National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[H] Evidence reviews for colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy

NICE guideline NG219

Evidence reviews underpinning recommendations 1.5.11 to 1.5.14 and research recommendations in the NICE guideline

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1.1 Review question: In people with gout (including people with gout and chronic kidney disease), what is the clinical and cost effectiveness of colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy?

1.1.1 Introduction

Long-term urate-lowering therapy (ULT) for gout aims to lower serum urate levels and prevent gout flares. However, ULT initiation and dose escalation commonly triggers gout flares in the first few months. ULT-induced flares are often perceived as indicating that ULT is not working, causing ULT to be stopped, and hence can contribute to poor uptake of and adherence to ULT. Prophylactic anti-inflammatory medications are often co-prescribed with ULT to prevent such flares.

The most commonly prescribed interventions to prevent flares when initiating ULT is colchicine. In people in whom colchicine is not tolerated, contraindicated or ineffective, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids can be used. Interleukin-1 inhibitors are rarely used for prophylaxis in clinical practice, owing to their expense and the wide availability of other treatments. This evidence review will determine the clinical and cost effectiveness of anti-inflammatory medication to prevent gout flares when initiating ULT.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (18 years and older) with gout about to start use of urate-lowering therapies or titration of urate-lowering therapies (initial and subsequent) Urate-lowering therapies: • Xanthine oxidase inhibitor - allopurinol and febuxostat • Uricosuric – fenofibrate, losartan and vitamin C • Uricase - rasburicase Strata: • People with chronic kidney disease (stage 3) • People with chronic kidney disease (stages 4-5) • People without chronic kidney disease or people with CKD stages 1-2 • Mixed population (people with CKD and people without CKD) Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout

Intervention(s)	• NSAIDs
	  ○ Celecoxib
	  ○ Diclofenac sodium
	  ○ Etoricoxib
	  ○ Ibuprofen
	  ○ Indomethacin
	  ○ Meloxicam
	  ○ Naproxen
	• Colchicine
	• Corticosteroids
	  ○ Methylprednisolone
	  ○ Prednisolone
	  ○ Triamcinolone
	• IL-1 inhibitors
	  ○ Anakinra
	  ○ Canakinumab
	• Combine all doses (doses much higher than standard doses will be excluded)
	• Within drug class comparisons will not be made, e.g. IL-1 inhibitors will be combined in analyses

Comparison(s)	• Compared to each other • No prophylaxis/treatment • Placebo
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/ joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • serum urate levels • adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) • admission (hospital and A&E/urgent care) • discontinuation of ULT Timepoints: short (up to two weeks), medium (two to six weeks) and long (> six weeks) term
Study design	RCT Systematic reviews of RCTs

If insufficient RCT evidence is available, search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders:

- Age
- Gender
- Previous treatment (non-pharmacological and pharmacological use)

Published NMAs will be considered for inclusion.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised trials comparing the clinical effectiveness of colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of flares during the initiation or titration of urate-lowering therapy for people with gout.

Three randomised controlled studies were included in the review [2, 13, 23] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

The three included studies evaluated pharmacological interventions in people with gout who do not have chronic kidney disease. Two studies evaluated the use of colchicine for preventing gout flares during the initiation or titration of urate-lowering therapies. The third study evaluated the use of canakinumab (versus colchicine) for preventing gout flares during the initiation or titration of urate-lowering therapies.

Non-randomised studies were searched for, but none were found that adequately adjusted for key confounders and therefore were excluded from the review.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Borstad 20042 RCT	Intervention (n=21): Allopurinol was initiated at 100 mg orally once a day. The dose of allopurinol was increased in 100 mg increments until a serum urate level of <6.5 mg/dl was attained. Participants received colchicine 0.6 mg orally twice a day. Colchicine was continued for at least 3 months after reaching target serum urate level (average duration = 5.21 months). Comparison (n=22): Allopurinol was initiated at 100 mg orally once a day. The dose of allopurinol was increased in 100 mg increments until a serum urate level of <6.5 mg/dl was attained. Participants received placebo orally twice a day. Placebo was continued for at least 3 months after reaching target serum urate level (average duration = 5.18 months).	n=43 People with crystal-proven gouty arthritis and frequent attacks of gout at least 3 attacks per year Age (mean): intervention - 63.5 years; comparison - 62.5 years Gender (male %): intervention - 81%; comparison - 91% Chronic kidney disease (chronic renal insufficiency, defined as a creatinine clearance of 20–50 ml/min): intervention – 14%; comparison – 9% USA	Frequency of flares (people experiencing one flare) at 6 months Frequency of flares (people experiencing >one flare) at 6 months Adverse events (gastrointestinal) at 6 months	Severity of flares measured using VAS – doesn't report how "severity" was defined – not extracted
Schlesinger 2011 13 RCT	Intervention (n=108): Allopurinol treatment (100–300 mg) was initiated at baseline	n=216	Frequency of flares (people experiencing ≥1 flares) at 4 months	Dosing study – 100mg and 200mg arms combined

Study	Intervention and comparison	Population	Outcomes	Comments
	or within 1 month before baseline and was administered to all randomised patients once daily for 24 weeks receive a single dose of canakinumab 100 mg and 200 mg. Comparison (n=108) Allopurinol treatment (100–300mg) was initiated at baseline or within 1 month before baseline and was administered to all randomised patients once daily for 24 weeks. Daily oral doses of colchicine 0.5 mg given for 16 weeks.	People with gouty arthritis at least two gouty arthritis flares in the previous year Age (mean): intervention – 52.0 years; comparison – 52.4 years Gender (male %): intervention - 90.8%; comparison – 93.5% Chronic kidney disease (low creatinine clearance): intervention – 7.4%; comparison – 5.6% Multicentre, 16 countries: Argentina, Belgium, Columbia, Czech Republic, Germany, Guatemala, Hungary, Poland, Portugal, Russia, Singapore, Slovakia, South Africa, Spain, Taiwan, Turkey, UK and USA	Adverse events (gastrointestinal) at 6 months	Other doses (not relevant): 25mg, 50mg, 300mg or 4-weekly intervals (50mg on day 1 and at week 4, and 25mg at weeks 8 and 12) Creatinine clearance determined using Cockcroft-Gault Equation
Yamanaka 2018 23: FORTUNE-1 trial RCT	Intervention (n=102) Febuxostat 40 mg/day from the start of the study for total duration of 24 weeks, with concomitant colchicine 0.5 mg/day for 12 weeks. Comparison (n=52) Febuxostat 40 mg/day from the start of the study for total duration of 24 weeks.	n=154 (n=255 for all randomised arms of the trial) People with gout who had at least one episode of gouty arthritis in the previous year Age (mean): intervention – 47.6 years; comparison – 46.4 years Gender (male %): 100% in all groups	Frequency of flares (patients who needed analgesic treatment with NSAIDs or adrenal corticosteroids to manage gout symptoms) at 3 months Adverse events (cardiovascular) at 6 months Adverse events (gastrointestinal) at 6 months	Percentage of patients whose serum urate decreased to 6.0mg/dL reported in Figure 1. Raw data not reported. Other arm of trial: stepwise dose increase of febuxostat from 10mg/day (4 weeks), 20mg/day (4 weeks) and 40mg/day

Study	Intervention and comparison	Population	Outcomes	Comments
		Chronic kidney disease: 0% (patients with serum creatinine level of 2.0 mg/dL or higher excluded from study) Japan	Adverse events (renal) at 6 months	

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Colchicine (colchicine plus febuxostat 40mg) versus no treatment (febuxostat 40mg)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with Colchicine
Frequency of flares at 3 months	145 (1 RCT)	MODERATE[a]	RR 0.53 (0.30 to 0.92)	360 per 1,000	169 fewer per 1,000 (252 fewer to 29 fewer)
Adverse events (cardiovascular) at 6 months	145 (1 RCT)	MODERATE[a]	RD 0 (0.03 to 0.03)[b]	0 per 1,000	0 fewer per 1,000 (30 fewer to 30 more)[b]
Adverse events (gastrointestinal) at 6 months	145 (1 RCT)	LOW[a]	Peto OR 4.60 (0.07 to 284.25)	0 per 1,000	10 more per 1,000 (30 fewer to 50 more)[c]
Adverse events (renal) at 6 months	145 (1 RCT)	LOW[a]	Peto OR 4.60 (0.07 to 284.25)	0 per 1,000	10 more per 1,000 (30 fewer to 50 more)[c]

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

b Zero events in both arms. Risk difference calculated in Review Manager.

c Absolute effects calculated using risk difference due to zero events in one of the arms.

Table 4: Clinical evidence summary: Colchicine (colchicine plus allopurinol) versus placebo (placebo plus allopurinol)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with Colchicine
Frequency of flares (people experiencing 1 flare) at 6 months	43 (1 RCT)	LOW[a,b]	RR 0.43 (0.23 to 0.82)	773 per 1,000	440 fewer per 1,000 (595 fewer to 139 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with Colchicine
Frequency of flares (people experiencing >1 flare) at 6 months	43 (1 RCT)	MODERATE[a]	RR 0.22 (0.08 to 0.67)	636 per 1,000	496 fewer per 1,000 (585 fewer to 210 fewer)
Adverse events (gastrointestinal) at 6 months	43 (1 RCT)	LOW[a,b]	RR 8.38 (1.14 to 61.37)	45 per 1,000	335 more per 1,000 (6 more to 1,000 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Tale 5: Clinical evidence summary: Canakinumab (canakinumab plus allopurinol) versus colchicine (colchicine versus allopurinol)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with Colchicine
Frequency of flares (people experiencing ≥1 flares) at 4 months	216 (1 RCT)	MODERATE[a]	RR 0.38 (0.23 to 0.60)	444 per 1,000	276 fewer per 1,000 (342 fewer to 178 fewer)
Adverse events (gastrointestinal) at 6 months	216 (1 RCT)	VERY LOW[a,b]	RR 2.67 (0.73 to 9.78)	28 per 1,000	46 more per 1,000 (8 fewer to 244 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but excluded due to a combination of limited applicability and methodological limitations[12]. This study is listed in Appendix J, with reasons for exclusion given.

