Online Supplemental File 1. Summary of findings tables

Relapse of Juvenile Idiopathic Arthritis Associated Uveitis After Discontinuation of Immunomodulatory Therapy **Ocul Immunol Inflamm. 2019 ; 27(4): 686–692. doi:10.1080/09273948.2018.1424341.**						
Ref ID,	**Author, Year**	**Study Type**	**Duration**	**Population Description**	**Treatment Given to relevant population**	**Results**
1	*Acharya et al. 2019*	Retrospective	Sep 14, 1988 to Jan 5, 2011	66 JIA-associated uveitis	51 (77%) on corticosteroid-sparing immunomodulatory therapy (IMT) 41/51 (80%) achieved uveitis control Main outcome: time to relapse defined by time from the date of initiation of the treatment taper or discontinuation until the date of relapse	19/51 (37%) attempts to stop IMT (could be multiple) 14/19 (74%) due to presumed remission 11/19 (58%) for reasons other than remission (AE, lack of efficacy, cost, pregnancy) 13/19 (68%) flared with a median time of 288 days 5/13 (38%) flared while they were in the process of tapering but had not stopped the treatment 9/11 (82%) with previous anti-TNF flared [in text 9/11, in table 8/11] Longer time to relapse and lower proportion of flare if taper done for presumed remission, compare to the other group (p=0.036-log rank permutation test) Median time of disease control longer in group with presumed remission 300 days vs 276 days No predictor of flare identified

Comparative Efficacy of Adalimumab and Etanercept in Children with Juvenile Idiopathic Arthritis Under 4 Years of Age Depending on Active Uveitis

The Open Rheumatology Journal, 2019, Volume 13

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
2	*Alexeeva, 2019*	Re-analysis of previous open-label prospective study	5 years.	74 patients. JIA patients with and without uveitis, ages <4, on ETN or ADA Subtypes: Oligo-ext 0% Oligo-per 41.67% RF- Poly 41.67% Psoriatic 16.67%		Percentage of patients achieved ACR50/70/90 by the end of the follow-up period was: 42/41/38 (85.7/83.7/77.6%) in ETA group 10/10/9 (76.9/76.9/69.2%) in ADA group with uveitis 9/7/5 (75/58.3/41.7) in ADA group without uveitis Comparable proportion of ETA patients and ADA patients with uveitis achieved remission (26 (53.1%) and 7 (53.8%), respectively), while only 3 (25%) of ADA patients without uveitis achieved long-term clinical remission (p-values insignificant).

Impact of Uveitis on Quality of Life in Adult Patients With Juvenile Idiopathic Arthritis

Arthritis Care & Research Vol. 69, No. 12, December 2017, pp 1895–1902

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
3	*Anne-Mike, 2017*	Retrospective cross-sectional, case control.	Patients recruited in Aug 2014.	Adult JIA patients (oligo persistent/extended and RF neg poly) total 194 respondents -with uveitis (n=31/67) -without uveitis (n=51/127).	3 validated QOL Questionnaires: NEI VFQ-25, SF-36, and EQ-5D	Baseline: 49% women, 29% men. 31 JIA-uveitis, 51 JIA without uveitis. Overall composite score of the NEI VFQ-25 was worse in the uveitis group compared to the non-uveitis group; 83.4 vs 94.9, p<0.0001, despite good visual acuity by SUN. (preserved findings when n=4(17%) patients with bilateral visual impairment/blindness removed) Nearly all subscales were lower in patients with uveitis than in patients without (P>0.0001) for all QOL still worse in uveitis patients when adjusting for duration of arthritis, JIA subtype, arthritis onset before or after 1990 and use of systemic immunomodulation No significant difference b/w groups for the SF-36 and EQ-5D Having uveitis in general has a substantial negative affect on the vision-related QoL in JIA in adulthood despite good visual acuity. General QOL not different between groups but systemic meds have a negative influence on general QOL scores in adult JIA patients. Supports need for studies to look at which specific medications affected QOL

Assessing Barriers to Uveitis Screening in Patients with Juvenile Idiopathic Arthritis Through Semi-Structured Interviews **Pediatr Qual Saf 2018;3:084.**						
Ref ID,	**Author, Year**	**Study Type**	**Duration**	**Population Description**	**Treatment Given to relevant population**	**Results**
4	*Ballenger L., 2018*	Qualitative study		Patients with JIA who were nonadherent with uveitis screening guidelines	Semi structured interviews with the patients or guardians	The rheumatologist interviewed 45 patients or guardians. The most common issues were: 1) System problems (Correct eye provider, Eye examination report not available, Appointment/scheduling problems) 2) access to care issues (Transportation, Insurance/financial) 3) knowledge deficits

Long-term Safety and Efficacy of Adalimumab and Infliximab for Uveitis Associated with Juvenile Idiopathic Arthritis

J Rheumatol 2018;45;1167-1172

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
5	*Cecchin et al 2018*	Prospective Observational ORCHIDEA Registry	Jan 2007 to Dec 2014	236 JIA patients with anterior uveitis treated with ADA or IFX after failure of other immunosuppressive treatment and/or corticosteroid dependent	Analysis of safety and efficacy in 154 patients with a 2-year treatment	Better remission rate for ADA (60 %) compare to IFX (20.3%) p<0.001 Significant decrease in number of flares at Y1 and Y2 with no differences in both groups Rate of ocular complications/100 PY significantly decreased at Y1 and Y2 in ADA group (p=0.08 and <0.001 respectively) Rate of ocular complication/100 PY higher in IFX vs ADA (p=0.015) Similar ocular complication in both groups except less cataract and CME in ADA group No identified predictor of outcome No SAEs: 1) Most common AE: infections 43% 2) Less AE with ADA 10.6 IR/100 PY vs IFX 25.0 IR/100 PY (p=0.008) 3) More multiple AE with IFX (p=0.014)

Frequency and Identification of Risk Factors of Uveitis in Juvenile Idiopathic Arthritis A Long-term Follow-up Study in a Cohort of Italian Children

J Clin Rheumatol 2019;00: 00–00

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
6	*Conti, 2019*	Observational, single centre (Italy) Study F/U = 13 yrs (authors admit - time of F/U "varied considerably" for those who did not develop end-point of JIA-U)	Recruited Jan 2000 to Dec 2013, followed until 1. End of study OR 2. 1° study end-point = diagnosis of JIA-U	108 Italian JIA pts. JIA ILAR Dx >3 mos duration. Note: in total cohort - relatively high "polyarthritis" (31%) versus "oligoarthritis" (35%) and also reported a separate category "monoarthritis" (4%)	Fulfilled "criteria for JIA" as reported from previous study. Evaluated every 3 months "clinical, lab, instrument". Defined: ANA+ $\geq$ 1:160 Both of the below, raise questions about the study cohort**:** 1. They report on the development of "acute" uveitis in 19 patients. 2. They report on type of uveitis detected and included "intermediate" uveitis (unilateral in 9% of patients, bilateral in 29%).	Main aim described: frequency and risk factors of JIA-U. Used x^2 to assess association between categorical variables. 21 patients developed JIA-U (19.44%) 20% overall cohort, ANA+ as defined. RR of uveitis 16.6, 95%CI 6.21-44.4 Oligoarthritis (total 38, 17 ANA+ ->14 JIA-U; 21 ANA neg -> 2 JIA-U). Risk factors: 1. ANA+ oligoarthritis subtype; reported on impact of "high levels" of ANA (see below). Do not see evaluation of any other risk factors. Do not see analysis of ANA and subtype as separate (did look at a given subtype as ANA+ or ANA negative). Kaplan-Meier analysis used to assess probability to develop JIA-U (end point) -> overall cohort ANA+ = RR 5.3 during mean F/U 36 mos vs ANA neg of 120 mos; oligo ANA+ 60 mos to JIA-U vs 120 mos (other subtypes).

Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis

Clin Rheumatol (2018) 37:549–553

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results

7	*Correll, 2018*	Retrospective chart review, no comparison cohort	Between January 2003 and November 2015	From 2 US American centers: 69 of patients identified on weekly adalimumab (Pediatric Rheumatologic Database); 60 included in the review
				
				Age (years) at start of weekly adalimumab 13.9 (4.78)
				
				Frequency (%)
				
				• Oligoarticular JIA, persistent 10 (16.7)
				• Oligoarticular JIA, extended 0 (0)
				• RF-positive polyarticular JIA 2 (3.3)
				• RF-negative polyarticular JIA 15 (25.0)
				• Enthesitis-related JIA 9 (15.0)
				• Arthritis associated with IBD 1 (1.7)
				• Psoriatic arthritis 9 (15.0)
				• Systemic JIA 3 (5.0)
				• Uveitis 17 (28.3)
				• Other 9 (15.0)
				
				Concurrent medications (%)
				
				• Methotrexate 50 (83)
				• NSAID 40 (67)
				• Oral prednisone 28 (47)
				• Hydroxychloroquine 8 (13.3)
				• Leflunomide 7 (11.7)
				• Sulfasalazine 6 (10.0)
				• Mycophenolate 4 (6.7)
					Adverse events including
					• Malignancies
					• New autoimmune diseases
					• Infections
					• Injection site reactions
					• Persistent transaminitis
					• Leukopenia
					• Anemia
					• Thrombocytopenia
						– Infection not requiring antimicrobials 24 (40.0%)
						– Infection requiring antimicrobials* 24 (40.0)
						  ○ Sinusitis 11 (18.3)
						  ○ Pharyngitis/tonsillitis 9 (15.0)
						  ○ Ear infection 8 (13.3)
						  ○ Respiratory infection/pneumonia 4 (6.7)
						  ○ Cellulitis 1 (1.7)
						  ○ Abscess 1 (1.7)
						  ○ Shingles 1 (1.7)
						  ○ Other 7 (11.7)
						– Infection requiring hospitalization 3 (5)
						  ○ Viral pharyngitis and Behcet's flare 1 (1.7)
						  ○ Sepsis 1 (1.7), concurrent treatment with cyclosporine, prednisone taper
						  ○ Acute appendicitis 1 (1.7)
						– Injection site reaction 4 (6.7)
						– Transaminitis 2 (3.3)
						– Leukopenia 1 (1.7) – thought not to be related to adalimumab
						– Anemia 3 (5) - thought not to be related to adalimumab
						– Other autoimmune disease 2 (3.3)
						  ○ Multiple sclerosis 1 (1.7)
						  ○ Autoimmune hepatitis 1 (1.7)
						– Malignancy 0 (0)
						– Death 0 (0)
						
						Conclusion: "The off-label use of weekly adalimumab was used most to treat

				• Cyclosporine 3 (5.0) • Azathioprine 2 (3.3) • Intravenous methylprednisolone 2 (3.3) • Rituximab 2 (3.3) • Abatacept 1 (1.7) • Intravenous immunoglobulin 1 (1.7) Number of weeks on weekly adalimumab (mean ± SD) **114.1 (107.4),** 16 patients on ongoing weekly adalimumab during the study		patients with uveitis and polyarticular JIA, and the mean duration of weekly dosing was 2 years. Serious adverse events were rare."

The risk of uveitis in patients with JIA receiving etanercept: the challenges of analyzing real-world data

RHEUMATOLOGY doi:10.1093/rheumatology/kez449

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
8	*Davies, 2019*	UK JIA national prospective treatment registries (JIA patients at start with biologic vs. methotrexate, non-randomized)	Etanercept Cohort Study (BSPAR-ETN) 2004 – 06/2018 Biologics for Children with Rheumatic Diseases (BCRD) study 2010 - 06/2018	non-systemic JIA registered at the point of starting MTX, biologic (etanercept, adalimumab or infliximab) who did not have a history of uveitis at the start of the registered drug; patients switched cohorts with respective change of treatment 2294 patients in the analysis; 943 MTX, 1047 etanercept and 304 adalimumab/infliximab Age, median (IQR), years MTX 10 (4-13) ETA 11 (6-14) ADA/INF 10 (6-13) Disease duration, median (IQR), years MTX 0 (0-1) ETA 2 (1-5) ADA/INF 2 (1-5) Oligoarthritis: persistent MTX 160 (17) ETA 55 (5) ADA/INF 16 (5) Oligoarthritis: extended MTX 149	Baseline, 6 months, 12 months and annually thereafter Newly diagnosed uveitis cases were defined as any reported adverse event of uveitis in patients that had no previous history of uveitis recorded at baseline. Uveitis information were captured from centres using specially designed proformas, which ask for the type, localization and course of uveitis, as well as establishing whether it is a new or recurrent event.	There were 44 new diagnoses of uveitis over a total of 5456 person-years of follow-up: 27 in patients on MTX, 16 in patients on etanercept (etanercept-combination = 11, etanercept-monotherapy = 5) and 1 in a patient on Adalimumab Crude incidence rates of uveitis (per 100 person-years) MTX 1.6 (1.0-2.3) ETA 0.6 (0.3-0.9) ADA/INF 0.1 (0-0.4) ETA mono 0.3 (0.1-0.7) ETA + MTX 1.0 (0.5-1.8) HR of uveitis diagnosis (95% CI), fully adjusted using propensity deciles (includes age, gender, CHAQ, JADAS, disease duration, ethnicity, comorbidity, baseline steroid use and ILAR category) MTX Ref ETA 0.5 (0.2, 1.1) ETA mono 0.3 (0.08, 1.0) ETA + MTX 0.6 (0.3, 1.6) ETA + MTX 2.6 (0.8, 8.8) (vs. ETA mono) Sensitivity analysis limited to patients younger than 12 years at JIA onset and sensitivity analysis limited to patients censored at their 12th birthday not significantly different (Patients < 12 yo more often screened for uveitis in the UK than patients > 12y)

				(16) ETA 205 (20) ADA/INF 48 (16) Polyarthritis: RF-negative MTX 330 (36) ETA 400 (39) ADA/INF 107 (35) Polyarthritis: RF-positive MTX 81 (9) ETA 122 (12) ADA/INF 39 (13) PsA MTX 82 (9) ETA 75 (7) ADA/INF 25 (8) Enthesitis-related arthritis MTX 72 (8) ETA 101 (10) ADA/INF 62 (21) Undifferentiated arthritis MTX 34 (4) ETA 48 (5) ADA/INF 1 (1)		Time from JIA diagnosis to uveitis diagnosis, median (IQR), years MTX 2 (1-3) ETA 4 (2-5) ADA/IFN 2 ETA mono 4 (4-5) ETA + MTX 4 (2-5) Age at uveitis diagnosis, median (IQR), years MTX 4 (3-9) ETA 7 (6-10) ADA/INF >15 ETA mono 7 (6.5-7.5) ETA + MTX 9 (6-10) No association was found between the use of etanercept and the occurrence of new uveitis when compared with those receiving MTX for the first time, although the crude incident rates were lower in patients receiving etanercept (most likely healthy user effect). Concurrent MTX use with etanercept did not appear to have a further protective effect in this cohort. The lower rates of uveitis among patients starting etanercept do not support a causative link between etanercept and the development of uveitis. A univariable analysis of risk factors showed significant associations between new onset uveitis and • younger age at baseline • shorter disease duration • being of non-white ethnicity and having • oligoarticular disease

Tocilizumab for refractory uveitis associated with juvenile idiopathic arthritis: A report of two cases

J Clin Pharm Ther. 2019;44:482–485.

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
9	*Dispasquale V., 2018*	Observational, Case report	-	two adolescents whose severe JIA-associated uveitis was unresponsive to DMARD and anti-TNF therapy	Tocilizumab 8 mg/kg, administered intravenously every 4 weeks	Pt1 previous treatments: CS, MTX, adalimumab Pt2 previous treatments: CS, MTX, infliximab, adalimumab Remission of uveitis - mean time of 3 weeks, and methotrexate was safely discontinued 1.5 years later. "These are the first reports of successful methotrexate withdrawal during tocilizumab treatment of JIA-associated uveitis."

Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

Seminars in Arthritis and Rheumatism 49 (2019) 43-55

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
10	*Heiligenhaus A. et al* *2018*	Guidelines (generated from literature review) 543 publications identified using ILAR and SUN classes Each publication reviewed by two delegates from each of 4 contributing groups, from rheumatology and ophthalmology Voting via consensus and Delphi process	1997-2017	Children with JIA (using ILAR) and uveitis (using SUN)		Those with ANA positive uveitis without JIA should be treated same as JIAU Treatment should begin immediately for uveitis (≥0.5 + AC cells) with target of elimination of all cells Topical steroids should be initial treatment for active disease (favor high potency topicals). Should commence as q1-2h x 1-3d, then tapered within 6w, and discontinued with < 0.5+ AC cells. Must monitor for topical and systemic effects of excess steroids. Cycloplegics should be used to treat or prevent synechiae. Topical steroid and/or NSAID must NOT be used as sole treatment for uveitis. May use topical monotherapy if inactivity can be reached within 3 months, using ≤ 2 drops per day of steroid maintenance therapy. If remission not achieved by 3 months (with maintenance of ≤ 2 drops / day), or if adverse effects or new complication, then DMARD recommended (+/- systemic steroid if risk factors for impending vision loss). Methotrexate first line (10-15mg/m2/w) po or SQ. • Imuran may only be considered if biologics contraindicated and intolerant of methotrexate • Recommended against CS-A, CYP, LFN

						• Unable to comment on MMF If unable to achieve remission within 16 weeks of MTX (≤ 2 drops / day) then TNFi should be added to MTX. May give bridging systemic steroids if impending vision loss risk factors. TNFi favored over adding second DMARD. • May consider TNFi monotherapy if intolerant of MTX • Adalimumab recommended 1st line • Golimumab or Infliximab to be considered if failed TNFi+MTX • Etanercept recommended against If unable to achieve remission (primary or secondary) within 16 weeks, may move on to alternate non-TNFi biologics. May add bridging systemic steroids if risk factors for acute vision loss. • TCZ preferred non-TNFi agent. • ABA may be considered alternative, but less favored to TCZ as data inconsistent. RTX may be considered alternative, but less favored to TCZ as it is not approved for JIA treatment. De-escalation may be considered no sooner than 2 years after remission Interventional procedures may be considered for impending vision loss or severe complications.

Adalimumab in Juvenile Idiopathic Arthritis–Associated Uveitis: 5-Year Follow-up of the Bristol Participants of the SYCAMORE Trial

Am J Ophthalmol 2019;207:170–174

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
11	*Horton, 2019*	Retrospective interventional case series	5 years	Children with JIA-associated uveitis refractory to topical or systemic steroids and methotrexate (recruited at the Bristol Eye Hospital into the SYCAMORE Trial)	Must have been recruited at the Bristol Eye Hospital Data extracted from clinical records for up to 5 years from the study randomization date	Following withdrawal of the investigational medicinal product (Adalimumab or placebo), 25/28 participants were started on Adalimumab for active JIA-U. Of the 12 participants in the active treatment arm of the SYCAMORE study, 11 (92%) were restarted on Adalimumab after withdrawal of the investigational medicinal product for active JIA-U (median time to flare 188 days [range 42-413 days). Two participants stopped Adalimumab for uncontrolled JIA-U. One participant had a reduction in vision to 0.3 owing to cataract. Mean visual acuity for the remaining 27 participants was -0.04 (right eye) and -0.05 (left eye). Conclusions: 1. Drug-induced remission of JIA-associated uveitis did not persist when Adalimumab was withdrawn after 1-2 years of tx. 2. Adalimumab was well-tolerated and visual acuity outcomes were excellent.

Cost-Effectiveness Analysis of Adalimumab for the Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis

Ophthalmology 2019;126:415-424

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
12	*Hughes., 2018*	Observational, cost-utility analysis	18 months	Children and adolescents 2 to 18 years of age with persistently active uveitis associated with jia	Methotrexate (up to 25 mg weekly) with or without fortnightly administered adalimumab (20 or 40 mg, according to body weight)	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). During the 18-month trial-based analysis, total costs were £15 980 (95%cr, £14 213-£17 943) and £6248 (95% cr, £3922-£8889), respectively, with most of the difference in costs (£8579 [88%]) attributable to the use of adalimumab. Adalimumab in combination with methotrexate generated more qalys but at a higher cost than methotrexate alone. 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. 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.

Prospective Determination of the Incidence and Risk Factors of New-Onset Uveitis in Juvenile Idiopathic Arthritis: The Research in Arthritis in Canadian Children Emphasizing Outcomes Cohort

Arthritis Care & Research 2019;71(11):1436-1443.

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
13	*Lee J et al.*	Cohort study AIMS: Estimate the annual incidence of new-onset uveitis following JIA diagnosis and the risk factors associated with its development.	Patient recruitment from Jan 2005 to Dec 2010	Pts with a new diagnosis of JIA made within 6 months of enrollment who had ≥1 follow-up visit and documentation on the presence or absence of uveitis.	N/A	1183 pts met inclusion criteria 100 patients were identified as having developed uveitis (13 patients had uveitis at the time of study enrollment and 87 developed new-onset uveitis during follow-up) The incidence of new-onset uveitis during the first 5 years was 2.8% per year. The annual incidence was highest in the first year after JIA diagnosis at 3.4% and lowest in the fifth year at 2.1% In secondary analyses, which included the prevalent cases (13 patients with uveitis at the time of enrollment), the incidence for the first year increased from 3.4% to 4.5% and the overall incidence increased from 2.8% to 3.0% per year The risk factors significantly associated with the development of uveitis in the multivariable analysis, were age <7 yrs at JIA diagnosis and a positive ANA These findings support continued vigilant surveillance for uveitis for at least the first 5 years after JIA diagnosis and support the idea that priority for screening should be placed on young age.

