National Institute for Health and Care Excellence

Guideline version (Draft for Consultation)

Gout: Diagnosis and Management

[D] Evidence reviews for pharmacological and non-pharmacological interventions for managing gout flares

NICE guideline <number>

Evidence reviews underpinning recommendations 1.3.1 to 1.3.5 and research recommendations in the NICE guideline

December 2021

Draft for Consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

1

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

1

1 Pharmacological and non-pharmacological interventions for managing gout flares

1.1 Review question: What is the clinical and cost effectiveness of pharmacological interventions (including NSAIDs, colchicine, corticosteroids and IL-1 inhibitors) and non-pharmacological interventions for managing gout flares?

1.1.1 Introduction

Recurrent flares are the most characteristic manifestation of gout and present with sudden onset of severe pain, swelling and inflammation, often overnight. Most flares present to and are managed in primary care.

Treatment of gout flares aims to provide rapid relief from joint pain and inflammation. The most commonly used pharmacological interventions to treat flares are non-steroidal anti-inflammatory drugs (NSAIDs), followed by colchicine and corticosteroids. However, many people with gout have contraindications to NSAIDs, such as peptic ulcer disease, chronic kidney disease and severe heart failure. Interleukin-1 inhibitors are a new approach to managing gout flares but are not commonly used in clinical practice. Non-pharmacological interventions such as rest and application of ice-packs to the affected joint are often employed as adjunctive treatment.

This evidence review will examine the clinical and cost effectiveness of pharmacological and non-pharmacological interventions to treat gout flares.

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 flares Strata: • People with chronic kidney disease (stage 3) • People with chronic kidney disease (stage 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 (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 • Triamcinolone • IL-1 inhibitors (commonly used in clinical practice in the UK) • Anakinra • Canakinumab • Non-pharmacological interventions - rest, elevation, bed cages and ice • Combinations (pharmacological + non-pharmacological) 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 • Standard care/usual care • Control/no intervention • 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 • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) • admissions (hospital and A&E/urgent care) • GP visits Timepoints: short-term (up to two weeks), medium-term (two to six weeks) and long-term (> six weeks)
Study design	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.

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

Eleven randomised controlled studies were included in the review[25,32,46,53,52,51,63,69,80,47,37] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 - Table 7).

The eleven randomised controlled studies evaluated pharmacological and non-pharmacological interventions for managing gout flares. One study evaluated the use of colchicine versus placebo. Four studies evaluated corticosteroids versus NSAIDs. Two studies compared NSAIDs versus colchicine. Three studies compared IL-1 inhibitors versus corticosteroids. One study compared ice therapy, corticosteroids and colchicine versus no ice therapy, corticosteroids and colchicine.

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

Five Cochrane reviews were excluded.[24,62,73,74,77] Janssens 2008[24] was excluded as two out of three included studies were not relevant, one of them had no pairwise analysis and another one included an inappropriate comparison (adrenocorticotropic hormone compared to triamcinolone). Sivera 2014[62] was excluded because one of the included studies had an inappropriate intervention (Rilonacept compared to indomethacin) and for other three studies outcomes were extracted at different time points (at 72 hours), whereas we used the last available timepoint across reviews. In this case the last available timepoint was 7 days. Van 2014[73] was excluded as only three out of twenty-three included studies were relevant. Studies were excluded due to inappropriate intervention, inappropriate comparison or they were not available. Van Echteld 2014[74] was excluded because one of two included studies used a very high dose of colchicine [6.7 mg] and common practice is 1 - 2 mg of Colchicine per day. Therefore, this study (Ahern 1987)[1] was excluded from our review. The other study (Terkeltaub 2010)[69] included high dose colchicine and low dose colchicine. We analysed the low dose and removed the high dose data. Wechalekar 2013[77] was excluded because this review had no included studies. All included studies in all five Cochrane reviews were checked for inclusion and 6 of them were included in our review

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
Janssens 200825 RCT	Intervention (n=60) Corticosteroids - Prednisolone 35mg once a day and look alike placebo naproxen twice a day for 5 days. Concurrent medication/care: no NSAIDs or other analgesics (including colchicine) within 24 h before baseline assessments or for the duration of the trial. Comparison (n=60) NSAIDs - Naproxen 500 mg twice a day and placebo capsule prednisolone for 5 days.	n=120 Participants were patients with monoarticular gout arthritis confirmed by identification of monosodium urate crystals in the synovial fluid of the affected joint Age - mean years (SD): Prednisolone group 57.3 (12.2), naproxen group 57.7 (13.4). Gender (M:F): Prednisolone group 54/6, naproxen group 53/7. Ethnicity: not reported Netherlands	Pain (VAS) at 90 hours Adverse events - gastrointestinal at 90 hours	
Liu 201932 RCT	Intervention (n=61) Colchicine. Patients in the colchicine group received colchicine 0.5 mg orally, 3 times daily, for 5 days, later changed to once daily (“later” was not specified) Comparison (n=61) NSAIDs - Etoricoxib. Patients in the etoricoxib group received	n=122 Patients from 18 to 70 years old with newly diagnosed acute gouty arthritis; an onset of acute gouty arthritis duration of less than 48 h and no administration of colchicine, NSAID or glucocorticoids; no administration of medications	Joint pain scores at 10 days Adverse events – gastrointestinal at 10 days	Gastrointestinal events included: diarrhoea, vomiting

Study	Intervention and comparison	Population	Outcomes	Comments
	etoricoxib 120mg orally (Hangzhou MSD Pharmaceutical Co., Ltd), once daily, for 5 days, later changed to 60 mg orally once daily. ("Later" was not specified)	affecting uric acid metabolism over the last 3 months; without diseases affecting uric acid metabolism. Age - mean years (SD): Etoricoxib group 44(9); Colchicine 43(9) Gender (M:F): Etoricoxib group 49/4; Colchicine 47/5 Ethnicity: not reported China		
Man 200737 RCT	Intervention (n=46) NSAIDs - Indomethacin. In the indomethacin group, each patient initially received diclofenac (3 mL; 75mg) intramuscularly, indomethacin 50 mg orally, acetaminophen 1 g orally, and 6 tablets of prednisolone like placebo orally and was observed for 120 minutes. The patient was then given a 5-day prescription of indomethacin (50 mg orally every 8 hours for 2 days, followed by indomethacin 25 mg every 8 hours for another 3 days), 6 tablets of prednisolone-like placebo once a day, and acetaminophen 1 g every 6	n=90 Patients were included if they had a clinical diagnosis of acute arthritis suggestive of gout. Age - mean years (SD): Indomethacin 66 (16) Prednisolone 64 (15) Gender (M/F): Indomethacin 39/7, Prednisolone 35/9 Ethnicity: not reported Australia	Adverse events – gastrointestinal events at 14 days Adverse events – cardiovascular events at 14 days	Gastrointestinal events included: epigastric pain, other abdominal pain, indigestion, vomiting, diarrhoea, gastrointestinal haemorrhage and nausea. Cardiovascular events included: chest pain

Study	Intervention and comparison	Population	Outcomes	Comments
	hours as required. Duration 5 days. Comparisons (n=44) Corticosteroids - Prednisolone. In the prednisolone group, each patient initially received an intramuscular placebo injection (3 mL), prednisolone 30 mg (6 times 5 mg) orally, acetaminophen 1g (2 tablets) orally, and indomethacin-like placebo (2 tablets) orally and was then observed for 120 minutes. The patient was then given a 5-day prescription of indomethacin-like placebo, prednisolone 30 mg orally once per day, and acetaminophen 1g every 6 hours as required.			
Rainer 201646 RCT	Intervention (n=208) NSAIDs - Indomethacin. In the indomethacin group, patients initially received 50 mg (two 25-mg tablets) of oral indomethacin 3 times a day and 6 tablets of oral placebo prednisolone once a day for 2 days, followed by 25 mg of indomethacin 3 times a day and 6 tablets of placebo prednisolone once a day for 3 days. Comparison (n=208)	n=416 Patients with the diagnosis of acute gout Age - mean years (SD): Indomethacin group 64.37(16.01); Prednisolone group 65.91(14.95) Gender (M/F): Indomethacin group 164/44; Prednisolone group 145/63	Patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - at rest at 14 days Patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - with activity at 14 days	Gastrointestinal events included: nausea, vomiting, abdominal pain, indigestion.

Study	Intervention and comparison	Population	Outcomes	Comments
	Corticosteroids - Prednisolone. In the prednisolone group, patients initially received 30 mg (three 10-mg tablets) of oral prednisolone once a day and 2 tablets of placebo indomethacin 3 times a day for 2 days, followed by 30 mg (three 10-mg tablets) of prednisolone once a day and 1 tablet of placebo indomethacin 3 times a day for 3 days. Patients took the first dose in the presence of one of the investigators.	Ethnicity: not reported Hong Kong (China)	Joint tenderness (mean change from baseline to day 14) at 14 days Adverse events - gastrointestinal Visited ED at 14 days Visited Outpatient department at 14 days GP visits at 14 days	
Roddy 202047 RCT	Intervention (n=200) NSAIDs – Naproxen - Single initial dose of oral naproxen 750 mg (three 250 mg tablets) followed by 250 mg (one tablet) every 8 hours for up to 7 days. Co-prescription of a proton-pump inhibitor was at the GP's discretion. Comparison (n=199) Oral colchicine 500 mg (one tablet) every 8 hours for 4 days. Participants prescribed a statin were advised to omit the statin during colchicine treatment	n=399 Participants consulting for a current gout flare Age mean- years (SD): Naproxen group - 58.7(14.4), Colchicine 60 (13.4) Gender (M/F): Naproxen group - 173/27; Colchicine group - 174/25 Ethnicity: not reported UK	Complete pain resolution at 7 days Complete pain resolution at 4 weeks Patient assessment of global treatment response (completely/much better) at 7 days Patient assessment of global treatment response (completely/much better) at 4 weeks	Gastrointestinal events included: nausea and vomiting, diarrhoea, dyspepsia, constipation, abdominal pain

Study	Intervention and comparison	Population	Outcomes	Comments
			Adverse events – gastrointestinal events at 7 days Adverse events – gastrointestinal events at 4 weeks Consultation re-attendance for gout during 4-week follow-up - emergency department Consultation Re-attendance for gout during 4-week follow-up - GP at 4 weeks	
Saag, 202150	Intervention (n=56) IL-1 inhibitors - Anakinra 100 mg by subcutaneous injection Comparison (n=55): Corticosteroids - Triamcinolone 40mg single injection on day 1	N= 165 (111 used in this analysis as anakinra 200mg group was not relevant to this review) Patients having a gout flare and who have had ≥1 episode of intolerance or non-responsiveness to NSAIDs and colchicine. Age (median, range): Anakinra 100mg group: 53.5 (25-79), Triamcinolone group: 56.0 (30-83) Gender: Anakinra 100mg group: 48 males (85.7%)	Pain - VAS change from baseline at 24-72 hours from the start of flares 1, 2 and 3 (during the 5 days treatment period) Any adverse event during the study period, including the extension period (up to 2 years)	There were two anakinra groups, only the 100mg group was relevant to the protocol and was included. Previous non-response to NSAIDs/ colchicine

Study	Intervention and comparison	Population	Outcomes	Comments
		Triamcinolone group: 48 males (87.3%) Ethnicity: Anakinra 100mg group: White 38 (67.9%), Black 15 (26.8%), Asian 3 (5,4%) Triamcinolone group: White 39 (70.9%), Black 15 (27.3%), Asian 1 (1.8%)		
Schlesinger 200253 RCT	Intervention (n=10) Combination interventions - Pharmacological plus non-pharmacological. received topical ice therapy, oral corticosteroids (prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and colchicine 0.6 mg/day. Ice therapy, by application of ice packs with self-ties on the inflamed target joint for 30 min 4 times/day, was given to all patients in Group A. The patients were followed for one week. Comparison (n=9) No Ice therapy + oral corticosteroids (prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and	n=19 Patients with acute gouty attacks Age - mean (SD): age not reported Gender (M/F): age not reported Ethnicity: not reported USA	Pain at 1 week Joint swelling/joint inflammation - joint circumference (cm) at 1 week	

Study	Intervention and comparison	Population	Outcomes	Comments
	colchicine 0.6 mg/day. No ice therapy. Duration 6 days.			
Schlesinger 201251: β-RELIEVED trial and β-RELIEVED II trial RCT	β-RELIEVED trial: Intervention - (n=115): IL-1 inhibitors - Canakinumab. canakinumab single dose 150 mg by subcutaneous injection Comparison (n=115): Corticosteroids - Triamcinolone acetonide single dose 40 mg intramuscular injection. β-RELIEVED-II trial: Intervention (n=112): IL-1 inhibitors - Canakinumab. canakinumab single doses 150 mg by subcutaneous injection Comparison (n=114): Corticosteroids - Triamcinolone. Triamcinolone acetonide 40 mg intramuscular injection (B-RELIEVED-II sub-study). Duration single dose.	n=456 Patients with acute arthritis of primary gout, with a history of ≥ three self-reported flares in the previous 12 months, having an acute flare for ≤five days characterised by baseline pain intensity ≥50 mm on a 0–100 mm visual analogue scale (VAS) Age - mean years (SD): Canakinumab group - 52.3 (11.8), triamcinolone group 53.6(11.5) Gender (M/F): 414/40 Ethnicity (%): Canakinumab group - Caucasian 74.2 %, Black – 11.6%; Asian -5.8%; Other – 8.419 Triamcinolone group - Caucasian – 76.9%; Black – 10.5%; Asian -5.2%; Other 7.4% USA	Physician assessment of swelling (OR) - β-RELIEVED at 7 days Pain 100-mm visual analogue scale at 72 hours (B-Relieved) Physician assessment of tenderness (OR) - β-RELIEVED at 7 days Patient global assessment (OR) - β-RELIEVED at 7 days Any adverse event - β-RELIEVED - long term at 24 weeks Physician assessment of swelling (OR) - β-RELIEVED-II at 7 days Pain 100-mm visual analogue scale at 72 hours (B-Relieved-II) Physician assessment of tenderness (OR) - β-RELIEVED at 7 days	The study also reported all outcomes at 72 hours

Study	Intervention and comparison	Population	Outcomes	Comments
			Patient global assessment (OR) - β-RELIEVED-II at 7 days Any adverse event - β-RELIEVED-II - long term at 24 weeks	
So 201063 (Schlesinger 201152) RCT	Intervention (n=28): IL-1 inhibitors - Canakinumab. Canakinumab 150 mg by subcutaneous injection and saline by intramuscular injection Comparison (n=57): Corticosteroids - Triamcinolone. triamcinolone acetonide (40 mg) intramuscularly and a subcutaneous placebo injection on day 1	n=85 Patients with a history of at least 1 previous gout flare, also required to have had an acute gout flare for ≤5 days, have a baseline pain intensity of ≥50 mm on a visual analogue scale (VAS) ranging from no pain (0 mm) to unbearable pain (100 mm), Age - mean years (SD): Canakinumab 50.6(15.38); Triamcinolone acetonide 52.4(11.55) Gender (M:F): Canakinumab 28/0; Triamcinolone acetonide 55/2 Ethnicity: Canakinumab vs triamcinolone acetonide White 85.7% vs 94.7% Black 3.6% vs 5.3% Asian 7.1% vs 0%	SF 36 - physical component at 7 days Pain - VAS change from baseline at 7 days Patient global assessment - Excellent at 7 days Patient global assessment - Good at 7 days Any adverse events at 7 days	Dose ranging study 150 mg single dose of Canakinumab was used for this review Other doses (not relevant): 10 mg, 25 mg, 50 mg or 90mg as a single dose;

Study	Intervention and comparison	Population	Outcomes	Comments
		Other 3.6% vs 0% USA		
Terkeltaub 201069 RCT	Intervention (n=74) Colchicine - (1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour for 5 hours [1.8 mg total]) Comparison (n=59) Placebo - (2 placebo capsules initially, followed by 1 placebo capsule every hour for 6 hours).	n=185 Male and postmenopausal female patients ≥18 years of age with a confirmed past diagnosis of gout (according to the American College of Rheumatology [ACR] classification criteria and having had ≥2 gout flares within the prior 12 months were eligible for randomization. Age - mean years (SD): 51.5 (11.12) Gender (M/F): 176/9 Ethnicity: Colchicine vs placebo American Indian/Alaska Native – 1.4% vs 0% Asian – 1.4% vs 1.7% Black/African American – 5.4% vs 18.6% White/Caucasian – 89.2% vs 79.7% Other – 2.7% vs 0%	Pain - treatment response based on target joint pain score 32 hours after first dose - ≥ 50% pain reduction (number of patients) at 32 hours Adverse events - Gastrointestinal	Low dose of Colchicine was used for this review Another dose was reported (not relevant) - high dose - (1.2 mg followed by 0.6 mg every hour for 6 hours [4.8 mg total])) Adverse events included: diarrhoea, nausea, vomiting

Study	Intervention and comparison	Population	Outcomes	Comments
		USA		
Xu 201680 RCT	Intervention (n=41) Corticosteroids - Prednisolone (35 mg daily, Comparison 1 (n=46) NSAIDs - Etoricoxib (120 mg qd, Duration 4 days. Comparison 2 (n=45) NSAIDs - Indomethacin. Etoricoxib (120 mg daily, Duration 4 days	n=132 Inclusion criteria were: 1) gout attacks within 72 hours of screening; 2) The degree of pain in the index joint was at least moderate (2 on a 5-point Likert scale) at baseline; and 3) the index joint was defined as the joint that was the most painful at the time of randomization. Age - mean (SD): prednisolone group - 44.03 (15.37), Etoricoxib 44.43 (15.08), indomethacin 43.81 (12.29). Gender (M:F): male (%) - prednisolone group - 100%, Etoricoxib 100%, indomethacin 97.2%. Ethnicity: not reported China	Pain at 4 days Swelling at 4 days Joint tenderness at 4 days Adverse events - gastrointestinal at 4 days	Adverse events included: gastric or abdominal pain

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Colchicine versus placebo

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Colchicine
Pain - Proportion with 50% or greater decrease in pain score (VAS) from baseline – Short-term (up to 2 weeks)	132 (1 RCT)	MODERATE[a]	RR 2.43 (1.30 to 4.54)	172 per 1,000	247 more per 1,000 (52 more to 610 more)
Adverse events - gastrointestinal (diarrhoea and vomiting) - Short-term (up to 2 weeks)	133 (1 RCT)	VERY LOW[a,b]	RR 1.26 (0.67 to 2.39)	203 per 1,000	53 more per 1,000 (67 fewer to 283 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. Established MIDs used for VAS scale (continuous outcomes) improvements of ≥ 10 points on a 1-100 scale. GRADE default MIDs used for all other outcomes, for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 4: Clinical evidence summary: Corticosteroids versus NSAIDs

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAIDs	Risk difference with Corticosteroids
Pain (VAS 0-100) at 90 hours - Short-term (up to 2 weeks)	118 (1 RCT)	LOW[a,b]	-	mean 12.9 (SD 18.1)	MD 3.9 higher (3.77 lower to 11.57 higher)
Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - at rest - Short-term (up to 2 weeks)	416 (1 RCT)	MODERATE[b]	RR 0.91 (0.75 to 1.10)	534 per 1,000	48 fewer per 1,000 (133 fewer to 53 more)
Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - with activity - Short-term (up to 2 weeks)	416 (1 RCT)	HIGH	RR 1.06 (0.95 to 1.19)	726 per 1,000	44 more per 1,000 (36 fewer to 138 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAIDs	Risk difference with Corticosteroids
Joint tenderness - Short-term (up to 2 weeks)	416 (1 RCT)	HIGH	-	The mean joint tendernesswas 0	MD 0.05 lower (0.33 lower to 0.23 higher)
Adverse events- gastrointestinal (abdominal pain) - Short-term (up to 2 weeks)	737 (4 RCTs)	MODERATE[c]	RR 0.48 (0.3 to 0.76)	132 per 1000	69 fewer per 1000 (93 fewer to 32 fewer)
Adverse events- gastrointestinal indigestion)- Short-term (up to 2 weeks)	506 (2 RCTs)	MODERATE[b]	RR 0.52 (0.30 to 0.91)	130 per 1000	62 fewer per 1000 (91 fewer to 12 fewer)
Adverse events- gastrointestinal (nausea)- Short-term (up to 2 weeks)	506 (2 RCTs)	HIGH	RR 0.26 (0.12 to 0.59)	106 per 1000	79 fewer per 1000 (94 fewer to 44 fewer)
Adverse events- gastrointestinal (vomiting)- Short-term (up to 2 weeks)	506 (2 RCTs)	HIGH	RR 0.10 (0.02 to 0.56)	55 per 1000	50 fewer per 1000 (54 fewer to 24 fewer)
Adverse events- gastrointestinal (diarrhoea) - Short-term (up to 2 weeks)	90 (1 RCT)	LOW[b]	Peto OR 0.14 (0.01 to 1.33)	65 per 1000	70 fewer per 1000 (from 150 fewer to 20 more)
Adverse events- gastrointestinal (GI haemorrhage) - Short-term (up to 2 weeks)	90 (1 RCT)	HIGH	Peto OR 0.13 (0.02 to 0.78)	109 per 1000	110 fewer per 1000 (from 210 fewer to 10 fewer)
Adverse events - cardiovascular - Short-term (up to 2 weeks)	90 (1 RCT)	LOW[b]	Peto OR 0.14 (0.00 to 7.13)	22 per 1000	19 fewer per 1000 (22 fewer to 115 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAIDs	Risk difference with Corticosteroids
Number of patients visited ED - Short-term (up to 2 weeks)	416 (1 RCT)	LOW[b]	RR 1.22 (0.73 to 2.04)	111 per 1000	24 more per 1000 (30 fewer to 115 more)
Number of patients visited outpatient department - Short-term (up to 2 weeks)	416 (1 RCT)	MODERATE[b]	Peto OR 0.13 (0.02 to 0.95)	19 per 1000	17 fewer per 1000 (19 fewer to 1 fewer)
GP visits - Short-term (up to 2 weeks)	416 (1 RCT)	MODERATE[b]	RR 0.58 (0.28 to 1.19)	91 per 1000	38 fewer per 1000 (66 fewer to 17 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. Established MIDs used for VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: joint tenderness (0.5 x baseline SD of control group as baseline values were not reported in the paper): 0.74.

c. Downgraded by 1 or 2 increments because: The point estimate varies widely across studies, subgroup analysis could not be performed. I^2 = 65%.

Table 5: Clinical evidence summary: NSAIDs versus colchicine

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Colchicine subgroup	Risk difference with NSAIDs
Joint pain scores (change score) - Short-term (up to 2 weeks)	105 (1 RCT)	HIGH	-	mean 0.96	MD 0.06 higher (0.28 lower to 0.4 higher)
Complete pain resolution - Short-term (up to 2 weeks)	344 (1 RCT)	LOW[a]	RR 1.01 (0.88 to 1.18)	667 per 1,000	7 more per 1,000 (80 fewer to 120 more)
Complete pain resolution – Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[a]	RR 1.02 (0.91 to 1.15)	747 per 1,000	15 more per 1000 (67 fewer to 112 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Colchicine subgroup	Risk difference with NSAIDs
Joint swelling scores - Short-term (up to 2 weeks)	105 (1 RCT)	HIGH	-	mean 0.73	MD 0.04 higher (0.19 lower to 0.27 higher)
Patient assessment of global treatment response (completely/much better) n - Short-term (up to 2 weeks)	344 (1 RCT)	VERY LOW[a,b]	RR 1.06 (0.91 to 1.24)	632 per 1,000	38 more per 1,000 (57 fewer to 152 more)
Patient assessment of global treatment response (completely/much better) n – Medium-term (2 to 6 weeks)	344 (1 RCT)	VERY LOW[a,b]	RR 1.00 (0.91 to 1.11)	822 per 1,000	0 fewer per 1,000 (74 fewer to 90 more)
Adverse events-gastrointestinal (vomiting) - Short-term (up to 2 weeks)	105 (1 RCT)	VERY LOW[a,b]	RR 1.96(0.18 to 20.99)	19 per 1000	19 per 1000
Adverse events-gastrointestinal (nausea and/or vomiting) - Short-term (up to 2 weeks)	344 (1 RCT)	MODERATE[b]	RR 0.72 (0.43 to 1.20)	172 per 1000	48 fewer per 1000 (98 fewer to 34 more)
Adverse events-gastrointestinal (diarrhoea) - Short-term (up to 2 weeks)	449 (2 RCTs)	HIGH	RR 0.47 (0.33 to 0.68)	305 per 1000	162 fewer per 1000 (205 fewer to 98 fewer)
Adverse events-gastrointestinal (dyspepsia) - Short-term (up to 2 weeks)	344 (1 RCT)	LOW[b]	RR 1.02 (0.57 to 1.83)	115 per 1,000	2 more per 1000 (49 fewer to 95 more)
Adverse events-gastrointestinal (abdominal	344 (1 RCT)	LOW[b]	RR 1.02 (0.53 to 1.98)	92 per 1000	2 more per 1000 (43 fewer to 90 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Colchicine subgroup	Risk difference with NSAIDs
pain) - Short-term (up to 2 weeks)					
Adverse events-gastrointestinal (constipation) - Short-term (up to 2 weeks)	344 (1 RCT)	HIGH	RR 0.46 (0.31 to 0.67)	385 per 1000	208 fewer per 1000 (266 fewer to 127 fewer)
Adverse events-gastrointestinal (nausea and/or vomiting) - Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[b]	RR 1.43 (0.46 to 4.43)	29 per 1,000	12 more per 1000 (16 fewer to 99 more)
Adverse events-gastrointestinal (dyspepsia) - Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[b]	RR 1.66 (0.71 to 3.91)	46 per 1000	30 more per 1000 (13 fewer to 134 more)
Adverse events-gastrointestinal (abdominal pain) - Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[b]	RR 0.51 (0.16 to 1.67)	46 per 1000	23 fewer per 1000 (39 fewer to 31 more)
Adverse events-gastrointestinal (constipation) - Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[b]	RR 1.54 (0.56 to 4.22)	34 per 1,000	19 more per 1000 (15 fewer to 111 more)
Adverse events-gastrointestinal (diarrhoea) - Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[b]	RR 0.51 (0.18 to 1.47)	57 per 1,000	28 fewer per 1000 (47 fewer to 27 more)
Consultation re-attendance for gout during 4-week follow-up -	344 (1 RCT)	VERY LOW[a,b]	Peto OR 1.02 (0.06 to 16.23)	6 per 1000	0 fewer per 1,000 (5 fewer to 80 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Colchicine subgroup	Risk difference with NSAIDs
Emergency department – Medium-term (2 to 6 weeks)					
Consultation re-attendance for gout during 4-week follow-up - GP – Medium-term (2 to 6 weeks)	344 (1 RCT)	LOW[a,b]	RR 0.68 (0.44 to 1.07)	224 per 1000	72 fewer per 1000 (126 fewer to 16 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. Established MIDs used for VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: joint pain scores: 0.435; joint swelling: 0.98.