1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 6: UK cost of NSAIDs for people without CKD

Drug	Cost per unit	Daily dose	Cost per day
Celecoxib 100mg capsules	£0.03	200mg – 400mg	£0.07 - £0.13
Diclofenac sodium 50mg gastro-resistant tablets / Misoprostol 200microgram tablets	£0.20	150mg daily	£0.60
Diclofenac sodium 50mg gastro-resistant tablets	£0.05		£0.15
Etoricoxib 60mg tablets	£0.10	120mg daily	£0.20
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21
Ibuprofen 600mg tablets	£0.06	1.8g daily	£0.17
Indomethacin 50mg capsules	£0.06	150mg – 200mg daily	£0.18 - £0.24
Meloxicam 15mg orodispersible tablets sugar free	£0.85	7.5mg – 15mg daily	£0.85
Meloxicam 15mg tablets	£0.16		£0.16
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85		£0.85
Meloxicam 7.5mg tablets	£0.11		£0.11
Naproxen 250mg effervescent tablets sugar free	£2.89	750mg – 1500mg daily	£8.66
Naproxen 250mg gastro-resistant tablets	£0.14		£0.41
Naproxen 250mg tablets	£0.05		£0.16
Naproxen 250mg/5ml oral suspension	£0.45		£1.35
Naproxen 500mg gastro-resistant tablets	£0.17		£0.51
Naproxen 500mg tablets	£0.06		£0.19

Source:
British National Formulary, Accessed October 2021[1]

Table 7: UK cost of NSAIDs for people with CKD stage 3

Drug	Cost per unit	Daily dose	Cost per day
Celecoxib 100mg capsules	£0.03	100mg – 400mg	£0.03 - £0.13
Diclofenac sodium 25mg gastro-resistant tablets	£0.06	75 – 150mg daily	£0.18
Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets	£0.26		£0.79
Diclofenac sodium 75mg gastro-resistant modified-release capsules	£0.14		£0.43
Diclofenac sodium 75mg modified-release capsules	£0.20		£0.61
Diclofenac sodium 75mg modified-release tablets	£0.31		£0.94
Etoricoxib 60mg tablets	£0.10	60mg – 120mg daily	£0.10 – £0.20
Etoricoxib 90mg tablets	£0.09	90mg daily	£0.09
Ibuprofen 200mg tablets	£0.04	600mg daily	£0.15
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21
Ibuprofen 600mg tablets	£0.06	1.8g daily	£0.17
Indomethacin 50mg capsules	£0.06	150mg – 200mg daily	£0.18 - £0.24
Meloxicam 15mg orodispersible tablets sugar free	£0.85	7.5mg – 15mg daily	£0.85
Meloxicam 15mg tablets	£0.16		£0.16
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85		£0.85
Meloxicam 7.5mg tablets	£0.11		£0.11
Naproxen 250mg effervescent tablets sugar free	£2.89	500mg – 1000mg daily	£5.78 – £11.56
Naproxen 250mg gastro-resistant tablets	£0.08		£0.16 – £0.32
Naproxen 250mg tablets	£0.05		£0.10 – £0.20
Naproxen 250mg/5ml oral suspension	£0.45		£0.90 – £1.80
Naproxen 500mg gastro-resistant tablets	£0.17		£0.17 - £0.34
Naproxen 500mg tablets	£0.06		£0.06 - £0.12

Source:
British National Formulary, Accessed October 2021[1]

Table 8: UK cost of NSAIDs for people with CKD stage 4-5

Drug	Cost per unit	Daily dose	Cost per day
Celecoxib 100mg capsules	£0.03	100mg – 200mg	£0.03 - £0.06
Diclofenac sodium 25mg gastro-resistant tablets	£0.06	75mg daily	£0.18
Etoricoxib 30mg tablets	£0.22	30mg daily	£0.22
Etoricoxib 60mg tablets	£0.10	60mg daily	£0.10
Ibuprofen			
Ibuprofen 200mg tablets	£0.04	600mg daily	£0.15
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21
Indomethacin 25mg capsules	£0.05	75mg – 100mg daily	£0.15 - £0.20
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85	7.5mg daily	£0.85
Meloxicam 7.5mg tablets	£0.11		£0.11
Naproxen 250mg effervescent tablets sugar free	£2.89	250mg – 750mg daily	£2.89 – £8.67
Naproxen 250mg gastro-resistant tablets	£0.08		£0.08 – £0.24
Naproxen 250mg tablets	£0.05		£0.05 – £0.15
Naproxen 250mg/5ml oral suspension	£0.45		£0.45 – £1.35
Naproxen 500mg gastro-resistant tablets	£0.17		£0.17
Naproxen 500mg tablets	£0.06		£0.06

Source:
British National Formulary, Accessed October 2021[1]

Table 9: UK cost of Colchicine

Drug	Cost per unit	Daily dose	Cost per day
Colchicine 500microgram tablets	£0.05	1mg – 2mg daily	£0.10 - £0.20

Source: NHS Drug Tariff, Accessed October 2021[10]

Table 10: UK cost of Corticosteroids

Drug	Cost per unit	Dosage
Methylprednisolone		
Methylprednisolone 40mg/1ml / Lidocaine 10mg/1ml (1%) suspension for injection vials	£3.94	1 injection on initiation or titration of ULT

Drug	Cost per unit	Dosage
Methylprednisolone 80mg/2ml / Lidocaine 20mg/2ml (1%) suspension for injection vials	£7.06	1 injection on initiation or titration of ULT
Methylprednisolone acetate 120mg/3ml suspension for injection vials	£8.96	1 injection on initiation or titration of ULT
Methylprednisolone acetate 40mg/1ml suspension for injection vials	£3.44	1 injection on initiation or titration of ULT
Methylprednisolone acetate 80mg/2ml suspension for injection vials	£6.18	1 injection on initiation or titration of ULT
Prednisolone		
Prednisolone 2.5mg tablets	£0.13	5mg – 7.5mg daily
Prednisolone 5mg tablets	£0.03	5mg – 7.5mg daily
Triamcinolone		
Triamcinolone acetonide 10mg/1ml suspension for injection ampoules	£0.89	1 injection on initiation or titration of ULT
Triamcinolone acetonide 40mg/1ml suspension for injection vials	£1.49	1 injection on initiation or titration of ULT
Triamcinolone acetonide 50mg/5ml suspension for injection vials	£3.63	1 injection on initiation or titration of ULT
Triamcinolone hexacetonide 20 mg/1ml suspension for injection ampules	£12.00	1 injection on initiation or titration of ULT

Source: NHS Drug Tariff, Accessed October 2021[10]

Table 11: UK cost of proton pump inhibitors (PPI's)

Drug	Cost per unit	Dosage
Omeprazole		
Omeprazole 10mg tablets	£0.33	1 tablet per day
Omeprazole 20mg tablets	£0.49	1 tablet per day
Omeprazole 40mg tablets	£0.98	1 tablet per day
Esomeprazole		
Esomeprazole 20mg tablets	£0.15	1 tablet per day
Esomeprazole 40mg tablets	£0.15	1 tablet per day
Lansoprazole		
Lansoprazole 15mg tablets	£0.13	1 tablet per day
Lansoprazole 30mg tablets	£0.18	1 tablet per day
Rabeprazole		
Rabeprazole 10mg tablets	£0.05	1 tablet per day
Rabeprazole 20mg tablets	£0.06	1 tablet per day
Pantoprazole		
Pantoprazole 20mg tablets	£0.06	1 tablet per day
Pantoprazole 40mg tablets	£0.06	1 tablet per day

Source: British National Formulary, Accessed October 2021[1]
Note: PPI's are a gastro-resistant tablet which can be prescribed in conjunction with NSAIDs and oral corticosteroids.

Table 12: UK cost of IL-1 Inhibitors

Drug	Cost per unit	Dosage
Anakinra		
Anakinra 100mg /0.67ml solution for injection pre-filled syringes	£26.23	Daily injections on initiation or titration of ULT[(a)]
Canakinumab		
Canakinumab 150mg per 1ml solution for injection vials	£9,928	1 injection on initiation or titration of ULT

Source: British National Formulary, Accessed October 2021[1]

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered the following outcomes as important for decision-making: health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, frequency of flares, patient global assessment of treatment success, serum urate levels, adverse events (cardiovascular, renal and gastrointestinal), admission (hospital and A&E/urgent care) and discontinuation of ULT. As the focus of the question is drug intervention to prevent flares when starting or titrating ULT the committee agreed frequency of flares outcome was of particular interest.

The committee decided to combine joint swelling and joint inflammation as they agreed that these outcomes are synonymous for people with gout. The committee also agreed to categorise timepoints reported in the included studies by short-term (up to two weeks), medium-term (two to six weeks) and long-term (more than six weeks).

Outcome data was available only for frequency of flares and adverse events (cardiovascular, renal and gastrointestinal). Outcome data was reported for long-term outcomes only (3-6 months).

1.1.11.2 The quality of the evidence

Three randomised controlled trials (RCTs) evaluating pharmacological prophylaxis in people with gout when initiating ULTs were included in this review. None of the studies evaluated pharmacological interventions in people with chronic kidney disease.

The three studies evaluated three comparisons; all these comparisons included a colchicine arm. Colchicine (plus febuxostat) was compared to no treatment (febuxostat only), placebo and canakinumab (an IL-1 inhibitor).

For colchicine (plus febuxostat) compared to no treatment (febuxostat only) frequency of flares and adverse events (gastrointestinal, renal and cardiovascular) were reported. The quality of this evidence ranged from low to moderate due to imprecision. The committee noted that this study used a 40mg dose of febuxostat but in the UK licensed doses are 80mg and 120mg, although the committee reported that in clinical practice a person might sometimes be started on 40mg or 80mg. This may be the case where people have moderate

hepatic impairment or where there is a high risk of gout flares during initiation of therapy. As a lower dose of ULT was used precipitation of flares may be less likely and the study underestimated the benefit of colchicine as prophylaxis. However, in clinical practice a slow increase in ULT may also result in fewer flares initially. The committee noted the uncertainty in the evidence results.

For the comparison of canakinumab versus colchicine, frequency of flares (people experiencing ≥1 flares) and adverse events (gastrointestinal) were reported. The quality of this evidence ranged from very low to moderate due to risk of bias (possible selection bias, as the sequence generation and allocation concealment were not detailed) and imprecision. For the comparison of colchicine versus placebo, frequency of flares (people experiencing 1 flare and people experiencing >1 flares) and adverse events (gastrointestinal) were reported in a small study (n=43). The quality of this evidence ranged from low to moderate due to risk of bias (possible selection bias, as the sequence generation and allocation concealment were not stated) and imprecision.