Timing of infliximab and adalimumab initiation despite methotrexate in children with chronic non-infectious anterior uveitis

Eye (2019) 33:629–639 https://doi.org/10.1038/s41433-018-0283-0

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
14	*McCracken, 2018*	Retrospective chart review	Recruited Sept 2011-July 2016. Enrollment at variable time points. Median study f/u 2.4 yrs	CAU (chronic active uveitis) – idiopathic (iCAU)=10 pts and JIA-U=36 pts. Mixed population, "volunteers" from larger uveitis epi study in a 3° care centre. Only 21 patients with initial ocular exams. Excluded acute AU.	All pts treated with MTX for uveitis (not for arthritis) - at any point during course. JIA - ILAR criteria. SUN criteria to define CAU, uveitis activity. Note: included only patients diagnosed after 1998 ("era of TNFi").	Primary outcome: Time to TNFi for active CAU using Kaplan Meier survival analysis (95%CI) and potential factors associated with addition - Cox regression. 1. MTX start median 5.0 months (CI 1.4-18.6), cumulatively 57% by 6 mos, 70% within 1 yr, 89% b/w 1-3 yrs. 56% addition of TNFi, median 19 mos (25-75%ile 7.1-46.9) after MTX. 4% required 2nd TNFi. TNFi median start 43 mos from uveitis Dx; after MTX, cumulatively -TNFi added 12% within 6 mos, 21% within 1yr, 39% within 2yr, 61% within 5yr. Factors for TNFi addition – conclusion – needs more investigation (and about the optimal timing). Increase use in iCAU at 3/12 but no difference at 1 yr. Earlier use in iCAU (6x higher at 3 mos). Factors not associated: age(<5 yr vs>5), sex (male vs female), race, ethnicity, bilateral disease, labs. Other potential factors to consider impact (other than uveitis severity) = responsiveness to topical; tolerance of/adherence to meds; physician, clinical support; pharmacogenetics with MTX in JIA-U. Explored changes in practice over time – time to treat longer in first cohort (2002-2011) but same proportion as TNFi use (2012-2015).

						Additional: ocular complications present “at some point” – JIA-U = 72%, defined vision loss =56% - felt to be similar to previous reports. Complications at presentation = 57%. Crucial comm between Rheum & Ophthal = shared decision making.

The economic burden of juvenile idiopathic arthritis–results from the German paediatric rheumatologic database

Clinical and Experimental Rheumatology 2009; 27: 863-869.

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
15	*Minden et al, 2009*	Cross-sectional sample from prospectively collected database	3 months in 2003 Normalized costs to 2008	369/1583 outpatients (263F:106M) aged 2-18 years with JIA enrolled in National Pediatric Rheumatology Database (NPRD) in Germany Inclusion: completed cost questionnaire Exclusion: no cost questionnaire data (1214/1583)	Direct JIA-related costs, families' out-of-pocket expenses, parents' income loss per patient and year used physicians' reports, parents' 3-month recall, and average prices as the basis.	Mean total cost of JIA = 4,663 euros/patient/year (95% CI: 3,987 to 5,415 euros) • RF+ pJIA = 16,172 euros • sJIA = 7,876 euros • Persistent oligoJIA = 2,904 euros • On biologics = 27,771; no biologic = 3,155 euros Direct costs: 4,403 euros (95% CI: 3,743 – 5,415) Healthcare costs = 89% of Total Cost (95% Direct costs) • Inpatient 40%; Oupatient 60% • medication 47% (77% for biologics) • MD visits 7% • Allied Health visits 3% • out-of-pocket cost 223 euros/yr/family Indirect cost (time loss from work) • 270 euros/yr/family • 8.4 days absent from school/yr Risk factors for higher costs: • increased disease activity (p=0.028) • pain (p<.001) • function (CHAQ) (p<.001) – In multiple Regression this was only significant risk factor (p=0.016) • disease duration (0.105) • time from symptom onset to first ped rheum visit (0.135) • uveitis (0.33)

JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis

Clinical Rheumatology https://doi.org/10.1007/s10067-019-04875-w

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
16	*Miserocchi, 2019*	Case Series	Between August 2018 and September 2019	**4 patients**. JIA-associated uveitis, severe, uncontrolled arthritis and/or uveitis despite conventional biologics and DMARDs.	Baricitinib (3 cases) and Tofacitinib (1 case). Rheumatologist and ophthalmologist assessment on same day. Response defined as two steps decrease of anterior chamber cells (SUN), reduction of flare by LFM (under 50 ph/ms) and resolution macular edema on OCT (under 300 um)	Baseline: Ages 18-43. Means: duration of articular disease 23 yrs, uveitis 21 years, age patients 30yrs. mean number of flare-up recurrences (2+ flare in ant chamber) before jakinibs 4.2/year to 1.4 per year after start Patients: 1) 42 female dx ANA neg JIA age 9, uveitis age 10, tx with Ifx 5 mg/kg q 4w, ADA 40 mg q2w, LFN, ABA, ritux and toci). Left eye retinal detachment and phthisis bulbi. Tofa 5 mg BID monotx started when uveitis inactive and remained so for 6 months on tx (started tofa for joints). Normal VA 2) 18 female, poly ANA + JIA, age 1 with uveitis at presentation, treated same as patient 1, also ritux, abatacept. Baricitinib March 2019 5 mg/day and mtx 15mg. uveitis inactive and topical steroids stopped. VA 20/40 OD, 20/200 OD 3) 37 female, oligo-extend ANA + dx age 2, uveitis onset age 3 controlled until age 20 – mtx, AZA and biologics as in case1 and 2 plus golimumab 50 mgq4weeks x 9 months, toci 162 mg/week x 6 months. Baricitinib august 2018 4mg/day- joints and eyes inactive x 13 months, VA 20/60 OU 4) 21 male, poly JIA ANA + RF – age 10. Age 15 uveitis tx with mtx, CyA TNfi biologics as above, and ABA, toci and ritux. Baricitinib 4mg/day with mtx

						15mg/week and pred 7.5mg/day. A/R 6 months taper off pred and VA normal. No reported AE – lab or infx. Mean fup time 7 months (4-13 months)

Specialty Practice and Cost Considerations in the Management of Uveitis Associated With Juvenile Idiopathic Arthritis

***J Pediatr Ophthalmol Strabismus*. 2016;53(4):246- 251.**

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
17	*Palestine et al, 2016*	Email Survey (cross-sectional)	Once	132/2,965 eligible physicians: • pediatric ophthalmologists • uveitis specialists • retina specialists • rheumatologists	Asked to choose therapy for hypothetical patient with JIA-associated uveitis Examined choice differences based on - Cost - Prior authorization - Specialty practice	38/192 (19.8%) uveitis specialists 25/742 retina specialists 44/1,179 (3.7%) ped ophthalmology 24/852 (2.8%) rheumatologists Methotrexate was the preferred first-line therapy for all specialty groups: 92.3% of uveitis specialists, 56% of retinal specialists, 75% of pediatric ophthalmologists, and 70.8% of rheumatologists (*P* = .0070). After equalization of cost/authorization: 82.1% of uveitis specialists, 48% of retina specialists, 72.7% of pediatric ophthal-mologists, and 54.2% of rheumatologists (*P* = .0139) choose MTX. Second line therapy: uveitis specialists, pediatric ophthalmologists, and rheu-matologists chose biologic agents No significant differences in distribution of second-line medication choices before and after equalization.

ADJUVITE: a double-blind, randomized, placebo controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis

Ann Rheum Dis 2018;77:1003–1011. doi:10.1136/annrheumdis-2017-212089

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
18	*Quartier, 2018*	Double-blind, randomized, placebo-controlled trial	12 months (primary outcome assessed at 2 months)	Children aged 4 years or older with ocular inflammation =/> 30 photon units/ms Inadequate response to well-conducted topical steroid tx and MTX at a dose of 0.3-0.6 mg/kg (max 25 mg) weekly for at least 3 months	Exclusion criteria: 1. Systemic JIA, RF +ve JIA, or ERA 2. Previous tx with TNFi monoclonal antibody 3. Any contra-indication to administration of immunosuppressive therapy 4. Complications requiring surgery	Primary outcome: at month two, among 31 patients included in intention-to-treat analysis, there were 9/16 responders on ADA and 3/15 on placebo (p=0.038, X test; relative risk=2.81, 95% CI 0.94 to 8.45; risk difference: 36.3%, 95% CI 2.1 to 60.6) There was no significant difference using the SUN classification criteria of improvement. 30 continued the trial after month two and received ADA (open-label phase), 29 reached month 12. There were 7 serious adverse events, none of which were related to study treatment.

Author(s): Quartier et al. 2017

Question: Adalimumab compared to placebo in JIA-associated uveitis with inadequate response to Methotrexate and topical steroids for at least 3 months

Setting: Double-blind, 1:1 randomized, placebo-controlled, multicenter, phase 3 trial

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adalimumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis												
1	Double-blind, randomized, placebo-controlled trial	No serious limitations. ITT principle, randomized patients, blinded injections, employed double blinding.	Not applicable. Single study, unable to compare differences in effect size across.	No serious limitations. Comparable populations, interventions, and outcome measures.	No serious limitations.	No serious concerns of publication bias.	16	16	RR = 2.81 (95% CI 0.94 to 8.45) for primary outcome		⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval

Tocilizumab in refractory JIA associated uveitis (APTITUDE) **Lancet Rheumatology 2020**							
Ref ID,	**Author, Year**	**Study Type**	**Duration**	**Population Description**	**Screening Given to relevant population**	**Intervention/Outcomes**	**Results**
19	*Ramanan AV et al. 2020*	Multicentre, single-arm, phase 2 trial 7 tertiary hospitals in the UK	24-weeks	Eligibility: 2-18 yrs with active JIA-associated uveitis PLUS inadequate response to MTX (min 12 week trial) and at least one anti-TNF (min 12 week trial) Active uveitis defn: Two or more readings of anterior cells of grade 1+ or more during the 6 wks preceding screening visit Exclusion criteria: - Previous exposure to tocilizumab - Receipt of more than 6 topical steroid drops per eye/day - Receipt of prednisone dose	Dose of MTX must be stable for 4 weeks before screening visit	Tocilizumab 162 mg sc q2 weeks (pt >30 kg) x 24 wks Tocilizumab 162 mg sc q3 weeks (pt <30 kg) x 24 wks All pts remain on MTX Outcomes: - Primary outcome: Response to treatment, defined as a two-step decrease in level of inflammation (AC cells) or decrease to zero between baseline and 12 weeks of treatment - Secondary outcomes: safety and tolerability of tocilizumab; compliance; corticosteroid use; ocular outcomes; ACR pedi30/50/70/90/100; # of pts with changes in biologic or dmards; # pts with arthritis flares; JADAS Primary Endpoint: If more than 7 patients responded to treatment then a phase 3 trial would be justified Intention to treat analysis	22 pts were enrolled, and 21 received treatment (one pt was found to be ineligible immediately after enrolment). All pts had received adalimumab, none had received other anti-tnfs. 17 (81%) of 21 pts discontinued treatment before 24 weeks, six (29%) discontinued before their 12-week visit, nine (43%) discontinued at 12 weeks, and two (10%) discontinued between weeks 12 and 24 Primary outcome: 7 (33%) of 21 pts achieved treatment response at week 12, a further three (14%) had a one-step improvement at week 24 with tocilizumab.

				more than 0.2 mg/kg/d			Secondary outcomes results of note: - Safety results were consistent with the known safety profile for tocilizumab. - Four (19%) pts had macular oedema at baseline, which resolved after treatment in 3 pts. Conclusion: Primary endpoint NOT MET

Author(s): Ramanan et al. 2020

Question: Tocilizumab compared to nil in anti-TNF refractory JIA-associated uveitis

Setting: multi centre, single-arm, phase 2 trial

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tocilizumab	nil	Relative (95% CI)	Absolute (95% CI)		
tocilizumab in patients with anti-TNF refractory JIA-associated uveitis (APTITUDE): a multi-centre, single-arm, phase 2 trial (follow up: 24 weeks; assessed with: SUN criteria - 2 step decrease or decreased to zero from baseline at week 12)												
1	Randomized multicentre, sing-arm, phase 2 trial.	No serious limitations.	Not applicable.	No serious limitations.	No serious limitations.	None.	-/21		Not estimable		⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval

High-dose intravenous methylprednisolone in juvenile non-infectious uveitis: A retrospective analysis

Clinical Immunology 211 (2020) 108327

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
20	*Schnabel, A et al, 2020*	Retrospective Chart Review at 2 sites Germany(electronic records reviewed)	IVMP received between 01.Jan 2003 and 31.Dec.2016	83 potential pts identified; 24 excluded because they did not meet diagnosis of non-infectious uveitis or did not receive IVMP; 3 had no data. 56 patients (under 16 y o) included, 52% female, median age 7.4 yrs (2.5-16.7) Rx with IVMP during the study period for active (new onset or flare of existing) non-infectious uveitis (SUN criteria met). 38 pts with idiopathic uveitis, 16 JIA and 1 IBD. Uveitis was bilateral in 36 pts, anterior in 24, intermediate in 17 and 3 had panuveitis. (Total of 93 eyes affected). All pts had failed topical RX (SHARE guidelines) or had predictors of poor outcome (17/56) including initial visual acuity (VA) < .3, low IOP, AC cells at least 2+, AC flare 1+, vitreous haze, glaucoma, cataract, macular edema, prolonged active uveitis, or uveitis onset under 5yo, before	IVMP 10-30 mg/kg/d (max 1000mg) X 3 d given for 1 to 5 courses at monthly intervals. At the time of the first IVMP, 49 also got topical CS, 13 MTX and 3 an anti- TNF. Most pts were subsequently Rx with additional topical CS, DMARD or a biologic at MDs discretion.	Primary outcomes were the effect of IVMP on intraocular inflammation and VA assessed at 4 wks, 3 and 6 mos. VA improved after 3 mos with further improvement at 6 mos (p<.001) Significant decrease in inflammation at 3 mos assessed by cells in AC (45%-18%, p=.01), deceased synechiae (47%-32%, p<.005), keratic precipitates (27%-18%, p<.001), papillary edema (30%-13%,p<.001), macular edema (15%-4%, p<.05). Assessment of 20 pts followed to 12 mos suggested ongoing reduction in inflammation; also a small # of patients with a uveitis flare on anti-TNF had improved VA after IVMP (p=.136). 18 pts Rx with 1 course of IVMP were compared with 27 pts Rx with 3-5 IVMP courses. 2/18 vs 12/27 had low VA (<.3) at baseline, and overall VA was lower in the 3-5 IVMP group; improved VA was reported in pts who got 3-5 IVMP at 3mos and 6 mos (p<.005). Despite more poor prognostic factors, 3-5 IVMP pts also had fewer relapses, less eye surgery for complications, less frequent need for a biologic, and the median time to first relapse was longer (but differences did not meet statistical significance).

				onset of JIA or within 6mos of arthritis onset). Median follow up was 2.7 yrs (0.3-17.8).		Overall cataracts were seen in 16% of pts; glaucoma in 5%. Cataracts were seen more often in pts who got I course of IVMP vs 3-5 (39%vs 7%, p<. 02). Limitations-retrospective design, SUN scoring system not used; used presence or absence of inflammation only; if AC cells not documented, AC was counted as “cell free”.

Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis associated uveitis **Arch Dis Child 2019;104:246–250. doi:10.1136/archdischild-2018-315060**						
Ref ID,	**Author, Year**	**Study Type**	**Duration**	**Population Description**	**Treatment Given to relevant population**	**Results**
21	*Skrabl-Baumgartner, 2018*	Observational study (prospective)	Up to 6 years	20 patients treated with active uveitis refractory to conventional disease-modifying antirheumatic drugs	Adalimumab (in the standard dose of 24 mg/m2 body surface (maximum dose 40 mg) subcutaneously every other week, without dose modification) Previous therapy with the cDMARDs: MTX, AZA or MMFwas continued, if tolerated. Patients with active uveitis at start of ADA treatment or in relapse received topical prednisolone acetate 1% in an initial dose of at least five drops or systemic prednisolone in an initial dose of 1 mg/kg/day	19 F/ 1 M 17 anterior -3 panuveitis 3 unilateral- 17 bilateral After 6 months, the uveitis response was complete in 14 and partial in 2. After 12 months, uveitis remained inactive in 15 patients and worsened in one. In the 12 patients receiving ADA treatment, at 24 months uveitis was inactive in 7, remained stable in 3 and had relapsed in 2. Anti-adalimumab antibodies (AAA) detected in 9 pts. Permanent AAA (7 pts) associated with loss of response Transient AAA (4 pts) not associated with loss of response (LOR) Conclusion: AAA-associated LOR frequently occurs in long-term treatment with ADA for JIA-associated uveitis. Concomitant immunosuppressive therapy significantly reduces the risk of LOR due to AAA.

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

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
22	*Jari M et al. 2020*	Systematic Review		13 total studies were reviewed 11875 patients; 10921 JAU (92%); rest were BD or SLE 632 /11875 (5% only) had MTX, across 8 papers from 1998-2016 (i.e. may have already been reviewed in other papers or by other group directly)	Methotrexate (for purpose of this analysis)	Were able to provide pooled response rate to ADA (68%), IFX (64.7%), and MTX (40%); remaining drugs TCZ, DCZ, RTX had insufficient evidence. Of the methotrexate group, there was a significant publication bias (P 0.016) and there was significant statical heterogeneity

Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach.

Rheumatology (Oxford). 2013 May;52(5):825-31

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
23	*Simonini G et al. 2013*	Systemic search of articles (Jan 1990 – June 2011) All included papers were retrospective chart reviews	22.5 mo median (range 1-96)	≤ 16y with chronic uveitis (not JAU). Of the 135 patients, 121 had JAU (remainder were sarcoid, TINU, idiopathic) Eligible patient: -vision-threatening non-infectious uveitis -autoimmune uveitis refractory to topical or systemic tx -onset <= 16y age -MTX monotherapy -SUN criteria for outcome measures -English language pub. **Excluded patients on other agents Positive response was a 2-step decrease in SUN grade, or grade 0 9/246 articles were used	Methotrexate monotherapy (dose 7.5-30mg/m2) 15mg/m2 was most common dose used	In total, 95/135 children responded to MTX alone (0.73, 95% CI 0.66-0.81) Discontinued MTX in 35/107 of patients: - 21/35 for sustained remission - 7/35 for inefficacy and 7/35 for intolerance/AE - 45/61 obtained remission over 3.5 months - 25/29 remained in remission for 10.6 months (3-27mo) - Steroid were tapered / dcd in 22/23 children - 11/13 showed improvement or remission, but not all papers agreed; Heilinghaus paper showed improvement in 71% but no remission over 27.6 months Of 107 MTX exposed patients, 21 (19.6%) had AE, primarily nausea and/or liver enzyme elevation.

Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach.

Rheumatology (Oxford). 2013 May;52(5):825-31

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
24	*Ferrara et al, 2018*	Guidelines on MTX use in JIA generated from SR and expert consensus meeting (MARAJIA group) 209 studies selected as most relevant (33 clinical trials, 51 reviews, 1 cochrane meta-analysis, 124 other types) Plus an additional 6 in updated search. Generated 10 recommendations from 9 PICO questions (up to Feb 2017)		All focused on methotrexate use in patients with JIA (includes section on JIA-uveitis)	Methotrexate	Recommend MTX for JIA-uveitis based on grade 4C evidence (all case series, case-control studies) Also recommends SC over PO if doses of 15mg/m2/week requested due to increased bioavailability (grade 4C evidence)

Efficacy of High-Dose Methotrexate in Pediatric Non-Infectious Uveitis.

Ocul Immunol Inflamm. 2019;27(8):1305-1313. doi: 10.1080/09273948.2018.1529800

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
25	*Wieringa W et al, 2019*	Retrospective observational cohort study	Median follow up 5.6 years (0.9 – 19.2 range)	Pediatric patients treated with MTX for uveitis for longer than 6 months between 1990-2014 at one centre in Netherlands - 44 patients (21 had JIA-uveitis; 10 oligo) - 25/44 had anterior uveitis	MTX PO/SC High dose = >/=15mg/m2 (25mg max) Low dose = <15mg/m2	- 12 JIA-uveitis patients received low dose MTX - 9 JIA-uveitis patients received high dose MTX - Overall, 28 (66.7%) patients reached remission on medication in (median) 22.5 months (IQR 10.4- 45). - Time to remission on medication in the low dose group (median 35.2, IQR 20.5 – 72.1 months) was significantly longer than in the high dose group (median 16.6, IQR 7.8 – 22.5 months) (p= 0.01). - data also indicate that an MTX dose of ≥15 mg/m2 /week administered by subcutaneous injection is the most effective in establishing rapid remission on medication - No statistically significant differences in ocular complications, steroid-sparing effect, cumulative dosage and side effects of MTX were found between

Methotrexate treatment may prevent uveitis onset in patients with juvenile idiopathic arthritis: experiences and subgroup analysis in a cohort with frequent methotrexate use.

Clin Exp Rheumatol. 2016 Jul-Aug;34(4):714-8.