Table 6: Clinical evidence summary: IL-1 inhibitors versus corticosteroids

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with corticosteroids	Risk difference with Il-1 inhibitors
Health related quality of life SF-36 - Physical Component - Short-term (up to 2 weeks)	85 (1 RCT)	VERY LOW[a,b]	-	mean 41.9	MD 6.4 higher (2.37 higher to 10.43 higher)
SF-36 Physical component – long-term (more than 6 weeks)	85 (1 RCT)	VERY LOW[a,b]	-	The mean SF-36 Physical component - long more than 6 weeks was 47.1	MD 5.7 higher (1.88 higher to 9.52 higher)
SF-36 - Mental component – long-	85 (1 RCT)	VERY LOW[a,b]	-	mean 49.1	MD 4.2 higher (0.22 higher to 8.18 higher)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with corticosteroids	Risk difference with Il-1 inhibitors
term (more than 6 weeks)					
Pain: 100-mm visual analogue scale - Short-term (up to 2 weeks)	454 (2 RCTs)	LOW[a,b]	-	mean 35.7	MD 10.56 lower (15.26 lower to 5.87 lower)
Pain 100-mm VAS % change Scale from: 0 to 100 follow up: mean 2 weeks	194 (2 RCTs)	VERY LOW[a,b,d]	-	mean -57.1	MD 10.32 lower (17.25 lower to 3.38 lower)
Joint swelling - Short-term (up to 2 weeks)	454 (2 RCTs)	LOW[a,b]	OR 1.58 (1.09 to 2.31)	Not provided	Could not be estimated[c]
Joint tenderness - Short-term (up to 2 weeks)	454 (2 RCTs)	MODERATE[a]	OR 2.16 (1.47 to 3.18)	Not provided	Could not be estimated[c]
Patient global assessment - Short-term (up to 2 weeks)	454 (2 RCTs)	MODERATE[a]	OR 1.98 (1.39 to 2.83)	Not provided	Could not be estimated[c]
Participant global assessment of response to treatment: good or excellent - Short-term (up to 2 weeks)	83 (1 RCT)	LOW[a]	RR 1.67 (1.29 to 2.17)	554 per 1000	371 more per 1000 (161 more to 648 more)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with corticosteroids	Risk difference with Il-1 inhibitors
Any adverse event-short -term (up to 2 weeks)	539 (3 RCTs)	LOW[a,b]	RR 1.20 (1.03 to 1.39)	507 per 1000	101 more per 1000 (15 more to 198 more)
Any adverse event-long-term >6 weeks	109 (1 RCT)	LOW[b]	RR 0.94 (0.59 to 1.49)	407 per 1000	24 fewer per 1000 (167 fewer to 200 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.Established MIDs for SF-36 physical/mental- 3.75; for VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.. Calculated MIDs for gout flares: 1, 2 and 3 were: 9.1, 10.3 and 5.9;

c. Absolute effect could not be estimated because studies only reported OR and did not report means separately for intervention and control arms. Inverse variance analysis method was used.

d. I^2= 79%, p=0.03

Table 7: Clinical evidence summary: ice plus prednisone and colchicine versus prednisone and colchicine

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with corticosteroids and colchicine	Risk difference with Ice and corticosteroids and colchicine
Pain (VAS 0-10) - Short-term (up to 2 weeks)	19 (1 RCT)	LOW[a,b]	-	mean 4.74	MD 3.94 lower (6.02 lower to 1.86 lower)
Joint circumference (joint swelling) (cm) - Short-term (up to 2 weeks)	19 (1 RCT)	VERY LOW[a,b]	-	mean 33.4 (cm)	MD 0.9 lower (9.45 lower to 7.65 higher)

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.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with corticosteroids and colchicine	Risk difference with Ice and corticosteroids and colchicine
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated, joint circumference: no baseline values reported so the control group SD was used:5.13.					

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study comparing naproxen and low-dose colchicine was included in this review[47]. This is summarised in the health economic evidence profile below (Table 8) and the health economic evidence table in Appendix H.

No additional health economic analyses comparing the other relevant comparisons listed in the protocol were identified for this review.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G

1.1.8 Summary of included economic evidence

Table 8: Health economic evidence profile: naproxen versus low-dose colchicine

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Roddy 2020 [47] (England)	Partially applicable [(a)]	Minor limitations [(b)]	• Within-RCT analysis (Open-label randomised pragramtic trial [CONTACT] comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care, Roddy 2020[47]) • Cost-utility analysis (QALYs) • Population: People 18 years and over consulting for a current gout flare. • Comparators: Naproxen versus low-dose colchicine Time horizon: 4 weeks	Saves £5.74[(c)]	0.0004 QALYs[(d)]	Naproxen dominates (less costly and more effective)	Probability naproxen cost effective (£20K threshold): 80%

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) The analysis uses EQ-5D-5L and so is not in line with the NICE reference case with preference for the EQ-5D-3L.
(b) Unit costs taken from 'standard UK sources' but no references provided, cost of PPIs not included for naproxen, short time horizon.
(c) 2015/16 costs. Cost components incorporated: Drug costs, GP costs, nurse costs, Emergency GP costs, A&E costs, intervention costs.
(d) QALYs adjusted for baseline values (both 'QALYs' and 'QALYs adjusted for baseline values' were reported in the study)

1.1.9 Economic model

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

1.1.10 Unit costs

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

Table 9: UK cost of NSAIDs for people without CKD

Drug[a]	Cost per unit	Daily dose	Cost per day	Cost per flare[b]
Celecoxib				
Celecoxib 100mg capsules	£0.03	200mg – 400mg	£0.07 - £0.13	£0.21 - £1.30
Diclofenac sodium				
Diclofenac sodium 50mg gastro-resistant tablets / Misoprostol 200microgram tablets	£0.20	150mg daily	£0.60	£1.80 - £6.00
Diclofenac sodium 50mg gastro-resistant tablets	£0.05		£0.15	£0.45 - £1.50
Etoricoxib				
Etoricoxib 60mg tablets	£0.10	120mg daily	£0.20	£0.60 - £2.00
Ibuprofen				
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21	£0.63 - £2.10
Ibuprofen 600mg tablets	£0.06	1.8g daily	£0.17	£0.51 - £1.70
Indomethacin				
Indomethacin 50mg capsules	£0.06	150mg – 200mg daily	£0.18 - £0.24	£0.54 - £2.90
Meloxicam				
Meloxicam 15mg orodispersible tablets sugar free	£0.85	7.5mg – 15mg daily	£0.85	£2.55 - £8.50
Meloxicam 15mg tablets	£0.16		£0.16	£0.48 - £1.60
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85		£0.85	£2.55 - £8.50
Meloxicam 7.5mg tablets	£0.11		£0.11	£0.33 - £1.10
Naproxen				
Naproxen 250mg effervescent tablets sugar free	£2.89	750mg – 1500mg daily	£8.66	£25.98 - £28.90
Naproxen 250mg gastro-resistant tablets	£0.14		£0.41	£1.23 - £4.10
Naproxen 250mg tablets	£0.05		£0.16	£0.48 - £1.60
Naproxen 250mg/5ml oral suspension	£0.45		£1.35	£4.05 - £13.50
Naproxen 500mg gastro-resistant tablets	£0.17		£0.51	£1.53 - £5.10
Naproxen 500mg tablets	£0.06		£0.19	£0.57 - £1.90

Sources:
(a) British National Formulary, Accessed October 2021[9]
Dosing: (b) Assuming people receive medication for 3 – 10 days

Table 10: UK cost of NSAIDs for people with CKD stage 3

Drug[(a)]	Cost per unit	Daily dose	Cost per day	Cost per flare[(b)]
Celecoxib				
Celecoxib 100mg capsules	£0.03	100mg – 400mg	£0.03 - £0.13	£0.09 - £1.30
Diclofenac sodium				
Diclofenac sodium 25mg gastro-resistant tablets	£0.06	75 – 150mg daily	£0.18	£0.54 - £1.80
Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets	£0.26		£0.79	£2.37 - £7.90
Diclofenac sodium 75mg gastro-resistant modified-release capsules	£0.14		£0.43	£1.29 - £4.30
Diclofenac sodium 75mg modified-release capsules	£0.20		£0.61	£1.83 - £6.10
Diclofenac sodium 75mg modified-release tablets	£0.31		£0.94	£2.82 - £9.40
Etoricoxib				
Etoricoxib 60mg tablets	£0.10	60mg – 120mg daily	£0.10 – £0.20	£0.30 - £2.00
Etoricoxib 90mg tablets	£0.09	90mg daily	£0.09	£0.27 - £0.90
Ibuprofen				
Ibuprofen 200mg tablets	£0.04	600mg daily	£0.15	£0.44 - £1.50
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21	£0.63 - £2.10
Ibuprofen 600mg tablets	£0.06	1.8g daily	£0.17	£0.51 - £1.70
Indomethacin				
Indomethacin 50mg capsules	£0.06	150mg – 200mg daily	£0.18 - £0.24	£0.54 - £2.40
Meloxicam				
Meloxicam 15mg orodispersible tablets sugar free	£0.85	7.5mg – 15mg daily	£0.85	£2.55 - £8.50
Meloxicam 15mg tablets	£0.16		£0.16	£0.48 - £1.60
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85		£0.85	£2.55 - £8.50
Meloxicam 7.5mg tablets	£0.11		£0.11	£0.33 - £1.10
Naproxen				
Naproxen 250mg effervescent tablets sugar free	£2.89	500mg – 1000mg daily	£5.78 – £11.56	£17.34 - £115.60
Naproxen 250mg gastro-resistant tablets	£0.08		£0.16 – £0.32	£0.48 - £3.20
Naproxen 250mg tablets	£0.05		£0.10 – £0.20	£0.20 - £2.00
Naproxen 250mg/5ml oral suspension	£0.45		£0.90 – £1.80	£2.70 - £18.00
Naproxen 500mg gastro-resistant tablets	£0.17		£0.17 - £0.34	£0.51 - £3.40

Naproxen 500mg tablets	£0.06		£0.06 - £0.12	£0.18 - £1.20

Sources:
(a) British National Formulary, Accessed October 2021[9]
Dosing: (b) Assuming people receive medication for 3 – 10 days

Table 11: UK cost of NSAIDs for people with CKD stage 4-5

Drug[(a)]	Cost per unit	Daily dose	Cost per day	Cost per flare[(b)]
Celecoxib				
Celecoxib 100mg capsules	£0.03	100mg – 200mg	£0.03 - £0.06	£0.09 - £0.60
Diclofenac sodium				
Diclofenac sodium 25mg gastro-resistant tablets	£0.06	75mg daily	£0.18	£0.54 - £1.80
Etoricoxib				
Etoricoxib 30mg tablets	£0.22	30mg daily	£0.22	£0.66 - £2.20
Etoricoxib 60mg tablets	£0.10	60mg daily	£0.10	£0.30 - £1.00
Ibuprofen				
Ibuprofen 200mg tablets	£0.04	600mg daily	£0.15	£0.44 - £1.50
Ibuprofen 400mg tablets	£0.07	1.2g daily	£0.21	£0.63 - £2.10
Indomethacin				
Indomethacin 25mg capsules	£0.05	75mg – 100mg daily	£0.15 - £0.20	£0.45 - £2.00
Meloxicam				
Meloxicam 7.5mg orodispersible tablets sugar free	£0.85	7.5mg daily	£0.85	£2.55 - £8.50
Meloxicam 7.5mg tablets	£0.11		£0.11	£0.33 - £1.10
Naproxen				
Naproxen 250mg effervescent tablets sugar free	£2.89	250mg – 750mg daily	£2.89 – £8.67	£8.67 - £86.70
Naproxen 250mg gastro-resistant tablets	£0.08		£0.08 – £0.24	£0.24 - £2.40
Naproxen 250mg tablets	£0.05		£0.05 – £0.15	£0.15 - £1.50
Naproxen 250mg/5ml oral suspension	£0.45		£0.45 – £1.35	£1.35 - £13.50
Naproxen 500mg gastro-resistant tablets	£0.17		£0.17	£0.36 - £1.20
Naproxen 500mg tablets	£0.06		£0.06	£0.18 - £0.60

Sources:
(a) British National Formulary, Accessed October 2021[9]
Dosing: (c) Assuming people receive medication for 3 – 10 days

Table 12: UK cost of Colchicine

Drug	Cost per unit	Daily dose	Cost per day	Cost per flare[(a)]
Colchicine 500microgram tablets	£0.05	1mg – 2mg daily	£0.10 - £0.20	£0.30 - £2.00

Source: NHS Drug Tariff, Accessed October 2021[43]
(a) Assuming people receive medication for 3 days

Table 13: 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 per gout flare
Methylprednisolone 80mg/2ml / Lidocaine 20mg/2ml (1%) suspension for injection vials	£7.06	1 injection per gout flare
Methylprednisolone acetate 120mg/3ml suspension for injection vials	£8.96	1 injection per gout flare
Methylprednisolone acetate 40mg/1ml suspension for injection vials	£3.44	1 injection per gout flare
Methylprednisolone acetate 80mg/2ml suspension for injection vials	£6.18	1 injection per gout flare
Prednisolone		
Prednisolone 5mg tablets	£0.03	30mg daily (costing £0.18 per day)
Triamcinolone		
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 per gout flare
Triamcinolone hexacetonide 20 mg/1ml suspension for injection ampules	£12.00	1 injection per gout flare

Source: NHS Drug Tariff, Accessed October 2021[43]

Table 14: 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[9]
Note: PPI's are a gastro-resistant tablet which can be prescribed in conjunction with NSAIDs and oral corticosteroids.

Table 15: UK cost of IL-1 Inhibitors

Drug	Cost per unit	Dosage
Anakinra		
Anakinra 100mg /0.67ml solution for injection pre-filled syringes	£26.23	3-5 injections per gout flare
Canakinumab		
Canakinumab 150mg per 1ml solution for injection vials	£9,928	1 injection per gout flare

Source: British National Formulary, Accessed October 2021[9]

1.1.11 Evidence statements

Economic

- One cost-utility analysis found that naproxen was cost effective compared to low-dose colchicine for the treatment of gout flares. Naproxen was the dominant strategy (less costly and more effective). This analysis was assessed as partially applicable with minor limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. 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, patient global assessment of treatment success, adverse events (cardiovascular, renal and gastrointestinal), admission (hospital and A&E/urgent care) and GP visits.

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).

1.1.12.2 The quality of the evidence

Eleven randomised controlled trials (RCTs) evaluating pharmacological therapy and one randomised controlled trial (RCT) evaluating combination therapy (pharmacological and non-pharmacological interventions) for managing gout flares were included in this review.

One RCT evaluated the use of colchicine versus placebo. The evidence was limited as only two outcomes were reported by the study. The outcome data was only available for pain (proportion of joints with 50% or greater decrease in pain score (on VAS) from baseline) and gastrointestinal adverse events (diarrhoea and vomiting). Both were reported as short-term outcomes (up to 2 weeks). The quality of pain (proportion of joints with 50% or greater decrease in pain score (on VAS) from baseline) outcome was graded as moderate due to high risk of selection bias. The quality of the gastrointestinal adverse events outcome was graded very low due to high risk of selection bias and imprecision.

Four studies evaluated the use of corticosteroids versus NSAIDs. The outcome data was reported for pain (VAS, number of patients with clinically significant change in pain score at

rest and number of patients with clinically significant change in pain score with activity), joint tenderness, adverse events (gastrointestinal and cardiovascular), number of patients visited ED, number of patients visited outpatient department and GP visits. All outcomes were reported as short-term (up to 2 weeks). The quality of evidence ranged from high to low quality due to lack of blinding, imprecision and inconsistency.

Two studies compared NSAIDs versus colchicine. The outcome data was reported for pain (change score), complete pain resolution, joint swelling scores, patient assessment of global treatment response (completely/much better), adverse events (gastrointestinal), number of patients visited ED and GP visits. Outcomes were reported as short term (up to 2 weeks) and medium-term (2 to 6 weeks). The quality of evidence ranged from high to very low quality due to lack of blinding, attrition bias and imprecision.

Three studies compared IL-1 inhibitors versus corticosteroids. The outcome data was reported for health-related quality of life SF 36 (physical and mental components), pain (VAS and VAS % change), joint swelling, joint tenderness, patient global assessment (OR), patient global assessment (good or excellent) and adverse events (any). Outcomes were reported as short term (up to 2 weeks) and long-term (more than 6 weeks). The quality of evidence ranged from moderate to very low quality due selection bias, lack of blinding and imprecision.

One study compared ice therapy plus corticosteroids and colchicine versus no ice therapy plus corticosteroids and colchicine. The outcome data was only reported for pain (VAS) and joint circumference (joint swelling). Both outcomes were reported as short-term (up to 2 weeks). The quality of evidence ranged from low to very low quality due to selection bias, lack of blinding and imprecision.

1.1.12.3 Benefits and harms

The evidence showed a clinical benefit for colchicine when compared with placebo for reducing pain (50% or greater decrease in pain scores from baseline), however the evidence indicated clinical harm for gastrointestinal adverse events (diarrhoea and vomiting) in the colchicine group in the short-term (up to 2 weeks).

The evidence showed a clinical benefit for corticosteroids when compared to NSAIDs for short-term (up to 2 weeks) gastrointestinal adverse events (abdominal pain, indigestion, nausea, vomiting, diarrhoea and GI haemorrhage). The evidence suggested that there was no clinically important difference for pain, joint tenderness, cardiovascular adverse events, number of patients who visited emergency and outpatient departments, and G.P. visits.

The evidence showed a clinical benefit for NSAIDs when compared to colchicine for short-term (up to 2 weeks) gastrointestinal adverse events (nausea and or vomiting, diarrhoea and constipation). There was no difference for abdominal pain, dyspepsia or vomiting at 2 weeks or any of these outcomes in the medium-term (2 to 6 weeks). The evidence suggested that there was no clinically important difference for pain outcomes (change score, complete pain resolution at short-term (up to 2 weeks) and medium term (2 to 6 weeks), joint swelling scores, patient assessment of global treatment response (completely/much better at short-term (up to 2 weeks) and medium-term (2 to 6 weeks)), number of patients visiting ED (medium-term 2 to 6 weeks) and number of GP visits (medium-term 2 to 6 weeks).

The evidence showed a clinical benefit for IL-1 inhibitors compared to corticosteroids for health related quality of life outcomes: SF36 physical component at short term (up to 2 weeks) and long-term (more than 6 weeks), SF-36 mental component long-term (more than 6 weeks), pain outcomes (VAS and VAS % change both short-term up to 2 weeks) and participant global assessment of response to treatment (good or excellent short up to 2 weeks). The evidence showed clinical benefit for corticosteroids compared to IL-1 inhibitors for any adverse events in the short-term. For joint swelling, joint tenderness and patient global assessment outcomes absolute effects and clinical significance could not be

estimated as studies only reported odds ratios and did not report means separately for intervention and control arms, but the results favoured corticosteroids.

The evidence showed a clinical benefit for combination therapy ice and corticosteroid and colchicine compared with no ice therapy and corticosteroid and colchicine for pain (VAS). The evidence suggested no clinical difference for joint circumference (joint swelling).

Treatment options for managing gout flares

Overall, the evidence showed no clinical difference for NSAIDs compared to colchicine and corticosteroids for most of the outcomes. There was some evidence of benefit for colchicine when compared to placebo for pain outcome. However, there was also evidence of harm for colchicine when comparing both to placebo and NSAIDs for gastrointestinal adverse events. The evidence also suggested that there is clinical benefit for corticosteroids when compared to NSAIDs for gastrointestinal adverse events. The committee discussed that in current practice NSAIDs, or colchicine would usually be prescribed first before using corticosteroids. The committee discussed when considering treatments for older patients, colchicine would not be the first choice because of risk of side effects, and when prescribing corticosteroids, the lowest dose would be used. The committee also noted NSAIDs are potentially nephrotoxic, with renal adverse effects including AKI, renal disease progression and hyperkalaemia. The risks are highest in those with more advanced CKD and are increased in older people and those taking inhibitors of the RAS and diuretics. They agreed NSAIDS would be prescribed taking into account patient characteristics, the CKD stage and duration of therapy.

After reviewing the evidence, the committee agreed that the evidence was not strong for any of the drugs and concluded recommendations should reflect current practice of considering either NSAIDs, colchicine or a corticosteroid based on the presence of any comorbidities, other medications being taken and the preference of the patient.

Based on their experience the committee decided to recommend considering co-prescribing proton pump inhibitor (PPI) for people taking an NSAID for a flare. They acknowledged PPI are not always prescribed if NSAIDS were only to be taken for a short period of time.

The committee noted intra-articular and intra-muscular corticosteroids are more commonly used to manage gout flare in secondary care than in GP practices, Oral corticosteroid can be given as a first-line option but corticosteroid by injection could be considered.

IL-1 inhibitors showed clinical benefit when compared to corticosteroids for the vast majority of outcomes, however the committee agreed the cost of IL1-inhibitors is high and there are effective alternative drugs available and therefore this drug would not usually be considered for the vast majority of people with a flare. The committee noted this treatment is used in very few centres in the UK and would only be considered appropriate for a very small population such as people with contraindications or non-response to all NSAIDS, colchicine and corticosteroids. Therefore, the committee decided to make a “do not offer” recommendation for IL-1 inhibitors unless the other drugs had been tried or were contraindicated or not tolerated.

The evidence showed clinical benefit for ice therapy compared to no ice therapy for pain (VAS) outcome. The committee considered evidence from only one small study to be limited, however in their experience applying ice can help to ease pain and inflammation and it is a simple and inexpensive treatment people can try. Therefore, the committee decided to recommend ice therapy as an adjunct to pharmacological treatments.

1.1.12.4 Cost effectiveness and resource use

One economic evaluation was identified for this review. The included health economic study compared naproxen to low-dose colchicine, illustrating that naproxen was the dominant

strategy (less costly and more effective). In addition, naproxen had an 80% chance of being cost effective at NICE's £20,000 threshold. The included health economic evidence only evaluated the cost effectiveness of naproxen and low dose colchicine and did not include other drugs relevant to this review question (NSAIDs other than naproxen, corticosteroids and IL-1 inhibitors), therefore unit costs were also presented to aid committee consideration of cost effectiveness.

The committee discussed the limitations of the included health economic study, noting that the cost of PPIs were not included for the total costs of naproxen. Although, the committee noted the cost of PPIs are relatively cheap, costing £0.06 – £0.98 per unit. The committee also acknowledged that PPIs may not be prescribed to all patients receiving NSAIDs if the duration of treatment is short and not anticipated to be long-term. For example, PPIs may not be required if a person is only anticipated to receive NSAIDs for the treatment of gout flares and they are only expected to experience one or two gout flares per year (where flares last for an average duration of four to five days).

Considering the costs of PPIs and the costs presented in the included health economic study, the committee concluded the overall results of the cost effectiveness analysis would unlikely be changed if the costs of PPIs had been included in the analysis. The total costs for naproxen and colchicine presented in the health economic study were £17.57 and £23.31 respectively. In the analysis, naproxen was prescribed for a total of seven days, therefore assuming a cost of £0.06 - £0.98 per day for the cost of a PPI, the total cost for naproxen would increase by £0.42 - £6.86 – resulting in a total cost of £17.99 - £24.43. Although £24.43 is more expensive than the total cost of colchicine (£23.31). The committee noted that the range for the cost of PPIs was predominately driven by the cost of Omeprazole 40mg, costing £0.98. Excluding the cost of Omeprazole 40mg, the cost of PPIs ranges from £0.06 - £0.49. When PPIs cost a maximum £0.49 the total cost for naproxen is £19.74 which is cheaper than the total cost of colchicine (£23.31).