Overall, the amount of evidence for Colchicine was low (based on three small RCTs) and the evidence had limitations. Furthermore, the studies were all followed-up between 3-6 months, and therefore showed indirectness for the initiation of therapy.

No evidence was found for NSAID or corticosteroid pharmacological prophylaxis.

1.1.11.3 Benefits and harms

The evidence showed a clinical benefit of colchicine when compared with placebo and no treatment for reducing the frequency of gout flares when initiating ULTs. When colchicine was compared with placebo there were gastrointestinal adverse events indicating clinical harm, although there was no clinical difference in terms of adverse events (gastrointestinal, renal and cardiovascular) when colchicine was compared to no treatment. The committee agreed gastrointestinal adverse events are common in clinical practice in people taking colchicine.

There were no studies evaluating outcomes during the initial titration of ULT e.g. less than 3 months. However, evidence review F on initiation of ULT confirms flares early in initiation and that the frequency of flares reduces as urate levels are lowered. This evidence although indirect is in keeping with the committee's experience of a risk of flares following the up-titration of ULT. Flares are painful and distressing and treatments to reduce flares is beneficial for the person with gout. The committee drew upon the indirect evidence within review F and therefore did not consider a research recommendation was of high priority. The committee decided not to search for cohort studies, as RCTs are more robust, and therefore preferential for a question about the effectiveness of drug treatments.

The committee agreed that the available evidence demonstrated colchicine resulted in a reduction in frequency of flares at 3 and 6 months, and decided to recommend colchicine to people with gout who have chosen to take medication to prevent flares during the initiation and titration of ULT.

The committee's experience is that patients commonly attribute flares to ULT and stop ULT as a result. Prophylaxis therefore also improves adherence to ULT by preventing ULT-induced flares. Given the importance of ULT for people with gout the committee considered it important that people are supported to persevere with the initiation of this treatment. The committee agreed a strong recommendation for people to be offered and informed about treatments to reduce flares during this important time.

The committee reported that current practice is to prescribe colchicine or NSAIDs when pharmacological prophylaxis is offered to people with gout. A recommendation to prescribe colchicine is therefore not a change in practice.

However, colchicine may not be appropriate for some individuals due to tolerability, patient preferences (e.g. past experiences with a particular intervention), co-morbidities (e.g. chronic kidney disease) and co-prescription (e.g. statins). In cases where colchicine is not tolerated, contraindicated or ineffective, use of NSAIDs or corticosteroids should be considered. The committee noted that in their experience NSAIDs are well tolerated in people with gout and can be easily accessed over the counter. Although no evidence had been identified for either NSAIDS or corticosteroids the committee agreed an alternative treatment option needs to be available to manage a person's pain which can be severe. The committee therefore decided to make a consensus recommendation to consider either an NSAID or corticosteroid if colchicine was not suitable during initiation of ULT. The committee also discussed adding a proton pump inhibitor for people prescribed either of these drugs as they might be used over several weeks or months, taking into account a person's risk factors for adverse events.

Because NSAID and corticosteroid drugs are widely prescribed in current practice, the committee agreed it was important to learn more about their clinical effectiveness in this situation to inform and extend choice of prophylactic interventions. The committee therefore agreed randomised controlled trials are required and made a research recommendation on the clinical and cost effectiveness of these drugs for the prevention of flares during initiation or titration of ULT.

The evidence review included one RCT comparing colchicine and canakinumab which showed clinical benefit for canakinumab for frequency of flares. IL-1 inhibitors are rarely prescribed to people with gout. Use of IL-1 inhibitors requires close monitoring and are currently only prescribed in secondary care for individuals with gout that is more severe. As most people with gout are managed in primary care the use of IL-1 inhibitors would require referral to rheumatology services which would add to cost and resource use. The committee weighed up these considerations alongside the evidence and concluded there is insufficient evidence to recommend IL-1 inhibitors over or instead of other treatments currently used routinely within clinical practice unless all of the other drug options are unsuitable.

The committee noted that some people may not want prophylactic treatment as they are already taking other pharmacological medications, they consider their condition not severe enough or they have had few flares. The committee discussed that it is important that healthcare professionals have a conversation with patients about the benefits and risks of using pharmacological interventions to prevent gout flares when initiating ULT and made recommendations for this discussion. Some of the discussion points to have with people could include the chance of gout flares without prophylaxis, noting one of the included studies reported that 3 in 4 participants had a flare after ULT initiation and that flares reduce in frequency when the target serum urate level has been reached. Healthcare professionals should explain the risk of gastrointestinal adverse events, so patients are prepared for this.

The BNF suggests colchicine 500 micrograms twice daily for short-term prophylaxis. In people with CKD, lower doses of Colchicine should be given and NSAIDs avoided. If there are any concerns around drug use and dosages for people with CKD, the committee suggested that GPs speak to the local renal team.

1.1.11.4 Cost effectiveness and resource use

No economic evaluations were identified for this review. Unit costs were presented to the committee to aid committee consideration of cost effectiveness.

The clinical evidence presented indicated a clinical benefit for colchicine; reducing the frequency of flares compared to no treatment and placebo. The committee noted that typically patients will receive prophylaxis for every month they are up titrated on their ULT until they achieve target serum urate levels. For example, someone achieving target serum urate levels on 400mg of allopurinol will receive 4 months of prophylaxis. The cost of one month of prophylaxis assuming 1-2mg of colchicine is prescribed per day is £3.04 - £6.08.

It was discussed that current practice varies with respect to offering prophylaxis for the prevention of gout flares. The committee noted that the benefits of prophylaxis should be discussed with all patients initiating and up titrating ULT, however the committee acknowledged that some people may choose not to receive prophylaxis because they are already on a large number of medications or because they decide the potential side effects outweighs the benefits of reduced flare frequency. The committee concluded that colchicine should be offered for those people who decide to use prophylaxis when initiating and up titrating ULT due to the low costs and clinical effectiveness associated with offering prophylaxis. This recommendation is not expected to result in a direct substantial resource impact. However, as a result of the recommendations made in this guideline more people are expected to be prescribed ULT and therefore this may also increase the number of people receiving prophylaxis.

There was no clinical evidence identified for the use of NSAIDs and corticosteroids for preventing gout flares. The committee acknowledged that when colchicine is not tolerated, NSAIDs and corticosteroids (specifically oral prednisolone) are suitable alternatives. The daily cost of NSAIDs ranges from £0.07 – £8.66 per day and the daily cost oral prednisolone is £0.03 – £0.39 per day. The monthly cost for NSAIDS and oral prednisolone for prophylaxis are £2.13 – £263.41 and £0.89 – £11.57 respectively. The committee noted that the large range observed for the cost of NSAIDs was largely driven by the cost of effervescent tablets for naproxen, which small numbers of people with gout would receive. Excluding these costs, the cost ranges from £0.07 - £1.806. Subsequently resulting in a monthly cost of £2.13 – £54.93.

The committee also discussed the use IL-1 inhibitors for prophylaxis and noted less than 1% of gout patients would be prescribed an IL-1 inhibitor. In general, the committee noted not only the high costs of IL-1 inhibitors, but also the additional costs associated, with respect to monitoring and costs associated with higher risk of infections, due to IL-1 inhibitors being immunosuppressive, compared to NSAIDs, colchicine, and corticosteroids. The committee also discussed the clinical evidence presented and acknowledged that although canakinumab was more effective than colchicine at reducing the frequency of flares (by 276 per 1,000 as defined by people experiencing ≥ 1 flare at 4 months), the benefits of reduced flare frequency could not be offset by the substantial cost differential (£9,928 per injection when initiating or up titrating ULT compared to £3.04 - £6.08 for one month of colchicine). Therefore, the committee concluded that canakinumab for the prevention of gout flares when initiating and titrating ULT would very unlikely be a cost-effective use of NHS resources if routinely prescribed to all people with gout.

The committee also discussed the use of anakinra, but noted no clinical evidence was found for this. In general, the committee discussed that anakinra would be prescribed in the form self-administered daily injections for the duration of initiation and up titration of ULT. The monthly cost of anakinra is £797.83. In addition, the committee noted that in clinical practice IL-1 inhibitors can only be prescribed in secondary care, and so may not be appropriate to use when patients are initiating or titrating ULT.

Overall due to the uncertainty surrounding the cost effectiveness of IL-1 inhibitors, the committee made a do not offer recommendation for the use of IL-1 inhibitors when initiating or titrating ULT for the prevention of gout flares unless colchicine, NSAIDs or corticosteroids are contraindicated, not tolerated, or ineffective. The committee also noted that for people where colchicine, NSAIDs or corticosteroids are contraindicated, not tolerated, or ineffective an option of ‘no prophylaxis’ is also appropriate. In addition, the committee noted that although anakinra is significantly cheaper than canakinumab, they concluded they could not make a recommendation for the use of anakinra as a first-line IL-1 inhibitor due to the lack of clinical evidence. However, the committee did discuss the efficacy of these drugs observed in clinical practice and concluded there were no significant differences in the efficacy of anakinra and canakinumab when used as prophylaxis. This recommendation is not expected

to result in a substantial resource impact as it is reflective of current practice in England. That is, approximately 1% of gout patients would receive IL-1 inhibitors.

Of note, the recommendations made as part of this guideline will likely result in an uptake of ULT and therefore more people may be prescribed prophylaxis.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.11 to 1.5.14 and the research recommendation on the clinical and cost effectiveness of NSAIDs or corticosteroids for preventing gout flares during the initiation or titration of urate-lowering therapy.

1.1.13 References

1. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://bnf.nice.org.uk/ Last accessed: September 2021.

2. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. Journal of Rheumatology. 2004; 31(12):2429-2432

3. Eminaga F, La-Crette J, Jones A, Abhishek A. Does the initiation of urate-lowering treatment during an acute gout attack prolong the current episode and precipitate recurrent attacks: a systematic literature review. Rheumatology International. 2016; 36(12):1747-1752

4. Feng X, Li Y, Gao W. Prophylaxis on gout flares after the initiation of urate-lowering therapy: a retrospective research. International Journal of Clinical and Experimental Medicine. 2015; 8(11):21460-21465

5. Karimzadeh H, Nazari J, Mottaghi P, Kabiri P. Different duration of colchicine for preventing recurrence of gouty arthritis. Journal of Research in Medical Sciences. 2006; 11(2):104-107

6. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology. 2014; 53(11):1920-1926

7. Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology. 2013; 52(7):1285-1292

8. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

9. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

10. NHS Business Services Authority. NHS electronic drug tariff: October 2020. 2020. Available from: http://www.nhsbsa.nhs.uk/PrescriptionServices/4940.aspx Last accessed: 30/10/2021.

11. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis and Rheumatism. 1974; 17(5):609-614

12. Robinson PC, Dalbeth N, Donovan P. Colchicine Prophylaxis of Gout Flares When Commencing Allopurinol is Very Cost Effective. Arthritis Care and Research. 2020; 17:17

13. Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Annals of the Rheumatic Diseases. 2011; 70(7):1264-1271

14. Schumacher HR, Jr., Sundy JS, Terkeltaub R, Knapp HR, Mellis SJ, Stahl N et al. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatism. 2012; 64(3):876-884

15. Seth R, Kydd AS, Falzon L, Bombardier C, van der Heijde DM, Edwards CJ. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. Journal of Rheumatology - Supplement. 2014; 92:42-47

16. Shiozawa A, Szabo SM, Bolzani A, Cheung A, Choi HK. Serum uric acid and the risk of incident and recurrent gout: A systematic review. Journal of Rheumatology. 2017; 44(3):388-396

17. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. Current Opinion in Rheumatology. 2011; 23(2):192-202

18. Stewart S, Tallon A, Taylor WJ, Gaffo A, Dalbeth N. How flare prevention outcomes are reported in gout studies: A systematic review and content analysis of randomized controlled trials. Seminars in Arthritis and Rheumatism. 2020; 50(2):303-313

19. Sundy JS, Schumacher HR, Kivitz A, Weinstein SP, Wu R, King-Davis S et al. Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: results of RESURGE, a phase III, international safety study. Journal of Rheumatology. 2014; 41(8):1703-1711

20. Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout - A systematic review. Rheumatology. 2006; 45(11):1422-1431

21. Vinik O, Wechalekar MD, Falzon L, Buchbinder R, van der Heijde DM, Bombardier C. Treatment of asymptomatic hyperuricemia for the prevention of gouty arthritis, renal disease, and cardiovascular events: a systematic literature review. Journal of Rheumatology - Supplement. 2014; 92:70-74

22. Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clinical Therapeutics. 2010; 32(14):2386-2397

23. Yamanaka H, Tamaki S, Ide Y, Kim H, Inoue K, Sugimoto M et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Annals of the Rheumatic Diseases. 2018; 77(2):270-276

24. Yu J, Qiu Q, Liang L, Yang X, Xu H. Prophylaxis of acute flares when initiating febuxostat for chronic gouty arthritis in a real-world clinical setting. Modern Rheumatology. 2018; 28(2):339-344

Appendices

Appendix A – Review protocols

Review protocol for colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	Colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy
2.	Review question	In people with gout (including people with gout and chronic kidney disease), what is the clinical and cost effectiveness of colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy?
3.	Objective	To determine which pharmacological therapy (e.g. colchicine, NSAIDs, corticosteroids and/or IL-1 inhibitors) is the most clinically and cost-effective for the prevention of gout flares during the initiation or titration of urate-lowering therapy.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Gout (including people with gout and chronic kidney disease)
6.	Population	Inclusion: Adults (18 years and older) with gout about to start use of urate-lowering therapies or titration of urate-lowering therapies (initial and subsequent)

		Strata: • People with chronic kidney disease (stage 3) • People with chronic kidney disease (stages 4-5) • People without chronic kidney disease or people with CKD stages 1-2 • Mixed population (people with CKD and people without CKD) Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout.
7.	Intervention/Exposure/Test	• NSAIDs (commonly used in clinical practice in the UK) • Celecoxib • Diclofenac sodium • Etoricoxib • Ibuprofen • Indomethacin • Meloxicam • Naproxen • Colchicine • Corticosteroids (commonly used in clinical practice in the UK) • Methylprednisolone • Prednisolone (oral) • Triamcinolone • IL-1 inhibitors (commonly used in clinical practice in the UK) • Anakinra • Canakinumab Combine all doses (doses much higher than standard doses will be excluded) Within drug class comparisons will not be made, e.g. IL-1 inhibitors will be combined in analyses Not including combinations of interventions
8.	Comparator/Reference standard/Confounding factors	• Compared to each other • No prophylaxis/treatment • Placebo
9.	Types of study to be included	RCT Systematic reviews of RCTs

		If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders: • Age • Gender • Previous treatment (non-pharmacological and pharmacological use) Published NMAs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	People with gout who use urate-lowering therapy to manage their condition can have gout flares. Pharmacological interventions (e.g. NSAIDS, colchicine, corticosteroids and IL-1 inhibitors) can be used to prevent gout flares, these are sometimes also offered at the initiation of urate-lowering therapies.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • serum urate levels • adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) • admission (hospital and A&E) • discontinuation of ULT Timepoints: short (up to two weeks), medium (two to six weeks) and long (> six weeks) term
13.	Secondary outcomes (important outcomes)	N/A
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the

		searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Evibase will be used for data extraction. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. If sufficient data is available and it is methodologically appropriate, network meta-analysis (NMA) will conducted. for the following outcomes.

		• GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.		
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Type of urate lowering therapySetting (primary and secondary) • Choice of prophylactic drug (drugs within the class, based on the intervention arm only • Initial vs subsequent titration of ULT		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]		
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
23.		Review stage	Started	Completed

	Stage of review at time of this submission	Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail gout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]		
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Sedina Lewis [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of		

		interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details	NA	
30.	Reference/URL for published protocol	NA	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]	
32.	Keywords	[Give words or phrases that best describe the review.]	
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[8] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

- In people with gout (including people with gout and chronic kidney disease), what is the clinical and cost effectiveness of colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[9]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 06 July 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 7 of 12 CENTRAL to 2021 Issue 7 of 12	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/

9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	Limit 25 to English language
27.	randomized controlled trial.pt.
28.	controlled clinical trial.pt.
29.	randomi#ed.ti,ab.
30.	placebo.ab.
31.	randomly.ti,ab.
32.	Clinical Trials as topic.sh.
33.	trial.ti.
34.	or/27-33
35.	Meta-Analysis/
36.	exp Meta-Analysis as Topic/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Epidemiologic studies/
47.	Observational study/
48.	exp Cohort studies/
49.	(cohort adj (study or studies or analys* or data)).ti,ab.

50.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
51.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	Controlled Before-After Studies/
53.	Historically Controlled Study/
54.	Interrupted Time Series Analysis/
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control studies/
57.	case control*.ti,ab.
58.	Cross-sectional studies/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/46-59
61.	26 and (34 or 45 or 60)

Embase (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to English language
25.	random*.ti,ab.
26.	factorial*.ti,ab.
27.	(crossover* or cross over*).ti,ab.
28.	((doubl* or singl*) adj blind*).ti,ab.
29.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

30.	crossover procedure/
31.	single blind procedure/
32.	randomized controlled trial/
33.	double blind procedure/
34.	or/25-33
35.	systematic review/
36.	meta-analysis/
37.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
38.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
39.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
40.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41.	(search* adj4 literature).ab.
42.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
43.	cochrane.jw.
44.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
45.	or/35-44
46.	Clinical study/
47.	Observational study/
48.	family study/
49.	longitudinal study/
50.	retrospective study/
51.	prospective study/
52.	cohort analysis/
53.	follow-up/
54.	cohort*.ti,ab.
55.	53 and 54
56.	(cohort adj (study or studies or analys* or data)).ti,ab.
57.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
58.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	exp case control study/
61.	case control*.ti,ab.
62.	cross-sectional study/
63.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
64.	or/46-52,55-63
65.	24 and (34 or 45 or 64)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Gout] explode all trees
#2.	gout*:ti,ab
#3.	toph*:ti,ab

#4.	podagra:ti,ab
#5.	pseudogout:ti,ab
#6.	(or #1-#5)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1946 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 14 June 2021 Quality of Life 1974 – 14 June 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	Uric Acid/
5.	uric acids*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter/

12.	editorial/
13.	news/
14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.

53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.
55.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
56.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
57.	(hui or hui1 or hui2 or hui3).ti,ab.
58.	(health* year* equivalent* or hye or hyes).ti,ab.
59.	discrete choice*.ti,ab.
60.	rosser.ti,ab.
61.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
62.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
63.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
64.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
65.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
66.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
67.	or/48-66
68.	30 and (47 or 67)

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/
5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/

25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/
46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	28 and (42 or 64)