Ref ID,	Author, Year	Study Type	Duration	Population Description	Treatment Given to relevant population	Results
26	*Kostik et al, 2016*	Retrospective chart review (observational cohort study)	Minimum 2 year follow up	- all consecutive JIA patients who had received a stable management for at least 2 years with or without MTX were reviewed - Russian cohort – 281 patients, 69.8% girls; ANA +'ve 40.4%; oligo in 217 Between Jan 2005-Jan 2013 Exclusion criteria: Treatment with any meds other than NSAID, MTX and IAC SJIA, RF +'ve, ERA Patients in whom uveitis occurred before arthritis or first observation in our centre	MTX 15mg/m2/week, SC and PO, (90% SC) 191 (68%) received MTX	During follow up, 64 patients (22.8%) developed uveitis Median of 1.6 years after disease onset The frequency of uveitis was lower in MTX-treated than in MTX-untreated patients (11.5% vs. 46.7%, respectively, OR=6.7 (95%CI: 3.7-12.3), p=0.0000001 Patients treated with MTX had more active joints, had more often polyarticular arthritis with involvement of the wrist and small joints of the hand. Patients who developed uveitis comparatively had a lower age, had more often oligoarticular arthritis, less active joints, higher levels of ESR and ANA positivity. There were no differences in uveitis frequency depending on MTX route of administration (oral or subcutaneous)

Online Supplemental File 2. Evidence to decision tables

Evidence to decision table ACR/AF Recommendation 1

QUESTION	
Should ophthalmic screening every 3 months (as per current guidelines) vs. screening at a longer frequency be used for children and adolescents with JIA at high risk of developing uveitis?	
POPULATION:	Children and adolescents with JIA at high risk of developing uveitis
INTERVENTION:	Ophthalmic screening every 3 months (as per current guidelines)
COMPARISON:	Screening at a different frequency
MAIN OUTCOMES:	Timely detection of (chronic, asymptomatic) uveitis
SETTING:	AMBULATORY PATIENTS
PERSPECTIVE:	RHEUMATOLOGIST, OPHTHALMOLOGIST, PATIENT
BACKGROUND:	Traditional screening for uveitis has been based on 2 different guidelines (AAP and German guidelines)
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes X Yes o Varies o Don't know	Yes, the panel has decided this is a priority question. Patients at high risk for uveitis are patients with JIA with onset at a young age (<7) and ANA positivity and have a 10-20% risk of developing uveitis over the first 5 years. No studies identified discuss the priority of determining the "most correct" screening interval in high risk patients with JIA (ANA positivity and oligoarticular disease course). From ACR guidelines: Two studies [Zanon 2012, Chia 2003) found that more severe uveitis was associated with a shorter time to onset from diagnosis of arthritis compared to mild	

	uveitis. Six studies found that ocular complications are not infrequent in patients with uveitis under the current screening guidelines. Recent Canadian study (Lee 2017): Incidence of new-onset uveitis during the first 5 years was 2.8% per year. The annual incidence was highest in the first year after JIA diagnosis at 3.4% and lowest in the fifth year at 2.1% In secondary analyses, which included the prevalent cases (13 patients with uveitis at the time of enrollment), the incidence for the first year increased from 3.4% to 4.5% and the overall incidence increased from 2.8% to 3.0% per year. The risk factors significantly associated with the development of uveitis in the multivariable analysis, were age <7 yrs at JIA diagnosis and a positive ANA Evaluation of timing of first screening (Papadopoulou, 2017) by BSPAR screening guidelines: First screen within 2-4 weeks of referral, then screening was q3-12 months based on risk factors. Median onset of uveitis +12mo after diagnosis (range -7mo to +72mo; only 1/32 patients after 4 years of JIA). Did not comment on how many had uveitis as presentation. Results ultimately support screening for uveitis at least as often as current guidelines and reiterates that ANA positivity and oligoarticular disease are risk factors for uveitis. Results also raise concern that males suspected of being at risk for uveitis be followed more closely given the potential for more severe disease. However, the results do not address what screening interval is associated with the least ocular complications.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X Large o Varies o Don't know	The ACR voting panel based on the combined AAP and German recommendations, high-risk children are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody (ANA) positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less. Low- or moderate-risk children are those with high-risk JIA categories but who are ANA negative, age 7 years or older at JIA onset, or have JIA duration of more than 4 years, and those with systemic JIA, polyarthritis (rheumatoid factor positive), and enthesitis-related arthritis. Low- or moderate-risk children should be screened every 6–12 months depending on their combination of risk factors. Because children who have enthesitis-related arthritis or are	The guideline group agreed that the early detection of uveitis and prompt treatment has the potential to have a significant impact on ocular complications and outcome thus screening frequency as specified in the ACR guidelines is required.

	carrying the HLA–B27 genotype are at risk of both AAU and CAU, they require screening as well. This recommendation was conditional, based on the low quality of evidence, although several reports have described factors that increase the risk of developing uveitis (19–24). Some children have significant eye disease at the time of screening under the current schedule, but there is a lack of data showing that more frequent screening is beneficial. Patients and parents supported the recommended frequency of screening and expressed a desire for frequent screening. No literature addresses the desirable anticipated effect of frequency of screening. One study [3], compared the AAP screening guidelines to Southwood guidelines and found that the Southwood guidelines identified a few uveitis patients earlier than the AAP guidelines. However, conversely, the AAP guidelines captured a few late onset cases that would have been missed by the Southwood guidelines. Appropriate screening guidelines should lead to optimal detection rates, with the least ocular complications. Even with adherence to screening (Papadopoulou, 2017) found 46.8% of patients with uveitis had ocular complications (most often synechiae, keratopathy, cataracts).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	Undesirable anticipated effects of frequent screening are not specifically addressed in the literature. The ACR guidelines state that some children have significant eye disease at the time of screening under the current schedule, but there is a lack of data showing that more frequent screening is beneficial. Patients and parents supported the recommended frequency of screening and expressed a desire for frequent screening. Minden (2009) examined cost associated with JIA. There was a trend for increased cost with JIA patients having uveitis, but this was not statistically significant in the final model. Mean (SD) annual total cost in euro for uveitis 5146 (6.9) vs 4530 (6.9) no uveitis, p=0.330. Frequent screening can be burdensome for patients and families. Young children may be reluctant or have difficulty complying with slit lamp examination. Families may have financial burden due to frequent screening – which could include the cost of parking,	

	missing work and school, babysitting/daycare costs for siblings. Anxiety and inconvenience of frequent monitoring may also be a factor if it were unnecessary.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low X Moderate o High o No included studies	The ACR recommendation is conditional and based on very low-quality evidence. Current guidelines are based on observational studies. Less frequent screening in high-risk patients will result in delayed diagnosis for a small proportion of patients, likewise more frequent screening in high risk patients will result in unnecessary exams for a proportion of patients. From ACR guidelines: Results ultimately support screening for uveitis at least as often as current guidelines and reiterates that ANA positivity and oligoarticular disease are risk factors for uveitis. Results also raise concern that males suspected of being at risk for uveitis be followed more closely given the potential for more severe disease. However, the results do not address what screening interval is associated with the least ocular complications.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability X Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	No research identified. The ACR guidelines voting panel included patients and parents who supported the recommended frequency of screening and expressed a desire for frequent screening.	Families may not value the main outcome (timely detection of chronic uveitis) if education about risk factors and asymptomatic nature of uveitis is not done appropriately. They may question necessity of frequent eye exams in “asymptomatic” children. Eye care specialists (ophthalmologists, optometrists) without significant pediatric experience may not have the necessary knowledge to value the outcome when weighed again the burden of frequent screening exams. They may question the need for frequent examinations

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	No research identified. Vision-related QOL in patients with uveitis is significantly decreased (Anne-Mike, 2017). Overall composite score of the NEI VFQ-25 was worse in the uveitis group compared to the non-uveitis group; 83.4 vs 94.9, p<0.0001, despite good visual acuity by SUN. Nearly all subscales were lower in patients with uveitis than in patients without (P>0.0001) for all. QOL still worse in uveitis patients when adjusting for duration of arthritis, JIA subtype, arthritis onset before or after 1990 and use of systemic immunomodulation.	Less frequent monitoring may result in undetected uveitis that is only detected after complications have already occurred (eg cataracts, posterior synechiae). Treatment of complications / severe uveitis can be more difficult than early on, leading to permanent damage and adverse visual outcomes. Determining optimal screening interval would manage expectations of burden on the family, if able to demonstrate that adverse outcomes would be minimized and therefore justified by frequent screening.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No research identified. Frequent screening requires more health care provider (optometrist, ophthalmologist) resources than less frequent screening. Resources required are health care provider time/availability, cost to the healthcare system (ie universal health care dollars / NIHB dollars), and costs to the family for transportation, parking, missed work and school, care for other children in the home.	Cost to society would be minimally increased if overall numbers of patients with ocular complications was reduced Ophthalmology costs are paid through provincial healthcare, whereas only some of optometry costs are reimbursed through provincial healthcare and other costs are billed to private insurance. Optometrists are reimbursed at lower rates than ophthalmologists, so conceivably reducing cost to society. And not all families will have private insurance, thereby creating inequities.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No research evidence.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No evidence identified. Uveitis detected at later stage (ie if screening is less frequent and therefore prolonged) can lead to ocular complications that require greater resources – more medications, surgeries and procedures, ophthalmic visits. Importantly, complications can lead to visual loss and impaired educational success and lifelong impact on employability.	The guidelines group agreed that more frequent screening is costly at the time of the intervention (ie cost of screening), but if prevents ocular complications then in the end is certainly a cost-saving measure.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased X Increased o Varies o Don't know	No evidence identified. Frequent screening in Canada should be possible for all patients with JIA. Universal healthcare pays for required optometrist and/or ophthalmology exams for all children under 18 years of age. Consideration for frequent ophthalmic exams in adults with JIA who require ongoing screening – coverage may vary by province but should still be covered as deemed medically necessary.	Adherence to screening guidelines for the high-risk group may be inequitable given the geographic distances of patients to qualified care providers (Ophthalmologists preferred over other ophthalmic providers) Inequity may also be an issue if all provinces do not cover screening tests

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The key stakeholders for the ACR guidelines voting panel include 15 pediatric rheumatologists, 2 ophthalmologists, both of whom were uveitis specialists, and 2 adult patients with JIA. In addition, a parent and patient panel, consisting of 9 adult patients with JIA and 2 parents of children with JIA and uveitis, reviewed the collated evidence and provided input on their values and preferences. The key stakeholders supported the recommended frequency of screening and expressed a desire for frequent screening.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No research evidence	The Canadian healthcare system may not have capacity to handle frequent visits to ophthalmologists, thus is imperative that there are trained optometrists willing and able to detect uveitis in young children. Access to optometry (and ophthalmology) may be limited for patients and families residing in remote communities, future considerations include telemedicine visits that include virtual slit lamp exams.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
O	O	O	O	O

CONCLUSIONS

Recommendation
Conditional recommendation for the intervention.
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 2

QUESTION	
Should ophthalmic monitoring within 1 month after each change of topical glucocorticoids vs. monitoring less frequently be used for children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids?	
POPULATION:	Children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids.
INTERVENTION:	Ophthalmic monitoring within 1 month after each change of topical glucocorticoids.
COMPARISON:	Ophthalmic monitoring less frequently than 1 month after each change of topical glucocorticoids.
MAIN OUTCOMES:	Timely detection of uveitis recurrence.
SETTING:	Outpatient.
PERSPECTIVE:	Ophthalmologist, rheumatologist, patients.
BACKGROUND:	Uveitis relapses potentially occur with tapering of topical steroids. Close monitoring is essential to recognize and effectively treat uveitis relapse to prevent ocular complications.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem		
Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel decided to make this question a priority. At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question. Recent interdisciplinary German guidelines for treatment of uveitis (Heiligenhaus et. al 2019) did not address monitoring pertaining to this question.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate o Large o Varies X Don't know	At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Large o Moderate o Small o Trivial o Varies o Don't know	Uveitis relapses potentially occur with tapering of topical steroids. Without close monitoring those relapses won't be recognized early and ocular complications such as synechiae or loss of vision may occur. Close monitoring seems to be essential to recognize and effectively treat uveitis relapses to prevent ocular complications.	Clinical experience: However, frequent visits every month raise costs for the healthcare system (physician visits, travel, etc.) as well as for the families (travel, missing days at work and school etc.), access to ophthalmologic care in this frequency can be difficult (Northern and rural communities), patients are exposed to stress, related to physician's visits and examinations.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question. No new studies have been identified addressing this question since then.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability X Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	No direct or relevant evidence identified.	To weigh and see benefits and risks of visiting a physician's office frequently may be difficult to judge for families and patients.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	No direct or relevant research evidence available.	Without close monitoring of uveitis, relapses may not be recognized early and ocular complications such as synechiae or loss of vision may occur. Overall, this issue would favor the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct or relevant research evidence available.	However, monthly eye exams will cost the healthcare system more dollars and provider resources than less frequent monitoring. It also will cost the patients and families time and money to attend the appointments (missed work, school, cost of transport and parking). Weigh this against resources required for a delay in diagnosis of reactivated uveitis. This can lead to adverse vision consequences which require increased resources – healthcare dollars/physician time for extra appointments, increased patient cost for the extra treatment/appointments

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant research evidence available.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No direct or relevant research evidence available.	Similar to the explanation for question 1, uveitis which is left untreated can lead to more ocular complications. Ultimately that would require greater resources and cost, than monthly eye exams while the treatment is being weaned. Catching a reactivation of uveitis early would allow less intense treatment and result in less complications. The cost effectiveness is not only monetary but there is a potential cost to the patient's vision. Vision loss can have lifelong consequences on quality of life, employability.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased X Increased o Varies o Don't know	No direct or relevant research evidence available.	Similar answer to the explanation for question 1. Increasing frequency of exams should be possible for all patients with JIA. Universal healthcare pays for medically necessary eye exams. While in some areas of Canada, without direct access to ophthalmological care, the access to appropriate eye exams may be more challenging, they should still be possible (may require travel etc).

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The key stakeholders for the ACR Guidelines “Strongly” supported this recommendation of monitoring patients within a month of tapering or discontinuing topical steroids, despite the lack of formal evidence.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research evidence available.	The frequency of once-a-month visits is most likely a challenge for patients from areas without direct access to an ophthalmologist such as Canadian rural and Northern communities. Ophthalmologists themselves need to have the resources available to provide close one-monthly monitoring for their patients. Significant concerns re: equity and access and who is able to provide this frequent monitoring (eg. Ophthalmology vs. optometry).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 3

QUESTION	
Should ophthalmic monitoring no less frequently than every 3 months vs. monitoring less frequently be used for children and adolescents with JIA and controlled uveitis on stable therapy?	
POPULATION:	Children and adolescents with JIA and controlled uveitis on stable therapy
INTERVENTION:	Ophthalmic monitoring no less frequently than every 3 months
COMPARISON:	Monitoring less frequently
MAIN OUTCOMES:	Presence of active uveitis which may be missed or not treated on time due to a delayed diagnosis
SETTING:	Ambulatory patients
PERSPECTIVE:	Pediatric Ophthalmologist, Rheumatologist. Parent/caregiver/patient
BACKGROUND:	JIA patients who are ambulatory and in addition, have well controlled uveitis. Patients are asymptomatic and attending regular surveillance.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	One of the main concerns when following JIA-U is detecting the recurrence or the early diagnosis of active inflammatory ocular disease. The uveitis related to JIA is mostly asymptomatic and requires active surveillance for its detection. Multiple studies identify that the consequences of undetected and untreated JIA-U are substantial ocular complications and vision loss. Also, not all patients respond completely to therapy and not all patients remain controlled over time. (Khotari 2015, Thorne 2010, Wolf 1987). There is no clear published evidence recommending what the ideal spacing for evaluations should be. From the perspective of earlier diagnosis, it makes more sense to continue with surveillance, no longer than every three months. Persistent intra-ocular inflammation without any treatment can be harmful to the eye, with significant sequelae such as glaucoma and vision loss. Although the timing is not completely clear, it is accepted that the longer duration of the inflammation, the more severe the sequelae will be (Thorne 2010).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X Large o Varies o Don't know	The desirable anticipated effect is the confirmation of ongoing clinical quiescence or control of JIA-U. Early diagnosis is important if there are recurrences from an existing diagnosis of uveitis or a new diagnosis. No direct evidence exists about the effect of screening more or less frequently on a patient who is stable from the JIA and uveitis perspective.	We consider the surveillance has to be active and frequent due to the fact the uveitis is silent (asymptomatic) and requires urgent and aggressive management.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large X Moderate o Small o Trivial o Varies o Don't know	The undesirable anticipated effect is not to detect an exacerbation or flare of JIA-U in a timely fashion in order to prevent the development or worsening of ocular complications. There is no evidence published on the undesirable effects of more frequent surveillance and monitoring.	By implementing more frequent surveillance, there is no risk to the eyes or the health of the patients. It is important to consider social aspects of more frequent vs less frequent evaluations. Considerations include parental time away from work, potential loss of wages if allotted time is finished, cost of parking. From the patient's perspective - missing school - reduction of social interactions and time for education, stigma of absenteeism or being seen as having an (invisible) condition requiring medical visits.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low X Moderate o High o No included studies	The existing guidelines were based on previous documents with low evidence. The early diagnosis and the consequences of a missed diagnosis are an important consideration when implementing surveillance at more frequent intervals. Note from Recommendation No 4 (but also relevant): Two additional studies have been published since the ACR guidelines that address the issue of uveitis recurrence after modifying systemic therapy (Acharya 2019, Horton 2019). Both studies report a high risk of uveitis recurrence, respectively 68% with a median time of 288 days (IQR 108-338), and 92% with a median time of 188 days (range 42-413).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	It is commonly accepted that frequent surveillance and monitoring is important for an early diagnosis and timely management of recurrences or new cases in otherwise stable JIA or JIA-U patients. No evidence on how much the main outcomes are valued.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o Don't know	No clear evidence.	Clinically, it makes sense to see the patients more often (3 monthly intervals), resulting in the possibility of making an early diagnosis of active uveitis. The patients benefit with possible reduction in secondary complications.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies X Don't know	No evidence.	There is no evidence of the overall cost for more frequent evaluations versus less frequent. It does require analysis of the economic and resource burden to the health system in addition to the potential social cost such as time off work for parents to take their child/youth to more frequent appointments or missed school and other factors (see above under Undesirable Effects).

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No evidence. There are no studies comparing the cost or consequences of every 3-month evaluation versus a longer interval to identify reactivation of uveitis at an earlier versus later time.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No evidence. No studies looking at the cost to the health system to have less frequent visits. Again, the cost from a social aspect needs to be considered.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced X Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	No evidence.	In consideration of the Canadian System and Health Act, all persons have the same access to evaluation and surveillance. All relevant costs are covered by the different provinces. It is important to recognize that there may be limited resources in a given location such as the number of ophthalmologists available to provide more frequent evaluations and this may indirectly affect general access to them by others. The concern is that it is there is variable expertise among Optometrists with respect to appropriately diagnosing uveitis.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No evidence.	Among clinicians, an accepted principle is the monitoring of stable patients according to the guidelines (ACR Guidelines 2019) to evaluate for the presence of uveitis and adjust treatment as required. It is even more important if there is a previous diagnosis of uveitis.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No evidence.	It is feasible to implement with most of the rheumatologists and ophthalmologists in agreement. There is an important group of comprehensive ophthalmologists who are willing to participate and are capable of following uncomplicated pediatric patients. Optometrists can represent a valuable resource particularly if they are guided and work collaboratively with the pediatric ophthalmologists.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
o	o	o	o	o