The committee noted the use of PPIs would not affect the effectiveness of NSAIDs and so naproxen would still be the dominant strategy (less costly and more effective) when all PPIs, except Omeprazole 40mg, are prescribed. When Omeprazole 40mg is prescribed, naproxen is more costly and more effective and the ICER is £2,800 per QALY gained. However, in general, the committee did note that the time horizon of the analysis (4 weeks) was not sufficiently long enough to capture the long-term adverse events for not prescribing a PPI.

Overall although the included health economic study illustrated that naproxen was the dominant strategy compared to low dose colchicine, due to potential limitations of this study and committee opinion, the committee made an 'offer' recommendation for; NSAIDs, low dose colchicine, and prednisolone as a first-line treatment for a gout flare. The committee noted that when prescribing therapeutic treatment for a gout flare – in the form of NSAIDs, low dose colchicine and oral prednisolone – it is important to take account of patient comorbidities, co-prescribing and patient preferences. The committee also considered the costs of NSAIDs, low dose colchicine, and prednisolone and concluded that all interventions would be cost effective at NICE's £20,000 threshold, whereby the most cost-effective intervention would be patient specific. For example, in people where NSAIDs or low dose colchicine are contraindicated or not tolerated, oral prednisolone would be the most cost-effective drug for managing gout flares. This recommendation is not expected to result in a substantial resource impact as the recommendation is reflective of current practice in England.

The committee discussed that in instances where NSAIDs, low dose colchicine or oral prednisolone are contraindicated, not tolerated or not effective, intra-articular or intra-muscular corticosteroid injection may also be appropriate. The committee acknowledged that, if clinically appropriate, oral prednisolone should be prescribed as a first-line corticosteroid because oral prednisolone is cheaper than intra-articular or intra-muscular corticosteroid injections. Oral prednisolone costs £0.18 per day and is typically prescribed for

five days, costing £0.90. Intra-articular or intra-muscular injections cost £1.49 - £12.00 per injection but will also have additional costs in terms of nurse administration time. Overall, the committee made a 'consider' recommendation for the use of, intra-articular or intra-muscular corticosteroid injections. This recommendation is not expected to have a substantial resource impact as it is reflective of current practice.

The committee also discussed the use of IL-1 inhibitors, noting that less than 1% of gout patients would be prescribed an IL-1 inhibitor for treatment of a gout flare. Clinical evidence was presented comparing canakinumab and intramuscular corticosteroids (triamcinolone). However, the cost of canakinumab is much greater than triamcinolone (£9,927 and £0.89 - £12.00 per injection respectively) therefore the committee concluded it was highly unlikely Canakinumab would be an effective use of NHS resources.

The committee also discussed the use of anakinra, which is the additional IL-1 inhibitor included in the clinical protocol. No clinical evidence was presented for anakinra, but the committee noted Anakinra is substantially cheaper than canakinumab. Anakinra costs £26.23 per unit and typically three to five doses of anakinra will be given to people for management of a gout flare, costing £78.69 - £131.15. Conversely, canakinumab costs £9,928 per unit, with one injection given for the treatment of a gout flare.

Overall, IL-1 inhibitors are substantially more expensive than NSAIDs, low dose colchicine, and corticosteroids. Therefore, the committee made a 'do not offer' recommendation for the use of IL-1 inhibitors. The committee did however acknowledge that in clinical practice IL-1 inhibitors are sometimes prescribed for patients with the most severe gout where all other treatment options have failed, noting people should be referred to rheumatology services before prescribing an IL-1 inhibitor. Based on clinical experience, the committee concluded that IL-1 inhibitors could be cost effective for patients where NSAIDs, low dose colchicine, and corticosteroids are contraindicated or not tolerated because gout flares can be extremely painful. This recommendation is not expected to have a substantial resource impact as it is reflective of current practice.

Non-pharmacological interventions for managing gout flares are typically recommended in conjunction with pharmacological interventions. The cost of ice is borne by patients themselves and so will not have a substantial resource impact.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1 to 1.3.5 and the research recommendation on the clinical and cost effectiveness of colchicine compared with corticosteroids for managing gout flares?

1.1.14 References

1. Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. Australian and New Zealand Journal of Medicine. 1987; 17(3):301-304

2. Alloway JA, Moriarty MJ, Hoogland YT, Nashel DJ. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. Journal of Rheumatology. 1993; 20(1):111-113

3. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. Journal of Rheumatology. 1988; 15(9):1422-1426

4. Anonymous. COX-2 effective for gout. Pharmaceutical Journal. 2002; 268(7204):898

5. Anonymous. Treatment of gout attacks. Prescrire International. 2008; 17(95):123

6. Araujo F, Cordeiro I, Ramiro S, Falzon L, Branco JC, Buchbinder R. Outcomes assessed in trials of gout and accordance with OMERACT-proposed domains: a systematic literature review. Rheumatology. 2015; 54(6):981-993

7. Balasubramaniam G, Parker T, Turner D, Parker M, Scales J, Harnett P et al. Feasibility randomised multicentre, double-blind, double-dummy controlled trial of anakinra, an interleukin-1 receptor antagonist versus intramuscular methylprednisolone for acute gout attacks in patients with chronic kidney disease (ASGARD): protocol study. BMJ Open. 2017; 7(9):e017121

8. Billy CA, Lim RT, Ruospo M, Palmer SC, Strippoli GFM. Corticosteroid or nonsteroidal antiinflammatory drugs for the treatment of acute gout: A systematic review of randomized controlled trials. Journal of Rheumatology. 2018; 45(1):128-136

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

10. Bruce SP. Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout. Annals of Pharmacotherapy. 2006; 40(12):2187-2194

11. Butler RC, Goddard DH, Higgens CS, Hollingworth P, Pease CT, Stodell MA et al. Double-blind trial of flurbiprofen and phenylbutazone in acute gouty arthritis. British Journal of Clinical Pharmacology. 1985; 20(5):511-513

12. Cheng TT, Lai HM, Chiu CK, Chem YC. A single-blind, randomized, controlled trial to assess the efficacy and tolerability of rofecoxib, diclofenac sodium, and meloxicam in patients with acute gouty arthritis. Clinical Therapeutics. 2004; 26(3):399-406

13. Daoussis D, Kordas P, Collaborators. ACTH vs betamethasone for the treatment of acute gout in hospitalized patients: A randomized, open label, comparative study. Mediterranean Journal of Rheumatology. 2018; 29(3):178-181

14. Denman M. Prednisolone was equivalent to indomethacin for pain reduction in acute gout: Commentary. Annals of Internal Medicine. 2016; 164(10):JC51

15. Dumusc A, So A. Interleukin-1 as a therapeutic target in gout. Current Opinion in Rheumatology. 2015; 27(2):156-163

16. Fravel MA, Ernst ME. Management of gout in the older adult. American Journal of Geriatric Pharmacotherapy. 2011; 9(5):271-285

17. Guillot X, Tordi N, Laheurte C, Pazart L, Prati C, Saas P et al. Local ice cryotherapy decreases synovial interleukin 6, interleukin 1beta, vascular endothelial growth factor,

prostaglandin-E2, and nuclear factor kappa B p65 in human knee arthritis: a controlled study. Arthritis Research & Therapy. 2019; 21(1):180

18. Hay CA, Prior JA, Belcher J, Mallen CD, Roddy E. Mortality in patients with gout treated with allopurinol: a systematic review and meta-analysis. Arthritis Care and Research. 2021; 73(7):1049-1054

19. Hu AM, Brown JN. Comparative effect of allopurinol and febuxostat on long-term renal outcomes in patients with hyperuricemia and chronic kidney disease: a systematic review. Clinical Rheumatology. 2020; 39(11):3287-3294

20. Huizinga T, Nigrovic P, Ruderman E, Schulze-Koops H. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: Results of a double-blind, randomised study - Commentary. International Journal of Advances in Rheumatology. 2011; 9(4):150

21. Huizinga T, Nigrovic P, Ruderman E, Schulze-Koops H. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Commentary. International Journal of Advances in Rheumatology. 2010; 8(3):120

22. Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, van de Laar M. Development and validation of a patient-reported gout attack intensity score for use in gout clinical studies. Rheumatology. 2019; 58(11):1928-1934

23. Janssen CA, Oude Voshaar MAH, Vonkeman HE, Jansen TLTA, Janssen M, Kok MR et al. Anakinra for the treatment of acute gout flares: A randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. Rheumatology. 2019; 58(8):1344-1352

24. Janssens H, Lucassen P, Van dLF, Janssen M, Van dLE. Systemic corticosteroids for acute gout. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005521. DOI: 10.1002/14651858.CD005521.pub2.

25. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet. 2008; 371(9627):1854-1860

26. Janssens HJEM, Janssen M, Van De Lisdonk EH, Van Riel PLCM, Van Weel C. [Prednisolone, a suitable first-choice treatment for gout pain: a randomized, double-blind, equivalent trial with naproxen as reference]. Nederlands Tijdschrift voor Geneeskunde. 2009; 153(23):1108-1116

27. Jomori T, Saitoh K, Hosoya T. Effects of topiroxostat on the serum urate levels and urinary albumin excretion in concomitant therapy or in primary disease of chronic kidney disease: -A post hoc analysis of multicenter, randomized, placebo-controlled, double-blind study in hyperuricemic stage 3 chronic kidney disease patients with or without gout. Japanese pharmacology and therapeutics. 2015; 43(1):39-50

28. Khanna PP, Gladue HS, Singh MK, FitzGerald JD, Bae S, Prakash S et al. Treatment of acute gout: a systematic review. Seminars in Arthritis and Rheumatism. 2014; 44(1):31-38

29. Lederman R. A double-blind comparison of Etodolac (Lodine) and high doses of naproxen in the treatment of acute gout. Advances in Therapy. 1990; 7(6):344-354

30. Li T, Chen SL, Dai Q, Han XH, Li ZG, Wu DH et al. Etoricoxib versus indometacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. Chinese Medical Journal. 2013; 126(10):1867-1871

31. Lin TM, Chi JE, Chang CC, Kang YN. Do etoricoxib and indometacin have similar effects and safety for gouty arthritis? A meta-analysis of randomized controlled trials. Journal of Pain Research. 2019; 12:83-91

32. Liu P, Chen Y, Wang B, Wang Z, Li C, Wang Y. Expression of microRNAs in the plasma of patients with acute gouty arthritis and the effects of colchicine and etoricoxib on the differential expression of microRNAs. Archives of Medical Science. 2019; 15(4):1047-1055

33. Liu X, Sun D, Ma X, Li C, Ying J, Yan Y. Benefit-risk of corticosteroids in acute gout patients: An updated meta-analysis and economic evaluation. Steroids. 2017; 128:89-94

34. Liu Y, Li ZC, Chen JB, Yu TT, Cui C, Zhang HB. [Therapeutic efficacy of small doses of colchicine combined with glucocorticoid for acute gouty arthritis]. Medical journal of chinese people's liberation army. 2015; 40(8):652-655

35. Lundberg GD. Prednisolone and naproxen both work for pain relief in acute gout. Medscape Journal of Medicine. 2008; 10(9):207

36. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Current Medical Research and Opinion. 1991; 12(7):423-429

37. Man CY, Cheung IT, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. Annals of Emergency Medicine. 2007; 49(5):670-677

38. Martina SD, Vesta KS, Ripley TL. Etoricoxib: a highly selective COX-2 inhibitor. Annals of Pharmacotherapy. 2005; 39(5):854-862

39. Moon KT. Low-dose colchicine effective for acute gout flare-ups. American Family Physician. 2011; 83(3):316

40. 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

41. 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

42. Navarra S, Rubin BR, Yu Q, Smugar SS, Tershakovec AM. Association of baseline disease and patient characteristics with response to etoricoxib and indomethacin for acute gout. Current Medical Research and Opinion. 2007; 23(7):1685-1691

43. 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.

44. Parperis K. Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care. Annals of the Rheumatic Diseases. 2019; Epub

45. Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ, Herrero-Beites A, Ruiz-Lucea E, Garcia-Erauskin G et al. Treatment of chronic gout in patients with renal function

impairment: an open, randomized, actively controlled study. JCR: Journal of Clinical Rheumatology. 1999; 5(2):49-55

46. Rainer TH, Cheng CH, Janssens HJ, Man CY, Tam LS, Choi YF et al. Oral prednisolone in the treatment of acute gout: A pragmatic, multicenter, double-blind, randomized trial. Annals of Internal Medicine. 2016; 164(7):464-471

47. Roddy E, Clarkson K, Blagojevic-Bucknall M, Mehta R, Oppong R, Avery A et al. Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care. Annals of the Rheumatic Diseases. 2020; 79(2):276-284

48. Roddy E, Mallen CD. Naproxen or low-dose colchicine for gout flares in primary care? Response to: 'Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care' by Parperis et al. Annals of the Rheumatic Diseases. 2019;

49. Rubin BR, Burton R, Navarra S, Antigua J, Londono J, Pryhuber KG et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis and Rheumatism. 2004; 50(2):598-606

50. Saag KG, Khanna PP, Keenan RT, Ohlman S, Osterling Koskinen L, Sparve E et al. A randomized, phase 2 study evaluating the efficacy and safety of anakinra in the treatment of gout flares. Arthritis & Rheumatology. 2021; 73(8):1533-1542

51. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Annals of the Rheumatic Diseases. 2012; 71(11):1839-1848

52. Schlesinger N, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V et al. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat Gouty Arthritis by suppressing inflammation: results of a randomized, dose-ranging study. Arthritis Research & Therapy. 2011; 13(2):R53

53. Schlesinger N, Detry MA, Holland BK, Baker DG, Beutler AM, Rull M et al. Local ice therapy during bouts of acute gouty arthritis. Journal of Rheumatology. 2002; 29(2):331-334

54. 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

55. Schlesinger N, Norquist JM, Watson DJ. Serum urate during acute gout. Journal of Rheumatology. 2009; 36(6):1287-1289

56. Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos-Vargas R, Li C. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. Journal of Rheumatology. 2012; 39(9):1859-1866

57. Schumacher HR, Jr., Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ. 2002; 324(7352):1488-1492

58. 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

59. Sharma E, Pedersen B, Terkeltaub R. Patients prescribed anakinra for acute gout have baseline increased burden of hyperuricemia, tophi, and comorbidities, and ultimate all-cause mortality. Clinical medicine insights Arthritis and musculoskeletal disorders. 2019; 12:1179544119890853

60. Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A et al. Management of gout: A systematic review in support of an American college of physicians clinical practice guideline. Annals of Internal Medicine. 2017; 166(1):37-51

61. Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. Annals of Emergency Medicine. 1995; 26(6):682-686

62. Sivera F, Wechalekar M, Andrés M, Buchbinder R, Carmona L. Interleukin-1 inhibitors for acute gout. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD009993. DOI: 10.1002/14651858.CD009993.pub2.

63. So A, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study. Arthritis and Rheumatism. 2010; 62(10):3064-3076

64. So A, DeMeulenmeester M, Ycel E, Arulmani U, Richard D, Murphy V et al. Canakinumab relieves symptoms of acute flares and improves health-related quality of life (HRQoL) in difficult-to-treat gouty arthritis patients by suppressing inflammation: results of a randomized, dose-ranging study. Journal of Allergy and Clinical Immunology. 2011; 127(2 Suppl 1):AB227

65. Solomon DH, Glynn RJ, MacFadyen JG, Libby P, Thuren T, Everett BM et al. Relationship of interleukin-1beta blockade with incident gout and serum uric acid levels: Exploratory analysis of a randomized controlled trial. Annals of Internal Medicine. 2018; 169(8):535-542

66. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Research & Therapy. 2020; 22(1):28

67. Stubbs DF, Freeman BE. Efficacy comparisons of flurbiprofen and other nonsteroidal anti-inflammatory drugs in arthritic diseases. Current Therapeutic Research - Clinical and Experimental. 1989; 46(3):511-528

68. Sturge RA, Scott JT, Hamilton EB, Liyanage SP, Dixon AS, Davies J et al. Multicentre trial of naproxen and phenylbutazone in acute gout. Annals of the Rheumatic Diseases. 1977; 36(1):80-82

69. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis and Rheumatism. 2010; 62(4):1060-1068

70. Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J et al. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Research & Therapy. 2013; 15(1):R25

71. Underwood M. Gout. Clinical Evidence. 2015; 2015

72. Valdes EF. Use of tenoxicam in patients with acute gouty arthritis. European Journal of Rheumatology and Inflammation. 1987; 9(2):133-136

73. van DC, Wechalekar M, Buchbinder R, Schlesinger N, van dHD, Landewé R. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD010120. DOI: 10.1002/14651858.CD010120.pub2.

74. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: 620615690. DOI: http://dx.doi.org/10.1002/14651858.CD006190.pub2.

75. van Echteld IA, van Durme C, Falzon L, Landewe RB, van der Heijde DM, Aletaha D. Treatment of gout patients with impairment of renal function: a systematic literature review. Journal of Rheumatology - Supplement. 2014; 92:48-54

76. Wechalekar MD, Vinik O, Moi JH, Sivera F, van Echteld IA, van Durme C et al. The efficacy and safety of treatments for acute gout: results from a series of systematic literature reviews including Cochrane reviews on intraarticular glucocorticoids, colchicine, nonsteroidal antiinflammatory drugs, and interleukin-1 inhibitors. Journal of Rheumatology - Supplement. 2014; 92:15-25

77. Wechalekar MD, Vinik O, Schlesinger N, Buchbinder R. Intra-articular glucocorticoids for acute gout. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: 23633379. DOI: https://dx.doi.org/10.1002/14651858.CD009920.pub2.

78. Weiner GI, White SR, Weitzner RI, Rubinstein HM. Double-blind study of fenoprofen versus phenylbutazone in acute gouty arthritis. Arthritis and Rheumatism. 1979; 22(4):425-426

79. Willburger RE, Mysler E, Derbot J, Jung T, Thurston H, Kreiss A et al. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. Rheumatology. 2007; 46(7):1126-1132

80. Xu L, Liu S, Guan M, Xue Y. Comparison of prednisolone, etoricoxib, and indomethacin in treatment of acute gouty arthritis: An open-label, randomized, controlled trial. Medical Science Monitor. 2016; 22:810-817

81. Xu Z, Zhang R, Zhang D, Yao J, Shi R, Tang Q et al. Peptic ulcer hemorrhage combined with acute gout: analyses of treatment in 136 cases. International Journal of Clinical and Experimental Medicine. 2015; 8(4):6193-6199

82. Yu J, Lu H, Zhou J, Xie Z, Wen C, Xu Z. Oral prednisolone versus non-steroidal anti-inflammatory drugs in the treatment of acute gout: a meta-analysis of randomized controlled trials. Inflammopharmacology. 2018; 26(3):717-723

83. Yu Y, Zhou Q, Yang N, Zhang J, Song X, Gao L et al. Treatment for acute flares of gout: An overview of systematic reviews. Chinese Journal of Evidence-Based Medicine. 2018; 18(10):1080-1085

84. Zeng L, Qasim A, Neogi T, Fitzgerald JD, Dalbeth N, Mikuls TR et al. Comparative efficacy and safety of pharmacological interventions in patients experiencing a gout flare: a systematic review and network meta-analysis. Arthritis Care Res (Hoboken). 2020;

85. Zhang S, Zhang Y, Liu P, Zhang W, Ma JL, Wang J. Efficacy and safety of etoricoxib compared with NSAIDs in acute gout: a systematic review and a meta-analysis. Clinical Rheumatology. 2016; 35(1):151-158

86. Zhang YK, Yang H, Zhang JY, Song LJ, Fan YC. Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout. International Journal of Clinical Practice. 2014; 68(5):633-638

Appendices

Appendix A – Review protocols

Review protocol for pharmacological and non -pharmacological interventions for managing gout flares

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	The clinical and cost effectiveness of pharmacological interventions including NSAIDs, colchicine, corticosteroids and IL-1 inhibitors and non-pharmacological interventions for managing gout flares
2.	Review question	What is the clinical and cost effectiveness of pharmacological interventions (including NSAIDs, colchicine, corticosteroids and IL-1 inhibitors) and non-pharmacological interventions for managing gout flares?
3.	Objective	To determine which pharmacological and non-pharmacological interventions are the most clinically and cost-effective for managing gout flares.
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 Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details) 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 flares Strata: • People with chronic kidney disease (stage 3) • People with chronic kidney disease (stage 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	• 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 • Triamcinolone • IL-1 inhibitors (commonly used in clinical practice in the UK) • Anakinra • Canakinumab • Non-pharmacological interventions - rest, elevation, bed cages and ice • Combinations (pharmacological + non-pharmacological)

		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 [This guideline will be updating and replacing the TA on canakinumab (TA281) - evidence included in this review will be relevant for this]
8.	Comparator	• Compared to each other • Standard care/usual care • Control/no intervention • 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	There are a range of pharmacological and non-pharmacological lifestyle interventions available to manage gout flares for adults (18 years and over) in various healthcare settings including primary care and secondary care.
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 • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) (total adverse events will be reported if the specific types of adverse events are not reported) • admissions (hospital and A&E) • GP visits Timepoints: short (up to two weeks), medium (two to six weeks) and long (> six weeks) term
13.	Secondary outcomes (important outcomes)	
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. EPPI Reviewer-5 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 be conducted. NMA will be prioritised for the following outcomes, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence: • 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 tenderness • admissions (hospital and A&E) • gout-specific QoL • 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

<table>
<tr><td></td><td></td><td colspan="3">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.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups that will be investigated if heterogeneity is present:

• Choice of drug (drugs within the class, based on the intervention arm only)
• Doses of colchicine (total daily dose: <=1mg, 1.5-2mg, >2mg)
• Setting (Primary vs secondary)
• Previous treatment</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">17th September 2020</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">13th June 2022</td></tr>
<tr><td rowspan="3">23.</td><td rowspan="3">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
</table>

		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 managementofgout@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		
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.	
32.	Keywords	Gout, NSAIDs, colchicine, corticosteroids and IL-1 inhibitors, gout flares, rest, ice, elevation	
33.	Details of existing review of same topic by same authors	NA	
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	

1

2

1 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.[40] **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.