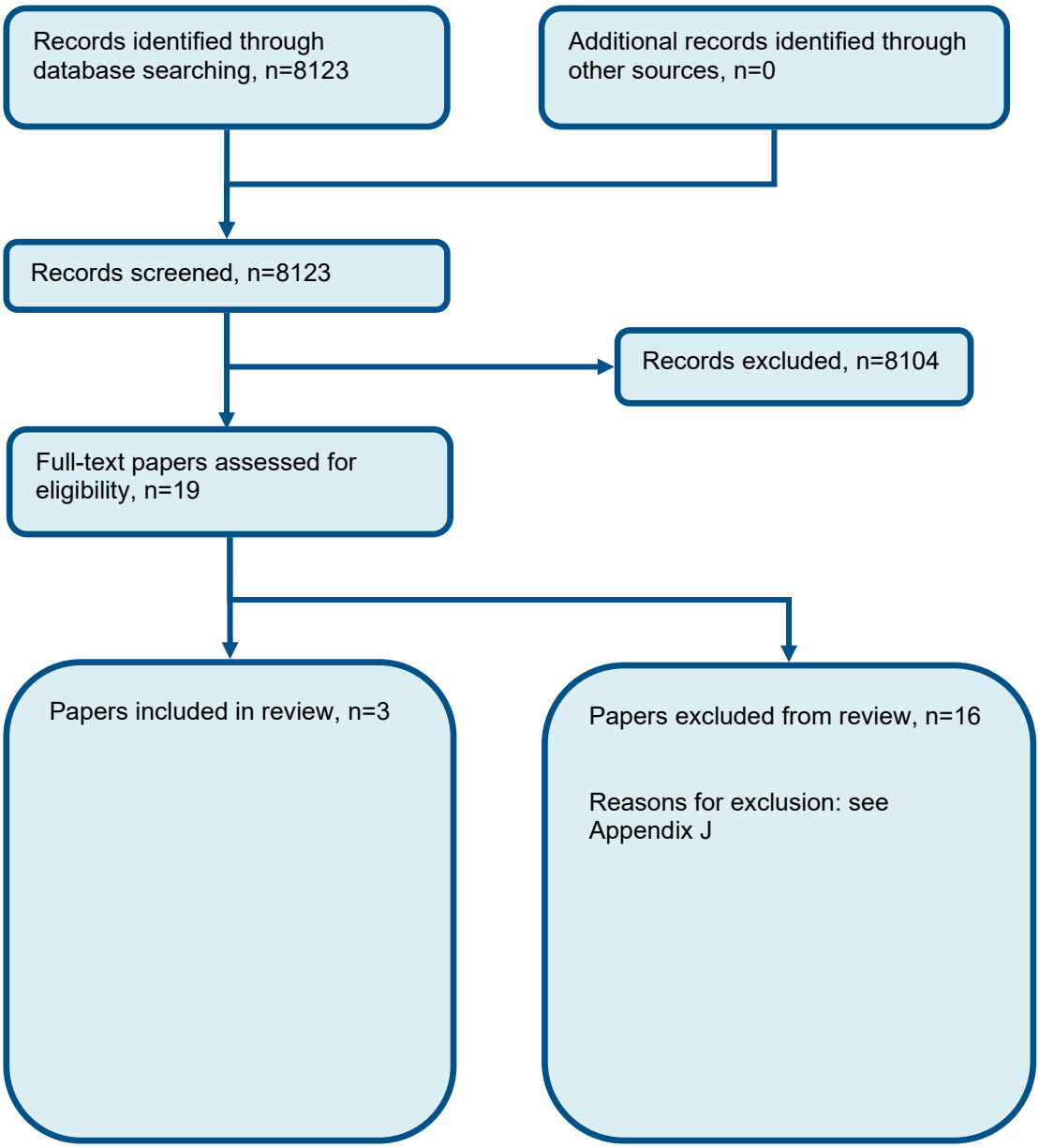
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES

#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES
#5.	(uric acid*)
#6.	((urate near (crystal* or sodium or mono sodium)))
#7.	MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES
#8.	((hyperuric* or hyper uric*))
#9.	(podagra)
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of colchicine, NSAIDs, corticosteroids and IL-1 inhibitors for the prevention of gout flares during the initiation or titration of urate-lowering therapy



Appendix D – Effectiveness evidence

Study	Borstad 2004[2]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=43)
Countries and setting	Conducted in USA; Setting: Rheumatology Department at Wilford Hall Medical Center, Texas, USA
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2: 11.5% of study population had chronic renal insufficiency
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects with crystal-proven gouty arthritis were chosen based on accepted criteria for allopurinol administration: presence of tophi, uric acid overproduction, frequent attacks of gout (≥3 attacks/year), elevated serum urate in the setting of chronic renal insufficiency (CRI), and nephrolithiasis.
Exclusion criteria	Subjects were excluded if they were under 19 years of age, had been given chronic colchicine within the past 3 months, had a history of allergic reaction to allopurinol or colchicine, had severe renal insufficiency (creatinine clearance < 20 ml/min), were female with childbearing potential, or had evidence of active hepatitis.
Recruitment/selection of patients	Recruited from the departments of internal medicine and rheumatology at Wilford Hall USAF Medical Centre, Texas, USA
Age, gender and ethnicity	Age - Mean (SD): 63.0 years (colchicine - 63.5 years; placebo - 62.5 years). Gender (M:F): 37/6 (male %: colchicine - 81%; placebo - 91%). Ethnicity: Caucasian race %: Colchicine - 67%; Placebo - 73%
Further population details	1. Initial vs subsequent titration: Initial titration (No further information provided). 2. Setting: Secondary care (Rheumatology Department in Wilford Hall Medical Centre).

Extra comments	Chronic kidney disease (chronic renal insufficiency, defined as a creatinine clearance of 20–50 ml/min): colchicine – 14%; placebo – 9%
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Colchicine. Participants starting allopurinol were randomised to colchicine 0.6 mg orally twice a day. Colchicine was continued for at least 3 months after reaching target serum urate level of < 6.5 mg/dl. . Duration At least 3 months (average duration = 5.21 months. Concurrent medication/care: Allopurinol was initiated at 100mg orally once a day. The dose of allopurinol was increased in 100mg increments until a serum urate level of < 6.5 mg/dl was attained. Serum urate levels were obtained at baseline, and at 2-3 week intervals. In the setting of chronic renal insufficiency (defined as a creatinine clearance of 20-50 ml/min), the dose was escalated in 50 mg increments. Chronic NSAID were not permitted, but short term NSAID use for acute gout flares was allowed (no details reported about how many participants used NSAID). Acute gout flares were managed in a manner deemed appropriate by individual physicians who enrolled and were following individual subjects. . Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine was administered). 2. Type of ULT: Xanthine oxidase inhibitor (Allopurinol was initiated). (n=22) Intervention 2: No prophylaxis/treatment - Placebo. Participants starting allopurinol were randomised to placebo orally twice a day. Placebo was continued for at least 3 months after reaching target serum urate level of < 6.5 mg/dl. . Duration At least 3 months (average duration = 5.18 months. Concurrent medication/care: Allopurinol was initiated at 100mg orally once a day. The dose of allopurinol was increased in 100mg increments until a serum urate level of < 6.5 mg/dl was attained. Serum urate levels were obtained at baseline, and at 2-3 week intervals. In the setting of chronic renal insufficiency (defined as a creatinine clearance of 20-50 ml/min), the dose was escalated in 50 mg increments. Chronic NSAID were not permitted, but short term NSAID use for acute gout flares was allowed (no details reported about how many participants used NSAID). Acute gout flares were managed in a manner deemed appropriate by individual physicians who enrolled and were following individual subjects. . Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine was administered in the intervention arm). 2. Type of ULT: Xanthine oxidase inhibitor (Allopurinol was initiated).
Funding	Academic or government funding (Research performed under United States Air Force Surgeon General-approved Clinical Investigation No. FWH19970125H)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLCHICINE versus PLACEBO	

Protocol outcome 1: Frequency of flares at long (> six weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: People experiencing one flare at 6 months; Group 1: 7/21, Group 2: 17/22; Comments: Percentages reported - used to calculate the number of events Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for factors including: age, gender, ethnicity and chronic renal insufficiency. But higher diuretic use at baseline in the colchicine group (57% versus 27%); Group 1 Number missing: 3, Reason: 1 subject had a stroke at 3 months, 1 subject discontinued the drug due to subjective muscle weakness at 2.5 months and 1 subject was lost to follow-up after being treated for 3 months; Group 2 Number missing: 4, Reason: 2 withdrawals due to high frequency of flares (at 2 and 3 months), 1 subject withdrew due to inadvertent medication discontinuation after 3 months and 1 subject whose frequent traveling prevented adequate follow-up after 4 months - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: People experiencing > one flare at 6 months; Group 1: 3/21, Group 2: 14/22; Comments: Percentages reported - used to calculate the number of events Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for factors including: age, gender, ethnicity and chronic renal insufficiency. But higher diuretic use at baseline in the colchicine group (57% versus 27%); Group 1 Number missing: 3, Reason: 1 subject had a stroke at 3 months, 1 subject discontinued the drug due to subjective muscle weakness at 2.5 months and 1 subject was lost to follow-up after being treated for 3 months; Group 2 Number missing: 4, Reason: 2 withdrawals due to high frequency of flares (at 2 and 3 months), 1 subject withdrew due to inadvertent medication discontinuation after 3 months and 1 subject whose frequent traveling prevented adequate follow-up after 4 months Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> six weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (gastrointestinal - diarrhoea) at 6 months; Group 1: 8/21, Group 2: 1/22; Comments: Percentages reported - used to calculate the number of events Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Comparable for factors including: age, gender, ethnicity and chronic renal insufficiency. But higher diuretic use at baseline in the colchicine group (57% versus 27%); Group 1 Number missing: 3, Reason: 1 subject had a stroke at 3 months, 1 subject discontinued the drug due to subjective muscle weakness at 2.5 months and 1 subject was lost to follow-up after being treated for 3 months; Group 2 Number missing: 4, Reason: 2 withdrawals due to high frequency of flares (at 2 and 3 months), 1 subject withdrew due to inadvertent medication discontinuation after 3 months and 1 subject whose frequent traveling prevented adequate follow-up after 4 months	
Protocol outcomes not reported by the study	Health-related quality of life at short (up to two weeks); Health-related quality of life at medium (two to six weeks); Health-related quality of life at long (> six weeks); Pain at short (up to two weeks); Pain at medium (two to six weeks); Pain at long (> six weeks); Joint swelling/joint inflammation at short (up to two weeks); Joint swelling/joint inflammation at medium (two to six weeks); Joint swelling/joint inflammation at long (> six weeks); Joint tenderness at short (up to two weeks); Joint tenderness at medium (two to six weeks); Joint tenderness at long (> six weeks); Patient global assessment of treatment success (response to treatment) at short (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium (two to six weeks); Patient global assessment of treatment success (response to treatment) at long (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks); Adverse events –

	cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (two to six weeks); Admissions (hospital & A&E) at short (up to two weeks); Admissions (hospital & A&E) at medium (two to six weeks); Admissions (hospital & A&E) at long (> six weeks); Discontinuation of ULT at medium (two to six weeks); Discontinuation of ULT at long (> six weeks); Discontinuation of ULT at short (up to two weeks); Frequency of flares at short (up to two weeks); Frequency of flares at medium (two to six weeks); Serum urate levels at short (up to two weeks); Serum urate levels at medium (two to six weeks); Serum urate levels at long (> six weeks)

