 28 trial participants [31%]) and visual acuity, which required a strong assumption of data being missing at random. • Study was reliant on a secondary outcome (visual impairment) for matching to the external dataset. The SYCAMORE trial was not powered to detect differences in visual impairment, and although the effect of adalimumab on the time to treatment failure (primary end point) was profound, there was no significant improvement in visual acuity. • There was no consideration of severe visual impairment or blindness, which is associated with high lifetime costs and significant impacts on quality of life, education, and employment. • Reliance on data from the Bristol cohort, which included patients who may not be comparable with or were managed differently from those recruited to the SYCAMORE trial.

Summary of other HTA agency decisions

A review of HTA reports and reimbursement decisions by international HTA agencies was conducted, the results are tabulated below (Table 3 and 4). Four of the selected agencies recommend adalimumab or etanercept for JIA if there has been an inadequate response to traditional DMARDs such as methotrexate. HITAP have not formally assessed this specific topic.

Table 3: Summary of Health Technology Assessment (HTA) agency decisions

Name	Included	Detail
National Institute for Health and Care Excellence (NICE)[11]	Yes	Adalimumab and etanercept 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
Canadian Agency for Drugs and Technologies in Health (CADTH)[1213]	Yes	Adalimumab for polyarticular JIA
		Etanercept for Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients aged four to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs.
Scottish Medicines Consortium (SMC)[14]	Yes	Advice of HTA MTA NICE adopted
Pharmaceutical Benefits Advisory Committee, Australian Government Department of Health[1516]	Yes	The Pharmaceutical Benefits Scheme (PBS) subsidises treatment with biological agents under the National Health Act 1953, section 85 and/or section 100 for adult and paediatric patients with severe active juvenile idiopathic arthritis (JIA). • Where the term 'biological agent' appears, it refers to adalimumab, etanercept and tocilizumab. • Patient must have demonstrated severe intolerance of, or toxicity due to, methotrexate; OR • Patient must have demonstrated failure to achieve an adequate response to 1 or more of the following treatment regimens: (i) oral or parenteral methotrexate at a dose of at least 20 mg per square metre weekly, alone or in combination with oral or intra-articular corticosteroids, for a minimum of 3 months; or (ii) oral methotrexate at a dose of at least 10 mg per square metre weekly together with at least 1 other disease modifying anti-rheumatic drug (DMARD), alone or in combination with corticosteroids, for a minimum of 3 months,
Health Intervention and Technology Assessment Program (HITAP)	No	Not assessed

Table 4. Summary Table of HTA reports

	HTA report 1	HTA report 2	HTA report 3	HTA report 4	HTA report 5
Country + HTA agency	NICE[11]	CADTH[12]	CADTH[13]	PBAC[15]	PBAC[16]
Year	2015	2013	2017	2002	2010
Indication	Juvenile Idiopathic Arthritis	Polyarticular Juvenile Idiopathic Arthritis patients (4 – 17 years) with inadequate response to one or more DMARDs	Polyarticular Juvenile Idiopathic Arthritis patients (4 – 17 years) with inadequate response to one or more DMARDs	Severe active polyarticular course juvenile idiopathic arthritis	Severe active polyarticular course juvenile idiopathic arthritis
Intervention	Abatacept, adalimumab, etanercept and tocilizumab	Adalimumab with or without methotrexate	Biosimilar etanercept – Erelzi®	Etanercept	Adalimumab with or without methotrexate
Comparator	Placebo and to each other	Placebo, methotrexate alone	Etanercept originator – Enbrel® (unable to find original submission)	Document not available	
Modelling approach	state-transition Markov model	state-transition Markov model	NA		NA
Type of analysis	CUA – conducted by assessors	CUA – conducted by manufacturer	Cost minimization		Cost minimization
Utility data utilised	Prince *et al.* 2011[10] study: Pre-biologic = 0.53; and 27 months post-biologic = 0.78	Unknown – manufacturer submission – utilities derived from DE038 trial (Lovell *et al.* 2008[17])	NA		NA
Results	1st biologic model (after insufficient response to methotrexate) ICER compared to each other not possible so ICER compared to methotrexate: • Adalimumab and methotrexate = $38 127 / QALY gained • Etanercept alone = $32 526 / QALY gained	Over a 7-year time horizon: $60 296 / QALY gained Over a lifetime horizon: $25 759 / QALY gained			
Major areas of uncertainty	Utilities of health states – lack of health-related quality of life. Lack of head-to-head data between agents. Long term benefits were not included.	No direct comparisons between adalimumab and other agents and data not available for patients with uveitis			
Ethical, social, legal issues	Age of onset and limit for authorization was discussed and it was recommended that people of all ages be covered.	None mentioned			
Recommendation	Recommended	Recommended	Recommended	Recommended	Recommended