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 4

QUESTION	
Should ophthalmic monitoring within 2 months of changing systemic therapy vs. monitoring less frequently be used for children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy?	
POPULATION:	Children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy
INTERVENTION:	Ophthalmic monitoring within 2 months of changing systemic therapy
COMPARISON:	Monitoring less frequently
MAIN OUTCOMES:	Timely detection of uveitis recurrence
SETTING:	Ambulatory patients
PERSPECTIVE:	Ophthalmologist, Rheumatologist, Patients/parents
BACKGROUND:	Patients with controlled uveitis are known to be at risk for recurrence when tapering/discontinuing systemic therapy. No consensus on best interval for monitoring
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Yes. This problem is a priority. Patients on systemic therapy for chronic uveitis are at high risk of flare when systemic therapy is modified (tapered or discontinued). It is well known that there is a serious risk for ocular complications and vision loss if identification of chronic uveitis is delayed. Also, it may be more difficult to get the disease back under control if not detected soon enough. No studies have directly addressed the issue of the optimal frequency of examinations when making changes to systemic therapy in controlled JIA uveitis. Three studies have indirectly addressed this issue. One retrospective study by Lerman in 2015 assessed the rate of uveitis recurrence in the year after stopping anti-TNF therapy in 19 patients with controlled uveitis (various systemic diagnosis, less than half with JIA). By 1 year 64% had recurred. The probability of reactivation was 18% at 3 months, 38% at 6 months and 55% at 9 months. Median time to failure was 3.9 months. A second retrospective study by Acharya in 2019 assessed the risk of uveitis recurrence after modifying systemic therapy. In this study 68% of patients eventually had a recurrence at a median interval of 288 days (IQR: 108-338). 38% flared while tapering systemic therapy. 82% of patients previously on anti-TNFs had a recurrence of uveitis. The last relevant study done by Horton in 2019 reports on patients previously included in the SYCAMORE trial. 11/12 patients previously on Adalimumab who had completed the trial (18 months) had to be restarted on that drug because of uveitis flare in a median time of 188 days (range 42-413 days). It is not stated in the paper whether the patients were still receiving MTX or not. Monitoring visits were done every 3 months.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X Large o Varies o Don't know	No literature directly addresses the desirable anticipated of frequent vs. infrequent screening for recurrence in controlled uveitis when systemic therapy is modified. The ACR panel strongly recommended frequent monitoring because the serious potential complications due to missed or delayed diagnosis of a recurrence, which is high. The ACR panel also agreed that the frequency of monitoring could be influenced by the half-life of the systemic therapy, but not to an interval beyond 2 months.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	This issue is not directly addressed in the literature. Patients involved in the ACR panel were concerned about the risk of infrequent examinations and felt there was little disadvantage associated with more frequent examinations.	Theoretical risks of increased screening include added stress on patients and families if they find ophthalmic examinations difficult as well as indirect costs including financial burden of office visits, parking, childcare, and time off from work. Other undesirable effects include too frequent changes in medication, cost to the healthcare system due to larger number of ophthalmology visits than would be unnecessary.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low o Low X Moderate o High o No included studies	The ACR guidelines were based on very low-quality evidence but the recommendation for screening frequency of at least every two months remained strong because of the potential harmful consequences of delayed identification of uveitis recurrences. Two additional studies have been published since the ACR guidelines that address the issue of uveitis recurrence after modifying systemic therapy (Acharya 2019, Horton 2019). Both studies report a high risk of uveitis recurrence, respectively 68% with a median time of 288 days (IQR 108-338), and 92% with a median time of 188 days (range 42-413).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability X Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	No direct research was identified. The ACR guidelines panel support a desire for frequent screening when systemic therapy is changed by patient/parents and physicians.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	No direct research was identified.	Frequent screening for recurrent uveitis after a change in systemic therapy requires increased provider resources than less frequent screening. There is an additional cost for medical visits. For families, these would include the cost of missed work, financial resources and time to travel to the appointments, parking, babysitters for other children, school absences etc.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct research was identified.	Frequent screening for recurrent uveitis after a change in systemic therapy requires increased provider resources than less frequent screening. There is an additional cost for medical visits. For families, these would include the cost of missed work, financial resources and time to travel to the appointments, parking, babysitters for other children, school absences etc.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct research was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No direct research was identified.	If detection of uveitis recurrence is delayed there is an increased risk for secondary complications and the inflammation may be more difficult to control. All of this may lead to increased number of visits, procedures, and surgeries. It may also require escalation in systemic therapy including the need for new biologic agents. Vision loss secondary to uncontrolled uveitis will additionally have impacts on education and employability on an ongoing basis.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased X Increased o Varies o Don't know	No direct research was identified.	Frequent assessment of patients undergoing a change in systemic therapy should be possible in all cases in Canada. All eye examinations for uveitis are covered by the Canadian healthcare system.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	ACR (American College of Rheumatology) guideline panel agreed that the quality of evidence was low, but that the intervention was acceptable given the serious consequences if recurrent uveitis if it is not recognized quickly.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct research was identified.	Patients with controlled JIA associated uveitis on systemic therapy are likely already being monitored by an ophthalmologist. Screening within two months of a change in systemic therapy may mean an increase in visits but is likely not a large increased burden on the physician or patient. However, access to a pediatric eye care provider may not always be easy in some remote areas, therefore more frequent visits may not be feasible

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 5

QUESTION	
Should using prednisolone acetate 1% topical drops vs. difluprednate topical drops be used for children and adolescents with JIA and active CAU?	
POPULATION:	Children and adolescents with JIA and active CAU.
INTERVENTION:	Using prednisolone acetate 1% topical drops.
COMPARISON:	Difluprednate topical drops.
MAIN OUTCOMES:	Control of the active Uveitis and possible complications.
SETTING:	AMBULATORY PATIENTS.
PERSPECTIVE:	OPHTHALMOLOGISTS, POSSIBLY OPTOMETRISTS.
BACKGROUND:	Patients with active uveitis who are being treated with topical steroids.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X No o Probably no o Probably yes o Yes o Varies o Don't know	The main concern when treating active Uveitis is the control of the inflammation and the prevention of complications. The accepted treatment among ophthalmologists and Uveitis specialists is the use of Prednisolone Acetate 1% due to its well-known efficacy and side effects. The majority of published literature is with this medication. (Kotari 2015, Thorne 2010). It has been proposed the use of Difluprednate as an alternative for the managements of active Uveitis. There is no published evidence in support of the use of the medication in Uveitis related to JIA. Sheppard et al published a non-inferiority trial comparing the two medications and found that Difluprednate four times a day was non-inferior to Prednisolone 1%, 8 times a day when treating active uveitis. The target population was acute uveitis in adults which may not extrapolate to our condition. This problem is not a priority as the proposed conventional treatment is effective, accepted and widely use worldwide with an acceptable cost.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Trivial o Small o Moderate o Large o Varies o Don't know	The effects are similar and does not provide a major difference. As per the NON inferiority trial, both substances have similar effects. The only difference is the frequency of application.	Difluprednate cost is considerable higher than Prednisolone (190 USD vs 29 USD). This adds a socioeconomic cost which can be detrimental for a population already using other medications to treat JIA.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small X Trivial o Varies o Don't know	No direct or relevant evidence.	The side effects of Difluprednate are similar to the ones from Prednisolone 1% as published in the document attached.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	No direct or relevant evidence. There are no published articles studying the efficacy of Difluprednate in patients with JIA and Uveitis.	The non-inferiority trial was performed in a different cohort, not applicable to our population.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability o Probably no important uncertainty or variability X No important uncertainty or variability	The main outcome is the control of inflammation and prevention of complications. There is only one goal in mind and is to control the inflammation. There is no variability in the outcome as all eye specialists will be aiming for the same objective.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X Don't know	The use of prednisolone is accepted and well known for the outcomes, side effects and widely available medication. There is no published evidence about the use of Difluprednate in patients with Uveitis and JIA (while comparing the two medications).	In terms of cost and accessibility, there is significant differences in the cost between the two medications being cheaper and more accessible the Intervention than the comparison.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct or relevant evidence from our literature search.	The management of JIA Uveitis requires a significant amount of time and resources, multiple appointments, use of medication for extended period of times. If we were to add an expensive medication such as Difluprednate to the existing protocol, it will be detrimental for families and health system in terms of cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant evidence from our literature search.	Same comments as the previous one.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o No included studies	No direct or relevant evidence from our literature search.	In terms of cost, there is a significant difference between the two medications. The Difluprednate is four times as expensive while compared to the Prednisolone Acetate 1%.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced X Probably no impact o Probably increased o Increased o Varies o Don't know	No direct or relevant evidence from our literature search.	In the adult studied (attached), both medications were similar in terms of efficacy, side effect. Difluprednate showed to be non-inferior to Prednisolone with expectation to have similar effects.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The intervention is widely accepted by Uveitis specialists, Pediatric Ophthalmologists with well-known side effects and outcomes. (Kotari 2015).	Prednisolone 1% is the current standard of care for uveitis due to JIA. This medication is affordable to the system, patients, and widely available. Pharmacies, hospitals and health care centers will have medications on their stocks.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The standard of care is with the Prednisolone 1%, favoring the intervention.	Affordable medication, reliable in treatments and well-known side effects. It is easier to implement this medication against the intervention as they are more expensive, relatively new and unclear exact efficacy in JIA patients with active uveitis.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
ubgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 6

QUESTION	
Should adding or increasing topical glucocorticoids for short-term control vs. adding systemic glucocorticoids be used for children and adolescents with JIA and active CAU?	
POPULATION:	Children and adolescents with JIA and active CAU.
INTERVENTION:	Adding or increasing topical glucocorticoids for short-term control.
COMPARISON:	Adding systemic glucocorticoids.
MAIN OUTCOMES:	Control of uveitis.
SETTING:	AMBULATORY PATIENTS
PERSPECTIVE:	RHEUMATOLOGIST, OPHTHALMOLOGIST, PATIENT
BACKGROUND:	Traditionally, adding or increasing topical steroids has been used over systemic steroids for short-term control of uveitis.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel has decided this is a priority question. Both the intervention and comparison are believed to be effective for controlling CAU although the scientific evidence is low. The potential for adverse events with each treatment modality are moderate to high (e.g. cataract formation and glaucoma from increased topical glucocorticoids, weight gain, stunted growth, insomnia, cushingoid appearance and from increased systemic glucocorticoids). All adverse events are duration and dose dependant for both the intervention and comparison. The question's importance relates to the efficacy versus the potential for adverse reaction to the two proposed treatment modalities.	The intervention and comparison are not mutually exclusive. In certain clinical settings, both an increase in topical as well as systemic steroids may be warranted. Examples of this include 1) severe active uveitis with complications that threaten permanent visual impairment in the short term, 2) treatment of post-operative uveitis in a patient with severe CAU.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	If uveitis can be controlled more effectively, the sequelae of uncontrolled inflammation will be reduced. Control of the inflammation is essential to maintaining visual function. The ACR panel "conditionally recommended" use of topical steroids over systemic steroids for short-term control of active CAU. Their guidelines only referenced one paper when looking at this PICO question (Wolf et al 1987) and based their recommendation on increased ocular complications of cataract and glaucoma with systemic steroid use. However, the 2020 Schnabel et al. paper found fewer ocular complications, better vision improvement and less need for DMARD's with use of pulse systemic steroids. While this was retrospective and did not compare systemic steroid directly with topical steroids, it shows that there is a potential benefit of 1-5 pulses of methylprednisolone, to bring uveitis under control.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	The 2020 Schnabel et al. did not have any severe systemic side effects from the use of pulse methylprednisolone. Potentially, there could be severe infection, high blood pressure, fractures, diabetes etc. The follow-up was only 6-12 months after the treatment, so long-term effects on growth and metabolism are not known. There are also potential ocular side effects with topical or systemic steroids. Systemic steroids are thought to cause more cataracts and glaucoma, as per the Wolf paper, but the Schnabel paper found the opposite. A 2010 report from Thorne et al. [10] reported on the risk of cataract development among children with JIA-related uveitis treated with topical corticosteroids. (note: This article was republished as a Retrospective Landmark paper in 2020[8], which is different from the 2010 report). This was a retrospective chart review. Over a median of 4 years, the incidence of new-onset cataract formations was 0.04/eye-year (EY). There was a dose-dependent increase in the rate of cataract development. The incidence of cataract formation was 0.01/EY for eyes treated with <3 drops daily and 0.16/EY for eyes treated with >3 drops daily (difference p=0.0006). For children receiving <2 drops/EY, the incidence of cataracts was 0/EY. The development of cataracts was significantly associated with posterior synechiae, active uveitis, and topical steroid use at presentation. Topical corticosteroid use was independently associated with cataract development independent of uveitis activity. There was an 87% lower risk of cataracts if <3 drops daily were used compared to > 3 drops daily. The effect of the duration of topical steroid use was not conveyed as a determinant of cataract formation. The data are expressed as per eye year, but it is difficult to ascertain how the duration of therapy impacted results. As the median follow-up was 4 years (range 6 months to 15 years) ascertaining the effects of more prolonged therapy even at low daily doses was not possible. Further, it was difficult to perfectly adjust for the potential for fluctuating topical steroid doses over time. Still, an effort was made to control for such fluctuations leading to the conclusion that ≤3 drops daily was associated with an 87% reduction risk. Kothari et al.[12], in a retrospective cohort study, evaluated the risk of topical and systemic steroids in JIA uveitis. The enrollment was over 29 years and follow-up assessed at 2 years. This was a risk factor study. The authors found that topical corticosteroid use (≥ 2 drops/day) was a strong risk factor for increased intraocular pressure. The hazard ratio increased with the number of drops per day. Systemic corticosteroids were not associated with increased intraocular pressure after adjusting for other factors.	While the side effects from steroids may be concerning, the uveitis itself can cause more long-term consequences, with potentially lifelong visual compromise. There can be challenges in administering frequent dosing of topical corticosteroids. Topical therapy is occasionally used as frequently as every hour while awake for short periods of time. This can constitute a burden for both pediatric patients and their parents.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	The ACR guidelines found one article (Wolf et al 1987) which pointed towards ocular complications such as cataract and glaucoma with systemic steroid use for uveitis. As a result, they recommended drops over systemic treatment for short-term control. The newer German Guidelines (Heiligenhaus et al 2019) referenced 1. Gaudo 2004 which states there is limited evidence for efficacy or safety for systemic steroids. 2. Wakefield 1986 which states that IV methylprednisolone can be an effective treatment of severe inflammation. Only 2 of the 17 patients in the study had CAU This guideline did not specifically address the question of short-term control. Schnabel et al. 2020, is a retrospective analysis of high dose methyprednisolone in uveitis. 56 patients, 1-5 monthly pulses. Despite worse vision at the start, those with 3-5 pulses vs 1-2 ended up with more vision improvement. Cataracts and glaucoma occurred less in the 3-5 pulse group vs 1-2 pulses. They also had less relapses, less DMARD therapy, less eye surgery. This study suggests that pulse systemic steroids can be an effective option for gaining control of uveitis. While it was retrospective and did not specifically compare topical vs systemic steroids, there is some evidence to support systemic steroid treatment. There are no comparative trials of topical versus systemic steroids in the short-term treatment of uveitis. The Wolf paper was retrospective and included patients from 1960-1985. Gaudo, Ocular Immunology and Inflammation, Volume 12, 2004 - Issue 3, 169 Wakefield, Arch Ophthalmol. 1986;104(6):847-851	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	No direct or relevant research identified. The ACR Guideline voting panel included patients and parents who "conditionally" recommended adding or increasing topical steroids vs adding systemic steroids.	While there is no research which concretely shows how much people value one choice over the other, control of uveitis (and avoiding of the associated complications) is agreed to be an important goal. Whatever treatment provides the best control would be valued more, but there is limited data on this.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X Don't know	There is a suggestion that the effect of using pulse systemic steroids is more desirable than that of increasing or adding topical steroids. However, this is based on only one paper (Schnabel et al.), which was a retrospective analysis. While it did look at pulse methyprednisolone, there was no direct comparison to topical steroid use. The ACR recommendation of using topical steroids was only "conditional" and based on an older retrospective review. That paper did not specifically compare to topical steroids and cited the side effects of systemic steroids as the reason not to use them. There needs to be more evidence to recommend one treatment over the other.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs X Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct or relevant research evidence identified.	The resources required for topical or oral corticosteroids are quite small (costs are very low), while IV pulse corticosteroids require moderate cost with the involvement of nursing personnel to administer the IV and monitor the patient.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low X Moderate o High o No included studies	There is a paucity of data published to compare the costs, but these treatment regimens are well defined and commonly administered.	Some topical glucocorticoids may require patients to pay out of pocket as may not be covered by private or public insurance. This may create inequities in access to therapy. Systemic glucocorticoids are covered by provincial/private payers.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No direct or relevant research identified. While the costs are low to moderate for both the intervention and the comparison, we have no reliable data to compare efficacy and therefor cost effectiveness cannot be assessed.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced X Probably no impact o Probably increased o Increased o Varies o Don't know	Probably no impact on healthy equity as the costs for both treatment modalities are low to moderate and access is generally available across Canada.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct evidence identified, but probably yes based on clinical experience.	For the intervention, patients and parents may find it more difficult to administer topical steroids more frequently, but this is still generally well accepted. For the comparison, there may be some resistance for patients and their parents to receive systemic corticosteroids due to their potential side effects.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes X Yes o Varies o Don't know	Yes, the intervention is feasible to implement and is already common practice and standard of care.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	X	○	○

CONCLUSIONS

Recommendation

There is insufficient evidence to compare efficacy and safety of short term increases in topical versus systemic corticosteroids. In retrospective data sets, both are shown to be effective in controlling active CAU. Treatment decisions need to be individualized.

Justification

There is insufficient evidence to compare the 2 treatment modalities for both efficacy and safety. Both are known to be effective and to have carry the potential for significant adverse events. Comparative trials are required.

Subgroup considerations

In some patients with severe active inflammation or in the immediate post-operative setting of patients with severe CAU, both increasing topical corticosteroids and systemic corticosteroids may be necessary to control the inflammation. Treatment decisions on whether to use topical or systemic corticosteroids may be influenced by patient characteristics including a history of steroid induced glaucoma, presence of diabetes, active infection, and others.

Implementation considerations

No specific concerns.

Monitoring and evaluation
None

Research priorities
A prospective comparative trial would be useful in determining which treatment modality is both most effective and acceptable from the side effects profile.

Evidence to decision table ACR/AF Recommendation 7

QUESTION	
Should topical glucocorticoids prior to changing/escalating systemic therapy vs. changing/escalating systemic therapy immediately be used for children and adolescents with JIA who develop new CAU activity despite stable systemic therapy?	
POPULATION:	Children and adolescents with JIA who develop new CAU activity despite stable systemic therapy.
INTERVENTION:	Topical glucocorticoids prior to changing/escalating systemic therapy.
COMPARISON:	Changing/escalating systemic therapy immediately.
MAIN OUTCOMES:	Avoidance of unnecessary change/escalation of therapy.
SETTING:	OUTPATIENT
PERSPECTIVE:	OPHTHALMOLOGIST, RHEUMATOLOGIST, PATIENTS
BACKGROUND:	Mild uveitis flares can be treated successfully with topical therapy and may not require a change or escalation in systemic therapy.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel made this question a priority. At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question. No new studies have been identified addressing this question since then. Traditionally, uveitis flares while on systemic therapy are initially treated with topical steroids before changes are made to systemic therapy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate o Large o Varies X Don't know	At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question. However, the ACR conditionally recommends topical glucocorticoids prior to changing/escalating systemic therapy over changing/escalating systemic therapy immediately unless there are contraindications. A successful trial of topical therapy could avoid making unnecessary changes in systemic therapy.	Additional consideration should be given to the duration of the trial of topical corticosteroid drops before determining a failure of treatment requiring escalation of systemic therapy. There are no publications addressing this issue. Additional consideration should be given to complications arising from topical corticosteroid drops, including elevated intraocular pressure. If complications occur, there is a stronger tendency to escalate systemic therapy.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	No direct or relevant evidence identified. Topical glucocorticoid therapy can contribute to ocular complications such as increased intraocular pressure and cataract formation (Thorne et al, 2010; Kothari et al, 2015). However, this risk is low over short periods of time. Those who require ongoing topical therapy for 3 or more months should be considered for a change/escalation in systemic therapy (as per ACR recommendation 9).	Administering eye drops may be cumbersome for some families depending on the required frequency, age, and cooperation of the child.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	At the time of the ACR guidelines, the literature searches did not identify any studies that addressed this PICO question. No new studies have been identified addressing this question since then. The ACR guidelines conditionally recommend topical glucocorticoids prior to changing/escalating systemic therapy over changing/escalating systemic therapy immediately. Therefore, quality of evidence is considered very low.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability X Probably no important uncertainty or variability ○ No important uncertainty or variability	No direct or relevant research identified. Based on consensus, probably no important uncertainty or variability in values from both the treating physicians and patients.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No direct or relevant research identified. A short course of topical therapy is a relatively simple and accessible intervention and is conditionally recommended as initial therapy for both new uveitis and uveitis flares (ACR recommendations 6 and 7). Balance of effects, therefore, probably favors the intervention.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies X Don't know	No direct or relevant research identified.	Topical therapy is less expensive than DMARD or biologic therapy. Changes in systemic therapy may require increased blood work monitoring. Both topical therapy and DMARD/biologic therapy would likely require the same frequency of eye examinations and therefore public resources.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant research identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o No included studies	No direct or relevant research identified, although probably favors the intervention due to the reduction in comorbidity and sequalae.	Topical glucocorticoids are less expensive than systemic therapies. Systemic therapies may also require regular blood work monitoring. A recent change in systemic therapy may require increased monitoring of uveitis.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	No direct or relevant research identified. Topical therapies are generally low cost and would be accessible for most patients in Canada. However, if a change in systemic therapy requires biologic therapy initiation or change, then extended health insurance benefits and provincially controlled access to certain biologic medication may serve as barriers to care and therefore reduce health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified. Topical therapy is generally accepted by patients and families, although it can be challenging for families if drops are required frequently. Changes in systemic therapy may lead to higher drug costs, greater chance of systemic side effects, and more blood work monitoring for patients and families.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes x Yes ○ Varies ○ Don't know	No direct or relevant research identified. The use of topical therapy as first line treatment for uveitis is already common clinical practice and therapy is accessible, therefore feasible in daily practice.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations

Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 8

QUESTION	
Should adding systemic therapy in order to taper topical glucocorticoids vs. not adding systemic therapy and maintaining on topical glucocorticoids only be used for children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy?	
POPULATION:	Children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy.
INTERVENTION:	Adding systemic therapy in order to taper topical glucocorticoids.
COMPARISON:	Not adding systemic therapy and maintaining on topical glucocorticoids only.
MAIN OUTCOMES:	Prevention of ocular complications, while maintaining control of uveitis
SETTING:	Ambulatory patients.
PERSPECTIVE:	Ophthalmologist, rheumatologist, patients
BACKGROUND:	Long term use of topical corticosteroid monotherapy for control of JIA uveitis may be associated with increased risk of ocular complications. Addition of systemic therapy may decrease corticosteroid treatment frequency.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel has decided that this is an important question. At the time of the ACR guidelines, there were 2 identified studies that indirectly addressed this issue. Kothari et. al 2015 showed that topical corticosteroid drops at a frequency of ≥2 drops/day was associated with a significantly increased risk for IOP elevation (risk increased as frequency increased). Thorne et. al 2010 showed that topical corticosteroids at a frequency of ≤3 drops/day was associated with significantly less risk of cataract formation when compared to a frequency of ≥4 drops/day. No additional references were identified.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X Large o Varies o Don't know	No studies were identified that directly compared the rate of cataract/glaucoma in JIA uveitis patients with and without the additional of systemic therapy to decrease topical corticosteroid burden. The anticipated effect is the prevention of corticosteroid related adverse effects, most commonly cataract formation and glaucoma. The ACR panel recommended systemic therapy be added based of the indirect evidence related to known complications of topical monotherapy as listed above, and also from the evidence of improved inflammatory control with the addition of systemic therapy.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large X Moderate o Small o Trivial o Varies o Don't know	The literature review did not directly address regarding the question of topical steroid monotherapy compared to systemic therapy.	The potential undesirable effects associated with this recommendation are the potential risks of systemic therapy in JIA uveitis including cost, access to medication, medication side effects, and long-term complications of immunosuppressive therapy. These are specifically addressed in other recommendations.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low X Moderate o High o No included studies	The recommendation is based on very low quality of evidence. The ACR panel and the German group remained comfortable with this recommendation despite the low quality of evidence because of serious ocular adverse events at risk to occur.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability X Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	No direct or relevant evidence was identified.	The theoretical effects and consequences of cataract and glaucoma on a child's health and functioning may be challenging for patients and family to understand.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	No direct or relevant evidence was identified.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct or relevant evidence was identified.	There may be a significant cost associated with the addition of systemic therapy which varies with the agent chosen. Both the development of cataract and glaucoma are associated with significant costs to the system in the form ophthalmologist visits, medications, procedures, and surgery. Additional costs to the family include time off of work, transportation, and childcare associated with the increased frequency of care required in managing these conditions. If there is loss of visual function related to these complications these can have long lasting effects on education and employment for the patient.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant evidence was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No direct or relevant evidence was identified regarding cost effectiveness. There are known costs associated with systemic therapy in JIA uveitis. Recent data by Hughes et al 2018 suggests that adalimumab may not be a cost-effective treatment for JIA uveitis in the UK. This may not be applicable to the Canadian system and all patients in the review were already on systemic therapy (methotrexate). There are known costs related to ophthalmologic complications related to the comparison treatment of topical steroids. No direct comparison studies available.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	No direct or relevant evidence was identified.	There should be no barriers to access of systemic therapy for JIA uveitis in Canadian children. With better control of uveitis and less topical corticosteroid use, there will be less clinic visits required which should improve equity for rural Canadians.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No direct or relevant evidence was identified. Despite this, the ACR panel felt this intervention was acceptable despite the low quality of evidence due to the potential of the serious risks from unmanaged uveitis.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No direct or relevant evidence was identified.	These patients are often already under the care of both an ophthalmologist and a rheumatologist. The treating ophthalmologist can share information about uveitis activity with the rheumatologist, who can guide addition of systemic therapy. However, if a patient is not on systemic therapy, he/ she may not be under care of a rheumatologist. Precondition to start systemic therapy should be to involve a pediatric rheumatologist; both, ophthalmologist and rheumatologist have to work as an interdisciplinary team sharing the same treatment goals and necessary information about treatment effects and adverse events.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 9

QUESTION	
Should changing or escalating systemic therapy vs. maintaining current systemic therapy be used for children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy for uveitis control?	
POPULATION:	Children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy for uveitis control.
INTERVENTION:	Changing or escalating systemic therapy.
COMPARISON:	Maintaining current systemic therapy.
MAIN OUTCOMES:	Adverse effects from topical steroid use, particularly cataracts and increased intraocular pressure.
SETTING:	GLOBAL, OPHTHALMOLOGY AND PEDIATRIC RHEUMATOLOGY CLINICS.
PERSPECTIVE:	CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS AND ASSOCIATED CHRONIC ANTERIOR UVEITIS. FROM A WHOLE POPULATION PERSPECTIVE JIA AND JIA UVEITIS ARE UNCOMMON BUT DO REPRESENT IMPORTANT CONDITIONS IN THE PEDIATRIC POPULATION. A CHILD AFFLICTED WITH BOTH ARTHRITIS AND ASSOCIATED UVEITIS, IF NOT OPTIMALLY TREATED, CAN HAVE COMPROMISED FUTURE QUALITY OF LIFE AND PRODUCTIVITY AND HAVE AN INCREASED IMPACT ON SOCIETAL RESOURCES, INCLUDING HEALTH CARE RESOURCES. FROM THE PATIENT AND FAMILY PERSPECTIVES JIA ALONE AND JIA COMPLICATED BY UVUEITIS CAN BE A STRESSFUL BURDEN AND COMPROMISE THE CHILD'S QUALITY OF LIFE AND NORMAL GROWTH AND DEVELOPMENT.
BACKGROUND:	Juvenile idiopathic arthritis (JIA) is among the most common chronic diseases of children. Chronic anterior uveitis is the most common extra-articular manifestation of JIA. Topical corticosteroid with mydriatics is accepted as conventional first-line therapy for JIA-uveitis. However, topical steroid use can be associated with adverse effects, including cataract formation and increased intraocular pressures. The adverse effects of topical ocular steroids appear to be dose and duration dependent. Second-line, immunomodulatory therapy is added to minimize topical steroid side effects and maximize disease control. Knowing the minimal dose of topical steroids that is required, in combination with systemic therapy, to control disease without promoting steroid-induced side effects would help guide the need to advance systemic therapy or, alternatively, to maintain the status quo. That is, if there is a minimal topical steroid dose that is safe (that is, which does not induce side effects), then systemic therapy can be maintained without escalation. Conversely, if the topical steroid dose that is required to control uveitis in combination with systemic therapy is so high as to induce adverse effects, then advancing systemic therapy to allow for a reduction of topical steroid dose would be indicated. *Notes:* 1. *The comments and recommendations referred to in this EtD relate only to prednisolone acetate 1% and not to any other topical steroid formulation. It is important that conclusions and recommendations that relate to prednisolone acetate 1% not be generalized to other topical, ocular steroid options. For example, difluprednate is another, more potent topical ocular steroid that induces adverse effects more frequently, including*

	increased intra-ocular pressure and cataracts, than prednisolone acetate 1%.[1,2] More potent formulations of topical corticosteroids (difluprednate) need to be used with great caution in chronic anterior pediatric uveitis as they are associated with a significantly increased risk of adverse events.[1,2] 2. *Topical prednisolone acetate 1% at 2 drops or less per day may be an adequate treatment, but sometimes still leads to adverse events like ocular hypertension or cataracts. The underlying disease subtype (that is, the JIA category), other concomitant treatment, or genetic vulnerability might conceivably account for the occurrence of adverse affects with weaker steroid therapies. The question under consideration might be intended to convey that there are no side effects from the topical steroids, but this is not explicitly stated in the question. Increasing immunosuppression in order to reduce the local burden of steroids in those patients who have steroid-induced adverse effects should be strongly considered. In contrast, those children whose uveitis is well controlled on prednisolone acetate 1% plus an immunosuppressant would not require changing or escalating therapy.* 3. *There is no evidence to evaluate how influential duration of prednisolone acetate 1% therapy is in inducing adverse effects. That is, it is conceivable that cumulative doses of topical ocular steroids over time might reach a tipping point, after which adverse effects are more likely to occur. Under these circumstances discontinuing topical steroids before adverse effects occur would be desirable. Again, however, there are no data available to ascertain if there is a tolerable duration of therapy.* 4. *Without knowing which alternate or additional systemic therapy is being considered it is difficult to ascertain the relative risks of maintaining current therapy or advancing/escalating therapy.*
CONFLICT OF INTERESTS:	No conflicts of interest to declare.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Topical corticosteroid use (prednisolone acetate 1%) continues to be the mainstay of first-line therapy for JIA-uveitis and a usual adjunctive therapy used with systemic therapies. However, topical corticosteroids used in high doses for prolonged periods increase the risk of adverse effects, including cataract formation and ocular hypertension. Knowing if there is a safe minimal does of topical steroids that can be used to maintain control either alone or in combination with systemic therapy would mitigate risks of topical steroid therapy. Cataract formation is a frequent complication of uveitis associated with JIA.[3-7] There is ample evidence of adverse effects of topical steroids.[4,7-11]	The issue of cataract formation and increased intraocular pressure due to topical steroid use is confounded by the fact that uveitis itself can be associated with the same adverse effects. Precisely discerning side effects due to steroid use and/or intraocular inflammation might not be possible. In this assessment, we have considered only prednisolone acetate 1% topical steroid drops; the use of other topical steroid options (such as difluprednate), sub-tenon injections or systemic corticosteroids can be further confounders in the assessment of adverse effects of topical steroids in JIA-uveitis.

	A 2010 report from Thorne *et al.* [12] reported on the risk of cataract development among children with JIA-related uveitis treated with topical corticosteroids. (note: This article was republished as a Retrospective Landmark paper in 2020[10] and should not be confused as different from the 2010 report). This was a retrospective chart review. Over a median of 4 years, the incidence of new-onset cataract formations was 0.04/eye-year (EY). There was a dose-dependent increase in the rate of cataract development. The incidence of cataract formation was 0.01/EY for eyes treated with <3 drops daily and 0.16/EY for eyes treated with >3 drops daily (difference p=0.0006). For children receiving <2 drops/EY, the incidence of cataracts was 0/EY. The development of cataracts was significantly associated with posterior synechiae, active uveitis, and topical steroid use at presentation. Topical corticosteroid use was independently associated with cataract development independent of uveitis activity. There was an 87% lower risk of cataracts if <3 drops daily were used compared to > 3 drops daily. The effect of the duration of topical steroid use was not conveyed as a determinant of cataract formation. The data are expressed as per eye year, but it is difficult to ascertain how the duration of therapy impacted results. As the median follow-up was 4 years (range 6 months to 15 years) ascertaining the effects of more prolonged therapy even at low daily doses was not possible. Further, it was difficult to perfectly adjust for the potential for fluctuating topical steroid doses over time. Still, an effort was made to control for such fluctuations leading to the conclusion that ≤3 drops daily was associated with an 87% reduction risk. Summary Thorne *et al.* Retrospective cohort study 60 eyes of 40 patients with JIA-uveitis Median age at diagnosis of uveitis 7 years (range 1-36 years) ≤2 drops per day: incidence of cataract 0/EY (95% CI 0-0.03 EY) 3 drops per day: incidence of cataract 0.01/EY (95% CI 0.02-0.14 EY 4 drops daily showed an incidence of cataract of 0.07/EY. >4 drops daily (5-12) drops daily: incidence of cataract (95% CI 0.09-0.21 EY)	In the report by Thorne *et al.* patients considered were seen between 1984 and 2005; therefore, as the last patient considered was seen 15 years ago, the findings might not necessarily reflect the effects of contemporary therapies. For example, it might be possible that the use of topical steroids at >3 drops daily plus immunomodulatory therapy might affect the risk of cataract development. Information about patients seen 15-36 years ago might be considered outdated in the context of current advanced therapies.

	≤ 3 drops per day was associated with an 87% reduction in the risk of new onset cataract when compared to ≥4 drops per day (RR 0.13, 95% CI 0.02-0.69, p=0.02) Although corticosteroids are known to be associated with increased risk of ocular hypertension[11], there is limited information relating to topical steroid use as an independent risk factor for glaucoma. In a report by **Stroh *et al.*[13]** patients with ocular hypertension were more likely to have been treated with topical corticosteroids (96.2% vs. 81.2%, *p* = 0.002), systemic corticosteroids (58.2% vs. 37.6%, *p* = 0.004), and immunosuppressive therapy (53.2% vs. 33.3%, *p* = 0.006) when the patient was first seen by the authors; during follow-up, systemic corticosteroids but not topical steroids were mentioned as a risk factor for increased intraocular pressure. The use of immunosuppressive therapy was associated with a lower incidence of ocular hypertension at follow-up. Kothari *et al.*[14], in a retrospective cohort study, evaluated the risk of tropical and systemic steroids in JIA uveitis. The enrollment was over 29 years and follow-up assessed at 2 years. This was a risk factor study. The authors found that topical corticosteroid use (≥ 2 drops/day) was a strong risk factor for increased intraocular pressure. The hazard ratio increased with the number of drops per day. Systemic corticosteroids was not associated with increased intraocular pressure after adjusting for other factors.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Trivial o Small o Moderate o Large o Varies o Don't know	No direct evidence or research was identified.	As the risks of low does topical therapy (1-2 drops per day) are associated with negligible adverse effects there is no indication to advance therapy when the uveitis is controlled assuming that the child has no side effects from the topical therapy. Reducing the dose- and duration-dependent risk of topical steroid-induced pathology in children with JIA-uveitis by using 1-2 drops per day should mitigate long term adverse effects. The aim is to control uveitis with a dose of topical steroid that is low enough to avoid inducing adverse effects (e.g. ≤ 2 drops per day) while controlling uveitis either with topical steroids alone or in combination with immunomodulatory therapies or with immunomodulatory

		therapies only (if low does topic steroids are not shown to provide any added benefit). However, there are no added benefits to advance other therapy to be able to discontinue topical steroids that, when used at low dose (1-2 drops per day), if the low does topical steroid therapy is not inducing any adverse effects. However, it must be acknowledged that even low dose topical prednisolone acetate 1% can be associated with adverse effects in some children.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large X Moderate o Small o Trivial o Varies o Don't know	From available evidence (although retrospective and not in the context of current real-world therapy) there are potential undesirable effects of using low dose topical steroids and not escalating therapy. Potentially moderate to large for escalating therapy unnecessarily if the child is well controlled on low-dose topical steroids and systemic therapy.	As the risks of 1-2 drops of topical steroids is generally small, advancing therapy in this context would be more undesirable than continuing current therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	Overall, the level of evidence is very low. There are no data derived from robust randomized controlled, prospective studies. There are no studies reporting risks of topical corticosteroids in the era of contemporary uveitis treatment regiments. The 2010 retrospective study report of Thorne *et al.* provides some support for the safety of low dose (≤2 drops per day). However, multiple confounders can influence interpretation of results.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability o Probably no important uncertainty or variability X No important uncertainty or variability	Overall, no relevant research or evidence. No important uncertainty or variability in how much people value the main outcome.	There is no evidence to support the judgement but intuitively one would suspect that people would value not having to escalate therapy. That is, not escalating therapy while maintaining control with therapy that is of low risk would be valued. As the dose of steroids is already as low as it can go (1-2 drops per day) then the choice is between no drops and 1-2 drops per day. However, as the low dose topical steroid is likely not associated with concerning adverse effects in most children, the status would likely be viewed as valuable. However, there is no evidence to support this supposition. Again, it is important to acknowledge that some children will develop adverse effects from topical prednisolone acetate 1% even at low doses. The reasons for vulnerability to topical ocular steroid toxicity are not clear but could relate to genetic vulnerability or the nature of the underlying primary disease (i.e. the JIA subtype).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	No direct or relevant research.	The non-escalation of therapy would be favored over escalation of therapy if there is no added efficacy or safety benefits.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No direct or relevant literature was available. Moderate to cost savings depending on what the nature of the escalation would be.	However, non-escalation of therapy would skew towards lower costs and savings. The degree of savings would depend on the nature of the escalation of therapy that would ensue. If the escalation of therapy took the form of adding a therapy, then there would be added costs. If the escalation involved substituting a new therapy for the current therapy, the cost could be incremental or decremental depending on the escalation treatment selected.

The certainty of the evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	The available information is very limited, and that which is available is retrospective, uncontrolled, and outdated. Overall evidence available is very low.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No direct evidence or literature is available. Cost effectiveness would likely favor the comparison (that is, favors no escalation of therapy).	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced X Probably no impact o Probably increased o Increased o Varies o Don't know	No relevant research evidence is available. Overall, probably no impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X No o Probably no o Probably yes o Yes o Varies o Don't know	No relevant research evidence is available. In this case the intervention would be escalating of therapy which, as escalating of therapy would be less desirable than no escalation, the intervention would not be acceptable to key stakeholders.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes X Yes o Varies o Don't know	No relevant research evidence is available.	Non-escalation of therapy (that is maintaining the status quo) is feasible. Intervention (escalating therapy) is also feasible but not desirable.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
o	X	o	o	o

CONCLUSIONS

Recommendation

There should be no escalation of therapy for children with JIA-uveitis whose uveitis is controlled on 1-2 drops of topical ocular steroids per day and systemic therapy. However, this recommendation is highly conditional on the absence of adverse effects from topical therapy, the duration of topical therapy, and the potential risk of the alternative immunosuppressant therapies being considered.

Justification

Based on limited indirect information, topical steroids in a dose of ≤2 drops per day is not associated with a high risk of topic steroid-induced adverse effects, although some risk does exist. Therefore, there would be no added benefit to escalating therapy for a child whose uveitis is well controlled on 1-2 drops of topical ocular steroid per day and systemic therapy assuming there are no current or anticipated adverse effects from the topical therapy in the individual patient. The evidence for this recommendation is very low. More information is required to judge the safety and efficacy of this recommendation for individual patients and specific JIA disease categories.

Subgroup considerations

There is insufficient information to adjudicate this recommendation for subgroups. Data are available for chronic uveitis rather than acute self-limited or acute episodic uveitis. Therefore, generalization to uveitis other than persistent chronic uveitis associated typically with oligoarticular and rheumatoid factor-negative polyarticular JIA is not possible.

Implementation considerations

Apart from disseminating guidelines supporting no escalation of therapy for those children with JIA-uveitis on ≤ 2drops per day of topical steroids and systemic therapy, there are no implementation considerations.

Monitoring and evaluation

Creating a registry of JIA-uveitis that tracks topical steroid dose and duration in the context of uveitis activity and ocular complications would help ascertain the appropriateness of this recommendation.

Research priorities

Prospective tracking of JIA-uveitis treatment regimens and outcomes would be valuable. It is unreasonable to consider that a randomized controlled, double-blind trial of topical steroid therapy of variable dose and duration is feasible or ethically acceptable. In studies of advanced therapies, such as biologically-based therapies, tracking the requirements of topical steroid dose, duration, and side effects would be informative.

Evidence to decision table ACR/AF Recommendation 10

QUESTION

Should subcutaneous methotrexate vs. oral methotrexate be used for children and adolescents with JIA and CAU who are starting systemic treatment for uveitis?

POPULATION:	Children and adolescents with JIA and CAU who are starting systemic treatment for uveitis.
INTERVENTION:	Using subcutaneous methotrexate.
COMPARISON:	Oral methotrexate.
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified.	Anecdotally, this has been a longstanding consideration in both JIA and uveitis, but no studies are available to support this question.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial X Small o Moderate o Large o Varies o Don't know	No direct or relevant research identified.	Many patients on methotrexate require escalation to biologic therapy. With treat-to-target approach, using oral route as initial choice may cause a delay in escalation to biologics as they may require an escalation to subcutaneous methotrexate prior to approval.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	No direct or relevant research identified.	There is no evidence that subcutaneous methotrexate is more effective than oral. Because the need for injection is the only meaningful difference known between oral vs. subcutaneous (no evidence could be found on differences in side effect profile in uveitis otherwise), undesirable effects were judged to be a small degree in this case.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	No direct or relevant research identified.	No papers addressed this issue that could be found.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability X Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	No direct or relevant research identified.	In pediatrics, convincing patients and families to accept SQ therapy (particularly when oral is an option) is highly challenging and can be a barrier to instituting therapy. Without evidence to support, many families will choose oral over subcutaneous, even if anecdotal evidence or expert opinion suggests starting with subcutaneous. Thus, I would consider this an important value in need of additional research.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	No direct or relevant research identified.	Would end up being either probably favoring intervention, or “don’t know”. Some articles will recommend SQ over oral without providing any evidence, but the consensus tends to be either favoring SQ or choosing either. No recommendations (even without evidence) available to suggest starting with oral has any benefit compared to SQ. Pharmacokinetic data (particularly at high doses) was not evaluated in this evidence gathering but is thought to favor subcutaneous in terms of efficacy. Undesirable effects would include strain on parent/child relationship with parent hesitancy to give SC injections. Child fear, avoidant behavior, pain should be considered.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies X Don't know	No direct or relevant research identified.	The full impact unknown as not studied. Certainly dispensation fees and associated fees (i.e. disposal kits, etc…) would suggest that intervention (SQ) has more costs, but no studies look at long term impacts (i.e. risk of flare, GI intolerance, need for additional supportive medications, compliance / lack thereof). As such, this question cannot be answered. Injections – parental training time, time invested in doing the injections/parental and child anxiety

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant research identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No direct or relevant research identified.	The cost of delay to change to biologic if requested also potential for time lost because patient on oral methotrexate and provincial/private payers specify failure of optimal dosing of subcutaneous methotrexate.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies X Don't know	No direct or relevant research identified.	Subcutaneous preparations have a shorter shelf-life and require more frequent refilling, which can be hard for remote patients. Is also harder to travel and requires more set-up than pills. Thus, favoring intervention (SC) likely reduces health equity, particularly in large country with non-dense population like Canada, but cannot say without evidence.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified.	As any further escalation of therapy (aside from JAK inhibitors) involves SQ therapy, and patients find this acceptable, then one would assume they are also okay with SQ MTX. Would put “yes” if there was any evidence.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified.	As above, could put Yes if there was any evidence to supportthis. Logically, there is no reason that it would be not feasible to implement, but uncomfortable with anything but “probably” without some research.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 11

QUESTION

Should starting methotrexate and a monoclonal antibody TNFi immediately vs. methotrexate as monotherapy be used for children and adolescents with JIA with severe active CAU and sight-threating complications?