1

Appendix B – Literature search strategies

- What is the clinical and cost effectiveness of pharmacological interventions (including NSAIDs, colchicine, corticosteroids and IL-1 inhibitors) and non-pharmacological interventions for managing gout flares?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[41]

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 16: 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)

1 **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 17: 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)

1 **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)

1 **NHS EED and HTA (CRD) search terms**

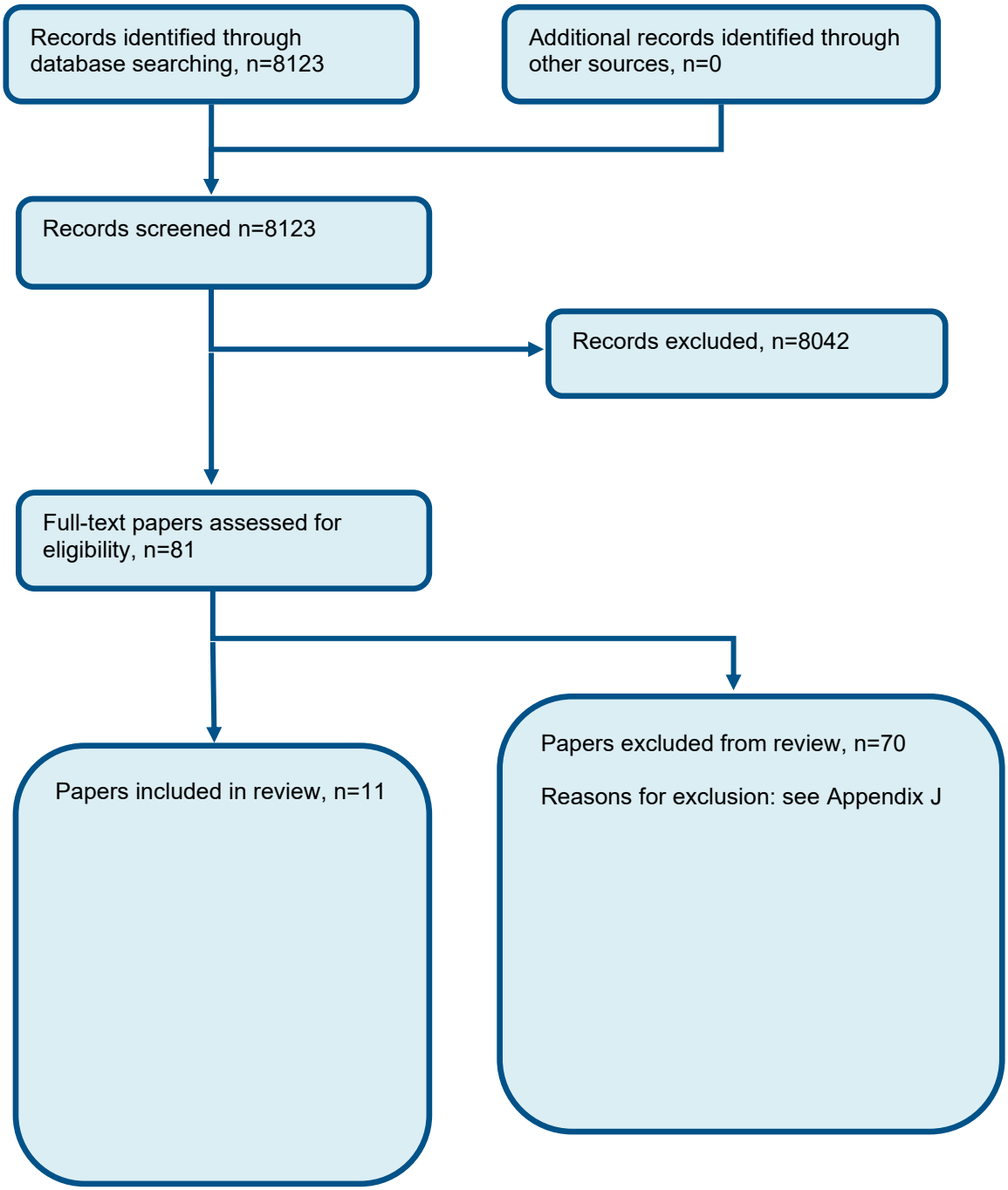
#1.	MeSH DESCRIPTOR Gout EXPLODE ALL TREES
#2.	(gout*)
#3.	(toph*)
#4.	MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES

#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

1
2

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of pharmacological and non-pharmacological management of gout flares



Appendix D – Effectiveness evidence

Study	Ahern 1987[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Australia; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: acute gout confirmed by joint aspiration and the demonstration of negatively birefringent needle-shaped crystals using a polarizing light microscope with first-order red compensator. Only minimal amounts of synovial fluid were extracted from the affected joints.
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with proven acute gout
Exclusion criteria	Not stated
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Colchicine 69(8), Placebo70(8). Gender (M:F): 40/3. Ethnicity: Not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Primary care
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Colchicine. The initial dose of (oral) Colchicine was 1 mg, followed by o.5 mg every two hours until complete response or toxicity (nausea, vomiting or diarrhoea) occurred. Duration 48 hours. Concurrent medication/care: No concomitant non-steroidal anti-inflammatory agents or analgesics were allowed 48 hours before entry or during the trial. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine). 2. Doses (historically high vs low): Define (The initial dose of (oral) Colchicine was 1 mg, followed by o.5 mg every two hours until complete response or toxicity (nausea, vomiting or diarrhoea) occurred.). (n=21) Intervention 2: Placebo. Matching oral placebo. Duration 48 hours. Concurrent medication/care: No concomitant

	non-steroidal anti-inflammatory agents or analgesics were allowed 48 hours before entry or during the trial. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (Placebo). 2. Doses (historically high vs low): Define (matching placebo).
Funding	Funding not stated

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

Protocol outcome 1: Pain at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: pain score - percentage of joints which showed a 50% decrease in baseline measures. at 48 hours after treatment; Group 1: 16/22, Group 2: 8/21; Comments: percentage of joints in Colchicine and placebo groups which showed 50 % decrease in baseline measures.
number of joints involved Colchicine group - 22, placebo group 22
Data was presented in percentages 73% vs 36%

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Joint swelling/joint inflammation at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Clinical score (compounded score comprising pain, tenderness on palpitation, swelling, and redness graded on four point scale(none 0, mild 1, moderate 2, severe 3) was also included) - percentage of joints which showed a 50% decrease in baseline measures. at 48 hours after treatment; Group 1: 14/22, Group 2: 5/21; Comments: percentage of joints in Colchicine and placebo groups which showed 50 % decrease in baseline measures.
number of joints involved Colchicine group - 22, placebo group 22
data was presented in percentages 64% vs 23%
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Diarrhoea and/or vomiting at median 24 hours (range 12-36 hours); Group 1: 22/22, Group 2: 5/21
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Health-related quality of life at short-term (up to two weeks); Health-related quality of life at medium-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at medium-term (two to six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at short-term (up to two weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at short-term (up to two weeks); Admissions (hospital & A&E) at medium-term (two to six weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at long-term (> six weeks); GP visits at short-term (up to two weeks)

Study	Janssens 2008[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Netherlands; Setting: trial centre
Line of therapy	1st line
Duration of study	Intervention + follow up: intervention 5 days + follow up 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were patients with monoarticular gout arthritis confirmed by identification of monosodium urate crystals in the synovial fluid of the affected joint
Stratum	People without chronic kidney disease or people with CKD stages 1-2: N/A
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Participants were patients with monoarticular gout arthritis confirmed by identification of monosodium urate crystals in the synovial fluid of the affected joint
Exclusion criteria	Unstable condition (prevalent angina pectoris, myocardial infarction, manifest heart failure, severe renal failure, renal transplant or cancer); chronic rheumatic diseases; current use of anticoagulants; and medical history of of upper gastrointestinal diseases.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): Prednisolone group 57.3(12.2), naproxen group 57.7(13.4). Gender (M:F): Prednisolone group 54/6, naproxen group 53/7. Ethnicity: not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Not stated / Unclear (trial centre).
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Corticosteroids - Prednisolone. Prednisolone 35 mg once a day and look alike placebo naproxen twice a day for 5 days. Duration 5 days. Concurrent medication/care: no NSAIDs or other analgesics (including colchicine) within 24 h before baseline assessments or for the duration of the trial. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (prednisolone +placebo). 2. Doses (historically high vs low): Define (prednisolone 35 mg once a day and look alike placebo). (n=60) Intervention 2: NSAIDs - Naproxen. Naproxen 500 mg twice a day and placebo capsule prednisolone for 5 days. Duration 5 days. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (naproxen). 2. Doses

	(historically high vs low): Define (500 mg twice a day for 5 days and placebo prednisolone capsule).
Funding	Equipment / drugs provided by industry (Pharmacy Riet (Rotterdam and the drug dispensing Primary care Centre Lobede (Lobith-Tolkamer) who prepared the study drugs)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREDNISOLONE versus NAPROXEN Protocol outcome 1: Pain at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (VAS) 90 hours after inclusion at 90 hours; Group 1: mean 16.8 (SD 24); n=59, Group 2: mean 12.9 (SD 18.1); n=59; Comments: Baseline VAS score: prednisolone group 61.5 (22.4); Naproxen 58.9 (20.8) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastric or abdominal pain at 90 hours; Group 1: 9/59, Group 2: 9/59 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (up to two weeks); Health-related quality of life at medium-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at medium-term (two to six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at short-term (up to two weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at short-term (up to two weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at short-term (up to two weeks); Admissions (hospital & A&E) at medium-term (two to six weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at long-term (> six weeks); GP visits at short-term (up to two weeks)

Study	**Liu 2019[32]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in China; Setting: Gout and Endocrinology Department of the Affiliated Hospital of Qingdao University
Line of therapy	1st line
Duration of study	Intervention + follow up: intervention 5 days +follow up 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnostic criteria were as follows: patients who met the 2015 ACR and EULAR diagnostic criteria for AGA [9], and the asymptomatic HUA diagnostic criteria.
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria were as follows: age 18–70 years; newly diagnosed AGA; an onset of AGA duration of less than 48 h and no administration of colchicine, NSAID or glucocorticoids; no administration of medications affecting uric acid metabolism over the last 3 months; without diseases affecting uric acid metabolism.
Exclusion criteria	The exclusion criteria were as follows: repeated or intermittent onset of AGA, or acute onset of chronic gout; chronic tophaceous gout, rheumatoid arthritis, traumatic arthritis or other types of arthritis; gouty nephropathy; pregnancy and lactation; diabetes; hypertension; severe dyslipidaemia; severe liver damage, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 2 times higher than upper limit of normal; severe cardiovascular and cerebral disease; malignancies.
Recruitment/selection of patients	In this study, 160 newly diagnosed AGA patients receiving outpatient therapies in the Gout and Endocrinology Department of the Affiliated Hospital of Qingdao University were selected as the screening subjects.
Age, gender and ethnicity	Age - Mean (SD): Etoricoxib group 44(9); Colchicine 43(9). Gender (M:F): Etoricoxib group 49/4; Colchicine 47/5. Ethnicity: Not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Gout and Endocrinology department of the Affiliated Hospital of Qingdao University)
Indirectness of population	No indirectness

Interventions	(n=61) Intervention 1: Colchicine. Patients in the colchicine group received colchicine 0.5 mg orally (Xishuangbanna Pharmaceutical Co., Ltd.), 3 times daily, for 5 days, later changed to once daily. Duration 5 days. Concurrent medication/care: All patients were given a low-purine diet and forbidden from smoking and drinking alcohol, and were required to drink enough water, 2500–3000 ml daily. All patients were also given sodium bicarbonate 1.0 g three times daily orally to alkalinize the urine. Meanwhile, all patients were required to stay in bed and avoid overtiring, cold and tension. . Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine). 2. Doses (historically high vs low): Define (Patients in the colchicine group received colchicine 0.5 mg orally (Xishuangbanna Pharmaceutical Co., Ltd.), 3 times daily, for 5 days, later changed to once daily). (n=61) Intervention 2: NSAIDs - Etoricoxib. Patients in the Etoricoxib group received Etoricoxib 120 mg orally (Hangzhou MSD Pharmaceutical Co., Ltd), once daily, for 5 days, later changed to 60 mg orally once daily. Duration 5 days. Concurrent medication/care: All patients were given a low-purine diet and forbidden from smoking and drinking alcohol, and were required to drink enough water, 2500–3000 ml daily. All patients were also given sodium bicarbonate 1.0 g three times daily orally to alkalinize the urine. Meanwhile, all patients were required to stay in bed and avoid overtiring, cold and tension. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Etoricoxib). 2. Doses (historically high vs low): (Patients in the Etoricoxib group received Etoricoxib 120 mg orally (Hangzhou MSD Pharmaceutical Co., Ltd), once daily, for 5 days, later changed to 60 mg orally once daily).
Funding	Academic or government funding (This work was supported by the National Natural Science Foundation of China (No. 81571625). The authors thank KangChen Bio-Tech Inc. for expert technical assistance.

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

Protocol outcome 1: Pain at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Joint pain scores at 10 days; Group 1: mean 0.96 (SD 0.91); n=52, Group 2: mean 1.02 (SD 0.84); n=53
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 ; Group 1 Number missing: 8, Reason: (severe vomit=1, loss to follow-up=2, joint pain and swelling can't be alleviated=5); Group 2 Number missing: 9, Reason: (severe diarrhoea=2, obvious liver damage=2; loss to follow-up=1, joint pain and swelling can't be alleviated=4) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Joint swelling scores at 5 days; Group 1: mean 0.73 (SD 0.64); n=52, Group 2: mean 0.77 (SD 0.57); n=53
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 ; Group 1 Number missing: 8, Reason: (severe vomit=1, loss to follow-up=2, joint pain and swelling can't be alleviated=5); Group 2 Number missing: 9, Reason: (severe diarrhoea=2, obvious liver damage=2; loss to follow-up=1, joint pain and swelling can't be alleviated=4) Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events - gastrointestinal (vomiting) at 10 days; Group 1: 1/52, Group 2: 2/53 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 ; Group 1 Number missing: 9, Reason: (severe vomit=1, loss to follow-up=2, joint pain and swelling can't be alleviated=5); Group 2 Number missing: 8, Reason: (severe diarrhoea=2, obvious liver damage=2; loss to follow-up=1, joint pain and swelling can't be alleviated=4) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events - gastrointestinal (diarrhoea) at 10 days; Group 1: 2/52, Group 2: 2/53 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 ; Group 1 Number missing: 9, Reason: (severe vomit=1, loss to follow-up=2, joint pain and swelling can't be alleviated=5); Group 2 Number missing: 8, Reason: (severe diarrhoea=2, obvious liver damage=2; loss to follow-up=1, joint pain and swelling can't be alleviated=4)	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (up to two weeks); Health-related quality of life at medium-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at medium-term (two to six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at short-term (up to two weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at short-term (up to two weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at short-term (up to two weeks); Admissions (hospital & A&E) at medium-term (two to six weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at long-term (> six weeks); GP visits at short-term (up to two weeks)

Study	Man 2007[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Australia; Setting: The ED of the Prince of Wales Hospital, a 1,400-bed teaching hospital in the New Territories of Hong Kong
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients older than 17 years, with an acute arthritis suggestive of gout, and presenting to the ED
Stratum	People without chronic kidney disease or people with CKD stages 1-2: N/A
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Patients were included if they had a clinical diagnosis of acute arthritis suggestive of gout, defined as the presence of pain and warmth in a joint, and presented within 3 days of the onset of pain and also had 1 or more of the following: metatarsal-phalangeal joint involvement; knee or ankle joint involvement and aspirate containing crystals; or typical gouty arthritis, with either gouty tophi present or previous joint aspiration confirming the diagnosis of gout.
Exclusion criteria	Patients were excluded if there was a clinical suspicion of sepsis or other joint disease; if follow-up was impossible because of lack of transport or lack of telephone contact; if there was significant comorbidity that would interfere with assessment; and if patients had dementia, confusion, active gastrointestinal symptoms, renal insufficiency with serum creatinine level greater than 200 µmol/L, bleeding disorder, allergy to a study drug, or joint aspirate that excluded the diagnosis of gout or were taking warfarin.
Age, gender and ethnicity	Age - Mean (SD): Indomethacin 66(16) Prednisolone 64(15). Gender (M:F): Indomethacin 39/7, Prednisolone 35/9. Ethnicity: Not reported
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Secondary care
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: NSAIDs - Indomethacin. In the indomethacin group, each patient initially received diclofenac (3 mL; 75mg) intramuscularly, indomethacin 50 mg orally, acetaminophen 1 g orally, and 6 tablets of prednisolone like placebo orally and was observed for 120 minutes. The patient was then given a 5-day prescription of indomethacin(50 mg orally

	every 8 hours for 2 days, followed by indomethacin 25 mg every 8 hours for another 3 days), 6 tablets of prednisolone-like placebo once a day, and acetaminophen 1 g every 6 hours as required. Duration 5 days. Concurrent medication/care: Indomethacin - IM diclofenac and paracetamol Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Indomethacin). 2. Doses (historically high vs low): Define (indomethacin (50 mg orally every 8 hours for 2 days, followed by indomethacin 25 mg every 8 hours for another 3 days)). (n=44) Intervention 2: Corticosteroids - Prednisolone. In the prednisolone group, each patient initially received an intramuscular placebo injection (3 mL), prednisolone 30 mg (6 times 5 mg) orally, acetaminophen 1 g (2 tablets) orally, and indomethacin-like placebo (2 tablets) orally and was then observed for 120 minutes. The patient was then given a 5-day prescription of indomethacin-like placebo, prednisolone 30 mg orally once per day, and acetaminophen 1 g every 6 hours as required. Both acetaminophen and intramuscular injection were given in accordance with common local practice. Many patients in Hong Kong believe that symptomatic relief will be faster if an injection is administered. The physician on duty was free to give extra doses or alternative analgesic if clinically required, and this was documented. Duration 5 days. Concurrent medication/care: Paracetamol. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Prednisolone). 2. Doses (historically high vs low): Define (prednisolone 30 mg orally once per day, and acetaminophen 1 g every 6 hours as required).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PREDNISOLONE

Protocol outcome 1: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Chest pain at 14 days; Group 1: 1/46, Group 2: 0/44
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (epigastric pain) at 14 days;
Group 1: 0/44, Group 2: 14/46
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (other abdominal pain) at 14 days;
3/46- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (indigestion) at 14 days;

Group 1: 4/44, Group 2: 14/46 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (nausea) at 14 days; Group 1: 3/44 Group 2: 12/46 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (vomiting) at 14 days; Group 1: 0/44, Group 2: 4/46 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (diarrhoea) at 14 days; Group 1: 0/44, Group 2: 3/46 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (gastrointestinal haemorrhage) at 14 days; Group 1: 0/44, Group 2: 5/46 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0	
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-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at short-term (up to two weeks); Pain at medium-term (two to six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at short-term (up to two weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at short-term (up to two weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at short-term (up to two weeks); Admissions (hospital & A&E) at medium-term (two to six weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at long-term (> six weeks); GP visits at short-term (up to two weeks)

Study	Rainer 2016[46]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=416)
Countries and setting	Conducted in Hong Kong (China); Setting: EDs of 4 acute hospitals (Prince of Wales Hospital, Queen Elizabeth Hospital, United Christian Hospital, and Pamela Youde Nethersole Eastern Hospital) out of 17 in Hong Kong
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for the study if they presented to the ED within 3 days of symptom onset, were considered to have gout by a specialist emergency physician and fulfilled the following 2 criteria for the diagnosis of acute gout (1, 19, 20). First, patients had to haven rapid onset of severe pain, swelling, tenderness, and erythema of an affected joint, which was maximal by 6 to 12 hours. Second, patients had to have at least 1 of the following clinical findings: 1) metatarsophalangeal (MTP) joint involvement (podagra) (category A), or 2) knee, ankle, wrist, or elbow joint involvement (category B) with gouty tophi (criterion B1), previous joint aspiration confirming a diagnosis of gout (criterion B2), hyperuricemia (criterion B3), or a clinical history of 1 or more clinical gouty arthritis attacks (criterion B4). If criteria B1 to B4 were not met, we sought to confirm the diagnosis by microscopic examination of aspirated fluid from the most affected joint for the presence of MSU crystals.
Exclusion criteria	Patients were excluded if they had received corticosteroids or indomethacin within 24 hours before recruitment, had a history of bleeding disorders or anticoagulant use, were allergic to a study drug, had suspected septic arthritis or another joint disease (such as rheumatoid arthritis), or had no MSU crystals found after joint aspiration. Other exclusion criteria included unstable cardiac conditions (angina pectoris, acute myocardial infarction, or heart failure), significant comorbidities that could interfere with assessment (dementia, confusion, or active gastrointestinal symptoms), a serum creatinine level greater than 200 µmol/L (>2.26 mg/dL), or an estimated glomerular filtration rate less than 30 mL/min/1.73 m2.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): Indomethacin group 64.37(16.01); Prednisolone group 65.91(14.95). Gender (M:F): Indomethacin group 164/44; Prednisolone group 145/63. Ethnicity: Not stated

Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: EDs of 4 acute hospitals
Indirectness of population	No indirectness
Interventions	(n=208) Intervention 1: NSAIDs - Indomethacin. In the indomethacin group, patients initially received 50 mg (two 25-mg tablets) of oral indomethacin 3 times a day and 6 tablets of oral placebo prednisolone once a day for 2 days, followed by 25 mg of indomethacin 3 times a day and 6 tablets of placebo prednisolone once a day for 3 days. Duration 5 days. Concurrent medication/care: All patients were prescribed oral paracetamol (1 g) to be taken every 6 hours as needed. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Indomethacin). 2. Doses (historically high vs low): Define (In the indomethacin group, patients initially received 50 mg (two 25-mg tablets) of oral indomethacin 3 times a day and 6 tablets of oral placebo prednisolone once a day for 2 days, followed by 25 mg of indomethacin 3 times a day and 6 tablets of placebo prednisolone once a day for 3 days.). (n=208) Intervention 2: Corticosteroids - Prednisolone. In the prednisolone group, patients initially received 30 mg (three 10-mg tablets) of oral prednisolone once a day and 2 tablets of placebo indomethacin 3 times a day for 2 days, followed by 30 mg (three 10-mg tablets) of prednisolone once a day and 1 tablet of placebo indomethacin 3 times a day for 3 days. Patients took the first dose in the presence of one of the investigators. Duration 5 days. Concurrent medication/care: All patients were prescribed oral paracetamol (1 g) to be taken every 6 hours as needed. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Prednisolone). 2. Doses (historically high vs low): Define (In the prednisolone group, patients initially received 30 mg (three 10-mg tablets) of oral prednisolone once a day and 2 tablets of placebo indomethacin 3 times a day for 2 days, followed by 30 mg (three 10-mg tablets) of prednisolone once a).
Funding	Academic or government funding (Health and Health Services Research Grant Committee of the Hong Kong Government

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PREDNISOLONE

Protocol outcome 1: Pain at short-term (up to two weeks)
- Actual outcome for people without chronic kidney disease or people with CKD stages 1-2: Patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - at rest at 14 days; Group 1: 111/208, Group 2: 101/208; Comments: clinically relevant range, defined for this study as ±13 mm on a 100-mm VAS. This equivalence limit was chosen because previous studies suggested that a clinically relevant difference in pain score on a 100-mm VAS is greater than 13 mm
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; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - with activity
at 14 days; Group 1: 151/208, Group 2: 160/208; Comments: clinically relevant range, defined for this study as ±13 mm on a 100-mm VAS. This equivalence limit was chosen because previous studies suggested that a clinically relevant difference in pain score on a 100-mm VAS is greater than 13 mm
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Joint tenderness at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Joint tenderness (mean change from baseline to day 14) at 14 days; Group 1: mean 2.37 (SD 1.48); n=208, Group 2: mean 2.32 (SD 1.44); n=208
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; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks)

- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – Gastrointestinal (nausea) at 14 days; Group 1:4/208, Group 2: 15/208
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; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – Gastrointestinal (vomiting) at 14 days; Group 1:1/208, Group 2: 10/208
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; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – Gastrointestinal (abdominal pain) at 14 days; Group 1:12/208, Group 2: 23/208
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; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – Gastrointestinal (indigestion) at 14 days; Group 1:13/208, Group 2: 19/208
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; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcome 4: Admissions (hospital & A&E) at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Visited ED at 14 days; Group 1: 23/208, Group 2: 28/208; Comments: data was presented for to time points: days 1 to 5 and days 6 to 14 those numbers were summed up
days 1 to 5 = 10 (Indomethacin group) vs 15 (Prednisolone group)

days 6 to 14 = 13 (Indomethacin group) vs 13 (Prednisolone group) 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; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Visited Outpatient department at 14 days; Group 1: 4/208, Group 2: 0/208; Comments: data was presented for to time points: days 1 to 5 and days 6 to 14 those numbers were summed up days 1 to 5 = 0 (Indomethacin group) vs 0 (Prednisolone group) days 6 to 14 = 4 (Indomethacin group) vs 0 (Prednisolone group) 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; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: GP visits at short-term (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: GP visits at 14 days; Group 1: 19/208, Group 2: 11/208; Comments: data was presented for to time points: days 1 to 5 and days 6 to 14 those numbers were summed up days 1 to 5 = 7 (Indomethacin group) vs 7 (Prednisolone group) days 6 to 14 = 12 (Indomethacin group) vs 4 (Prednisolone group) 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; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (up to two weeks); Health-related quality of life at medium-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at medium (two to six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at short-term (up to two weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks); Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at medium-term (two to six weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at long-term (> six weeks)

Study	**Roddy 2020[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=399)

Countries and setting	Conducted in United Kingdom; Setting: primary care setting
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A clinical diagnosis of gout was made by the GP without joint aspiration, blood tests, imaging, or diagnostic criteria.
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion - Eligibility was assessed by the GP during a routine consultation. Participants were aged 18 years and over, consulting for a current gout flare, and had capacity and willingness to give consent and complete trial documentation. A clinical diagnosis of gout was made by the GP without joint aspiration, blood tests, imaging, or diagnostic criteria.
Exclusion criteria	Exclusion criteria were unstable medical conditions (e.g. ischaemic heart disease, impaired liver function); known stage 4/5 chronic kidney disease (estimated glomerular filtration rate/creatinine clearance <30 mL/min); recent surgery or gastrointestinal bleed; history of gastric ulcer; current anticoagulant use; allergy to aspirin or NSAID; previous inability to tolerate naproxen or low-dose colchicine; other contraindication to either study drug described in the Summary of Product Characteristics; prescription of naproxen or colchicine in the previous 24 hours; pregnancy or lactation; potentially vulnerable patients; and participation in the CONTACT trial during a previous gout flare or involvement in another clinical trial in the last 90 days or other research within the last 30 days.
Age, gender and ethnicity	Age - Mean (SD): Naproxen group - 58.7(14.4), Colchicine 60(13.4). Gender (M:F): Male - Naproxen group - 173/27; Colchicine group - 174/25. Ethnicity: not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Primary care
Indirectness of population	No indirectness
Interventions	(n=200) Intervention 1: NSAIDs - Naproxen. NSAIDS - Single initial dose of oral naproxen 750 mg (three 250 mg tablets) followed by 250 mg (one tablet) every 8 hours for up to 7 days. Co-prescription of a proton-pump inhibitor was at the GP's discretion. Duration 7 days. Concurrent medication/care: not stated. Indirectness: No indirectness. Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Naproxen). 2. Doses (historically high vs low):

	Define (Single initial dose of oral naproxen 750 mg (three 250 mg tablets) followed by 250 mg (one tablet) every 8 hours for up to 7 days.). (n=199) Intervention 2: Colchicine. Oral colchicine 500 mg (one tablet) every 8 hours for 4 days. Participants prescribed a statin were advised to omit the statin during colchicine treatment Duration 7 days. Concurrent medication/care: not stated. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine). 2. Doses (historically high vs low): 500 mg (one tablet) every 8 hours for 4 days).
Funding	Academic or government funding (The CONTACT trial was funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR). CDM is funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and an NIHR Research Professorship in General Practice (RP_2014-04-026). EMH is an NIHR Senior Investigator. MB was funded by the NIHR School for Primary Care Research. CH and KRM are supported by the NIHR School for Primary Care Research Evidence Synthesis Working group (NIHR SPCR ESWG project 390). CH is also supported by the NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and is an NIHR Senior Investigator.