Conclusion

A rapid search of evidence on quality of life found only one study that matched the medicine review PICO question. The cohort study explored the impact of etanercept on quality of life and found the associated improvement to be moderate, but statistically significant.

Two cost-effectiveness studies were also identified. One cost-effectiveness study was conducted specifically on patients with both JIA and uveitis, and was associated with numerous limitations and received several published responses. Notwithstanding, it noted that the price of adalimumab would need to be reduced substantially (by 84%) in order to be deemed cost-effective. The second cost-effectiveness analysis, which did not distinguish between the presence of uveitis, informed the NICE HTA report (2015) which recommended that adalimumab and etanercept be reimbursed for individuals older than 2 years old, who have not responded adequately to one or more DMARDs.

Despite cited limitations around quality-of-life estimates and cost-effectiveness analyses, several HTA agencies recommend TNF-inhibitors for JIA in patients with inadequate response to traditional DMARDs. In respect of uveitis, no differentiation is made for patients with or without uveitis in these decisions. Considering these recommendations made by HTA agencies, it is unlikely that new evidence on quality of life for this specific group of patients will emerge.

APPENDIX A

PUBMED

#	Query	Search Details	Results
9	#5 AND #7	(("tumor necrosis factor inhibitors"[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 "infliximab"[MeSH Terms] OR "adalimumab"[Title/Abstract] OR "etanercept"[Title/Abstract] OR "golimumab"[Title/Abstract] OR "infliximab"[Title/Abstract]) AND "arthritis, juvenile"[MeSH Terms]) OR "juvenile idiopathic arthritis"[Title/Abstract]) AND ("quality of life"[MeSH Terms] OR "quality of life"[Title/Abstract] OR "QALY"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QoL"[Title/Abstract]) AND ("cost benefit analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost effectiveness analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms])	29
8	#5 AND #6	(("tumor necrosis factor inhibitors"[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 "infliximab"[MeSH Terms] OR "adalimumab"[Title/Abstract] OR "etanercept"[Title/Abstract] OR "golimumab"[Title/Abstract] OR "infliximab"[Title/Abstract]) AND "arthritis, juvenile"[MeSH Terms]) OR "juvenile idiopathic arthritis"[Title/Abstract]) AND ("quality of life"[MeSH Terms] OR "quality of life"[Title/Abstract] OR "QALY"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QoL"[Title/Abstract]) AND (("systematic review"[Publication Type] OR "meta analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta analysis"[Title/Abstract]) NOT "animals"[Title/Abstract])	41
7	Cost analyses	"cost benefit analysis"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "cost effectiveness analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms]	263 629
6	Systematic reviews & meta-analyses	(((((Systematic Review[Publication Type])) OR (Meta-analysis[Publication Type])) OR (systematic review[Title/Abstract])) OR (meta-analysis[Title/Abstract])) NOT (animals[Title/Abstract])	412 753
5	#3 AND #4	(("tumor necrosis factor inhibitors"[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 "infliximab"[MeSH Terms] OR "adalimumab"[Title/Abstract] OR "etanercept"[Title/Abstract] OR "golimumab"[Title/Abstract] OR "infliximab"[Title/Abstract]) AND "arthritis, juvenile"[MeSH Terms]) OR "juvenile idiopathic arthritis"[Title/Abstract]) AND ("quality of life"[MeSH Terms] OR "quality of life"[Title/Abstract] OR "QALY"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QoL"[Title/Abstract])	595
4	Quality of life	"quality of life"[MeSH Terms] OR "quality of life"[Title/Abstract] OR "QALY"[Title/Abstract] OR "DALY"[Title/Abstract] OR "QoL"[Title/Abstract]	436 405
3	#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
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

COCHRANE LIBRARY

search	Query	Results
#1	MeSH descriptor: [Arthritis, Juvenile] explode all trees	381
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	119
#3	#1 AND #2	2