POPULATION:	Children and adolescents with JIA with severe active CAU and sight-threating complications.
INTERVENTION:	Starting methotrexate and a monoclonal antibody TNFi immediately.
COMPARISON:	Methotrexate as monotherapy.
MAIN OUTCOMES:	Time to control/loss of control of uveitis, side effect of therapy, improvement/normalization of visual acuity.
SETTING:	Ambulatory outpatient.
PERSPECTIVE:	Rheumatologist, Ophthalmologist (uveitis vs glaucoma specialist), patient, population.
BACKGROUND:	Traditionally, systemic corticosteroids are added in addition to topical corticosteroids with early introduction of methotrexate. Due to potential permanent vision loss, combining methotrexate with monoclonal TNFi may be valuable at onset as well as later in the disease course.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	Yes, panel has decided this is a priority question. Severe uveitis may lead to permanent vision loss and structural complications. Current guidelines recommend TNFi as adjunct therapy after failure to achieve remission with	

	DMARD therapy, especially methotrexate. In patients with severe uveitis, use of combination methotrexate and TNFi may be a potential therapeutic option to explore. The ACR Uveitis guideline did not identify any studies addressing this PICO, but supported conditional recommendations based on low quality evidence, risk of permanent vision loss, and anticipated differences in patient values. Updated literature review did not identify new literature to address PICO.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate X Large ○ Varies ○ Don't know	No literature addressed the anticipated desirable effects of combination TNFi and methotrexate in severe uveitis and JIA. Due to the potential for permanent vision loss and ocular complications, the predicted desirable effects are potentially large.	Uncontrolled chronic uveitis has well-documented and potentially permanent complications, which can be avoided with sufficient treatment. These include synechiae, cataracts, glaucoma, and vision loss. Areas to explore potential desirable effects in future research could include time to remission, complications, visual outcomes, steroid related side effects.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Large o Moderate o Small o Trivial o Varies o Don't know	No literature addressed anticipated undesirable effects pertaining to this question. However, the side effects of TNFi therapy is well documented. Immunosuppression from biologic use may be compounded in those requiring systemic corticosteroids due to sight threatening complications.	TNF inhibitor use includes side effects such as immunosuppression, drug-induced lupus, demyelinating disease, and more. Multiple systemic therapy use may add to caregiver burden and discomfort to patients. Population level effects include added costs to healthcare system without substantial evidence of improved outcome. Immediate use of TNFi therapy may delay timing of surgical intervention due to risk of complications associated with biologic use (i.e glaucoma surgery). Immediate use of anti-TNFi may replace the use of systemic corticosteroids for sight threatening complications and if ineffective may lead to worse outcomes.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	The updated literature review did not identify new literature to address PICO. The ACR uveitis guidelines did not identify any studies addressing this PICO, but supported conditional recommendations based on risk of permanent vision loss, and anticipated differences in patient values.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	ACR guidelines and updated literature review did not identify relevant research. In patients with severe uveitis, both physicians, and families will likely share equal value in importance of main outcome.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	The ACR Uveitis guidelines and updated literature review did not identify specific research. Although there is a paucity of direct evidence, newer studies have shown a significant number of non-responders to adalimumab despite early treatment and a proportion of patients may respond well to methotrexate monotherapy. Recent guidelines by Heiligenhaus et al. also support somewhat later addition of TNFi if unable to achieve remission within 16 weeks of MTX. Sight threatening uveitis may be better treated with aggressive systemic corticosteroid regimen rather than immediate addition of a TNFi. Summary of relevant research: Quartier et al 2018 – Double blind randomized control trial of early use of adalimumab in patients with active uveitis and inadequate response to methotrexate showed that by 2 months, 9/16 patients responded to adalimumab compared to 3/15 in placebo. Almost half of patients on adalimumab did not respond by 2 months. McCracken et al 2018 – Retrospective chart review of patients with chronic anterior uveitis, showed that mean time to addition of TNFi therapy was 43 months and only 12% at 6 months. Patients with idiopathic CAU had 6x higher use of TNFi at 3 months.	The use of TNFi therapy and biologics may also carry additional risk compared to methotrexate monotherapy.

	Heiligenhaus et al 2019 – Review recommended addition of TNFi therapy if unable to achieve remission within 16 weeks of MTX (<2 drops/day topical GC). Palestine et al 2018 – 92.3% of uveitis specialists prefer methotrexate as first line therapy. Schnabel et al 2020 – Retrospective chart review that showed possible benefit of pulse IVMP for sight-threatening uveitis.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	Hughs et al. 2018 – Observational cost-utility analysis in patients with JIA-associated uveitis and demonstrated significantly higher costs of adalimumab with methotrexate combination therapy compared to methotrexate monotherapy during the 18-month trial. Conclusion was that addition of TNFi was not cost-effective. However, total number of patients with sight-threatening complications may have less impact to resources.	Anti-TNFi medications carry notable financial costs to the health care system, which are a shared resource in a universal health care system. However, complications arising from uncontrolled uveitis are also potentially costly including surgical intervention, medication use, costs to family (time off work, transportation), and more. No evidence to quantify the magnitude of costs.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Overall the certainty of evidence is limited given that there is only one study on this topic. Hughs et al. 2018 – Observational cost-utility analysis in patients with JIA-associated uveitis and demonstrated significantly higher costs of adalimumab with methotrexate combination therapy compared to methotrexate monotherapy during the 18-month trial. Conclusion was that addition of TNFi was not cost-effective. However, total number of patients with sight-threatening complications may have less impact to resources.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	Hughs et al. 2018 – Observational cost-utility analysis in patients with JIA-associated uveitis and demonstrated significantly higher costs of adalimumab with methotrexate combination therapy compared to methotrexate monotherapy during the 18-month trial. Conclusion was that addition of TNFi was not cost-effective. However, total number of patients may have less impact to resources.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced X Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	No direct or specific research identified. The addition of biologics would be less equitable compared to MTX monotherapy.	Universal healthcare covers medication use for essential medical conditions, including both methotrexate and TNFi biologics. Barriers to TNFi use may include pre-biologic screening (TB, hepatitis), administration (IV or SQ), and time delay. Access to biologics may differ across provinces.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No X Probably no o Probably yes o Yes o Varies o Don't know	Although there is no direct evidence to support, recent guidelines and uveitis expert consensus would not favor immediate use of TNFi. Heiligenhaus et al 2019 – Review recommended addition of TNFi therapy if unable to achieve remission within 16 weeks of MTX (<2 drops/day topical GC). Palestine et al 2018 – 92.3% of uveitis specialists prefer methotrexate as first line therapy.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No X Probably no o Probably yes o Yes o Varies o Don't know	No direct or relevant research identified. Barriers to TNFi use may include pre-biologic screening (TB, hepatitis), administration (IV or SQ), and time delay. Criteria to access biologics may vary across provinces. Some provinces may require failure of DMARD therapy before approval of biologics.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 12

QUESTION	
Should starting a monoclonal antibody TNFi versus etanercept be used for children and adolescents with JIA and active CAU?	
POPULATION:	Children and adolescents with JIA and active CAU starting a TNFi agent.
INTERVENTION:	Starting a monoclonal antibody TNFi.
COMPARISON:	Etanercept.
MAIN OUTCOMES:	Control of uveitis, prevention of flare of uveitis, adverse events.
SETTING:	Ambulatory outpatient.
PERSPECTIVE:	Rheumatologist, Ophthalmologist, Patient
BACKGROUND:	Adalimumab has been shown to be effective in treating uveitis in a randomized control trial. It is therefore considered the first choice of biologic treatment for CAU. Reports of flare of uveitis on etanercept have led to concern using this TNFi in patients with CAU.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no o Probably yes X Yes o Varies o Don't know	Severe and untreated uveitis may lead to blindness. A significant proportion of patients fail to respond to MTX for treatment of JIA and CAU, therefore optimal choice of a TNFi is clinically important. The current guidelines recommend the use of a TNFi if DMARD fails to achieve control of uveitis. The ACR uveitis guidelines conditionally recommend ADA over ETA (Recommendation # 12; PICO # 15).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	Overall there is no high quality evidence to directly answer this question that IFX or ADA are better than ETA. There is good evidence for the efficacy of ADA for the treatment of active CAU. There are no good studies on efficacy of ETA for CAU. Many patients find ADA injections very painful. Ramanan et al, 2017; RCT, ADA treated CAU better than placebo + stable MTX. N=60 ADA vs N=30 placebo. This provided good evidence for efficacy of ADA but does not specifically address this question regarding advantage of ADA over ETA. Tynjala,P et al, Ann Rheum Dis 2007; Retrospective observational study – did directly address this question. Compared ETA vs IFX for JIA pts with uveitis; N=21 ETA vs N=24 IFX; no significant difference found at 24 mos for uveitis activity, uveitis remission or SAE. The authors suggested perhaps some advantage to IFX, but the mean occurrence of new uveitis cases during TNFi Rx was not significantly different between ADA and ETA. However, very low quality of evidence due to study design and very low number of patients. Smith et al, Arthritis Rheum 2005; RCT DB for 6 mos; then open label ETA to 12 mos. Total of 12 pts with JIA and CAU treated: N=7 ETA (3/7+MTX); N=5 placebo (4/5+MTX). No difference found between groups but not adequately powered to detect a difference, thus very low quality evidence.	Some patients may prefer every 2-week injection of ADA to weekly injection of ETA. While initially they agree that every 2-weekly injection (ADA) seems more ideal than once weekly injection (ETA), there is a big difference in how well these injections are tolerated. Could consideration be given for offering ETA as a treatment arm and prospectively following? It seems unfortunate to exclude a medication that could potentially be equally efficacious and better tolerated than ADA.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o Varies X Don't know	Overall, there is no high-quality direct evidence to address the question of a difference in SAE between CAU patients treated with monoclonal Ab TNFi vs ETA. Increased SAE have been reported in patients treated with TNFi vs placebo or MTX: • Ramanan et al, 2017, SAE increased in patients on ADA vs Placebo. • Klotsche, 2016, SAE (infection) increased on TNFi vs MTX. No high quality research on the undesirable effect of possible increased risk of uveitis flare on ETA. Observational studies (low quality) suggest there may not be an increased risk of CAU in JIA patients treated with ETA in general, but do not look at this specifically in patients with active uveitis: • Davies, 2019; Large UK Registry study, 2294 patients in analysis; no association of ETA with new onset CAU; no significant difference in the risk of uveitis btw pts receiving ETA vs MTX; too few events to make definitive comparison of patients on ETA vs ADA/IFX. Lower rates of uveitis seen among patients on ETA vs MTX- authors thought this was due to patients receiving ETA later in the course of their disease. • Foeldvari, 2015; Observational study looked at ETA vs ADA/other TNFi for treatment of JIA (not for Rx of uveitis) and occurrence of uveitis; found no significant difference in uveitis events in ADA vs ETA groups. • Saurenmann, 2006; Observational study also found no significant difference in risk of developing uveitis for JIA patients on MTX, or MTX+ADA vs ETA. No high quality evidence for efficacy of ETA for active uveitis (see section above on desirable effects).	Increased SAE have been reported in patients treated with TNFi vs placebo or MTX. No high quality direct evidence to address the question of a difference in SAE between CAU patients treated with monoclonal Ab TNFi vs ETA. The UK registry data and 2 other observational studies suggest that ETA does not increase the risk of CAU, but quality of evidence is low.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Very low-quality evidence directly comparing IFX to ETA (Tynjala, 2007). There is very low quality of evidence from observational studies on risk of uveitis in JIA patients treated with ETA. There is very low quality of evidence on efficacy of ETA for treatment of uveitis (Tynjala, 2007; Smith, 2005). There is good quality evidence for efficacy of ADA for treatment of CAU (Ramanan et al, 2017).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	No research evidence pertaining to variability in values.	Physicians and patients likely share high value in the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	Ramanan et al, 2017 is the only high-quality evidence to support the use of a TNFi for the treatment of active uveitis; there is no high quality evidence to directly answer the question posed regarding a comparison of ADA/IFX with the efficacy of ETA for uveitis. Ramanan et al, 2017; RCT, ADA controlled CAU better than placebo + stable MTX. N=60 ADA vs N=30 placebo. This paper provides good evidence for efficacy of ADA but does not specifically address this Question regarding advantage of ADA over ETA.	Further research is needed to determine the efficacy of ETA for CAU. I suspect that a formal trial of determining the efficacy of ETA will be challenging to arrange. One thought could be to develop 2 recommended treatment arms and prospectively follow in "real time".

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	Hughes et al 2018; Observational cost-utility analysis- concluded that addition of TNFi (ADA) was not cost-effective vs MTX in the UK.	This question I think will only be answered by prospective data collection. If use of TNFi can prevent blindness, then the cost of adding TNFi to MTX will not only be measured in "actual" medication cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Overall, there is minimal evidence to answer this question. Hughes et al 2018; Observational cost-utility analysis- concluded that addition of TNFi (ADA) was not cost-effective vs MTX in the UK.	Due to the potentially significant outcome of blindness in children, the weighing of medication costs may not be appropriate or possible.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No evidence to assess cost-effectiveness of monoclonal Ab TNFi vs ETA.	ETA may be less costly as it is given at home vs some monoclonal Ab (IFX) given in infusion centers; require time off work/ higher indirect expenses.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	No direct or relevant research identified.	Access to all TNFi are likely similar, particularly ADA + ETA as both are approved for Juvenile Idiopathic Arthriits. Time off work to go to an infusion center for IFX may not be possible for single parent/low income family/ less job security and serve as a barrier to care.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	The RCT of ADA for CAU has led to wide acceptance of this therapy by physicians and families; there is still no high quality study to show efficacy of ETA for CAU. Some patients may prefer less frequent ADA injections; others may prefer less painful ETA injections. Ramanan et al, 2017; RCT, ADA controlled CAU better than placebo + stable MTX. N=60 ADA vs N=30 placebo. This provided good evidence for efficacy of ADA but does not specifically address this Question regarding advantage of ADA over ETA.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified.	ADA/IFX are now currently used in many patients with CAU and their use over ETA is recommended in the ACR Uveitis Guidelines as a conditional recommendation.

SUMMARY OF JUDGEMENTS

JUDGEMENT

TYPE OF RECOMMENDATION

CONCLUSIONS

Recommendation
Justification
Subgroup considerations

Implementation considerations
Monitoring and evaluation
Research priorities

Evidence to decision table ACR/AF Recommendation 13

QUESTION	
Should escalating the dose and/ or frequency to above standard vs. switching to another monoclonal antibody TNFi be used for children and adolescents with JIA and active CAU who have an inadequate response to 1 monoclonal antibody TNFi at standard JIA dose?	
POPULATION:	Children and adolescents with JIA and active CAU who have an inadequate response to 1 monoclonal antibody TNFi at standard JIA dose.
INTERVENTION:	Escalating the dose and/ or frequency to above standard therapy.
COMPARISON:	Switching to another monoclonal antibody TNFi.
MAIN OUTCOMES:	Inducing remission of CAU.
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	Overall, there is very little evidence. This is a conditional recommendation as per PICO 13 in the ACR Uveitis Guidelines. One of the challenges is that there are no consensus guidelines regarding the specific dose or frequency for escalating the dose and/or frequency. In the above paper, the authors quoted the references 37-39. In these observational studies, doses as high as infliximab 20 mg/kg/q 2 weekly and adalimumab weekly have been reported and utilized.	In Canada, there is variability between approval for infliximab for uveitis which may limit biologic options

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o **Moderate** o Large o Varies o **Don't know**	Again, limited evidence (reference 37-39 in the above paper). One of the papers is relatively old (2006) and the others are from 2013 and 2018	If dose and/or frequency escalation is recommended and is successful in a patient, this may prevent exposure of a second biologic DMARD. In patients who require escalated dose/frequency, they likely are already on MTX.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o Varies X Don't know	In a retrospective chart review of patients on weekly adalimumab (no comparator group), serious adverse events were rare (reference 38 in the cited paper).	In Canada, National Guidelines with corresponding changes to Provincial Drug Coverage guidelines would be developed to support the recommendation of doses that exceed product monograph. Furthermore, a national biologics database would allow real world assessment of efficacy and monitoring for any potential increase risk of adverse effects associated with increased dose and/or frequency of biologic agents.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	Overall there is limited evidence (The referenced ACR manuscript and references 37-39).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability X Probably no important uncertainty or variability ○ No important uncertainty or variability	There is limited evidence in literature. This area has not been well studied. However, it would seem reasonable that remission of uveitis would be a valued outcome between care providers, parents, and patients.	It may be easier to convince a family to increase dose/frequency of a medication with which they are already comfortable with than switching to a new medication. However, moving to a weekly painful injection (from every other week) may be challenging for some if already using adalimumab. Another option would be to increase the dose but maintain injection frequency at the original level (eg q 2 weekly for adalimumab). However, the dose might be too large for single injection, plus there is no literature to support this practice. For infliximab, arranging q 2 weekly infusions would add to the cost and this may reduce the overall acceptability of this option

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	Overall, there is limited evidence.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs X Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	There is limited evidence in literature.	The resources required will likely increase for those who require more frequent IV infusions which includes missed time from work, school. travel to and costs associate with attendance at an infusion centre/hospital. The financial impact will be less pronounced if it were SQ injections rather than IV infusions.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	There is limited evidence in literature.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	There is limited evidence in literature.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	There is limited evidence in literature.	If we were able to make national guidelines and ensure that all approval biologics are available in all provinces, then there could be a positive impact. Currently, this would depend on access to biologics across the country. There would have to be provincial coverage for biologics at increased dosing/frequency to ensure equitable access otherwise considerable costs may be incurred.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	There is limited evidence in literature.	Who do we define as "key stakeholders"? Patients Their parents Health Canada Provincial drug regulation? For patients and their families, it may be easier for families to continue a medication they are familiar with but at increased dosing/frequency rather than switching to a new medication. However, moving to a weekly painful injection (from every other week) may be challenging for some if this was favoured over increasing the dose but maintaining original injection frequency.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Please see references 37-39 in the ACR guidelines for uveitis.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations

Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 14

QUESTION	
Should changing to another monoclonal antibody TNFi vs. a biologic in another category be used for children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency?	
POPULATION:	Children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency.
INTERVENTION:	Changing to another monoclonal antibody TNFi.
COMPARISON:	A biologic in another category.
MAIN OUTCOMES:	The main outcome is to achieve uveitis remission using anti-TNFi therapy.
SETTING:	**GLOBAL; PEDIATRIC OPHTHALMOLOGY AND RHEUMATOLOGY CLINICS**
PERSPECTIVE:	**CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS AND ASSOCIATED CHRONIC ANTERIOR UVEITIS. FROM A WHOLE POPULATION PERSPECTIVE JIA AND JIA UVEITIS ARE UNCOMMON BUT DO REPRESENT IMPORTANT CONDITIONS IN THE PEDIATRIC POPULATION. A CHILD AFFLICTED WITH BOTH ARTHRITIS AND ASSOCIATED UVEITIS, IF NOT OPTIMALLY TREATED, CAN HAVE COMPROMISED QUALITY OF LIFE, IMPAIRED GROWTH AND DEVELOPMENT, AND LIMITATIONS IN FUTURE PRODUCTIVITY AND HAVE AN INCREASED ADVERSE IMPACT ON SOCIETAL RESOURCES, INCLUDING HEALTH CARE RESOURCES. FROM THE PATIENT AND FAMILY PERSPECTIVES JIA ALONE AND JIA COMPLICATED BY UVUEITIS CAN BE A STRESSFUL BURDEN.**
BACKGROUND:	Juvenile idiopathic arthritis (JIA) is among the most common chronic diseases of children. Chronic anterior uveitis is the most common extra-articular manifestation of JIA. Topical corticosteroids and mydriatics remain the standard first-line treatment of JIA-uveitis. Immunomodulatory therapies, notably methotrexate or, less frequently, cyclosporine, are examples of usual second-line treatments. Biologically-based therapies, particularly tumor necrosis factor inhibitors (TNFis), have emerged as transformative options in the therapeutic armamentarium for JIA-uveitis. Failure or intolerance of first and second-line therapies prompts consideration of adding an TFNi to the treatment regimen.