Study	FORTUNE-1 trial: Yamanaka 2018[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=255 (n=154 for the two relevant randomised arms))
Countries and setting	Conducted in Japan; Setting: 24 centres in Japan
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2: Patients with serum creatinine level of 2.0 mg/dL or higher excluded from study
Subgroup analysis within study	Not applicable:
Inclusion criteria	Men with gout who had at least one episode of gouty arthritis within 1 year before study entry, whose serum urate exceeded 7.0 mg/dL (416.39 µmol/L) and who had not received treatment with any urate-lowering drugs for at least 1 month prior to entry. Diagnosis of gout was based on the 1977 criteria.
Exclusion criteria	People experiencing gouty arthritis within 2 weeks before study entry were excluded. Other exclusion criteria were age <20 years, history of allergic reaction to febuxostat, colchicine or NSAIDs, presence of serious comorbidities including serum creatinine level of 2.0 mg/dL or higher and the judgement of the investigator is that the patient was not an appropriate candidate for study participation.
Recruitment/selection of patients	Conducted between August 2013 and February 2015.
Age, gender and ethnicity	Age - Mean (SD): 47.5 years (colchicine - 47.6 years; control – 46.4 years) . Gender (M:F): 100% male in both arms. Ethnicity: Not reported
Further population details	1. Initial vs subsequent titration: Initial titration (Initial titration of febuxostat). 2. Setting: Not stated / Unclear (Not clearly reported).
Extra comments	Other arm of trial: stepwise dose increase of febuxostat from 10 mg/day (4 weeks), 20 mg/day (4 weeks) and 40 mg/day Chronic kidney disease: 0% (patients with serum creatinine level of 2.0 mg/dL or higher excluded from study.
Indirectness of population	No indirectness

Interventions	(n=102) Intervention 1: Colchicine. Participants randomised to febuxostat with concomitant colchicine 0.5 mg at the same time one time per day for 12 weeks. . Duration 24 weeks. Concurrent medication/care: Febuxostat 40 mg was taken once a day for 12 weeks (randomised period) and for another 12 weeks (observation period). Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine was administered). 2. Type of ULT: Xanthine oxidase inhibitor (Febuxostat was initiated). (n=52) Intervention 2: No prophylaxis/treatment. Participants randomised to febuxostat only. Duration 24 weeks. Concurrent medication/care: Febuxostat 40 mg was taken once a day for 12 weeks (randomised period) and for another 12 weeks (observation period). Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine was administered in the intervention arm). 2. Type of ULT: Xanthine oxidase inhibitor (Febuxostat was initiated).
Funding	Study funded by industry (This investigator-initiated study was supported by a grant from Teijin Pharma Limited.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLCHICINE versus NO PROPHYLAXIS/TREATMENT

Protocol outcome 1: Frequency of flares at long (> six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patients who needed analgesic treatment with NSAIDs or adrenal corticosteroid to manage gout symptoms at 3 months; Group 1: 18/95, Group 2: 18/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for confounders including: age, gender, prior urate-lowering therapy use and any comorbidity; Group 1 Number missing: 20, Reason: Did not receive allocated intervention (n=7), safety reasons (n=2), not examined (n=5), withdrew consent (n=2), withdrawn by investigators (n=4); Group 2 Number missing: 13, Reason: Did not receive allocated intervention (n=2), safety reasons (n=1), not examined (n=3), withdrew consent (n=5), withdrawn by investigators (n=2)

Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (cardiovascular - vascular disorders) at 6 months; Group 1: 0/95, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for confounders including: age, gender, prior urate-lowering therapy use and any comorbidity; Group 1 Number missing: 20, Reason: Did not receive allocated intervention (n=7), safety reasons (n=2), not examined (n=5), withdrew consent (n=2), withdrawn by investigators (n=4); Group 2 Number missing: 13, Reason: Did not receive allocated intervention (n=2), safety reasons (n=1), not examined (n=3), withdrew consent (n=5), withdrawn by investigators (n=2)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (gastrointestinal) at 6 months; Group 1: 1/95, Group 2: 0/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for confounders including: age, gender, prior urate-lowering therapy use and any comorbidity; Group 1 Number missing: 7, Reason: Did not receive allocated intervention; Group 2 Number missing: 2, Reason: Did not receive allocated intervention - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (renal - renal and urinary disorders) at 6 months; Group 1: 1/95, Group 2: 0/50 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for confounders including: age, gender, prior urate-lowering therapy use and any comorbidity; Group 1 Number missing: 20, Reason: Did not receive allocated intervention (n=7), safety reasons (n=2), not examined (n=5), withdrew consent (n=2), withdrawn by investigators (n=4); Group 2 Number missing: 13, Reason: Did not receive allocated intervention (n=2), safety reasons (n=1), not examined (n=3), withdrew consent (n=5), withdrawn by investigators (n=2)	
Protocol outcomes not reported by the study	Health-related quality of life at short (up to two weeks); Health-related quality of life at medium (two to six weeks); Health-related quality of life at long (> six weeks); Pain at short (up to two weeks); Pain at medium (two to six weeks); Pain at long (> six weeks); Joint swelling/joint inflammation at short (up to two weeks); Joint swelling/joint inflammation at medium (two to six weeks); Joint swelling/joint inflammation at long (> six weeks); Joint tenderness at short (up to two weeks); Joint tenderness at medium (two to six weeks); Joint tenderness at long (> six weeks); Patient global assessment of treatment success (response to treatment) at short (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium (two to six weeks); Patient global assessment of treatment success (response to treatment) at long (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (two to six weeks); Admissions (hospital & A&E) at short (up to two weeks); Admissions (hospital & A&E) at medium (two to six weeks); Admissions (hospital & A&E) at long (> six weeks); Discontinuation of ULT at medium (two to six weeks); Discontinuation of ULT at long (> six weeks); Discontinuation of ULT at short (up to two weeks); Frequency of flares at short (up to two weeks); Frequency of flares at medium (two to six weeks); Serum urate levels at short (up to two weeks); Serum urate levels at medium (two to six weeks); Serum urate levels at long (> six weeks)

Study	Schlesinger 2011[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=432 (n=216 for the three relevant randomised arms)
Countries and setting	Conducted in Argentina, Belgium, Colombia, Czech Republic, Germany, Guatemala, Hungary, Multiple countries, Poland, Portugal, Russia, Singapore, Slovakia, South Africa, Spain, Taiwan, Turkey, United Kingdom, USA; Setting: Multi-centre study in 75 centres, further details not reported.
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2: 6.5% of study population had low renal function
Subgroup analysis within study	Not applicable
Inclusion criteria	People age 18-80 years, diagnosis of gouty arthritis as defined by the American College of Rheumatology 1977 preliminary criteria, having had at least two gouty arthritis flares in the previous year, body mass index of ≤40 kg/m2 and willingness to initiate allopurinol treatment or having initiated allopurinol treatment with 1 month of screening.
Exclusion criteria	People having a gouty arthritis flare within 2 weeks of screening, present at screening, or having pain associated with a flare at screening, history of allergy, contraindication, or intolerance to allopurinol or colchicine.
Recruitment/selection of patients	Between December 2008 and August 2009, patients from 75 centres in 16 countries.
Age, gender and ethnicity	Age - Mean (SD): 52.2 years canakinumab – 52.0 years; colchicine – 52.4 years). Gender (M:F): 92.1%/7.9%-(male %): canakinumab - 90.8%; colchicine – 93.5%. Ethnicity: Caucasian - 73.2%; Black - 3.7% ; Asian - 10.8%; Other - 12.3%
Further population details	1. Initial vs subsequent titration: Initial titration (Initial titration reported). 2. Setting: Not stated / Unclear (Not specified).
Extra comments	Other doses of canakinumab included in the 7-arm trial: 25 mg, 50 mg, 300 mg or 4-weekly intervals (50 mg on day 1 and at week 4, and 25 mg at weeks 8 and 12) % of participants using allopurinol before baseline – Canakinumab - 16.7%; Colchicine – 11.1%

	Chronic kidney disease (low creatinine clearance): canakinumab – 7.4%; colchicine – 5.6% Creatinine clearance determined using Cockcroft-Gault Equation. Normal range for women aged: 16–50 years, 65–110 ml/min; 51–70 years, 50–90 ml/min; 71–110 years, 35–60 ml/min. Normal range for men aged: 16–50 years, 80–125 ml/min; 51–70 years, 55–100 ml/min; 71–110 years, 40–75 ml/min
Indirectness of population	No indirectness
Interventions	(n=108) Intervention 1: IL-1 inhibitors - Canakinumab. Participants taking allopurinol treatment randomised to receive a single dose of canakinumab (100 mg and 200 mg). . Duration 24 weeks (6 months). Concurrent medication/care: Allopurinol treatment (100-300mg) was initiated at baseline or within 1 month before baseline and was administered to all randomised patients once daily for 24 weeks. Participants could receive rescue medication as needed. . Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Canakinumab administered). 2. Type of ULT: Xanthine oxidase inhibitor (Allopurinol initiated). (n=108) Intervention 2: Colchicine. Participants taking allopurinol treatment randomised to receive daily oral doses of colchicine 0.5 mg given for 16 weeks. Duration 16 weeks (4 months). Concurrent medication/care: Allopurinol treatment (100-300mg) was initiated at baseline or within 1 month before baseline and was administered to all randomised patients once daily for 24 weeks. Participants could receive rescue medication as needed. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Canakinumab administered in intervention arm). 2. Type of ULT: Xanthine oxidase inhibitor (Allopurinol initiated).
Funding	Study funded by industry (The study was funded by Novartis Pharma AG, Basel, Switzerland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CANAKINUMAB versus COLCHICINE

Protocol outcome 1: Frequency of flares at long (> six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: People experiencing ≥1 flares at 4 months; Group 1: 18/108, Group 2: 48/108;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Canakinumab 100 mg and 200 mg arms combined; Indirectness of outcome: No indirectness ; Baseline details: Comparable for factors including: age, gender, ethnicity and creatinine clearance; Group 1 Number missing: 13, Reason: Discontinued; Group 2 Number missing: 11, Reason: Discontinued

Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (> six weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events (gastrointestinal - diarrhoea and nausea) at 6 months; Group 1: 8/108, Group 2: 3/108 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Canakinumab 100 mg and 200 mg arms combined; Indirectness of outcome: No indirectness ; Baseline details: Comparable for factors including: age, gender, ethnicity and creatinine clearance; Group 1 Number missing: 13, Reason: Discontinued; Group 2 Number missing: 11, Reason: Discontinued	
Protocol outcomes not reported by the study	Health-related quality of life at short (up to two weeks); Health-related quality of life at medium (two to six weeks); Health-related quality of life at long (> six weeks); Pain at short (up to two weeks); Pain at medium (two to six weeks); Pain at long (> six weeks); Joint swelling/joint inflammation at short (up to two weeks); Joint swelling/joint inflammation at medium (two to six weeks); Joint swelling/joint inflammation at long (> six weeks); Joint tenderness at short (up to two weeks); Joint tenderness at medium (two to six weeks); Joint tenderness at long (> six weeks); Patient global assessment of treatment success (response to treatment) at short (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium (two to six weeks); Patient global assessment of treatment success (response to treatment) at long (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (two to six weeks); Admissions (hospital & A&E) at short (up to two weeks); Admissions (hospital & A&E) at medium (two to six weeks); Admissions (hospital & A&E) at long (> six weeks); Discontinuation of ULT at medium (two to six weeks); Discontinuation of ULT at long (> six weeks); Discontinuation of ULT at short (up to two weeks); Frequency of flares at short (up to two weeks); Frequency of flares at medium (two to six weeks); Serum urate levels at short (up to two weeks); Serum urate levels at medium (two to six weeks); Serum urate levels at long (> six weeks)

Appendix E – Forest plots

E.1 Colchicine (plus febuxostat 40mg) versus no treatment (febuxostat 40mg)

Figure 2: Frequency of flares at 3 months

	Colchicine		No treatment		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Yamanaka 2018	18	95	18	50	0.53 [0.30, 0.92]

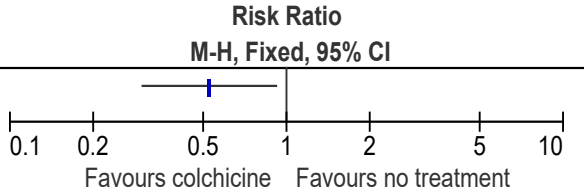


Figure 3: Adverse events (cardiovascular) at 6 months

	Colchicine		No treatment		Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Yamanaka 2018	0	95	0	50	0.00 [-0.03, 0.03]

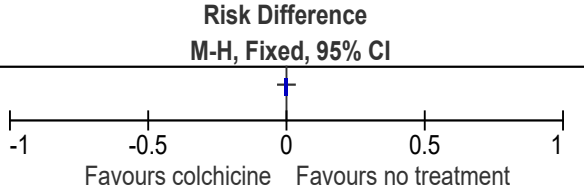


Figure 4: Adverse events (gastrointestinal) at 6 months

	Colchicine		No treatment		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Peto, Fixed, 95% CI
Yamanaka 2018	1	95	0	50	4.60 [0.07, 284.25]

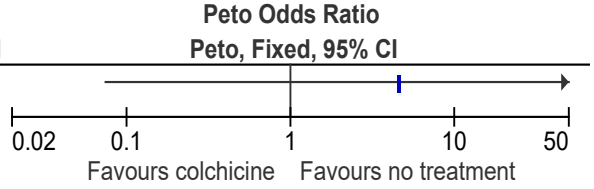
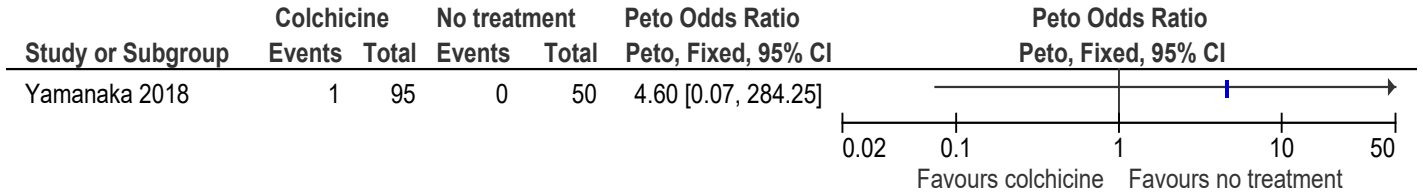


Figure 5: Adverse events (renal) at 6 months



E.2 Colchicine (colchicine plus allopurinol) versus placebo (placebo plus allopurinol)

Figure 6: Frequency of flares (people experiencing 1 flare) at 6 months

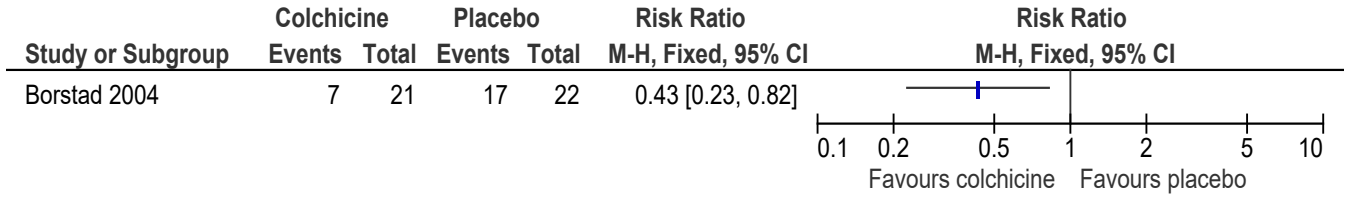


Figure 7: Frequency of flares (people experiencing >1 flare) at 6 months

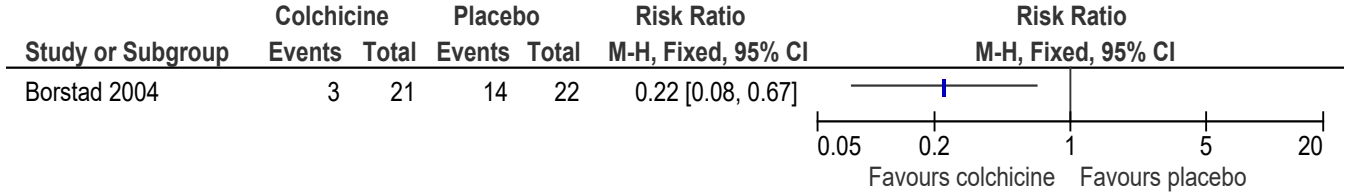
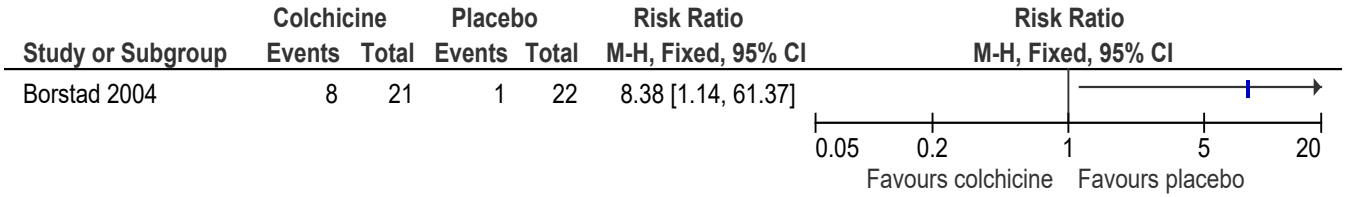


Figure 8: Adverse events (gastrointestinal) at 6 months



E.3 Canakinumab (Canakinumab plus allopurinol) versus colchicine (colchicine versus allopurinol)

Figure 9: Frequency of flares (people experiencing ≥1 flares) at 4 months

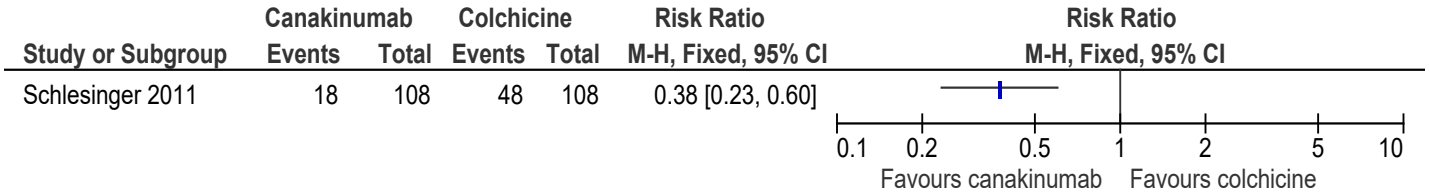
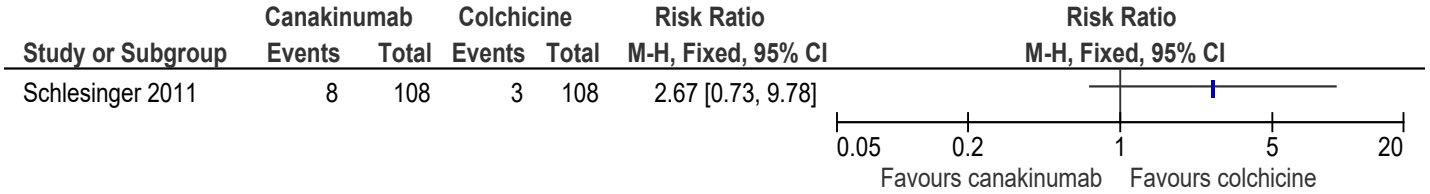


Figure 10: Adverse events (gastrointestinal) at 6 months



Appendix F – GRADE tables

Table 15: Clinical evidence profile: Colchicine (colchicine plus febuxostat 40mg) versus no treatment (febuxostat 40mg)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	No treatment	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares at 3 months												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	18/95 (18.9%)	18/50 (36.0%)	RR 0.53 (0.30 to 0.92)	169 fewer per 1,000 (from 252 fewer to 29 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (cardiovascular) at 6 months												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	0/95 (0.0%)	0/50 (0.0%)	RD 0 (0.03 to 0.03 [b]	0 fewer per 1,000 (from 30 fewer to 30 more) [b]	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	No treatment	Relative (95% CI)	Absolute (95% CI)		
Adverse events (gastrointestinal) at 6 months												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/95 (1.1%)	0/50 (0.0%)	Peto OR 4.60 (0.07 to 284.25)	10 more per 1,000 (from 30 fewer to 50 more) [c]	⊕⊕◯◯ LOW	CRITICAL
Adverse events (renal) at 6 months												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/95 (1.1%)	0/50 (0.0%)	Peto OR 4.60 (0.07 to 284.25)	10 more per 1,000 (from 30 fewer to 50 more) [c]	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

b. Zero events in both arms. Risk difference calculated in Review Manager

c. Absolute effects calculated using risk difference due to zero events in one of the arms