TUFTS CEA REGISTRY

search	Query	Results
#1	Utilities Filter: Juvenile Idiopathic Arthritis	3
#2	Keyword filter: Juvenile Idiopathic Arthritis	4
#3	Utilities Filter: JIA	8

INTERNATIONAL HTA DATABASE (INAHTA)

search	Query	Results
#1	Juvenile arthritis [MeSH term]	11

APPENDIX B

LIST OF EXCLUDED STUDIES

Citation	Reason
Luca NJ, Burnett HF, Ungar WJ, Moretti ME, Beukelman T, Feldman BM, Schwartz G, Bayoumi AM. Cost-Effectiveness Analysis of First-Line Treatment With Biologic Agents in Polyarticular Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2016 Dec;68(12):1803-1811. doi: 10.1002/acr.22903. Epub 2016 Oct 21. PMID: 27059807.	Wrong population and timing of therapy
Angelis A, Kanavos P, López-Bastida J, Linertová R, Serrano-Aguilar P; BURQOL-RD Research Network. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: a cost-of-illness study in the United Kingdom. BMC Musculoskelet Disord. 2016 Aug 2;17:321. doi: 10.1186/s12891-016-1129-1. PMID: 27484740; PMCID: PMC4971720.	QoL not specific to interventions
Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015 Jul;119(7):964-79. doi: 10.1016/j.healthpol.2014.12.016. Epub 2014 Dec 30. PMID: 25661982.	No information on QoL
Lapadula G, Marchesoni A, Armuzzi A, Blandizzi C, Caporali R, Chimenti S, Cimaz R, Cimino L, Gionchetti P, Girolomoni G, Lionetti P, Marcellusi A, Mennini FS, Salvarani C. Adalimumab in the treatment of immune-mediated diseases. Int J Immunopathol Pharmacol. 2014 Jan-Mar;27(1 Suppl):33-48. doi: 10.1177/03946320140270S103. PMID: 24774505.	Narrative review
Abdul-Sattar A, Magd SA, Negm MG. Associates of school impairment in Egyptian patients with juvenile idiopathic arthritis: Sharkia Governorate. Rheumatol Int. 2014 Jan;34(1):35-42. doi: 10.1007/s00296-013-2871-4. Epub 2013 Sep 26. PMID: 24071936.	No children on TNF-inhibitors
Abdul-Sattar AB, Elewa EA, El-Shahawy Eel-D, Waly EH. Determinants of health-related quality of life impairment in Egyptian children and adolescents with juvenile idiopathic arthritis: Sharkia Governorate. Rheumatol Int. 2014 Aug;34(8):1095-101. doi: 10.1007/s00296-014-2950-1. Epub 2014 Jan 28. PMID: 24469640.	No children on TNF-inhibitors
Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. Arthritis Care Res (Hoboken). 2012 Sep;64(9):1392-404. doi: 10.1002/acr.21695. PMID: 22504867.	QoL not specific to interventions
Baars RM, Atherton CI, Koopman HM, Bullinger M, Power M; DISABKIDS group. The European DISABKIDS project: development of seven condition-specific modules to measure health related quality of life in children and adolescents. Health Qual Life Outcomes. 2005 Nov 13;3:70. doi: 10.1186/1477-7525-3-70. PMID: 16283947; PMCID: PMC1326227.	QoL not specific to interventions
Kuhlmann A, Schmidt T, Treskova M, López-Bastida J, Linertová R, Oliva-Moreno J, Serrano-Aguilar P, Posada-de-la-Paz M, Kanavos P, Taruscio D, Schieppati A, Iskrov G, Péntek M, Delgado C, von der Schulenburg JM, Persson U, Chevreul K, Fattore G; BURQOL-RD Research Network. Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe. Eur J Health Econ. 2016 Apr;17 Suppl 1:79-87. doi: 10.1007/s10198-016-0786-1. Epub 2016 Apr 16. PMID: 27086322.	QoL not specific to interventions

References

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[2] Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, ten Cate R, et al. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children register. Rheumatology 2011;50:1131–6.

[3] Hughes DA, Culeddu G, Plumpton CO, Wood E, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot Lacassagne S, Hardwick B, Hickey H, Woo P, Beresford MW, Ramanan AV. 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. PMID: 30336181.

[4] 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. PMID: 27135404; PMCID: PMC4867422.

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