	The question is, If the first selected TNFi is ineffective and/or not tolerated should an alternate TNFi be used instead or should the decision be to switch to a biologic agent in a different (non-TNFi) category? **Ambiguity of the question:** This question will be difficult to address definitively as the question does not stipulate a distinction in the TNFi options. Some TNFi have been shown to be more efficacious in treating JIA-uveitis than others. Thus, if a most efficacious TNFi option (e.g. adalimumab) is the current therapy then switching to a less efficacious TNFi (e.g. etanercept) would not ordinarily be suitable. Alternatively, if a less efficacious TNFi (e.g. etanercept) is the current therapy then switching to a more efficacious TNFi (e.g adalimmab or infliximab) could be justified. If the first TNFi is discontinued because of intolerance or adverse effects, then switching to an alternate TNFi could be considered but the question relates to failure of efficacy of the original TNFi as the trigger for change, not adverse effects of the original TNFi. If a new question is created, it should include not only specifics with respect the TNFi options but also specifics about which alternate biologic categories are considered.
CONFLICT OF INTERESTS:	No conflicts of interest to declare.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Probably yes. In general, the literature suggests that TNFi efficacy in JIA-uveitis is ranked adalimumab >infliximab>golimumab.[1-15] Etanercept is not recommended.[8,11,16-20] Thus, based on the relative efficacies there is some support for the idea of switching from etanercept, golimumab, and infliximab to adalimumab. However, there is no substantive support, for example, to switch from adalimumab to etanercept.	Because the context of the question does not reference the specific TNFi, assessing the priority of the problem is difficult to ascertain. If the problem is lack of awareness of relative efficacies of certain TNFis, then the problem is a priority. The recognition of the relative efficacies of TNFis in treating the uveitis associated with JIA and monitoring and predicting TNFi treatment response is a priority. Knowing what clinical, genetic, and biomarker attributes might predict TNFi response and inform which biologic category would most likely be effective in an individual patient would be a high priority. Access to certain TNFis might restricted in certain provincial jurisdictions. Therefore, selecting TNFi options might be

	However, the general question – should unresponsiveness to one TNFi trigger a switch to another TNFi or a medication from another biologic category - cannot be answered without knowing the respective biologic agents under consideration. More recent evidence suggests the efficacy of two other non-TNFi classes of biologic agents that respectively block interleukin 6 (tocilizumab) and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) costimulatory blockade (abatacept).[21]	limited to a limited selection of publicly- or privately funded TNFis. Selecting a TNFi or alternate biologic therapy that requires intravenous administration might preclude easy access for patients residing in locales remote from an infusion centre in which case non-Intravenous options might be more desirable. As more experience and evidence accumulates regarding the efficacy of other non-TNFi biologics (as examples, tocilizumab and abatacept) switching to a non-TNFi biologic might be undertaken more quickly and with more confidence if the evidence for efficacy is strong.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate o Large o Varies o Don't know	The desirable effects are likely moderate. Foldvari *et al.*[16] reported results from an uncontrolled survey of 15 centres following 404 patients receiving TNFi for treatment of uveitis. All 3 patients taking adalimumab were responders. Infliximab was statistically significantly more efficacious for the treatment of JIA-associated uveitis than etanercept (chi-square p = 0.004). Trachana *et al.*[9] reported on 26 patients enrolled prospectively in an observational study to assess the efficacy of adalimumab in JIA. Nine patients were switched to adalumumab after being unresponsive to another TNFi. Two of the nine patients developed uveitis and for this reason were switched to adalimumab (one from infliximab and one from etanercept); both responded (with respect to uveitis) to adalimumab. Miserocchi *et al.*[22] undertook a retrospective chart review of 13 patients with severe JIA-associated uveitis and four with HLA-B27-associated uveitis who were treated with golimumab because of non-response to another TNFi. Patients had been on one to four TNFis prior to starting golimumab; 12 had received etanercept, 14 infliximab, and 15 adalimumab. Fourteen of the 17 patients, all of whom had recalcitrant, severe uveitis on other TNFis, responded to golimumab having no active uveitis at last follow-up while three patients did not respond. Dhingra *et al.*[23] reported their uncontrolled experience in seven patients, four of whom had JIA-uveitis, in switching from one TNFi to another. The four JIA-uveitis patients all were switched from infliximab to adalimumab and responded favorably. Calvo-Rio *et al.*[24] studied the use of intravenous tocilizumab prospectively in 25 children with JIA-uveitis after failure of a variety of corticosteroid, conventional immunosuppressive	Again, the anticipated effects cannot be judged because it is unclear if the change in TNFi will be from a poor efficacy option to a superior efficacy option or from a superior efficacy option to an inferior option. This assumes that there is evidence to discern differences in efficacy among the various TNFis.

	drugs, and biologic agents including adalimumab in 24, etanercept in 8, infliximab in 7, abatacept in 6, rituximab in 2, and anakinra in 1. Within 6 months of starting tocilizumab 79% improved and by one year 88% had improved. Tappeniner *et al.*[25] prospectively studied intravenous tocilizumab in 17 patients with JIA-uveitis who had failed earlier therapies including biologics. Of the 17, 10 achieved remission within 6 months and in 7 of those remission was sustained without recurrence during the 12-month follow-up period. In general, tocilizumab allowed for reduction of steroid and other non-steroid therapies. Ramana *et al.*[26] reported results of a multicenter, single-arm, phase 2 trial of tocilizumab in children with JIA-uveitis who were all on stable doses of methotrexate and had failed TNFi therapy. Of the 21 participants receiving treatment only seven responded to treatment. The study results were felt not to meet the standards to proceed to a phase 3 trial. The authors concluded that, because some patients did respond to tocilizumab, this might still be an option for some patients. There is accumulated literature reporting on treatment of JIA-uveitis with abatacept after TNFi therapy with varying success rates.[21] Birolo *et al.*[27] reported on 31 patients with JIA-uveitis comparing abatacept as a first-line biologic therapy (N=14) and as a "rescue" treatment (N=17). 17 of 31 patients had no uveitis flares for more than 6 months when on abatacept. Tappeiner *et al.*[28], in a retrospective report of 21 children with JIA-uveitis resistant to earlier therapies and treated with abatacept, reported that 11 of 21 children (52%) had periodic inactive disease during the one year of follow-up but flares also occurred while on the therapy and it was not possible to taper concomitant system and local therapies. In a group of seven children with severe uveitis associated with JIA, Zulian *et al.*[29] reported retrospective findings. In all patients a two-degree decrease in inflammation or disappearance of active uveitis occurred in the first six months of therapy. Four patients were able to discontinue or reduce steroid therapy. Small anecdotal case series or case reports in which rituximab was used to treat uveitis have been reported have produced variable results. However, the limited information available tends to show some efficacy prompting consideration of the need for future, larger scale assessments of rituximab in JIA-uveitis. Currently, data are insufficient to draw conclusions about the efficacy of rituximab in JIA-uveitis.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	Undesirable effects are likely small.	If the impetus to switch from a current TNFi to another TNFi or a biologic in another category is because of lack of efficacy and/or intolerance of the first TNFi then discontinuing the original therapy should not have adverse effects. However, depending on which alternate TNFi or which alternate drug from a different category is considered, the effects could be desirable or undesirable depending on efficacy and tolerance. Cost and access may be an issue if for example infliximab is the only other monoclonal available.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	Overall, the certainty of evidence is very low. There are no studies that explicitly address the research question although there are studies which compare different TNFis to each other and TNFis to other biologic categories (see above).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability	Probably no important uncertainty or variability.	The goal is to completely control uveitis so that it becomes inactive (on medication). Thus, this goal is likely to be desired unless it comes at the expense of unacceptable

o No important uncertainty or variability		adverse effects from switching or not switching biologic categories.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison X Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	Does not favor either the intervention or the comparison. Again, it is difficult to answer this question without knowing the specific TNFi and the relatively efficacies and safety profiles of the various TNFis with respect to uveitis. Assuming the preferred TNFi is the current therapy then the balance would favor the comparison. If a less efficacious TNFi is the current therapy, then the comparison would favor the intervention.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies X Don't know	Based on the evidence we are unable to determine the resources required,	As the specific treatment options are unknown ascertaining resource requirements is not possible.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	The certainty of evidence of required resources is very low.	As the question under consideration is ambiguous it is difficult to determine certainty of resource requirements.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	There are no included studies that discuss cost effectiveness.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced X Probably no impact o Probably increased o Increased o Varies o Don't know	There is probably no impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	Assuming that the current TNFi is not efficacious, then choosing a different treatment option is likely to be acceptable.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	Switching from one biologic (either another TNFi or another biologic in a different category) is feasible.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	X	○	○

CONCLUSIONS

Recommendation
It is not possible to make a recommendation as the question is ambiguous. Without a context of which TNFis are being considered no recommendation can be made.
Justification
Insufficient context to answer the question.
Subgroup considerations
No information is available.
Implementation considerations
Further prospective studies designed to address switching biologics in the treatment of JIA-uveitis are required.
Monitoring and evaluation
Insufficient data and context to inform monitoring and evaluation

Research priorities
Further prospective studies designed to address switching biologics in the treatment of JIA-uveitis are required.

Evidence to decision table ACR/AF Recommendation 15

QUESTION	
Should the use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options vs. be used for children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency be considered as reasonable alternatives?	
POPULATION:	Children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency be considered as reasonable alternatives.
INTERVENTION:	The use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options.
COMPARISON:	
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Multiple studies and guidelines on suggestions for therapy in patients who fail TNFi (lack of response) or are intolerant, suggesting that these patients exist and require intervention. No new evidence identified.	The access to various biologic and non-biologic DMARDs may vary from province to province.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o X Moderate o Small o Trivial o Varies o Don't know	There are potential AE from alternate medications suggested in this recommendation. May consider listing side effects for toci, abatacept, mmf, cyclosporine and leflunomide?? No worsening of inflammation and no new complications, no SAE. Tocilizumab: new-onset macular edema (Tappeiner 2016, APTITUDE 2020) – unclear if related to TCZ directly or due to inefficacy in treating uveitis. Also known to cause neutropenia, thrombocytopenia, mild transaminitis, and Immune suppression. Abatacept: Immune suppression (but no increase in infections commented on in the studies looking at it); seems to be very well tolerated amongst the therapeutic options. MMF, CS-A, LFN: Adverse effects as per warnings on medication. No specific side effects suggested in these medications when used in uveitis compared to other uses.	Too many variables to consider in PICO question in order to make informed judgement. Each medication must be considered in turn or separately. However, the undesirable impacts of all above therapies felt to be less significant than the persistence of refractory JAU.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o **Low** o Moderate o High o No included studies	This question combines multiple medications making it difficult to evaluate. Some studies continued background methotrexate. Three case series addressing this for abatacept (reviewed by ACR committee) 1. Tappeiner C. (2015): retrospective case-series of 21 JIA patients with uveitis (n=21) and arthritis (n=18), all were refractory or intolerant to at least one TNFi. Initial inactivity in 11/21, but 8/11 had recurrence while on abatacept. 3/4 patients without baseline complications developed while on therapy. Sustained response low (<15%). 2. Birolo C. (2016): retrospective case series of 31 JAU patients refractory to TNFi (38% had failed 2); n=14 for first-line biologic, and n=17 for second-line biologic. 17/35 (54.8%) achieved clinical remission; preexisting ocular	For Abatacept: evidence is low (favor low); there are 3 case series (and one recommendation guideline derived from same) suggesting it has some efficacy; inactivity rate of 48-86%. Only one looked at abatacept as an option after failing two TNFi (most used it as second-line after initial failure or intolerance, or sometimes as primary). Thus cannot grade as high evidence as question not exactly answered (verbatim) and type of studies is of weaker caliber (case series). However, Birolo (Zulian) note longer treatment duration associated with progressive improvement in response. For Tocilizumab: evidence is low based on more recent studies. Initial studies showed much more benefit than most

	7/21 (33%) achieved treatment response by 12 weeks, additional 3/14 (14%) had one-step improvement by week 24. Only 4 pts completed 24 week treatment. Primary end point WAS NOT MET. No study addressing Mycophenolate (reviewed by ACR committee) initially. They included one 2008 study in their review, but these patients had only been treated previously with methotrexate, not biologic. No studies addressing this in the intervening time. No study addressing Leflunomide (reviewed by ACR committee) initially. They included two studies in their review, but both of these were not in patients who had previously failed TNFi. No additional studies since ACR publication as well. No study addressing CsA (reviewed by ACR committee initially). They included two studies on CS-A, but there was none that looked at it specifically in biologic refractory patients. There was not enough subgroup analysis to come to a conclusion on the use of CS-A as a treatment choice in those who have been refractory to TNFi (one or more).	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No research evidence	Though not supported by evidence, logic dictates that it is important for one to know about alternatives to TNFi in refractory JAU patients. The main outcome (i.e. remission, decrease flare rate) discussed in majority of papers would be what everyone values particularly when faced with lack of response to previous treatments. Overall – what is valued more by the patient ? vision versus potential for side effects. • Not specifically studied, but both of us would assume that preservation of vision is of paramount importance.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Evidence is limited; each study on TCZ and ABA that were reviewed discussed adverse effect profiles, but did not weigh specifically against the risk of JAU. However, Tappeiner (2015) does comment on the development of new complications and this would need to be considered. Overall the risk of uncontrolled JAU is felt to be higher in both rate, severity and subsequent complications than that of an intervention, but this was not evaluated definitively.	To consider – how much do patients values inactive/lower disease activity (fewer drops) versus side effects from medications. For example – less drops but risk of GI perf from toci. Along this theme – palatability, twice daily dosing of some of these meds, travel time to infusion centre, income loss etc As before is quite challenging to answer this because we have multiple interventions to study, in the context of considering “two or more TNFi” which has not been studied at all. We will review this aspect of it again, however, to see if any specific adverse effects were described. TCZ: can be given SQ/IV same as TNFi. Risk of GI perforation is mentioned in TCZ, but not reported in any of the uveitis studies specifically (would have to be inferred from data in RA, which was outside the scope of our review). Aba: can be given SQ/IV same as TNFi. As TCZ, the values piece has not been studied in uveitis specifically. MMF, CS-A, LFN: because the efficacy for these are so poor (when considering those who are refractory to double TNFi) we feel that it is not worth commenting on the balance of adverse effects, simply because the therapy is very unlikely to be efficacious. Again there are no specific studies on it, but it is known to be inferior to TNFi to begin with.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ **Don't know**	No evidence to make decision however, medications such as abatacept and tocilizumab are expensive (?$25,000/year).	- cost/travel etc for infusion medications (toci /abatacept) versus resources to administer twice daily medication in young child for example Obviously many more resources are required for IV > SC > home oral therapy, but this has yet to be studied in uveitis in particular. Ultimately we felt that efficacy was the most important question, because if a therapy is not efficacious, then the resource issue doesn't matter because the drug itself doesn't work.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	No evidence to make decision.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o **No included studies**	No direct evidence	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o **Varies** o Don't know	No evidence to make decision	to consider - cost/access/health literacy access to these health Canada approved medications varies greatly between provinces creating disparities. We feel there is province-to-province variability; however, in the question as posed (dealing with patients who have failed two TNFi) we are not aware of any province that would mandate failure of an additional non-biologic DMARD (LFN,CS-A, MMF) in order to qualify for another biologic (ABA, TCZ).

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	No direct evidence to make decision	All interventions are used by rheumatologists , and thus side effect profiles reasonable to consider. All interventions (TCZ, ABA, CSA, MMF, LFN) have been used to treat juvenile arthritis with variable success. It is established that complications from uveitis can be more severe and important than those from arthritis alone.. Therefore, it is reasonable that stakeholders would support the intervention, since there is some evidence for response (albeit limited) particularly when faced with this potentially sight-threatening condition. Patients preference and values to consider potential AE with new treatment versus risk of vision loss/ side effects of drops. • Agree with your comment that it should be considered, but it has not been studied. Our assumption is that one would want to preserve vision over any other side-effect (blindness being a major side effect of non-intervention), which is why we chose “probably yes” instead of “yes”.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	No direct evidence	All medications are currently available in the Canadian market and health care insurance (provincial or private) is available to offset cost if criteria met. Same reasoning as above Access not equivalent across the country. Agree (hence “probably yes” instead of “yes”)

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 16

QUESTION

Should strongly recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis vs. be used for children and adolescents with spondyloarthritis?

POPULATION:	Children and adolescents with spondyloarthritis
INTERVENTION:	Strongly recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis
COMPARISON:	No education.
MAIN OUTCOMES:	Delay in treatment, duration of symptoms, complications of iritis.
SETTING:	Outpatient clinics.
PERSPECTIVE:	Rheumatologist, nurse, ophthalmologist, patient.
BACKGROUND:	Patients may not know the signs/symptoms of iritis and when they should seek assessment/treatment.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies	Overall, there is 'very low' research evidence to support this recommendation. The PICO in question is of high clinical priority, but possibly not a high research priority.	

o Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X Large o Varies o Don't know	The literature review did not show any direct evidence. Chang et al. 2011 showed that 10% of patients with HLA-B27 related acute anterior uveitis suffered legal blindness or severe visual impairment, 7% with decreased final visual acuity. The most common sequelae were cystoid macular edema. As the complications can be significant and devastating, education could have the desired effect of avoiding the potentially severe consequences of not treating.	Educating patients could promote earlier consultation, leading to earlier treatment, potentially decreasing complications.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small X Trivial o Varies o Don't know	The literature review did not show any direct evidence.	The undesirable effects of education were trivial. It would take more time and resources for the treating team and the patient. Perhaps it could cause some stress to the patient.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	The literature review did not show any direct evidence.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability o Probably no important uncertainty or variability X No important uncertainty or variability	The literature review did not show any direct evidence.	Although this has not been formally studied, we can presume there is low uncertainty or variability in how much patients or care providers would value the outcomes of decreasing delay in treatment, decreasing duration of symptoms, and decreasing complications of iritis.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o Don't know	The literature review did not show any direct evidence. However, the balance of effects would strongly favor the intervention (education) in this case over the alternative (no education).	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings X Large savings o Varies o Don't know	The literature review did not show any direct evidence. However, for the small and inexpensive input of education, there is likely a large savings in terms of the costs associated with delays in treatment, longer duration of symptoms, and complications of iritis.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	The literature review did not show any direct evidence.	There may be a small cost associated with time involved in educating patients. These resources invested by the health care team may include the following: time, dissemination of education to other providers, reminders to the group, and more. Overall, these resources are minimal compared to potential outcomes.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o No included studies	The literature review did not show any direct evidence.	However, the low cost of education is likely very cost effective in this situation.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	The literature review did not show any direct evidence.	However, increased education would likely help increase the equity between patients in terms of knowledge of their condition and when to seek help.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No studies identified, but education is likely acceptable to the educators and the patients.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No studies identified, but this is a low cost, very feasible intervention to implement.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Although there is low evidence for that recommendation, given the low cost, low resources and high desirable effects of the intervention, we strongly recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis.
Justification
See above for justification.
Subgroup considerations
Implementation considerations
Need to develop clear guidelines as to what to include in the education tools (which signs, when to consult, etc). Need to define who is going to deliver thje educational activity (ophthalmologist, rheumatologist, nurse, etc). Need to explore most effective ways of delivering the information to the patient (written pamphlet, emails, verbal teaching, etc).
Monitoring and evaluation

Research priorities
This is a clinical priority, but possibly not a very high research priority.

Evidence to decision table ACR/AF Recommendation 17

QUESTION	
Should conditionally recommend against switching systemic immunosuppressive therapy immediately in favor of treating with topical glucocorticoids first vs. be used for children and adolescents with spondyloarthritis otherwise well controlled with systemic immunosuppressive therapy (DMARDs, biologics) who develop AAU?	
POPULATION:	children and adolescents with spondyloarthritis otherwise well controlled with systemic immunosuppressive therapy (DMARDs, biologics) who develop AAU
INTERVENTION:	treating with topical glucocorticoids first
COMPARISON:	switching systemic immunosuppressive therapy
MAIN OUTCOMES:	Time to inactive disease, side effect of therapy, visual outcome
SETTING:	ambulatory outpatient
PERSPECTIVE:	rheumatologist, ophthalmologist, patient
BACKGROUND:	Patients with SPA-related AAU are episodic and short-lived, potentially benefit from topical therapy first before adjusting systemic therapy
CONFLICT OF INTERESTS:	none

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	Yes, panel has decided this is a priority question due to lack of relevant studies and risk of permanent vision loss. Chang et al. 2011- 10% of patients with HLA B-27 related AAU suffered legal blindness or severe visual impairment, 7% with decreased final visual acuity. Most common sequelae were cystoid macular edema. Acute anterior uveitis associated with spondyloarthropathy may lead to permanent vision loss. Current ACR guidelines recommend treatment with topical glucocorticoids over adjusting systemic immunosuppressive therapy due to good response to topical glucocorticoids and short duration. ACR guideline did not identify any studies addressing this PICO. Updated literature review did not identify new literature to address PICO. If patient has recurrent episodes despite topical GC therapy, no guidance towards threshold before adjusting systemic therapy.	However, we would consider it an important question because it is a big deal to switch systemic medication in children and adolescents with spondyloarthritis. There are a limited number of medications available and once a patient is switched, it is rare for them to go back on the original medication.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	No direct or relevant research identified.	Short term benefits include avoiding need for additional or switch in systemic therapy and get away with topical treatment only. Long term benefits include potential to prevent permanent vision loss and disability.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large X Moderate o Small o Trivial o Varies o Don't know	No direct or relevant research identified.	Overall the inconvenience of using short-term topical glucocorticoids and possible side effects thereof are likely outweighed by the avoidance of a switch in systemic treatment. Frequent utilization of topical GC therapy may cause iatrogenic effects (cataracts, raised IOP), increase patient and caregiver burden. However, switching biologics may flare systemic manifestations, increase healthcare costs, and have systemic side effects. The threshold of when to switch from topical GC therapy to systemic therapy is unclear. Sequelae of spondyloarthropathy associated uveitis include permanent vision loss, morbidity, reduced quality of life, vocation, disability.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	ACR guideline didn't identify studies addressing PICO, therefore supported conditional recommendation for topical GC over systemic therapy change due to low quality evidence, response to topical GC, and short duration of episodes. Updated literature review identified no new studies.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	ACR guidelines and updated literature review did not identify relevant research.	We think that it is clear that both patients and caregivers would value the main outcome in this case. Patients with symptomatic and acute uveitis are more likely to perceive importance of screening and treatment compared to patients with CAU as their disease is usually symptomatic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o Don't know	ACR guidelines and updated literature review did not identify relevant research.	Although no direct studies to address PICO, spondyloarthropathy associated AAU known to respond favorably to topical GC therapy. Due to short duration of episodes, ease of medication access, and immediate efficacy, topical GC appears reasonable choice. We would think that the balance of effects favours the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings X Varies o Don't know	No direct or relevant research identified.	From resource perspective, topical glucocorticoid has benefits of ease of drug access, and lower costs compared to most immunosuppressive therapy (DMARDs and biologics). Potentially large savings by not switching systemic medications, depending on the switch that would have occurred.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant research identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention X Favors the intervention o Varies o No included studies	No direct or relevant research identified.	From resource perspective, topical glucocorticoid has benefits of ease of drug access, and lower costs compared to most immunosuppressive therapy (DMARDs and biologics). It is much less expensive to use topical glucocorticoids than to switch to a new systemic therapy.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact X Probably increased o Increased o Varies o Don't know	No direct or relevant research identified. Overall, topical GC therapy compared to systemic immunosuppressive therapy is more accessible due to relative availability in community, reduced cost, lack of pre-biologic screening (TB and hepatitis).	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no X Probably yes o Yes o Varies o Don't know	No direct or relevant research identified. Due to short duration and response to topical GC therapy, both treating physician and family will likely value a graded approach. Benefits of topical GC therapy include ease of administration, immediate onset, and demonstrated efficacy. Less costly to health system.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	No direct or relevant research identified. Topical GC is feasible due to wide availability and low cost. Barriers to topical GC use include frequent administration, patient discomfort, and adherence.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations

Monitoring and evaluation

Research priorities
Other – Threshold to switch from topical GC to adjusting systemic therapy.