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

Protocol outcome 1: Pain at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Complete pain resolution at 7 days; Group 1: 115/170, Group 2: 116/174
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25

Protocol outcome 2: Pain at medium-term (two to six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Complete pain resolution at 4 weeks; Group 1: 130/170, Group 2: 130/174
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25

Protocol outcome 3: Patient global assessment of treatment success (response to treatment) at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patient assessment of global treatment response (completely/much better) n at 7 days; Group 1: 114/170, Group 2: 110/174
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25

Protocol outcome 4: Patient global assessment of treatment success (response to treatment) at medium-term (two to six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patient assessment of global treatment response (completely/much better) n at 4 weeks; Group 1: 140/170, Group 2: 143/174
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25

Protocol outcome 5: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (diarrhoea) at 7 days; Group 1: 30/170, Group 2: 67/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (nausea and/ or vomiting) at 7 days; Group 1: 21/170, Group 2: 30/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (dyspepsia) at 7 days; Group 1: 20/170, Group 2: 20/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (abdominal pain) at 7 days; Group 1: 16/170, Group 2: 16/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (constipation) at 7 days; Group 1: 30/170, Group 2: 67/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (nausea and/ or vomiting) at 4 weeks; Group 1: 7/170, Group 2: 5/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (dyspepsia) at 4 weeks; Group 1: 13/170, Group 2: 8/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (abdominal pain) at 4 weeks; Group 1: 4/170, Group 2: 8/174
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25

- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (constipation) at 4 weeks; Group 1: 9/170, Group 2: 6/174 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25 - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events – gastrointestinal (diarrhoea) at 4 weeks; Group 1: 5/170, Group 2: 10/174 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25 Protocol outcome 6: Admissions (hospital & A&E) at medium (two to six weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Consultation Re-attendance for gout during 4-week follow-up - Emergency department at 4 weeks; Group 1: 1/170, Group 2: 1/174 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25 Protocol outcome 7: GP visits at long (> six weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Consultation Re-attendance for gout during 4-week follow-up - GP at 4 weeks; Group 1: 26/170, Group 2: 39/174; Comments: Number of times GP consultation 1 time - 14 (Naproxen group) vs 27 (Colchicine group) 2 times 8 (Naproxen group) vs 10 (Colchicine group) 3 times 2 (Naproxen group) vs 2 (Colchicine group) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 25	
Protocol outcomes not reported by the study	Health-related quality of life at short-term (up to two weeks); Health-related quality of life at medium-term (two to six weeks); Health-related quality of life at long-term (> six weeks); Pain at long-term (> six weeks); Joint swelling/joint inflammation at short-term (up to two weeks); Joint swelling/joint inflammation at medium-term (two to six weeks); Joint swelling/joint inflammation at long-term (> six weeks); Joint tenderness at short-term (up to two weeks); Joint tenderness at medium-term (two to six weeks); Joint tenderness at long-term (> six weeks); Patient global assessment of treatment success (response to treatment) at long-term (> six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium-term (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks); Admissions (hospital & A&E) at short-term (up to two weeks); Admissions (hospital & A&E) at long-term (> six weeks); GP visits at medium-term (two to six weeks); GP visits at short-term (up to two weeks)

Study	**Anakinra in Gout (anaGO0 NCT03002974) trial: Saag 2021[50]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=165 (111 used in this analysis as anakinra 200mg group was not relevant to this review))
Countries and setting	Conducted in USA; Setting: multicentre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days treatment, 15 days follow-up (extension phase could last up to 2 years).
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR/EULAR 2015 criteria
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	≥18 years, have a diagnosis of gout according to 2015 ACR/ EULAR criteria, have had ≥1 self-reported gout flare within the 12 months prior to randomisation and have had the onset of an going flare (characterised by baseline pain intensity in the index joint of ≥50 on a 0-100 VAS and defined by tenderness and swelling in the index joint of ≥1 on a 0-4 Likert scale) within 4 days prior to randomisation. In addition, patients had to have had ≥1 episode of intolerance or non-responsiveness to NSAIDs and colchicine or have had these treatments judged to be contraindicated or not appropriate. Signs of non-responsiveness to NSAIDs and colchicine were prespecified and included lost efficacy over time, failure to treat acute gout pain, inadequate/ unsatisfactory pain relief, or incapacity to achieve/maintain adequate dose regimen of these agents.
Exclusion criteria	Patients taking specified pain relief medications or biologic agents were excluded. Other exclusions were the presence of a contraindication to triamcinolone treatment or the presence of rheumatoid arthritis, polyarticular gouty arthritis (involving >4 joints), infectious/septic arthritis, or any other acute inflammatory arthritis.
Recruitment/selection of patients	Not reported

Age, gender and ethnicity	Age - Median (range): Anakinra 100mg group: 53.5 (25-79), Triamcinolone group:56.0 (30-83). Gender (M:F): Anakinra 100mg group: 48 males (85.7%) Triamcinolone group: 48 males (87.3%). Ethnicity: Anakinra 100mg group: White 38 (67.9%), Black 15 (26.8%), Asian 3 (5,4%) Triamcinolone group: White 39 (70.9%), Black 15 (27.3%), Asian 1 (1.8%)
Further population details	1. Previous treatment: Pharmacological (patients had to have had ≥1 episode of intolerance or non-responsiveness to NSAIDs and colchicine or have had these treatments judged to be contraindicated or not appropriate.). 2. Setting: Not stated / Unclear
Extra comments	Mean disease duration 8.7 years Mean number of self-reported flares during the past year: 4.5
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: IL-1 inhibitors - Anakinra. Anakinra 100mg S/C once daily for 5 days. In accordance with the double dummy design, patients received one IM injection and two S/C injections on day 1 and two S/C injections on days 2-5. Treatments were initiated on the day of randomisation (visit 1) and were supervised or given by the investigator (or delegated study staff) at the outpatient clinic, emergency department or hospital. If a patient was treated at an outpatient clinic or was discharged from hospital before the end of the 5-day drug administration period, the daily S/C injections were administered at home by the patients themselves or a caregiver. Duration 5 days. Concurrent medication/care: Allowed rescue medication was paracetamol and/ or codeine, short-acting tramadol and topical ice/ cold packs. If relief was insufficient, prednisone or prednisolone was permitted. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Anakinra). 2. Doses (historically high vs low): Define (100mg). Comments: 50% of patients (28) were receiving ULT at baseline. (n=55) Intervention 2: Corticosteroids - Triamcinolone. Triamcinolone 40mg single injection. In accordance with the double dummy design, patients received one IM injection and two S/C injections on day 1 and two S/C injections on days 2-5. Treatments were initiated on the day of randomisation (visit 1) and were supervised or given by the investigator (or delegated study staff) at the outpatient clinic, emergency department or hospital. If a patient was treated at an outpatient clinic or was discharged from hospital before the end of the 5-day drug administration period, the daily S/C injections were administered at home by the patients themselves or a caregiver. Duration 5 days. Concurrent medication/care: Allowed rescue medication was paracetamol and/ or codeine, short-acting tramadol and topical ice/ cold packs. If relief was insufficient, prednisone or prednisolone was permitted. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids

	(Triamcinolone). 2. Doses (historically high vs low): Define (40mg). Comments: 41.8% of patients (23) were receiving ULT at baseline.
Funding	Study funded by industry (Swedish Orphan Biovitrum)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANAKINRA 100MG versus TRIAMCINOLONE

Protocol outcome 1: Pain at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (VAS change) - flare 1 at 24-72 hours; Group 1: mean -41.8 (SD 26.5121); n=56, Group 2: mean -39.4 (SD 26.8472); n=55; VAS 0-100 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Anakinra 100mg group mean disease duration was 9.7 years; triamcinolone group was 7.7 years.
ULT use: anakinra group: 50%; triamcinolone group: 41.8%; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (VAS change)- flare 2 at 24-72 hours; Group 1: mean -35.3 (SD 25.7); n=22, Group 2: mean -31.1 (SD 26.3); n=17; VAS pain 0-100 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Anakinra 100mg group mean disease duration was 9.7 years; triamcinolone group was 7.7 years.
ULT use: anakinra group: 50%; triamcinolone group: 41.8%; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (VAS change)- flare 3 at 24-72 hours; Group 1: mean -40.4 (SD 18); n=13, Group 2: mean -51.2 (SD 14.1); n=5; VAS pain 0-100 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Anakinra 100mg group mean disease duration was 9.7 years; triamcinolone group was 7.7 years.
ULT use: anakinra group: 50%; triamcinolone group: 41.8%; Group 1 Number missing: 0; Group 2 Number missing:0

Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at long (>6 weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events at whole study period (up to 2 years); Group 1: 21/55, Group 2: 22/54
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Anakinra 100mg group mean disease duration was 9.7 years; triamcinolone group was 7.7 years.

ULT use: anakinra group: 50%; triamcinolone group: 41.8%; Group 1 Number missing: 0; Group 2 Number missing: 0	
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 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 medium (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Study	Schlesinger 2002[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: intervention 6 days + 1 week follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients had arthrocentesis during the acute gouty attacks and had confirmation of intracellular monosodium urate crystals. Synovial fluid leukocyte counts >2000/mm3 or > 10 leukocytes per high power field (HPF) were seen in 16 patients. Three patients with synovial fluid leukocyte counts < 2000/mm3 but with a clinical picture of acute gout were also included in the study (of these patients 2 were in the group treated with ice and one was in the control group).
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Nineteen patients with acute gouty attacks seen in the Rheumatology Clinic and during hospitalization at the Philadelphia VA Medical Center between February 1, 1996, to May 1, 1997, were enrolled into an institutional review board approved protocol. All patients had arthrocentesis during the acute gouty attacks and had confirmation of intracellular monosodium urate crystals. Synovial fluid leukocyte counts > 2000/mm3 or > 10 leukocytes per high power field (HPF) were seen in 16 patients. Three patients with synovial fluid leukocyte counts < 2000/mm3 but with a clinical picture of acute gout were also included in the study (of these patients 2 were in the group treated with ice and one was in the control group).
Exclusion criteria	not stated
Age, gender and ethnicity	Age - Other: age not stated. Gender (M:F): not stated. Ethnicity: not stated
Further population details	1. Previous treatment: Pharmacological (Allopurinol treatment was continued in the same dose if patients were receiving it prior to the attack.). 2. Setting: Define (Rheumatology Clinic and during hospitalization at the Philadelphia VA Medical Center).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Combination interventions - Pharmacological + non-pharmacological. received topical ice therapy, oral corticosteroids (prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and colchicine 0.6 mg/day. Ice therapy, by application of ice packs with self-ties (Stay-dry ice packs, Tecnol model 11427) on the inflamed target joint for 30 min 4 times/day, was given to all patients in Group A. The patients were followed for one week. Duration 6 days. Concurrent medication/care: Allopurinol treatment was continued in the same dose if patients were

	receiving it prior to the attack. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (Ice and prednisolone and colchicine). 2. Doses (historically high vs low): Define (received topical ice therapy, oral corticosteroids (prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and colchicine 0.6 mg/day. Ice therapy, by application of ice packs with self-ties (Stay-dry ice packs, Tecnol model 11427) on the inflamed target joint for 30 min 4 times/day, was given to all patients in Group A.). (n=9) Intervention 2: Combination interventions - Pharmacological + non-pharmacological. oral corticosteroids (prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and colchicine 0.6 mg/day. no ice therapy. Duration 6 days. Concurrent medication/care: Allopurinol treatment was continued in the same dose if patients were receiving it prior to the attack. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (Prednisolone +colchicine). 2. Doses (historically high vs low): Define ((prednisone tapered from 30 mg to 0 over 6 days (30 mg 2 days, 20 mg × 2 days, 10 mg × 2 days) and colchicine 0.6 mg/day).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHARMACOLOGICAL + NON-PHARMACOLOGICAL versus PHARMACOLOGICAL + NON-PHARMACOLOGICAL

Protocol outcome 1: Pain at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain at 1 week; Group 1: mean 0.8 (SD 1.1); n=10, Group 2: mean 4.74 (SD 3.011); n=9
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: standard deviation calculated by NGC using pain scores for each patient that were provided by paper; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Joint swelling/joint inflammation at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: joint circumference (cm) at 1 week; Group 1: mean 32.5 centimetres (SD 8.57); n=10, Group 2: mean 33.4 centimetres (SD 10.25); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: standard deviation calculated by NGC using joint circumference for each patient that were provided by paper; Group 1 Number missing: 0; Group 2 Number missing: 0

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 medium (two to six weeks); Pain at long (> six 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); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Study	Schlesinger 2012[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=456)
Countries and setting	Conducted in USA; Setting: N/A
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Mixed population (people with chronic kidney disease and people without chronic kidney disease)
Subgroup analysis within study	Not applicable
Inclusion criteria	The studies enrolled patients: aged 18–85 years, meeting the American College of Rheumatology 1977 preliminary criteria for the classification of acute arthritis of primary gout,21 with a history of ≥three self-reported flares in the previous 12 months, having an acute flare for ≤five days characterised by baseline pain intensity ≥50 mm on a 0–100 mm visual analogue scale (VAS), having contraindications for, intolerance of, or unresponsiveness to NSAIDs and/or colchicine (as determined by the investigator, and with a body mass index (BMI) ≤45 kg/m2. Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study.
Exclusion criteria	Key exclusion criteria included: use of specified pain relief medications or biologics (including corticosteroids, narcotics, paracetamol/acetaminophen, ibuprofen, colchicine, IL-blocker and tumour necrosis factor inhibitor) within specified periods prior to study entry , rheumatoid arthritis, infectious/septic arthritis, or other acute inflammatory arthritis, history of malignancy, active, chronic, or recurrent infections, including tuberculosis, or HIV infection or hepatitis B or C infection.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): Pooled: Canakinumab group - 52.3(11.8), triamcinolone group 53.6(11.5). Gender (M:F): 414/40. Ethnicity: Canakinumab group Caucasian 167, black - 26, Asian-13, other19, Triamcinolone group Caucasian 176, black - 24, Asian-12, other17
Further population details	1. Previous treatment: Pharmacological (Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study). 2. Setting: Not stated / Unclear
Indirectness of population	No indirectness

Interventions	(n=115) Intervention 1: IL-1 inhibitors - Canakinumab. canakinumab 150 mg by subcutaneous injection - (B-RELIEVED sub-study). Duration single dose. Concurrent medication/care: Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study. Patients experiencing a new flare visited the study site as soon as possible (within 5 days of flare onset) for treatment with the same baseline study drug. The minimum period between two consecutive study drug administrations was 14 days. Patients having difficulty tolerating their pain or experiencing a flare within 14 days of receiving the study medication could take rescue medication (see online supplementary text). During the extension studies, patients continued to be treated on-demand for any new flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Canakinumab). 2. Doses (historically high vs low): Define (150 mg). (n=115) Intervention 2: Corticosteroids - Triamcinolone. Triamcinolone acetonide 40 mg intramuscular injection (B-RELIEVED sub-study). Duration single dose. Concurrent medication/care: Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study. Patients experiencing a new flare visited the study site as soon as possible (within 5 days of flare onset) for treatment with the same baseline study drug. The minimum period between two consecutive study drug administrations was 14 days. Patients having difficulty tolerating their pain or experiencing a flare within 14 days of receiving the study medication could take rescue medication (see online supplementary text). During the extension studies, patients continued to be treated on-demand for any new flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Triamcinolone). 2. Doses (historically high vs low): Define (40 mg). (n=112) Intervention 3: IL-1 inhibitors - Canakinumab. canakinumab 150 mg by subcutaneous injection - (B-RELIEVED-II sub-study). Duration single dose. Concurrent medication/care: Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study. Patients experiencing a new flare visited the study site as soon as possible (within 5 days of flare onset) for treatment with the same baseline study drug. The minimum period between two consecutive study drug administrations was 14 days. Patients having difficulty tolerating their pain or experiencing a flare within 14 days of receiving the study medication could take rescue medication (see online supplementary text). During the extension studies, patients continued to be treated on-demand for any new flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Canakinumab). 2. Doses (historically high vs low): Define (150 mg). (n=114) Intervention 4: Corticosteroids - Triamcinolone. Triamcinolone acetonide 40 mg intramuscular injection (B-RELIEVED-II sub-study). Duration single dose. Concurrent medication/care: Patients taking ULT were on a stable dose and regimen for at least 2 weeks prior to randomisation and were expected to remain on a stable regimen during the study.

	Patients experiencing a new flare visited the study site as soon as possible (within 5 days of flare onset) for treatment with the same baseline study drug. The minimum period between two consecutive study drug administrations was 14 days. Patients having difficulty tolerating their pain or experiencing a flare within 14 days of receiving the study medication could take rescue medication (see online supplementary text). During the extension studies, patients continued to be treated on-demand for any new flares. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Triamcinolone). 2. Doses (historically high vs low): Define (40 mg).
Funding	Other author(s) funded by industry (This study was supported by Novartis Pharma AG, Basel, Switzerland.

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

Protocol outcome 1: Joint swelling/joint inflammation at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Physician assessment of swelling (OR) - β-RELIEVED at 7 days; OR; , Comments: OR (95% CI) =2.02 (1.2 to 3.5).

The study also reported swelling at 72 hours OR (95% CI) =1.72 (1.1 to 2.8).

Proportional odds regression with study, treatment group and body mass index at baseline as covariates

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 ; Group 1 Number missing: 2; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: 100-mm visual analogue scale at 72 hours (B-Relieved) at 7 days; Group 1: mean 28.1 (SD 26.19); n=113, Group 2: mean 39.5 (SD 26.19); n=115
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 ; Group 1 Number missing: 2; Group 2 Number missing: 0

Protocol outcome 2: Joint tenderness at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Physician assessment of tenderness (OR) - β-RELIEVED at 7 days; OR (95% CI) =2.25 (1.3 to 3.8)

The study also reported Tenderness at 72 hours OR (95% CI) =2.00 (1.2 to 3.4)

Proportional odds regression with study, treatment group and body mass index at baseline as covariates;
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; Group 1 Number missing: 2; Group 2 Number missing: 0

Protocol outcome 3: Patient global assessment of treatment success (response to treatment) at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patient global assessment (OR) - β-RELIEVED at 7 days; OR; , Comments: OR (95% CI) = 1.83 (1.1 to 3.0)

The study also reported patient global assessment at 72 hours OR (95% CI) = 1.74 (1.1 to 2.8)

Proportional odds regression with study, treatment group and body mass index at baseline as covariates;
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; Group 1 Number missing: 2; Group 2 Number missing: 0

Protocol outcome 4: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Any adverse event - β-RELIEVED - long term at 24 weeks; Group 1: 71/113, Group 2: 56/115
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; Group 1 Number missing: 2; Group 2 Number missing: 0

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

Protocol outcome 1: Joint swelling/joint inflammation at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Physician assessment of swelling (OR) - β-RELIEVED-II at 7 days; Mean; , Comments: OR (95% CI) = 1.21 (0.7 to 2.1)

The study also reported swelling at 72 hours OR (95% CI) = 1.76(1.1 to 2.9)

Proportional odds regression with study, treatment group and body mass index at baseline as covariates;
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: 100-mm visual analogue scale at 72 hours (B-Relieved-II) at 72 hours; Group 1: mean 22.1 (SD 24.92); n=112, Group 2: mean 31.9 (SD 24.92); n=114
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 ; Group 1 Number missing: 2; Group 2 Number missing: 0

Protocol outcome 2: Joint tenderness at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Physician assessment of tenderness (OR) - β-RELIEVED-II at 7 days; OR; ,

Comments: OR (95% CI) = 2.07(1.2 to 3.6) The study also reported tenderness at 72 hours OR (95% CI) = 2.34(1.4 to 4.0) Proportional odds regression with study, treatment group and body mass index at baseline as covariates 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Patient global assessment of treatment success (response to treatment) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patient global assessment (OR) - β-RELIEVED-II at 7 days; OR; , Comments: OR (95% CI) = 2.14(1.3 to 3.5) The study also reported tenderness at 72 hours OR (95% CI) = 2.71(1.7 to 4.5). Proportional odds regression with study, treatment group and body mass index at baseline as covariates 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Any adverse event - β-RELIEVED-II - long term at 24 weeks; Group 1: 78/112, Group 2: 65/114 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0	
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 medium (two to six weeks); Joint swelling/joint inflammation at long (> six 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 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 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Study (subsidiary papers)	**So 2010[63] (Schlesinger 2011[52])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in Switzerland; Setting: N/A
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	The study enrolled patients ages 18–80 years with a history of at least 1 previous gout flare who met the American College of Rheumatology 1977 preliminary criteria for acute gout (22). Patients were also required to have had an acute gout flare for ≤5 days, have a baseline pain intensity of ≥50 mm on a visual analogue scale (VAS) ranging from no pain (0 mm) to unbearable pain (100 mm), have disease that was refractory to or have contraindications to NSAIDs and/or colchicine according to their treating physician, and have a body mass index (BMI) of ≤40 kg/m2. Patients receiving urate-lowering therapy were required to be on a stable dose regimen and were expected to remain on this regimen throughout the study.
Exclusion criteria	Key exclusion criteria included the use of any of the following medications within specified periods before screening: ibuprofen, acetaminophen, aspirin, diclofenac, naproxen, cyclooxygenase 2 inhibitors, other NSAIDs, systemic or intraarticular corticosteroids, anakinra, rilonacept, any tumour necrosis factor inhibitor, or use of >1 dose of 0.6 mg colchicine in the 24 hours before screening, if not taking a stable dose. Patients were excluded if they had rheumatoid, infectious/septic, or other inflammatory arthritis; severe renal function impairment; drug allergies; idiopathic thrombocytopenic purpura; contraindication to intramuscular injection; donation or loss of ≥400 ml of blood in the 8 weeks before dosing; live vaccination in the 3 months before the start of the study; active or recurrent infection at enrolment; active pulmonary disease; requirement for antibiotics against latent tuberculosis; risk factors for tuberculosis; any surgical or underlying hepatic, hematologic, pulmonary, infectious, or gastrointestinal condition that compromised the immune system and/or would place the patient at unacceptable risk if they received immunomodulatory therapy; or long QT syndrome or QTc >450 msec for men and >470 msec for women. Women of childbearing age were required to be using an acceptable method of contraception.
Recruitment/selection of patients	N/A

Age, gender and ethnicity	Age - Mean (SD): Canakinumab 50.6(15.38); Triamcinolone acetonide 52.4(11.55). Gender (M:F): Canakinumab 28/0; Triamcinolone acetonide 55/2. Ethnicity: Not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: IL-1 inhibitors - Canakinumab. Canakinumab 150 mg by subcutaneous injection and saline by intramuscular injection. Duration single dose. Concurrent medication/care: 6 (22.2%) patients received rescue medication (Acetaminophen 5 (18.5%); Codeine 1(3.7%); Prednisolone 2 (7.4%)); 32 % of the patients were taking Allopurinol in the Canakinumab (150 mg) group. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): IL-1 inhibitors (Canakinumab). 2. Doses (historically high vs low): Define (150 mg). (n=57) Intervention 2: Corticosteroids - Triamcinolone. triamcinolone acetonide (40 mg) intramuscularly and a subcutaneous placebo injection on day 1. Duration single dose. Concurrent medication/care: 31 patients received rescue medication (Acetaminophen 23 (41.1%); Codeine 9(16.1%%); Prednisolone 16 (28.6%%)); 35 % of the patients were taking Allopurinol in triamcinolone group). Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Triamcinolone). 2. Doses (historically high vs low): Define (40 mg).
Funding	Study funded by industry (Supported by Novartis Pharma AG, Basel, Switzerland.