Table 16: Clinical evidence profile: Colchicine (colchicine plus allopurinol) versus placebo (placebo plus allopurinol)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares (people experiencing 1 flare) at 6 months												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	7/21 (33.3%)	17/22 (77.3%)	RR 0.43 (0.23 to 0.82)	440 fewer per 1,000 (from 595 fewer to 139 fewer)	⊕⊕◯◯ LOW	CRITICAL
Frequency of flares (people experiencing >1 flare) at 6 months												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	3/21 (14.3%)	14/22 (63.6%)	RR 0.22 (0.08 to 0.67)	496 fewer per 1,000 (from 585 fewer to 210 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events (gastrointestinal) at 6 months												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	8/21 (38.1%)	1/22 (4.5%)	RR 8.38 (1.14 to 61.37)	335 more per 1,000 (from 6 more to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 17: Clinical evidence profile: Canakinumab (Canakinumab plus allopurinol) versus colchicine (colchicine plus allopurinol)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Canakinumab	Colchicine	Relative (95% CI)	Absolute (95% CI)		
Frequency of flares (people experiencing ≥1 flares) at 4 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Canakinumab	Colchicine	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	18/108 (16.7%)	48/108 (44.4%)	RR 0.38 (0.22 to 0.63)	276 fewer per 1,000 (from 342 fewer to 178 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

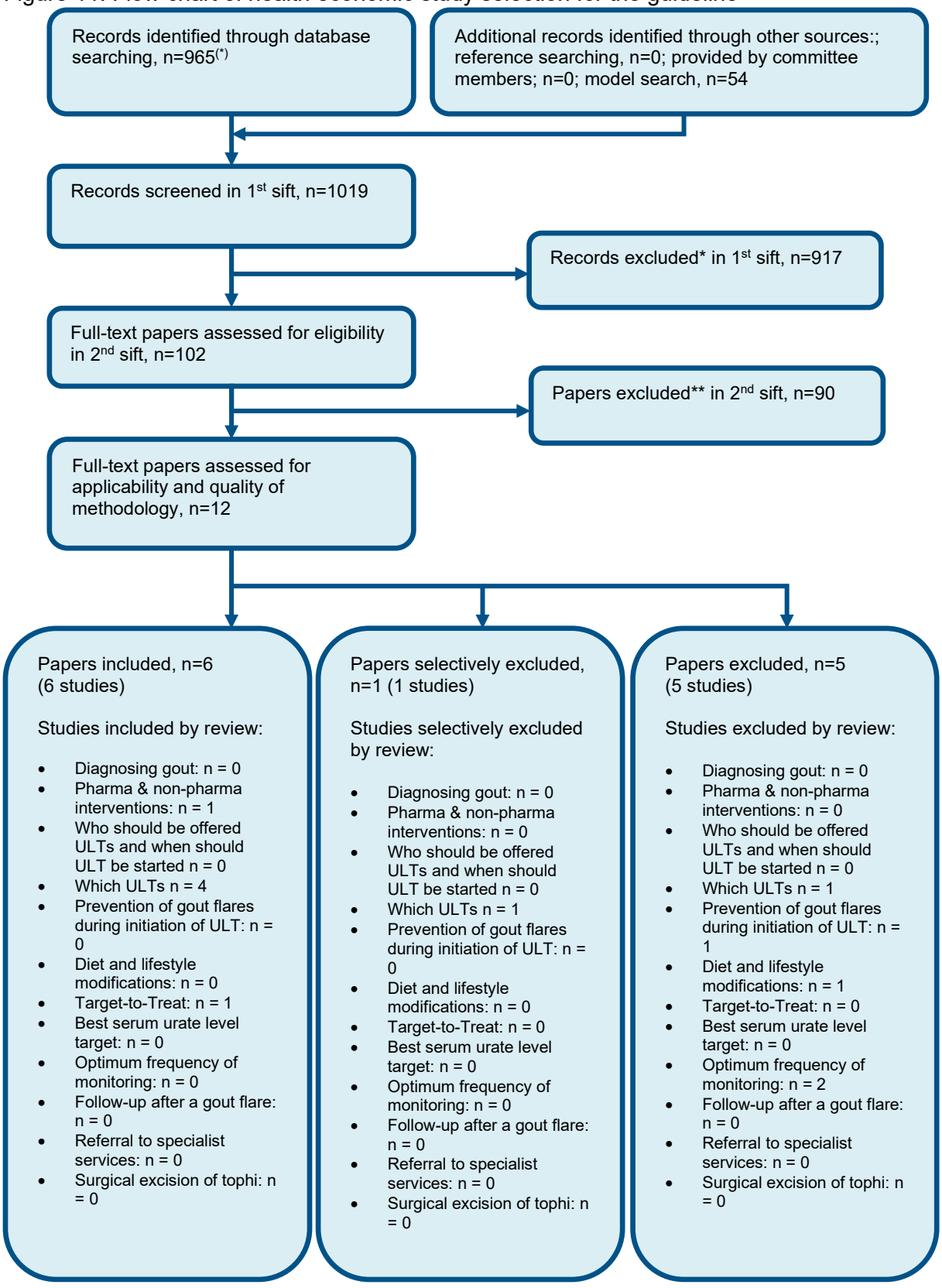
Adverse events (gastrointestinal) at 6 months

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	8/108 (7.4%)	3/108 (2.8%)	RR 2.67 (0.73 to 9.78)	46 more per 1,000 (from 8 fewer to 244 more)	⊕◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Appendix G – Economic evidence study selection

Figure 11: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original health economic modelling was conducted for this review question.

Appendix J – Excluded studies

Clinical studies

Table 18: Studies excluded from the clinical review

Study	Exclusion reason
Eminaga 2016[3]	Systematic review references were checked; no relevant studies identified
Feng 2015[4]	Incorrect study design: retrospective cohort study. Unadjusted outcome data reported
Karimzadeh 2006[5]	Incorrect comparison: different durations of colchicine
Latourte 2014[6]	Systematic review references were checked; relevant studies previously identified and included
Mitha 2013[7]	Incorrect intervention: rilonacept
Paulus 1974[11]	Incorrect population: probenecid initiated during the study
Schumacher 2012[14]	Incorrect intervention: rilonacept
Seth 2014[15]	Systematic review references were checked; relevant studies previously identified and included
Shiozawa 2017[16]	Systematic review references were checked; no relevant studies identified
Singh 2011[17]	Systematic review references were checked; no relevant studies identified
Stewart 2020[18]	Systematic review references were checked; relevant studies previously identified and included
Sundy 2014[19]	Incorrect intervention: rilonacept
Sutaria 2006[20]	Systematic review references were checked; no relevant studies identified
Vinik 2014[21]	Systematic review references were checked; no relevant studies identified
Wortmann 2010[22]	Systematic review references were checked; no relevant studies identified
Yu 2018[24]	Incorrect study design: retrospective cohort study. Unadjusted outcome data reported

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 19: Studies excluded from the health economic review

Reference	Reason for exclusion
Robinson 2020[12]	Excluded due to a combination of applicability and methodological limitations. The analysis presented results from an American and Australian health care perspective; however, a breakdown of costs was only presented for the American analysis. In general, it was unclear how resource use was obtained. The primary source of

Reference	Reason for exclusion
	utility values was from an unpublished study and it was unclear how these values were elicited. The economic evaluation was based on Borstad 2004 which was included in our clinical review, but the trial only had 43 participants. In addition, the model assumed a colchicine dose reduction due to diarrhoea would not affect flare rates.

Appendix K Research recommendations – full details

J.1.1 Research recommendation

In people with gout (including people with gout and chronic kidney disease), what is the clinical and cost effectiveness of non-steroidal anti-inflammatory drugs or corticosteroids for preventing gout flares when starting or titrating urate-lowering therapy (ULT)?

J.1.2 Why this is important

Gout flares are common during the initiation and titration of urate lowering therapy and these are prevented commonly by co-prescribing ULTs with colchicine. NSAIDs and corticosteroids are also used in clinical practice, especially when colchicine is contraindicated or not tolerated. RCT evidence shows the effectiveness of colchicine but no RCTs evaluating the use of NSAIDs and corticosteroids were identified.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Although colchicine is the most prescribed intervention to prevent flares when initiating ULT, there are people in whom colchicine is not tolerated, contraindicated or ineffective. In these patients NSAIDs or corticosteroids may be an option.
Relevance to NICE guidance	This guideline recommends offering colchicine as first line when starting or titrating ULT, and NSAIDs or corticosteroids as second line. No RCTs on the use of NSAIDs or corticosteroids were identified for the prevention of gout flares during the initiation or titration of ULT. Further evidence would allow more informed recommendations on the use of NSAIDs and corticosteroids
Relevance to the NHS	Long-term ULT is an important aspect in the prevention of painful flares and long-term joint complications. However, ULT initiation and dose titration can cause acute flares in the short term. This causes poor ULT medication compliance, leading to poor gout control, long-term joint damage, and a greater NHS burden. The outcome would provide evidence of therapies as alternative to colchicine which is not always well tolerated.
National priorities	None
Current evidence base	3 RCTs were identified in the evidence review evaluating the use of therapies for the prevention of gout flares during the initiation or titration of urate-lowering therapy. However, no RCTs on the use of NSAIDs or corticosteroids were identified
Equality considerations	None known

J.1.4 Modified PICO table

Population	People with gout, where colchicine is not tolerated, contraindicated or ineffective, who are initiating or dose titrating ULT
Intervention	NSAID, Corticosteroid.
Comparator	Placebo, Corticosteroid, NSAID
Outcome	quality of life, pain, joint swelling/ joint inflammation, joint tenderness, frequency of flares serum urate levels, costs.
Study design	RCT
Timeframe	short (up to two weeks), medium (two to six weeks) and long (> six weeks) term
Additional information	None