Evidence to decision table ACR/AF Recommendation 18

QUESTION	
Should tapering topical glucocorticoids first vs. systemic therapy be used for children and adolescents with JIA and CAU that is controlled on systemic therapy but who remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent)?	
POPULATION:	Children and adolescents with JIA and CAU that is controlled on systemic therapy but who remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent).
INTERVENTION:	Tapering topical glucocorticoids first.
COMPARISON:	Tapering systemic therapy.
MAIN OUTCOMES:	Prevent complications of prolonged topical glucocorticoids; prevent uveitis flare.
SETTING:	Outpatient.
PERSPECTIVE:	Patients, rheumatologist, ophthalmologist.
BACKGROUND:	Traditionally, topical therapy is tapered first to prevent complications while systemic therapy is continued to maintain disease control.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel has decided this is a priority question. At the time of the ACR guidelines, two retrospective cohort studies (Kothari et al, 2015; Thorne et al, 2010) reported ocular complications associated with prolonged use of topical glucocorticoids. Despite the very low quality of evidence, they strongly recommend tapering topical glucocorticoids first once uveitis is controlled. This is supported by recommendation 19 that encourages at least two years of relapse free systemic therapy before weaning. No new studies that address this PICO question have been identified since then.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	Kothari et al (2015) report that topical corticosteroid use (≥2 drops/day) was a strong risk factor for intraocular pressure (IOP) elevation in multivariate analysis. The hazard ratio increased with number of drops/day. Thorne et al (2010) report that use of < 3 corticosteroid drops daily was associated with an 87% reduction in the risk of new onset cataract when compared to > 4 drops daily (RR = 0.13, 95% CI: 0.02- 0.69, P = 0.02). Thus, weaning topical steroids first can prevent these complications. Furthermore, weaning systemic therapy first may lead to increased uveitis flares and even more exposure to topical therapies.	Stopping topical glucocorticoid eyedrops is more convenient for families.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	Undesirable effects of weaning topical therapy in uveitis has not been specifically addressed in the literature. However, weaning topical corticosteroids may lead to uveitis flare, thus requiring more drops at increased frequency. Active uveitis is also associated with significant complications. Those who require ongoing topical therapy for 3 or more months should be considered for a change/escalation in systemic therapy (as per ACR recommendation 9).	Undesirable effects of weaning systemic therapies first include increased risk of uveitis flare and the need for more intensive topical therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Although only 2 retrospective cohort studies addressed this PICO question and the quality of evidence is considered very low, the ACR strongly recommends tapering topical corticosteroids before systemic therapy once uveitis is well controlled.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	No specific research or evidence was identified. Topical corticosteroids are known to be associated with complications (glaucoma and cataracts) from the papers described above. Uveitis itself can also cause these complications and others. It is current standard practice to taper topical therapies before systemic therapy.	ACR recommends at least 2 years of inactive disease on systemic therapy before weaning systemic therapy (ACR recommendation 19).

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	No specific evidence was identified. It is standard practice to taper topical therapy first before systemic therapy. Kothari et al (2015) and Thorne et al (2010) demonstrate ocular complications associated with prolonged topical therapy. ACR conditionally recommends at least 2 years of inactive disease on systemic therapy before weaning systemic therapy (ACR recommendation 19) based on 3 studies.	Undesirable effects would include a flare of uveitis that is unnoticed by the patient.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies X Don't know	No specific evidence was identified. Topical therapy is less expensive than DMARD or biologic therapy. Thus, weaning topical therapy first saves less than weaning systemic therapy. Tapering either topical therapy and DMARD/biologic therapy would likely require the same frequency of eye examinations.	Some topical therapy may be more expensive than systemic therapy with methotrexate. Coverage for topical drops varies by province and private payer.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No specific evidence was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No specific evidence was identified. Topical glucocorticoids are less expensive than systemic therapies. However, development of ocular complications would require additional treatments (more medications, surgical intervention, more frequent assessments). Systemic therapies require regular blood work monitoring. If uveitis flares with tapering either topical or systemic therapy, increased costs both for medications and assessments.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies X Don't know	No specific evidence was identified.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no x Probably yes o Yes o Varies o Don't know	No specific research or evidence was identified. It is standard practice to taper topical therapy first, thus likely acceptable for rheumatologists and ophthalmologists. Topical eyedrops can be cumbersome for patients and families to administer, so tapering is likely acceptable. Patients and families who experience side effects from systemic therapy, have needle phobia or other concerns may prefer tapering systemic therapy first, but are likely more concerned about the complications of active uveitis.	Families may prefer to stop drops over wean of systemic therapy if disease control with systemic for convenience.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes x Yes o Varies o Don't know	No specific research or evidence was identified. Standard practice and simple to implement.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 19

QUESTION

Should there be at least 2 years of well-controlled disease before tapering therapy vs. less be used for children and adolescents with uveitis that is well controlled on DMARD and biologic systemic therapy only?	
POPULATION:	Children and adolescents with uveitis that is well controlled on DMARD and biologic systemic therapy only.
INTERVENTION:	There be at least 2 years of well-controlled disease before tapering therapy.
COMPARISON:	Less duration of well-controlled disease.
MAIN OUTCOMES:	Recommended duration of systemic therapy for well controlled uveitis to prevent disease flare.
SETTING:	Ambulatory patients.
PERSPECTIVE:	Families, ophthalmologist, rheumatologist.
BACKGROUND:	No consensus on optimal duration of systemic therapy in patients with controlled uveitis.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes **X** Yes o Varies o Don't know	This problem is a priority There is a high risk of uveitis flare when systemic therapy is modified. However, some patients may continue in remission when systemic therapy is stopped. It is important to be	

	able to remove systemic therapy if not needed especially because some of these medications have potential side effects. The ACR panel based their recommendation on very low evidence. They identified three studies in which this issue was addressed. Breitbach in 2016 reported 20 patients who stopped adalimumab. Three were able to stop the medication after more than 2 years of complete disease inactivity. One retrospective study by Lerman in 2015 assessed the rate of uveitis recurrence in the year after stopping anti-TNF therapy in 19 patients with controlled uveitis (various systemic diagnosis, less than half with JIA). By 1 year 64% had recurred. There was no role of the duration of the immunosuppression as treatment for more than 1,5 years with anti-TNF, does not appear to impact the risk of reactivation. In the third study by Ayuso, 22 JIA patients were treated with MTX for active uveitis. Results showed that longer inactivity under MTX therapy was independently protective for relapses after the withdrawal (hazard ratio = 0.07; 95% confidence interval 0.01-0.86; P = .038), which means that 1-year increase of duration of inactive uveitis before the withdrawal of MTX results in a decrease of hazard for new relapse of 93%. Relapse-free survival after the withdrawal of MTX was significantly longer in patients who had been treated with MTX longer than 3 years, children who were older than 8 years at the moment of the withdrawal, and patients who had an inactivity of longer than 2 years before the withdrawal of MTX. **New references have been identified since the publication of the ACR guidelines.** Heiligenhaus et al in 2019 updated their guidelines for anti-inflammatory treatment of uveitis associated with JIA. One of the recommendations is that de-escalation of treatment with DMARDs should be preceded by period of at least 2 years of uveitis inactivity based on the retrospective data included in the ACR guidelines by Lerman and Ayuso. They acknowledged	

	that there was no published data to show whether gradual dose reduction should be preferred to abrupt discontinuation Acharya in 2019 assessed the risk of uveitis recurrence after modifying systemic therapy. 68% of patients eventually had a recurrence at a median interval of 288 days (IQR: 108-338). Of these, 38% flared while tapering systemic therapy. 82% of patients previously on anti-TNFs had a recurrence of uveitis. For patients who had their treatment modified based on a presumed disease remission, there was a longer time to relapse and a lower proportion of flare compare to the other group (p=0.036-log rank permutation test). No predictor of flare was identified Dipasquale et al reported 2 patients treated with Tocilizumab for uveitis refractory to anti-TNF and MTX. Both patients had a remission of uveitis within 3 weeks, and methotrexate was safely discontinued 1.5 years later. These are the first reports of successful methotrexate withdrawal during tocilizumab treatment of JIA-associated uveitis. Horton 2019 reported on patients who took part of the SYCAMORE trial. 12 patients had received Adalimumab for 18 months as part of the trial. 11/12 patients had to restart Adalimumab while off because of uveitis flare (median time of 188 days). No information was available on treatment with MTX. Their conclusion is that drug-induced remission of JIA-associated uveitis did not persist when Adalimumab was withdrawn after 1-2 years of treatment	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate **X** Large ○ Varies ○ Don't know	No literature directly addresses the desirable anticipated effects for the timing of weaning systemic therapy for well controlled uveitis.	Every systemic therapy has potential side effects. Therefore, it is important to consider weaning medications when they become less needed. However, since there is a high risk of uveitis flare, the weaning cannot occur too quickly. To establish the adequate duration of treatment once uveitis is well controlled is key to balance benefits/risks of treatment vs complications secondary to uveitis

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small o Trivial o Varies o Don't know	No research evidence identified.	Maintaining systemic therapy that is not needed has potential undesirable effects in the short and long term, pain and distress of injections, missing work to attend appointment to infusion clinics. Other undesirable effects include medication cost.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low **X** Moderate o High o No included studies	The ACR recommendation is based on very low quality evidence based on 3 reports. Ayuso reported 22 JIA patients on MTX for active uveitis. Relapse-free survival after the withdrawal of MTX was significantly longer in patients who had been treated with MTX longer than 3 years, children who were older than 8 years at the moment of the withdrawal, and patients who had an inactivity of longer than 2 years before the withdrawal of MTX. Lerman assessed the rate of uveitis recurrence in the year after stopping anti-TNF therapy in 19 patients with controlled uveitis (various systemic diagnosis, less than half with JIA). By 1 year 64% had recurred. Of patients who discontinued anti-TNFα, two-thirds (68.4%) were on anti-TNFα for more than 1 year after achieving quiescence, but only one third were on anti-TNFα for more than 2 years after achieving quiescence (36.8%). The median time on anti-TNFα from achievement of quiescence to discontinuation was 1.73 years (IQR: 0.25-2.15). The likelihood of uveitis reactivation was higher after anti-TNFα discontinuation (63.8%) than before (24.4%). Additional studies have confirmed that longer duration of systemic therapy is associated with a decrease risk of uveitis recurrence. NEW EVIDENCE In Horton's report, 92% of patients who stopped adalimumab after a treatment for 18 months had to be restarted on it because of a recurrence of their uveitis (median time of 188 days). Their conclusion was that drug-induced remission of JIA-associated uveitis did not persist when Adalimumab was withdrawn after 1-2 years of treatment.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability **X** Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence identified.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No research evidence identified.	Longer duration of medication exposure would incur greater chances of costs, adverse effects, mediation related pain, monitoring labs.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs **X** Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	No research evidence identified.	Biologic agents used to treat chronic uveitis have a high cost. Therefore, it is important to define the optimal duration of treatment. Continuing a treatment that is unnecessary is costly. Some DMARDs are given in infusion center or at local clinics. This can be a burden for families with missed work/school, transportation, parking etc. On the other hand, uveitis recurrence may lead to an increased number of medical visits.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High **X** No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison **X** Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o No included studies	No research evidence identified.	Uveitis recurrence is associated with an increased risk for secondary complications and the inflammation may be more difficult to control. All of this may lead to increased number of visits, procedures, and surgeries. It may also require escalation in systemic therapy including the need for new biologic agents. Biologic agents are medications with a high cost.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced **X** Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	No research evidence identified.	Barriers to health equity include ongoing costs, travel time, burden to families. These indirect costs are particularly pronounced if patients are on infusions or require the use of clinics for injections.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes **X** Yes o Varies o Don't know	No research evidence identified.	Patient values would include the balance of inactive uveitis while on treatment with minimal side effects.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Not weaning systemic therapy prior to 2 years of well controlled uveitis seems feasible. The cost of medication may be an issue. However biologic agents are covered by provincial or private insurance plans. The access should be similar for all families. Patients may experience medication side effects that impact on quality of life and ability to continue treatment. Families may become less compliant to treatment.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations

Monitoring and evaluation

Research priorities

Evidence to decision table ACR/AF Recommendation 20

QUESTION	
Should methotrexate be used as first-line DMARD therapy over other DMARDs for children with JIA-uveitis not controlled with topical therapy?	
POPULATION:	Children and adolescents with JIA and uveitis not controlled with topical therapy.
INTERVENTION:	Methotrexate (SC or PO route).
COMPARISON:	Other conventional DMARDS.
MAIN OUTCOMES:	Disease control.
SETTING:	Outpatient.
PERSPECTIVE:	Rheumatologist, ophthalmologist, patient.
BACKGROUND:	MTX is traditionally recommended as first-line DMARD therapy for uveitis.
CONFLICT OF INTERESTS:	None.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	The panel has decided this is a priority question even though the ACR uveitis guideline did not specifically recommend review this question. The SHARE 2018 uveitis guidelines do recommend MTX as first-line DMARD therapy for JIA-uveitis (4D evidence) based on 5 retrospective chart reviews. The MARAJIA systematic review and expert consensus meeting from 2018 recommend MTX as first-line DMARD therapy for JIA-uveitis (4C evidence) based on same articles from SHARE and other small retrospective studies in idiopathic uveitis.	Limited evidence to recommend SC (subcutaneous) route over PO (oral). Family preference, accessibility, dose and provincial health authority requirements should be considered when deciding upon SC vs PO route. MARAJIA guidelines recommend MTX SC over PO if doses of 15mg/m2/wk are requested due to greater bioavailability (grade 4C).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	Overall, there are no head-to-head trials comparing methotrexate with other conventional DMARDs. There are multiple sources citing efficacy of methotrexate as below. Evidence for other DMARDs (azathioprine, MMF, cyclosporine, leflunomide) have been reviewed elsewhere in the ACR uveitis recommendations and is even more limited than MTX evidence. There are no study addressing Mycophenolate (reviewed by ACR committee) initially. They included one 2008 study in their review, but these patients had only been treated previously with methotrexate, not biologic. No studies addressing this in the intervening time. There are no studies addressing Leflunomide (reviewed by ACR committee) initially. They included two studies in their review, but both of these were not in patients who had previously failed TNFi. No additional studies since ACR publication as well. There are no study addressing CsA (reviewed by ACR committee initially). They included two studies on CS-A, but there was none that looked at it specifically in biologic refractory	

	patients. There was not enough subgroup analysis to conclude on the use of CS-A as a treatment choice in those who have been refractory to TNFi (one or more). Papadopoulou et al 2013 found that 10.3% of MTX-treated patients developed uveitis compared to 20.2% of MTX-untreated patients, suggesting potential preventative effect of MTX in children with JIA. Sijssens et al 2007 found that early treatment with MTX (within 1 year of uveitis diagnosis) was associated with a delay in development of cataract requiring surgery. Shetty et al 1999 showed significant or mild improvement in uveitis in 4 patients treated with MTX; all reduced steroid doses and no adverse events reported during therapy. Foeldvari et al 2005 found that 21/25 patients with JIA-uveitis responded to MTX therapy. 4 patients required additional immunosuppressive therapy. Heiligenhaus et al 2007 found that 32/35 patients with JIA-uveitis improved on MTX. Only 3 patients had adverse effects. Weiringa et al 2019 found that 66.7% MTX-treated patients reached remission on MTX. Data suggested longer time to remission with low dose MTX (<15mg/m2/wk). Data also suggested that at doses of MTX=/>15mg/m2/week, SC dosing was more effective at establishing remission. No significant differences in complications, steroid-sparing effect or side effects between high or low dose groups. Kostik et al 2016 also found that frequency of uveitis in JIA patients was lower in those treated with MTX compared to MTX-untreated patients (11.5% vs 46.7%). Risk factors for uveitis also higher in MTX-untreated group (younger, more oligo JIA, high ANA positivity). Simonini et al. 2013 systemic review showed 73% of children (CI 0.66-0.81) responded to MTX monotherapy, but dosing ranged as high as 30 mg/m2 (majority 15 mg/m2).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate X Small o Trivial o Varies o Don't know	Evidence from afore mentioned studies shows MTX is generally well-tolerated. However, commonly reported side effects include nausea, vomiting, fatigue after dosing. These side effects should be balanced against considerable undesirable effects of active uveitis including impaired vision. The side effects of MTX should also be balanced with the potential adverse effects of alternate DMARDs, all of which have significant potential adverse effect profiles. There are no head-to-head trials comparing the respective adverse effect profiles of various DMARDS.	SC route of MTX may cause pain and discomfort for patients. Additional considerations for SC route include family comfort with administering medications, time away to physicians office for injections, and indirect costs of time away from school and work. Treatment with methotrexate may delay certain childhood vaccinations. Treatment with methotrexate may restrict ability to travel (if taking SQ dosing) due to storage of vials.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Evidence comes from small retrospective cohort studies/chart reviews. Systematic reviews have been performed but evidence is still low grade.	Traditionally, MTX is recommended by most rheumatologists as first-line therapy for uveitis despite the lack of high-quality evidence. MTX is also a reasonable option as concurrent Juvenile Idiopathic Arthritis is also responsive to this treatment.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability X Probably no important uncertainty or variability o No important uncertainty or variability	Henderson et al 2016 assessed the practice patterns in treatment of JIA-uveitis using the CARRA registry (656 patients with JIA-uveitis, 92 with idiopathic uveitis). 85% JIA-uveitis patients received MTX (both SC and PO in similar rates). This was used far more often than other DMARDs.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison X Probably favors the intervention o Favors the intervention o Varies o Don't know	Limited evidence available to compare methotrexate to other DMARDS. Overall, methotrexate is favoured based on limited evidence. Evidence for other DMARDs (azathioprine, MMF, cyclosporine, leflunomide) has been reviewed elsewhere in ACR recommendations and is even more limited than MTX evidence. Evidence for methotrexate vs. placebo would favor methotrexate.	Treatment of methotrexate should be weighed against the significant short and long term burden of non-treatment (i.e. progressive uveitis or long-term complications from excessive use of topical steroids).

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings X Varies o Don't know	No direct or relevant research was identified.	PO MTX is not expensive compared to biologic medications. SC MTX is not expensive but may require indirect resources and costs (doctor's visits, syringes, alcohol wipes, etc). This would be similar when considering other biologics though. MTX is likely obtained more easily than some other DMARDs (for example, MMF is more expensive and may require special authority. Patients are easier to qualify for methotrexate given the underlying diagnosis of JIA associated uveitis. All interventions require blood work monitoring and regular follow up with rheumatology and ophthalmology.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies	No direct or relevant research was identified. Resources may vary based on location, insurance, psychosocial factors.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies X No included studies	No direct or relevant research identified.	Although there is no literature to compare the costs of methotrexate to other DMARDs, the cost of untreated uveitis is high.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies X Don't know	No direct or relevant research identified.	SC MTX may be challenging for some families living remotely if unable to administer injections at home.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o Yes o Varies X Don't know	No direct or relevant research identified.	PO MTX likely more acceptable to families than SC. Once weekly dosing likely easier than daily or BID dosing of other DMARDS. Side effects may not be tolerated by patients. Most adverse effects of other DMARDs are similar in magnitude, but no head-to-head studies comparing them.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes X Yes o Varies o Don't know	No direct or relevant research identified. Methotrexate is also standard and common practice for Juvenile Idiopathic Arthritis and prescribed by most pediatric rheumatologists in Canada.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation
Justification
Subgroup considerations
Implementation considerations
Monitoring and evaluation
Research priorities