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

Protocol outcome 1: Health-related quality of life at long (> six weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: SF 36 - physical component at 7 days; Group 1: mean 48.3 (SD 8.6); n=28, Group 2: mean 41.9 (SD 9.5); n=57
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: SF 36 - physical component at 8 weeks; Group 1: mean 52.8 (SD 6.7); n=28, Group 2: mean 47.1 (SD 11.2); n=57
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: SF 36 - Mental component at 8 weeks; Group 1: mean 53.3 (SD 7.4); n=28, Group 2: mean 49.1 (SD 11.1); n=57

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 2: Pain at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain - VAS % change from baseline at 7 days; Group 1: mean -92.7 (SD 12.1); n=27, Group 2: mean -74.8 (SD 32.7); n=56 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 3: Patient global assessment of treatment success (response to treatment) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Patient global assessment of response to treatment: good or excellent at 7 days; Group 1: 25/27, Group 2: 31/56 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 4: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Any adverse events at 7 days; Group 1: 9/28, Group 2: 24/57; Comments: Any serious adverse events - were cerebrovascular disorder (in 1 patient in the triamcinolone acetonide group) 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0	
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); 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 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 medium (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Study	Terkeltaub 2010[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=185) with gout flare. A key aspect of the study design was that patients were enrolled and were dispensed a double-blinded blister card of study medication, at screening, prior to the onset of a gout flare (n=575).
Countries and setting	Conducted in USA; Setting: 54 centres in the US
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and postmenopausal female patients ≥18 years of age with a confirmed past diagnosis of gout (according to the American College of Rheumatology [ACR] classification criteria and having had ≥2 gout flares within the prior 12 months were eligible for randomization.
Exclusion criteria	Not stated
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): 51.5 (11.12). Gender (M:F): 176/9. Ethnicity: American Indian/Alaska native - 1, Asian - 2, Black/African American - 25, White/Caucasian - 153, Other - 4
Further population details	1. Previous treatment: Not stated / Unclear (Not stated). 2. Setting: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Colchicine – "low-dose" colchicine (1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour for 5 hours [1.8 mg total]). Duration 1 day. Concurrent medication/care: A stable regimen of urate-lowering therapy was permitted. Concurrent allopurinol use: Colchicine group 29 (39.2%), Placebo group 15 (25.4). Most rescue medications used in this trial were NSAIDs, with indomethacin predominating. Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose colchicine group, 18 patients (34.6%) in the high-dose colchicine group, and 29 patients (50.0%) in the placebo group. These patients were considered non-responders. Compared with patients receiving placebo, significantly fewer patients in the low-dose colchicine group (odds ratio [OR] 0.45 [95% CI 0.22–0.92], P 0.027) took rescue medication prior to hour 24. Fewer patients in the high-dose colchicine group than in the placebo group (OR 0.53 [95% CI 0.25–1.14]) took rescue medication prior to hour 24, although the difference did not reach

	statistical significance (P = 0.103). Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Colchicine (Colchicine). 2. Doses (historically high vs low): Lower dose ((1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour for 5 hours [1.8 mg total])). (n=59) Intervention 2: Placebo - (2 placebo capsules initially, followed by 1 placebo capsule every hour for 6 hours). Most rescue medications used in this trial were NSAIDs, with indomethacin predominating. Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose colchicine group, 18 patients (34.6%) in the high-dose colchicine group, and 29 patients (50.0%) in the placebo group. These patients were considered non-responders. Compared with patients receiving placebo, significantly fewer patients in the low-dose colchicine group (odds ratio [OR] 0.45 [95% CI 0.22–0.92], P 0.027) took rescue medication prior to hour 24. Fewer patients in the high-dose colchicine group than in the placebo group (OR 0.53 [95% CI 0.25–1.14]) took rescue medication prior to hour 24, although the difference did not reach statistical significance (P = 0.103). Duration 1 day. Concurrent medication/care: A stable regimen of urate-lowering therapy was permitted. Concurrent allopurinol use: Colchicine group 29(39.2%), Placebo group 15 (25.4). Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (Placebo). 2. Doses (historically high vs low): Define (1 placebo capsule every hour for 6 hours).
Funding	Equipment / drugs provided by industry (URL Pharma funded the study and choose United BioSource Corporation to be the Contract Research Organization to run the study. Dr. Davis is the Chief Medical Officer for URL Pharma and had key roles in the study design, data collection, data analysis, and writing of the manuscript. Prior to the start of the study, URL Pharma agreed that the authors had full rights to submit the manuscript for publication, URL Pharma approval of the content of the submitted manuscript was not required, and publication of the manuscript was not contingent upon the approval of URL Pharma. The authors had full access to all data, and Dr. Terkeltaub made the final editorial decisions.

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

Protocol outcome 1: Pain at short-term (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain - treatment response based on target joint pain score 32 hours after first dose - ≥ 50% pain reduction (number of patients) at 32 hours; Group 1: 31/74, Group 2: 10/58
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 ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short-term (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Adverse events - gastrointestinal at 32 hours; Group 1: 19/74, Group 2: 12/59 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 ; Group 1 Number missing: 0; Group 2 Number missing: 0	
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 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 medium (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Study	Xu 2016[80]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=132)
Countries and setting	Conducted in China; Setting: Department of Endocrinology of Nanfang Hospital affiliated to Southern Medical University between April 2015 and August 2015.
Line of therapy	1st line
Duration of study	Intervention + follow up: 4 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People without chronic kidney disease or people with CKD stages 1-2
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were: 1) gout attacks within 72 h of screening; 2) The degree of pain in the index joint was at least moderate (2 on a 5-point Likert scale) at baseline; and 3) the index joint was defined as the joint that was the most painful at the time of randomization.
Exclusion criteria	Exclusion criteria were: 1) chronic gouty arthritis stage; 2) clinical suspicion of joint infection or other joint disease; 3) polyarticular gout involving more than four joints; 4) coronary heart disease, heart failure, gastrointestinal haemorrhage, or a history of peptic ulcer; 5) the digestive tract operation history, inflammatory bowel disease, or malignant tumor; 6) using NSAIDs or corticosteroids within 72 h before the baseline assessments; 7) allergic to any of the study drugs; 8) abnormal liver function with transaminase levels higher than 2 times the upper limit of normal; or 9) renal insufficiency with serum creatinine levels greater than 200 µmol
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): prednisolone group - 44.03(15.37), etoricoxib 44.43(15.08), indomethacin 43.81(12.29). Gender (M:F): male (%) -prednisolone group - 100%, etoricoxib 100%, indomethacin 97.2%. Ethnicity: not stated
Further population details	1. Previous treatment: Not stated / Unclear 2. Setting: Define (department of Endocrinology of Nanfang affiliated to southern medical university).
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Corticosteroids - Prednisolone. prednisolone (35 mg qd, Tianjin Lisheng Pharmaceutical Co., Ltd., Shenzhen, China; n=41). Duration 4 days. Concurrent medication/care: no concomitant treatment. Indirectness: No indirectness

	Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): Corticosteroids (Prednisolone). 2. Doses (historically high vs low): Define (35 mg). (n=46) Intervention 2: NSAIDs - Etoricoxib. Etoricoxib (120 mg qd, Merck Frost, Montreal, Canada; n=46. Duration 4 days. Concurrent medication/care: no concomitant treatment. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Etoricoxib). 2. Doses (historically high vs low): Define (120 mg). (n=45) Intervention 3: NSAIDs - Indomethacin. Etoricoxib (120 mg qd, Merck Frost, Montreal, Canada; n=45). Duration 4 days. Concurrent medication/care: No concomitant treatment. Indirectness: No indirectness Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): NSAIDs (Indomethacin). 2. Doses (historically high vs low): Define (120 mg).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREDNISOLONE versus ETORICOXIB

Protocol outcome 1: Pain at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (Prednisolone vs etoricoxib) at 4 days; MD; , Units:
Comments: Mean difference (Standard error) = 0.12 (0.131);
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 2

Protocol outcome 2: Joint swelling/joint inflammation at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Swelling (Prednisolone vs etoricoxib) at 4 days; MD; , Comments: Mean difference (Standard error) = 0.21(0.125);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 2

Protocol outcome 3: Joint tenderness at short (up to two weeks)
- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: tenderness (Prednisolone vs etoricoxib) at 4 days; MD; , Comments: Mean difference (Standard error) = 0.11 (0.097);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 2

Protocol outcome 4: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastric or abdominal pain (Prednisolone vs etoricoxib) at 4 days; Group 1: 2/33, Group 2: 0/44 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 2 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREDNISOLONE versus INDOMETHACIN Protocol outcome 1: Pain at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Pain (Prednisolone vs indomethacin) at 4 days; Mean difference (Standard error) = 0.11 (0.116); Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9 Protocol outcome 2: Joint swelling/joint inflammation at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Swelling (Prednisolone vs indomethacin) at 4 days; Mean difference (Standard error) = 0.33 (0.131); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9 Protocol outcome 3: Joint tenderness at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: tenderness (Prednisolone vs indomethacin) at 4 days; Mean difference (Standard error) = 0.13 (0.102); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9 Protocol outcome 4: Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two weeks) - Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: Gastric or abdominal pain (Prednisolone vs indomethacin) at 4 days; Group 1: 2/33, Group 2: 3/36 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 9	
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 medium (two to six weeks); Pain at long (> six weeks); Joint swelling/joint inflammation at medium (two to six weeks); Joint swelling/joint inflammation at long (> six 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 medium (two to six weeks); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at short (up to two 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); GP visits at medium (two to six weeks); GP visits at long (> six weeks); GP visits at short (up to two weeks)

Appendix E – Forest plots

E.1 Colchicine versus placebo

Figure 2: Proportion joints with 50% or greater decrease in pain score from baseline – short-term up to 2 weeks (better indicated by higher score)

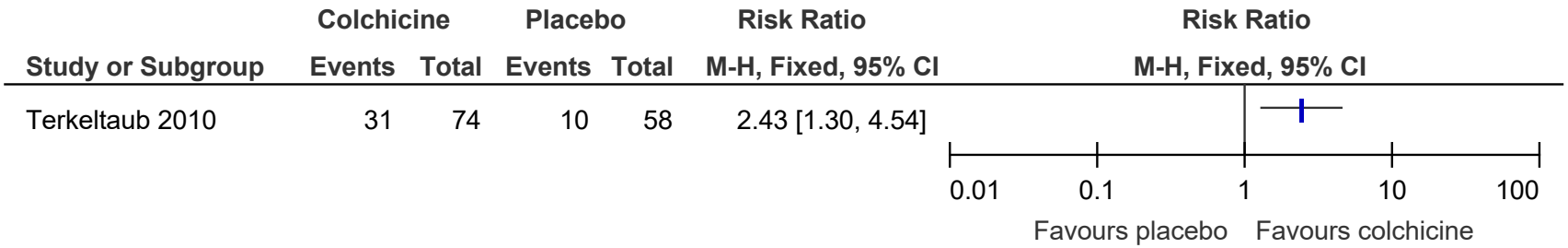
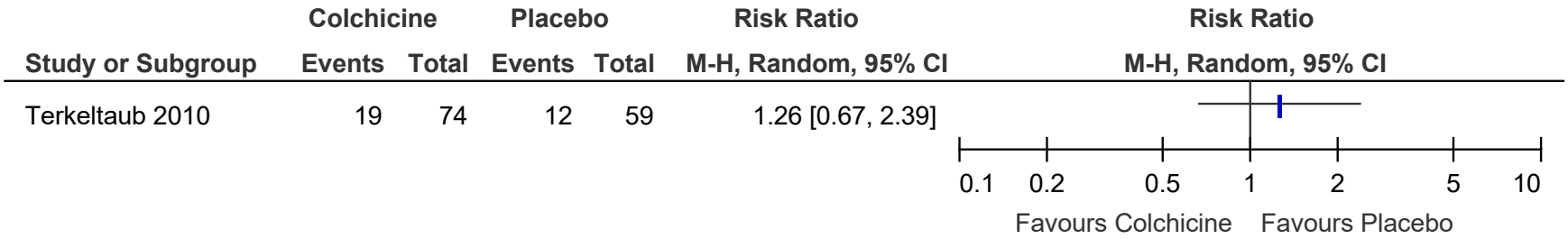


Figure 3: Adverse events – Gastrointestinal events (diarrhoea and nausea) – short-term up to 2 weeks (better indicated by lower score)



E.2 Corticosteroids versus NSAIDs

Figure 4: Pain VAS at 90 hours – Short-term up to 2 weeks (better indicated by lower score)

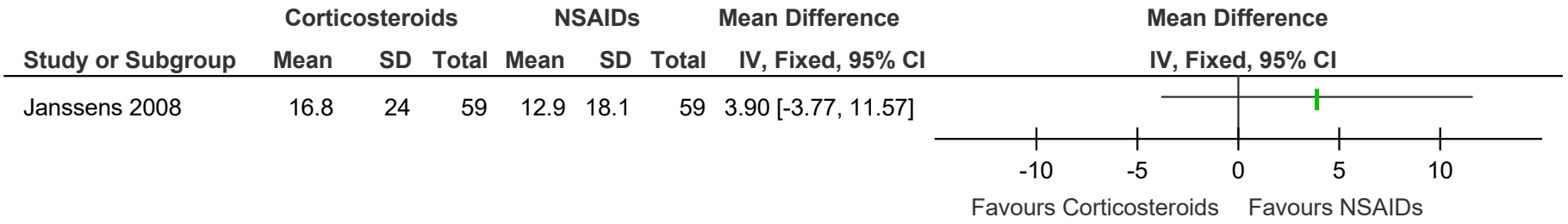


Figure 5: Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - at rest – short-term up to 2 weeks (better indicated by higher score)

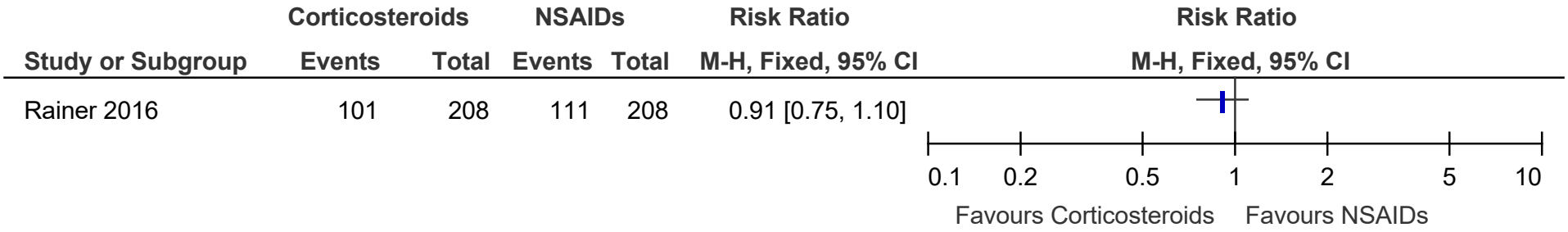


Figure 6: Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - with activity – short-term up to 2 weeks (better indicated by higher score)

	Corticosteroids		NSAIDs		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Rainer 2016	160	208	151	208	1.06 [0.95, 1.19]	

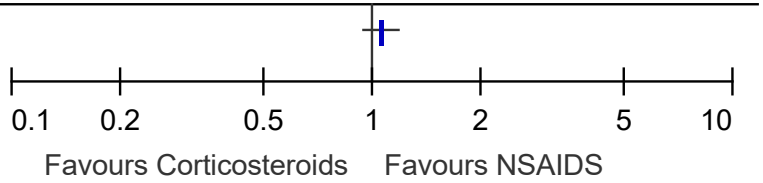


Figure 7: Joint tenderness – short-term up to 2 weeks (better indicated by lower score)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rainer 2016	2.32	1.44	208	2.37	1.48	208	-0.05 [-0.33, 0.23]	

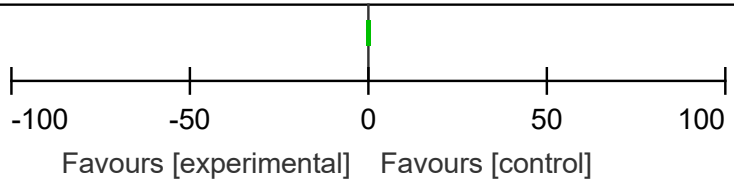
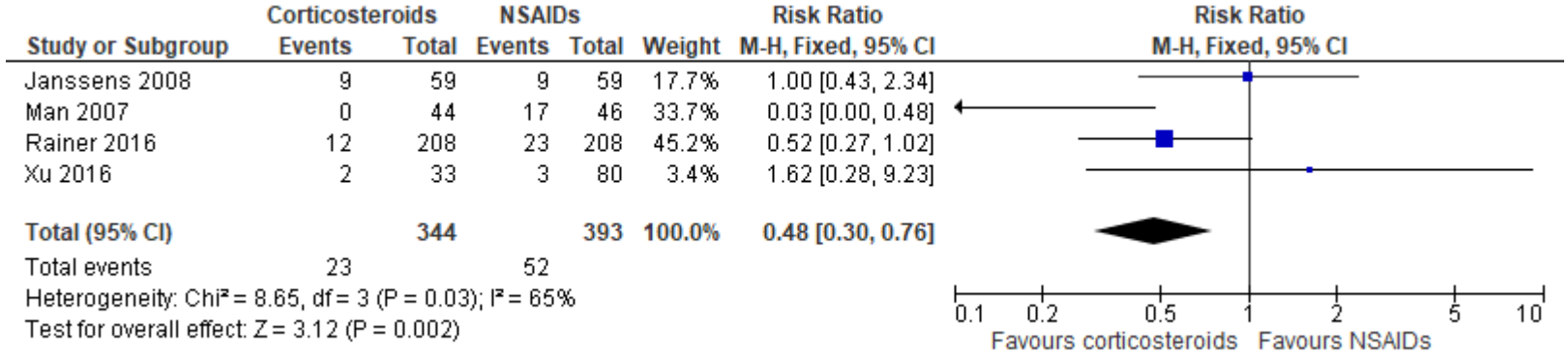


Figure 8: Adverse events- gastrointestinal (abdominal pain) - short term up to 2 weeks (better indicated by lower score)



'Abdominal pain' includes abdominal and gastric pain reported by Janssens 2008 and Xu 2016, abdominal pain reported by Rainer 2016 and epigastric and other abdominal pain reported by Man 2007.

Figure 9: Adverse events- gastrointestinal (indigestion) - short term up to 2 weeks (better indicated by lower score)

Source: <Insert Source text here>

Figure 10: Adverse events- gastrointestinal (nausea) - short term up to 2 weeks (better indicated by lower score)

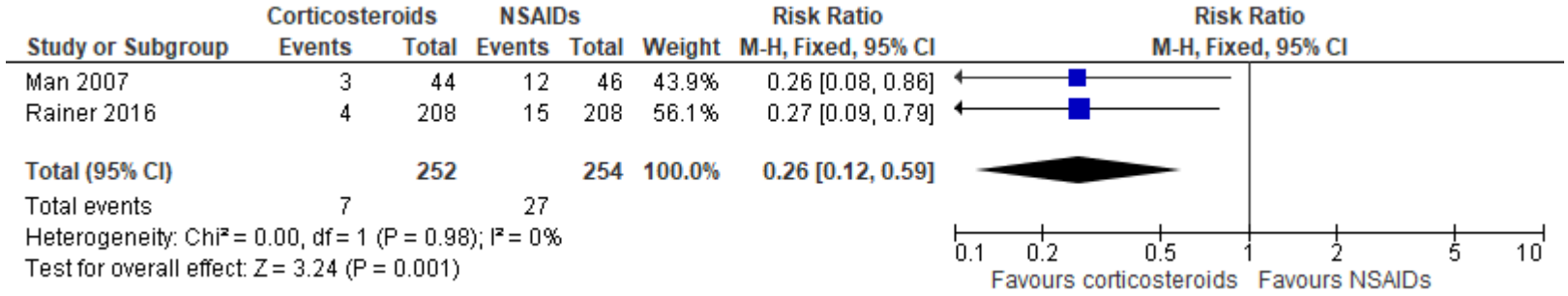


Figure 11: Adverse events- gastrointestinal (vomiting) - short term up to 2 weeks (better indicated by lower score)

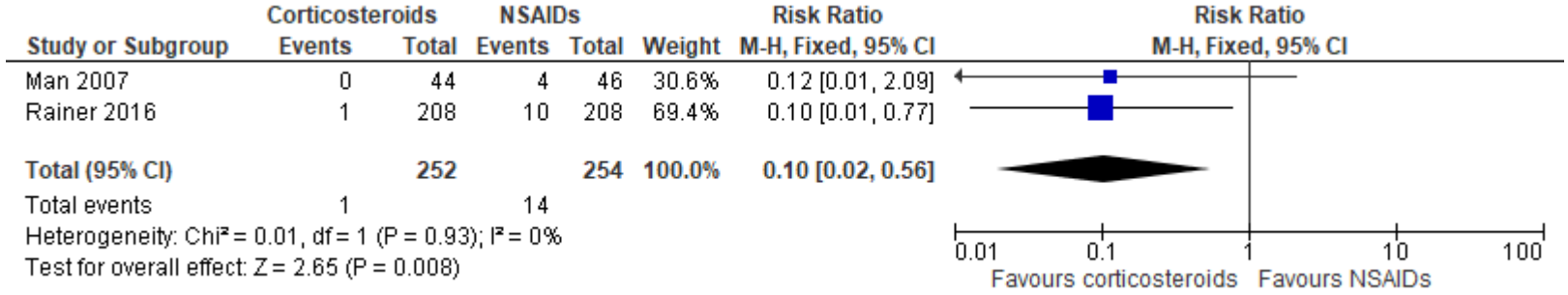


Figure 12: Adverse events- gastrointestinal (diarrhoea) - short term up to 2 weeks (better indicated by lower score)

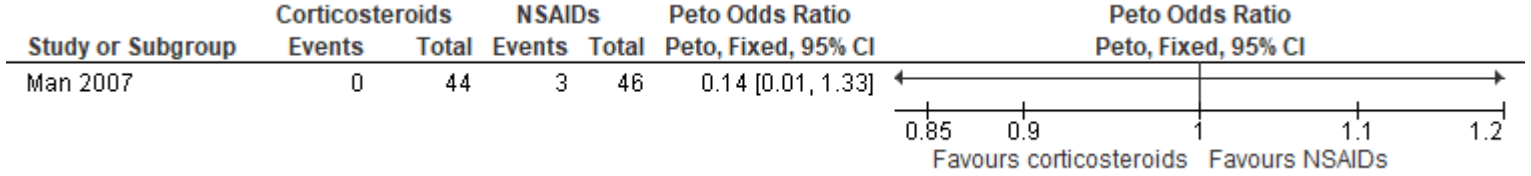


Figure 13: Adverse events- gastrointestinal (GI haemorrhage) - short term up to 2 weeks (better indicated by lower score)

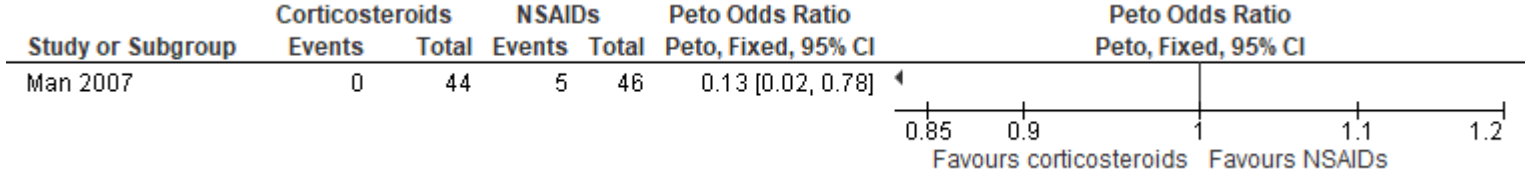


Figure 14: Adverse events – cardiovascular – short-term up to 2 weeks (better indicated by lower score)

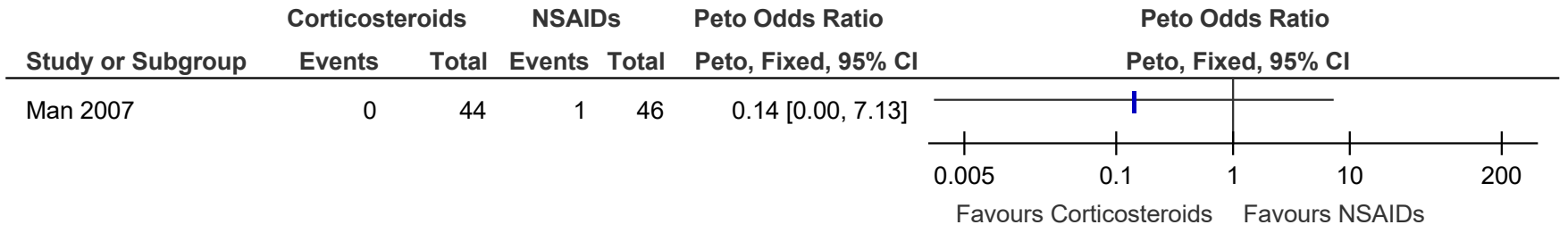


Figure 15: Number of patients who visited the Emergency Department – short-term up to 2 weeks (better indicated by lower score)

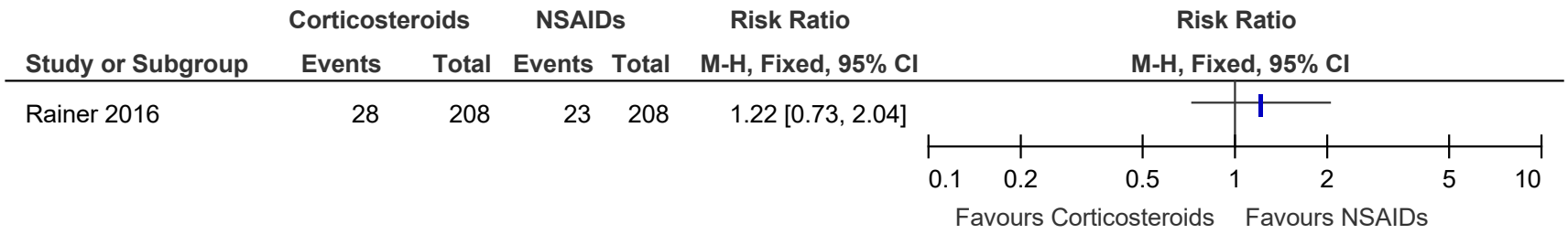


Figure 16: Number of patients visited the outpatient department – short-term up to 2 weeks (better indicated by lower score)

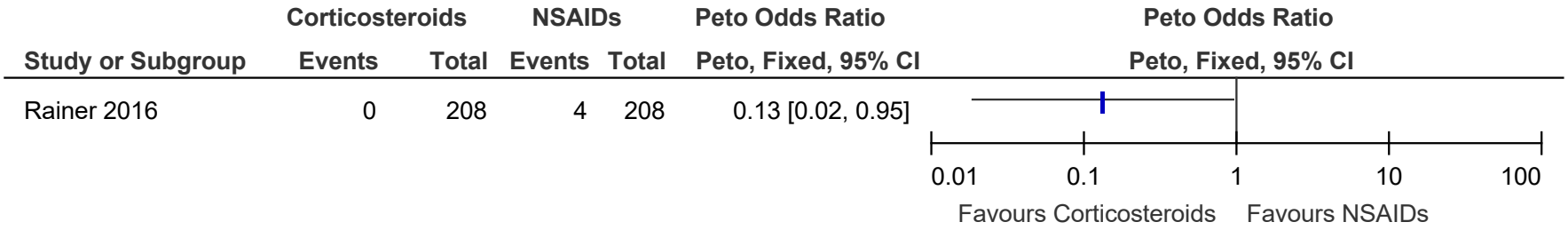
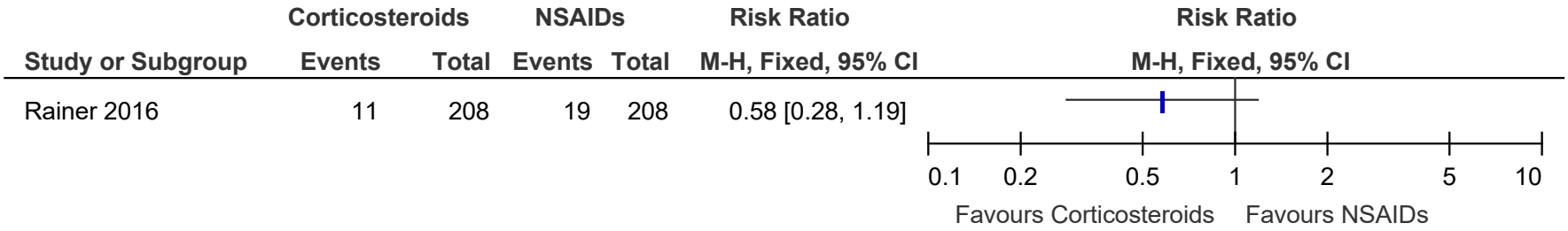


Figure 17: GP visits – short-term, up to 2 weeks (better indicated by lower score)



E.3 NSAIDs versus colchicine

Figure 18: Joint pain scores – short-term up to 2 weeks (better indicated by lower score)

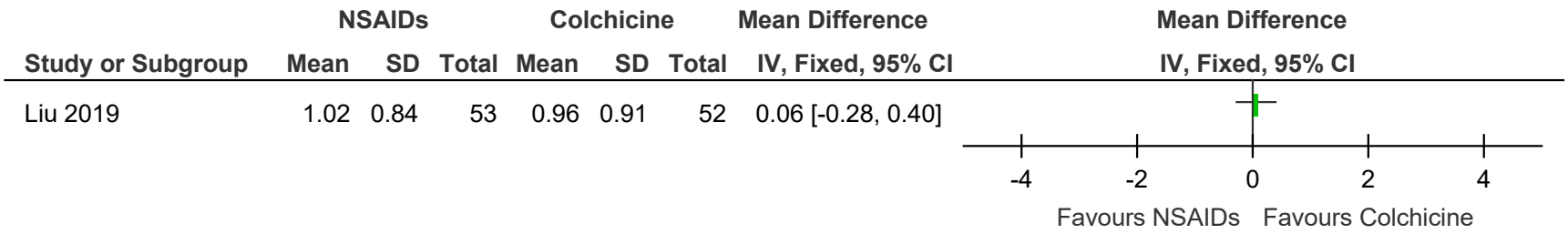


Figure 19: Complete pain resolution – short-term up to 2 weeks (better indicated by higher score)

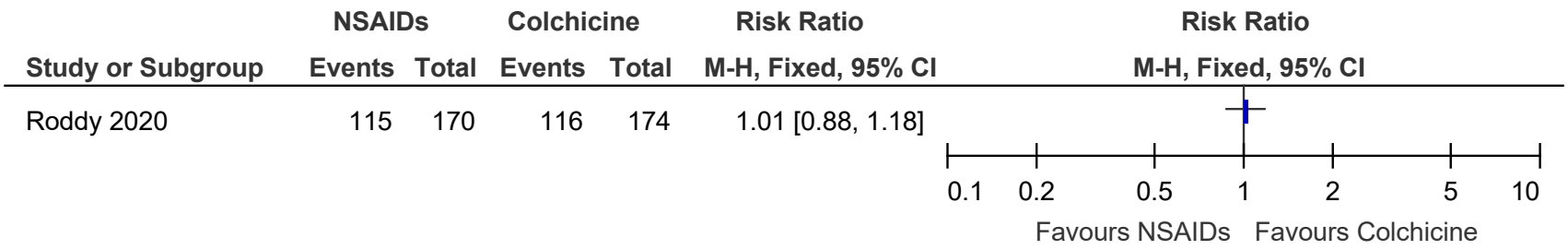


Figure 20: Complete pain resolution – medium-term 2 to 6 weeks (better indicated by higher score)

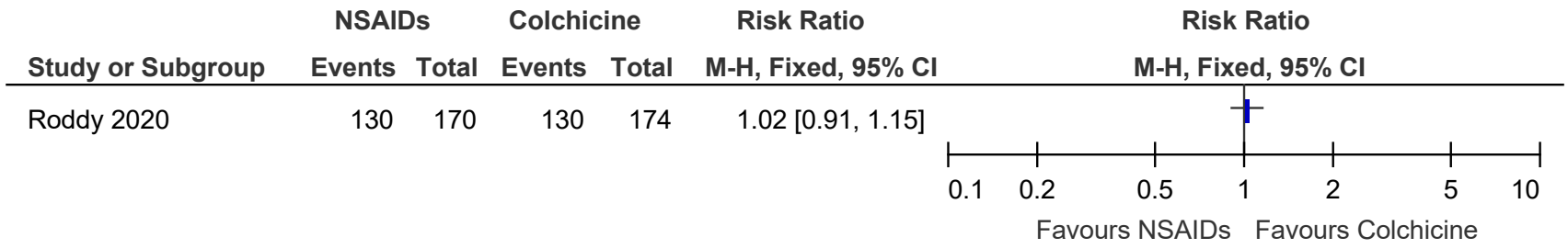


Figure 21: Joint swelling scores – short-term up to 2 weeks (better indicated by lower score)

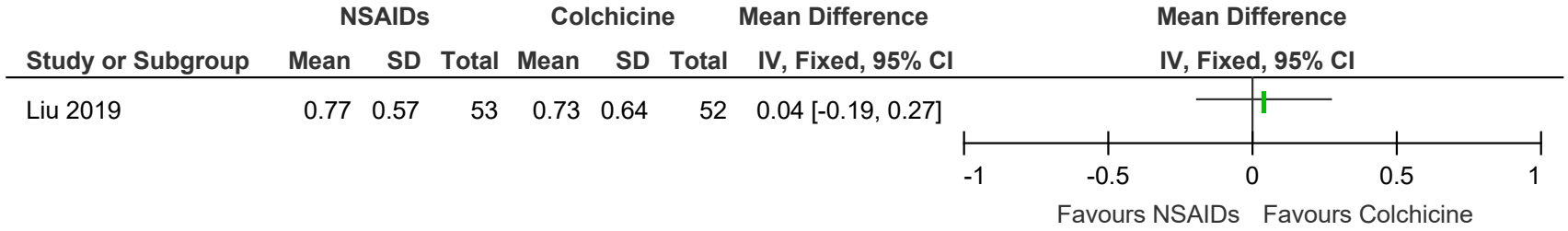


Figure 22: Patient assessment of global treatment response (completely/much better) – short-term up to 2 weeks (better indicated by lower score)

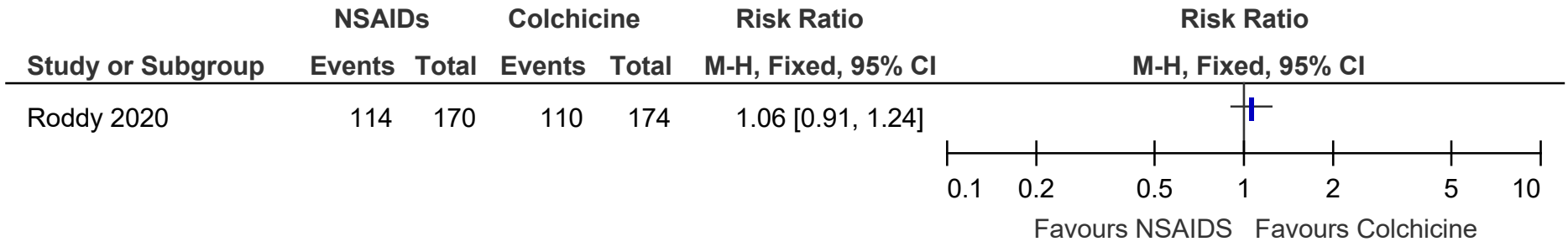


Figure 23: Patient assessment of global treatment response (completely/much better) – medium-term 2 to 6 weeks (better indicated by lower score)

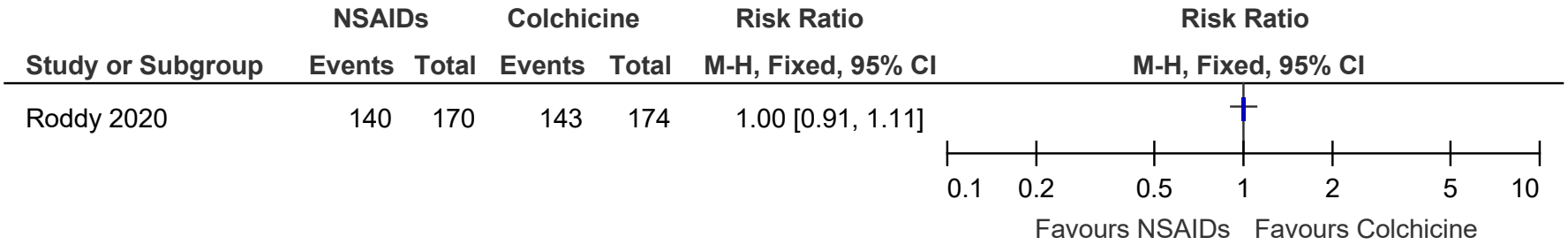


Figure 24: Adverse events- gastrointestinal (vomiting)- short-term (up to 2 weeks) better indicated by lower score

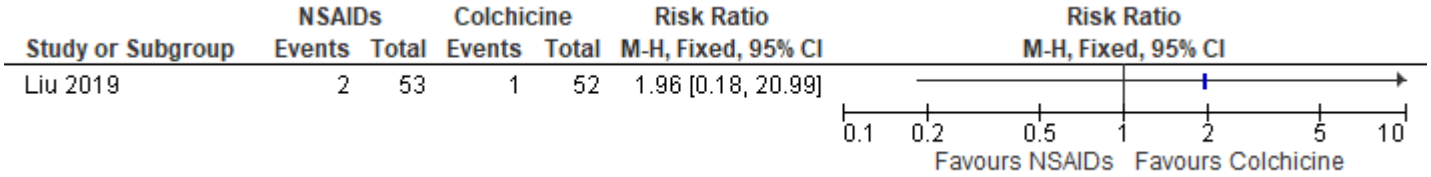


Figure 25: Adverse events- gastrointestinal (nausea and/or vomiting)- short-term (up to 2 weeks) better indicated by lower score

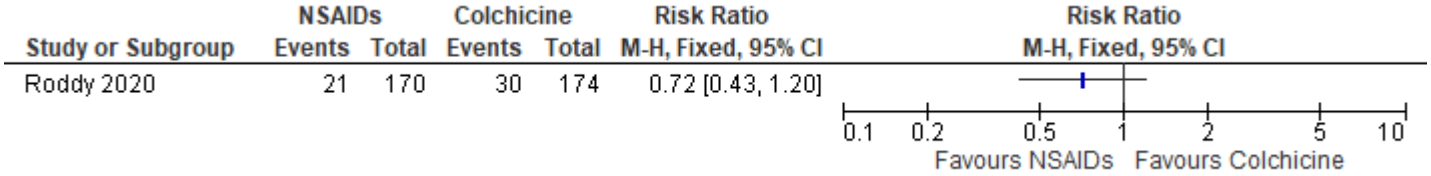


Figure 26: Adverse events- gastrointestinal (diarrhoea)- short-term (up to 2 weeks) better indicated by lower score

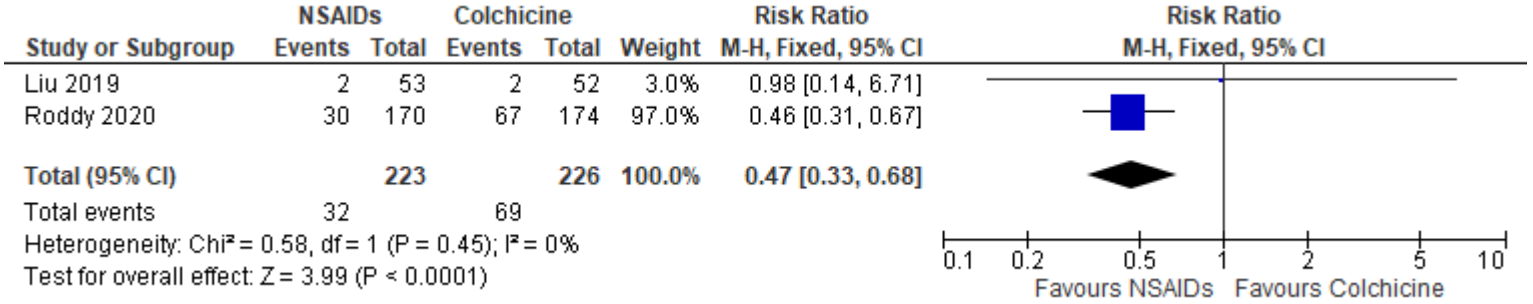


Figure 27: Adverse events- gastrointestinal (dyspepsia)- short-term (up to 2 weeks) better indicated by lower score

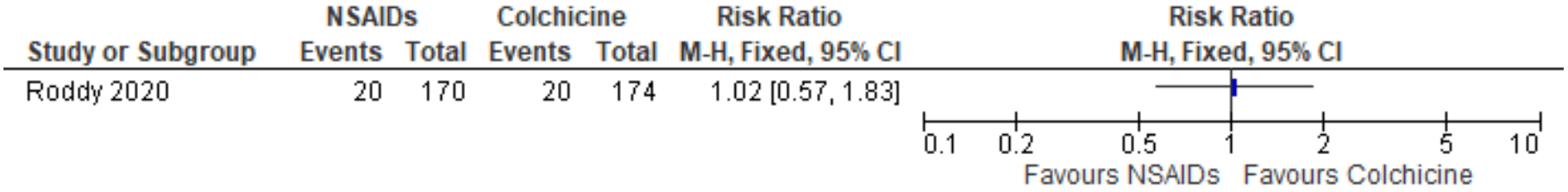


Figure 28: Adverse events- gastrointestinal (abdominal pain)- short-term (up to 2 weeks) better indicated by lower score

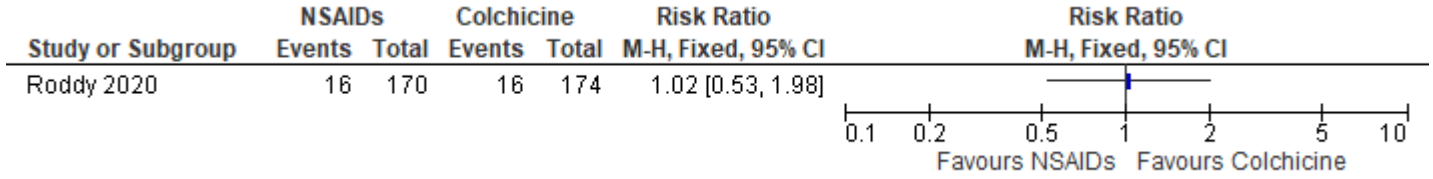


Figure 29: Adverse events- gastrointestinal (constipation)- short-term (up to 2 weeks) better indicated by lower score

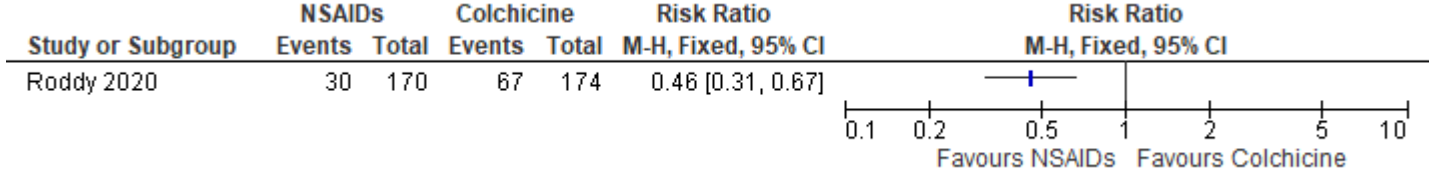


Figure 30: Adverse events- gastrointestinal (nausea and/or vomiting)- medium-term (2 to 6 weeks) better indicated by lower score

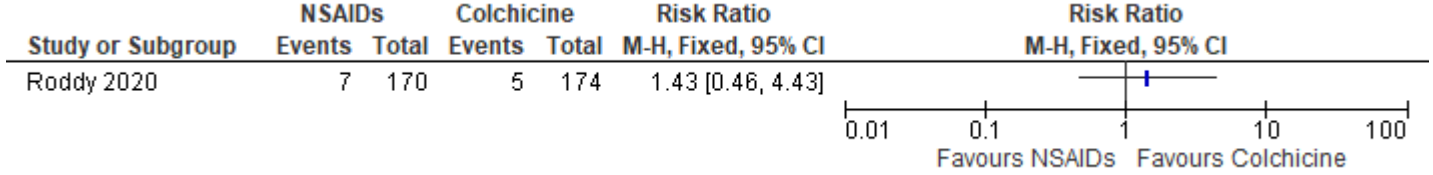


Figure 31: Adverse events- gastrointestinal (dyspepsia)- medium-term (2 to 6 weeks) better indicated by lower score

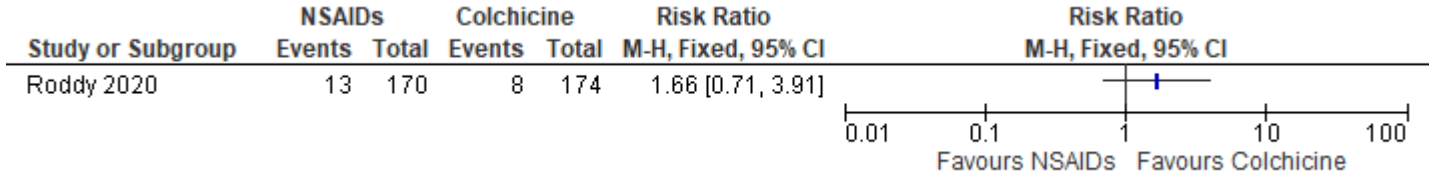


Figure 32: Adverse events- gastrointestinal (abdominal pain)- medium-term (2 to 6 weeks) better indicated by lower score

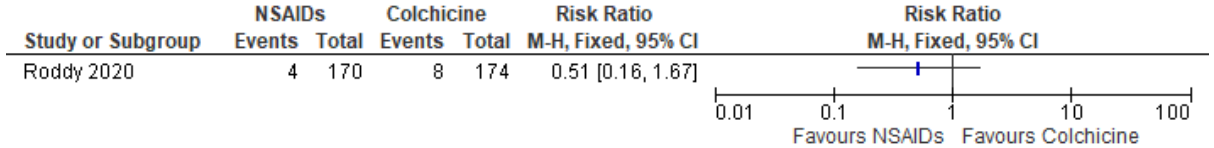


Figure 33: Adverse events- gastrointestinal (constipation)- medium-term (2 to 6 weeks) better indicated by lower score

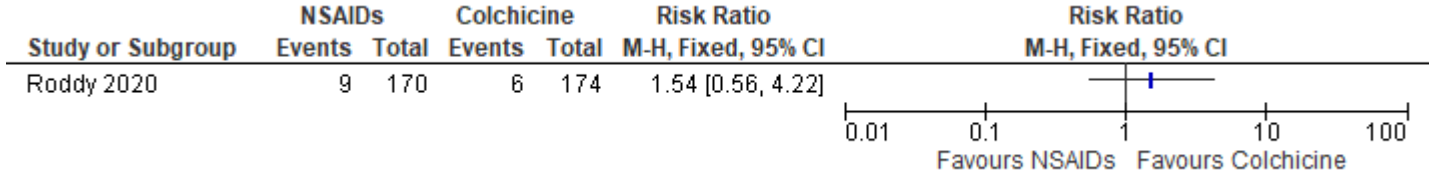


Figure 34: Adverse events- gastrointestinal (diarrhoea)- medium-term (2 to 6 weeks) better indicated by lower score

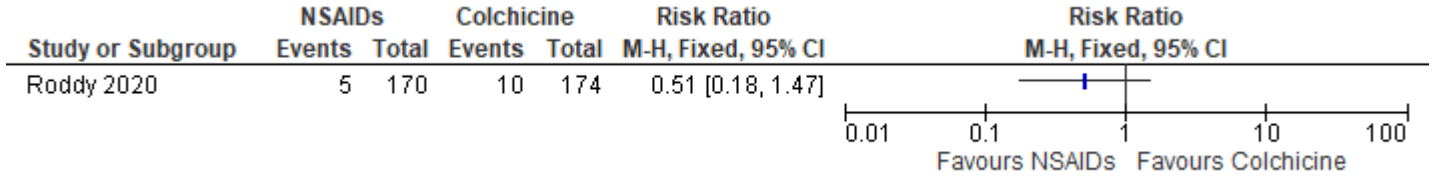


Figure 35: Consultation re-attendance for gout during 4-week follow-up - Emergency department – medium-term 2 to 6 weeks (better indicated by lower score)

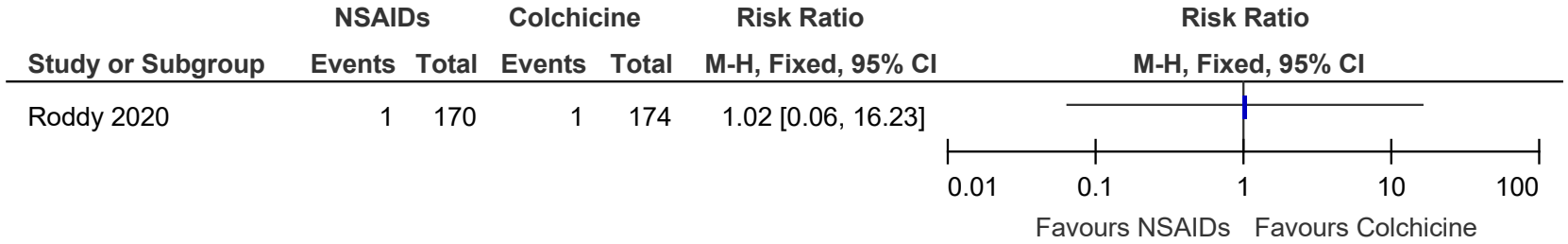
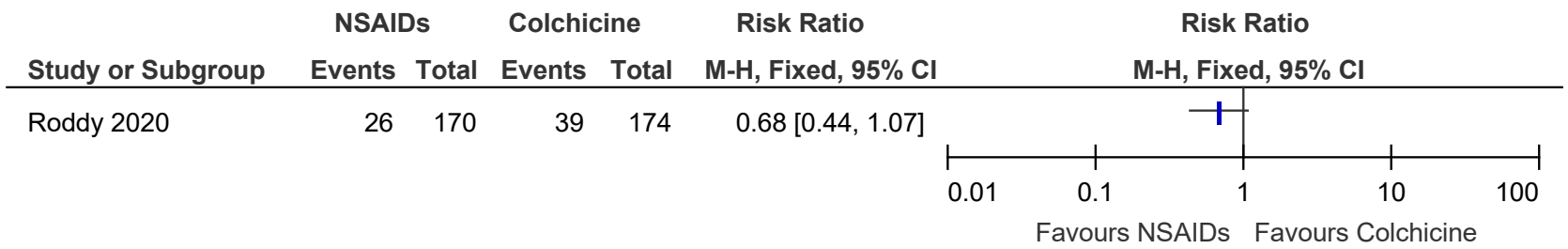


Figure 36: Consultation re-attendance for gout during 4-week follow-up - GP medium-term 2 to 6 weeks (better indicated by lower score)



E.4 IL1-inhibitors versus corticosteroids

Figure 37: SF 36 - Physical component – short-term up to 2 weeks (better indicated by higher score)

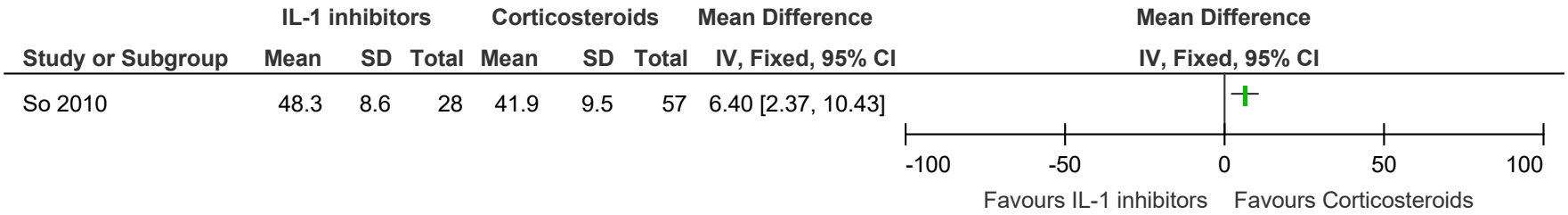


Figure 38: SF 36 - Physical component – medium-term 2 to 6 weeks (better indicated by higher score)

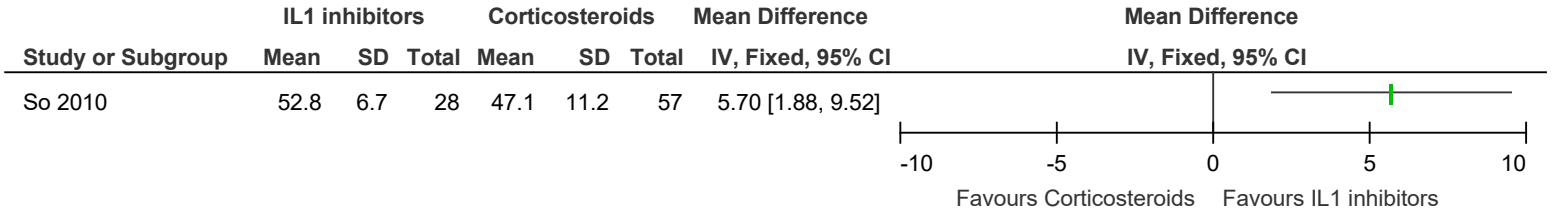


Figure 39: SF 36 - Mental component – short-term up to 2 weeks (better indicated by higher score)

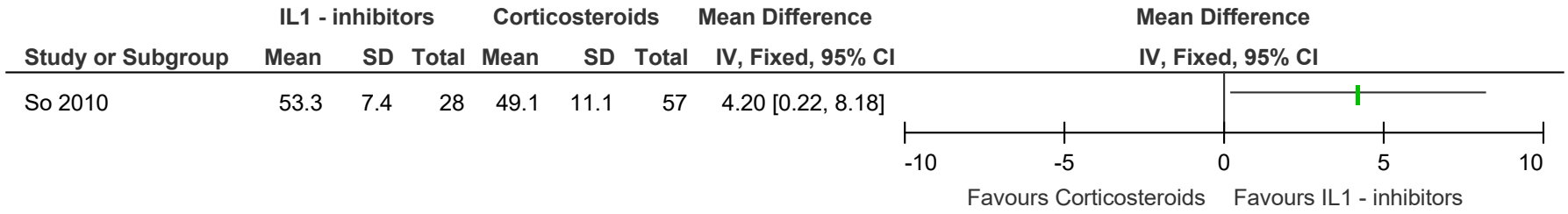


Figure 40: Pain: 100-mm visual analogue scale – short-term up to 2 weeks (at 72 hours) (better indicated by lower score)

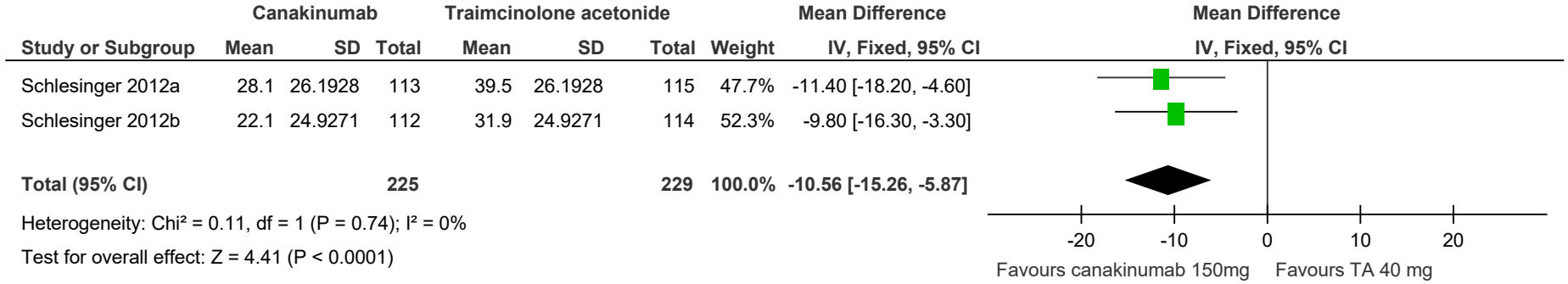


Figure 41: Pain: % change 100-mm visual analogue scale – short-term up to 2 weeks (better indicated by higher score)

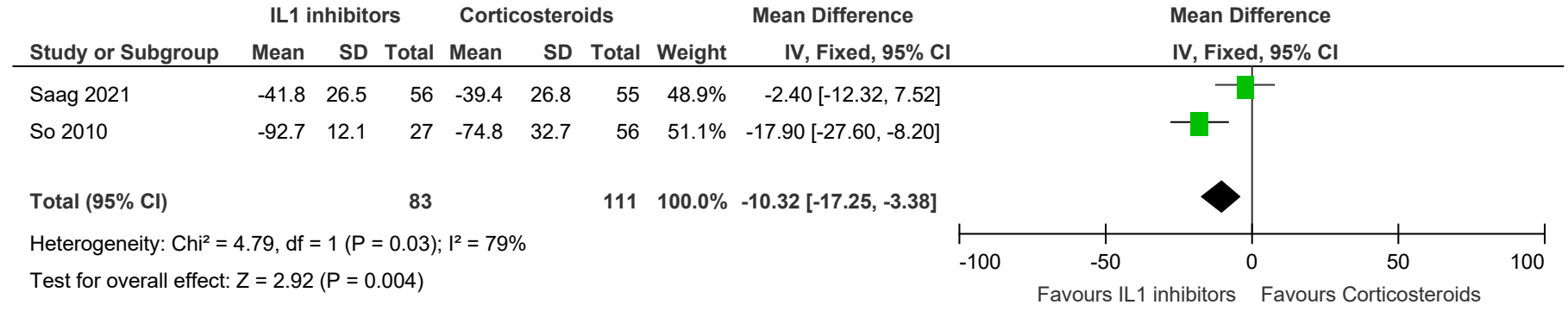


Figure 42: Joint swelling – short-term up to 2 weeks (better indicated by lower score)

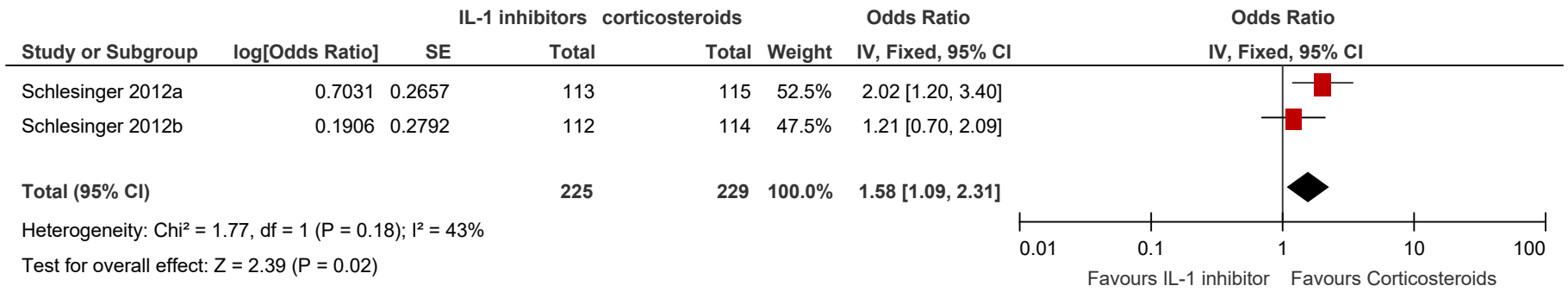


Figure 43: Joint tenderness – short-term up to 2 weeks (better indicated by higher score)

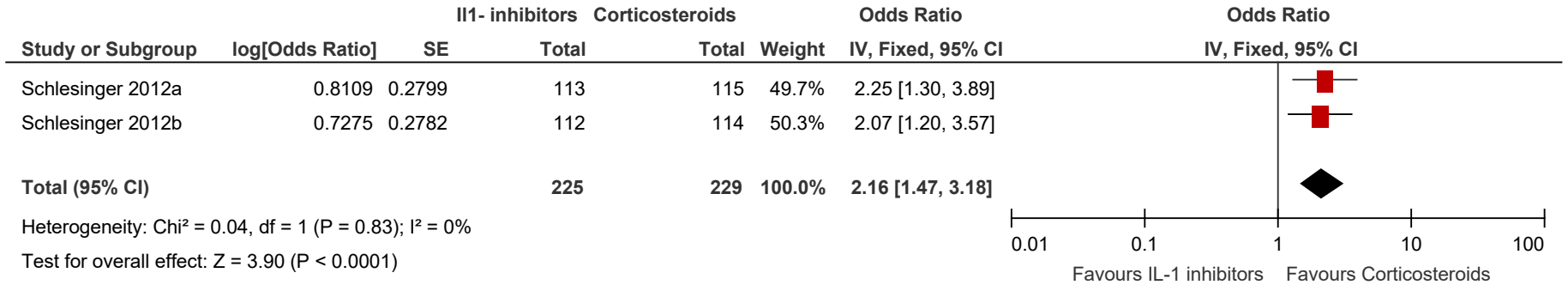


Figure 44: Patient global assessment – short-term up to 2 weeks (better indicated by lower score)

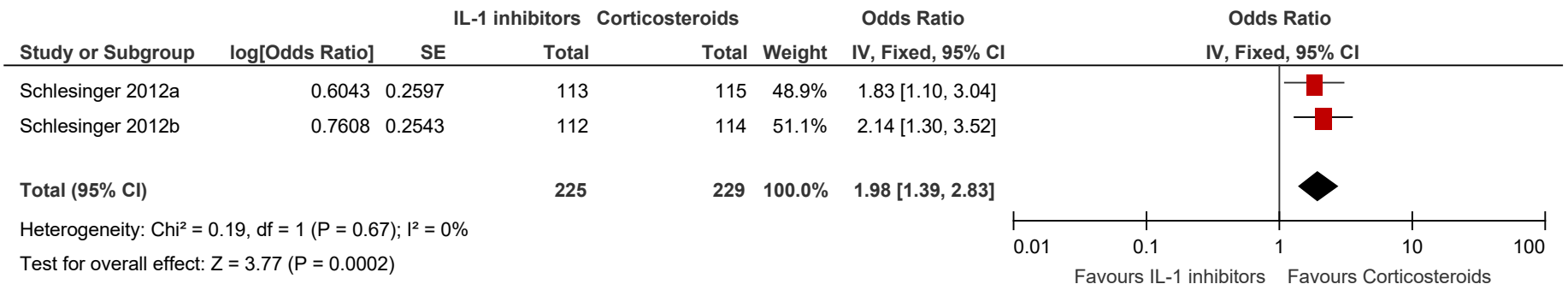


Figure 45: Participant global assessment of response to treatment: good or excellent – short-term up to 2 weeks (better indicated by lower score)

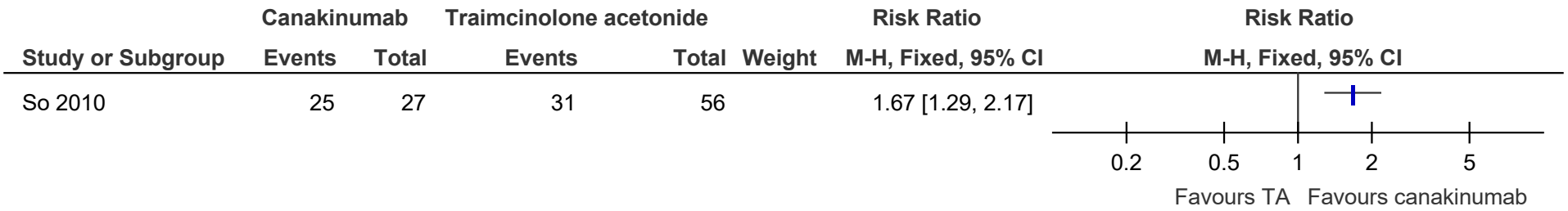


Figure 46: **Figure 47: Any adverse event- short-term up to 2 weeks**

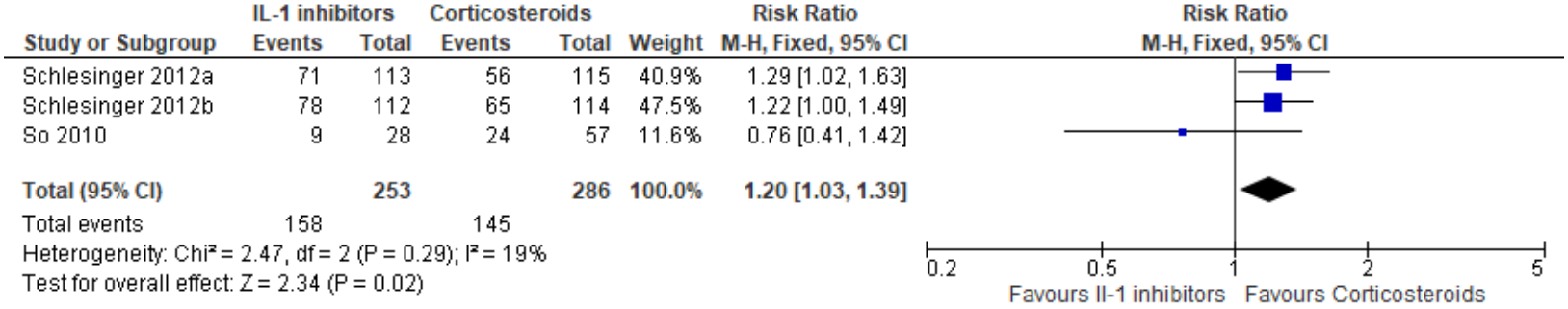
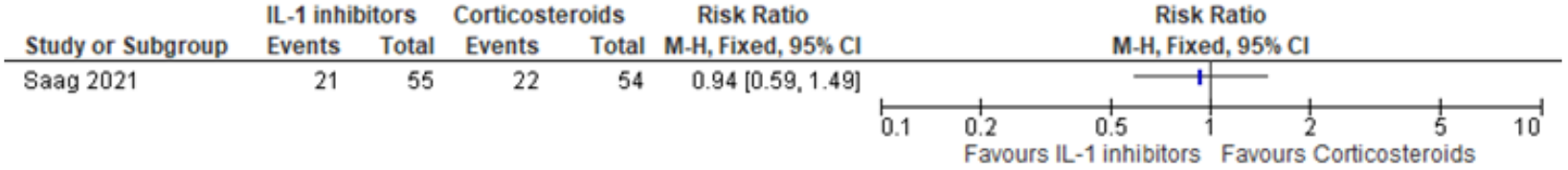


Figure 48: Any adverse event- long-term >6 weeks



E.5 Ice therapy plus corticosteroids and colchicine versus corticosteroids and colchicine

Figure 49: Pain (VAS 0-10) – Short-term up to 2 weeks (Better indicated by lower score)

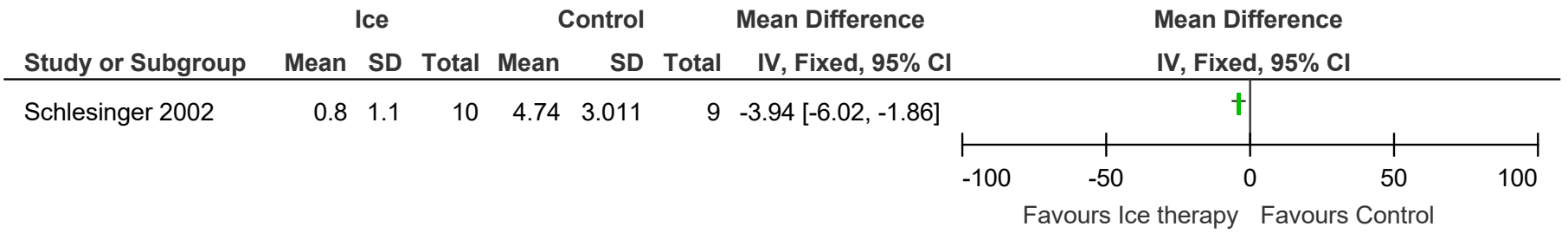
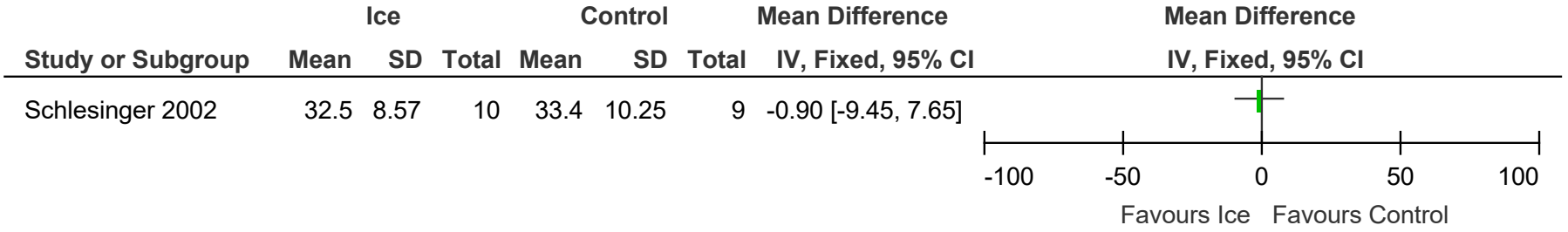


Figure 50: Joint circumference (cm) – Short-term up to 2 weeks (Better indicated by lower score)



Appendix F – GRADE tables

Table 18: Clinical evidence profile: Colchicine versus placebo

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)		
Pain - Proportion with 50% or greater decrease in pain score (VAS) from baseline – short-term (up to 2 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	31/74 (41.9%)	10/58 (17.2%)	RR 2.43 (1.30 to 4.54)	247 more per 1,000 (from 52 more to 610 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events - gastrointestinal (diarrhoea and vomiting) – short-term (up to 2 weeks) - Colchicine small dose (1.8 mg total)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	19/74 (25.7%)	12/59 (20.3%)	RR 1.26 (0.67 to 2.39)	53 more per 1,000 (from 67 fewer to 283 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. Established MIDs for VAS scale (continuous outcomes) improvements of ≥ 10 points. GRADE default MIDs used for all other outcomes, for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

Table 19: Clinical evidence profile: Corticosteroids versus NSAIDs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS) at 90 hours – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	59	59	-	MD **3.9 higher** (3.77 lower to 11.57 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - at rest – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	101/208 (48.6%)	111/208 (53.4%)	**RR 0.91** (0.75 to 1.10)	**48 fewer per 1,000** (from 133 fewer to 53 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Pain - Number of patients with clinically significant change in pain score (13 mm on a 100-mm VAS) - with activity – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	160/208 (76.9%)	151/208 (72.6%)	**RR 1.06** (0.95 to 1.19)	**44 more per 1,000** (from 36 fewer to 138 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Joint tenderness – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	208	208	-	MD 0.05 lower (0.33 lower to 0.23 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events- gastrointestinal (abdominal pain)- Short-term (up to 2 weeks)												
4	randomised trials	not serious	serious [a]	not serious	not serious	none	23/344 (6.7%)	52/393 (13.2 %)	RR 0.48 (0.30 to 0.76)	69 fewer per 1,000 (from 93 fewer to 32 fewer)	⊕⊕⊕◯MODERATE	CRITICAL
Adverse events- gastrointestinal (indigestion)- Short-term (up to 2 weeks)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	17/252 (6.7%)	33/254 (13.0%)	RR 0.52 (0.30 to 0.91)	62 fewer per 1,000 (from 91 fewer to 12 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events- gastrointestinal (nausea)- Short-term (up to 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious	none	7/252 (2.8%)	27/254 (10.6%)	RR 0.26 (0.12 to 0.59)	79 fewer per 1,000 (from 94 fewer to 44 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events- gastrointestinal (vomiting)- Short-term (up to 2 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	1/252 (0.4%)	14/254 (5.5%)	RR 0.1 (0.02 to 0.56)	50 fewer per 1,000 (from 54 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events- gastrointestinal (diarrhoea)- Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	0/44 (0.0%)	3/46 (6.5%)	Peto OR 0.14 (0.01 to 1.33)	70 fewer per 1,000 (from 150 fewer to 20 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events- gastrointestinal (GI haemorrhage)- Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/44 (0.0%)	5/46 (10.9%)	Peto OR 0.13 (0.02 to 0.78	110 fewer per 1,000 (from 210 fewer to 10 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Adverse events - cardiovascular (Chest pain) – Short-term (up to 2 weeks) (follow up: mean 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	0/44 (0.0%)	1/46 (2.2%)	Peto OR 0.14 (0.00 to 7.13)	19 fewer per 1,000 (from -- to 115 more)	⊕⊕◯◯ LOW	CRITICAL
Number of patients visited ED – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	28/208 (13.5%)	23/208 (11.1%)	RR 1.22 (0.73 to 2.04)	24 more per 1,000 (from 30 fewer to 115 more)	⊕⊕◯◯ LOW	CRITICAL
Number of patients visited outpatient department – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	0/208 (0.0%)	4/208 (1.9%)	Peto OR 0.13 (0.02 to 0.95)	17 fewer per 1,000 (from 19 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
GP visits – Short-term (up to 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	NSAIDs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [b]	none	11/208 (5.3%)	19/208 (9.1%)	RR 0.58 (0.28 to 1.19)	38 fewer per 1,000 (from 66 fewer to 17 more)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Downgraded by 1 or 2 increments because: the point estimate varies widely across studies, subgroup analysis could not be performed. I^2=65%.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.. Established MIDs VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: joint tenderness (0.5x baseline SD of control group as baseline values were not reported in the paper): 0.74. c. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, subgroup analysis could not be performed. I^2=65%.

Table 20: Clinical evidence profile: NSAIDs versus colchicine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
Joint pain scores (change score) - Short term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	53	52	-	MD 0.06 higher (0.28 lower to 0.4 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete pain resolution – Short-term (up to 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	115/170 (67.6%)	116/174 (66.7%)	RR 1.01 (0.88 to 1.18)	7 more per 1,000 (from 80 fewer to 120 more)	⊕⊕◯◯ LOW	CRITICAL
Complete pain resolution – Medium-term (2 to 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	130/170 (76.5%)	130/174 (74.7%)	RR 1.02 (0.91 to 1.15)	15 more per 1,000 (from 67 fewer to 112 more)	⊕⊕◯◯ LOW	CRITICAL
Joint swelling scores – Short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	53	52	-	MD 0.04 higher (0.19 lower to 0.27 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Patient assessment of global treatment response (completely/much better) n – Short-term (up to 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	114/170 (67.1%)	110/174 (63.2%)	RR 1.06 (0.91 to 1.24)	38 more per 1,000 (from 57 fewer to 152 more)	⊕◯◯◯ VERY LOW	CRITICAL
Patient assessment of global treatment response (completely/much better) n – Medium-term (2 to 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	140/170 (82.4%)	143/174 (82.2%)	RR 1.00 (0.91 to 1.11)	0 fewer per 1,000 (from 74 fewer to 90 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events - gastrointestinal (vomiting) -short-term (up to 2 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/53 (3.8%)	1/52 (1.9%)	RR 1.96 (0.18 to 20.99)	18 more per 1,000 (from 16 fewer to 384 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events - gastrointestinal (diarrhoea) -short-term (up to 2 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	32/223 (14.3%)	69/226 (30.5%)	RR 0.47 (0.33 to 0.68)	162 fewer per 1,000 (from 205 fewer to 98 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
Adverse events - gastrointestinal (nausea+/or vomiting) - short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	serious [b]	none	21/170 (12.4%)	30/174 (17.2%)	RR 0.72 (0.43 to 1.20)	48 fewer per 1,000 (from 98 fewer to 34 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events - gastrointestinal (dyspepsia) -short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	20/170 (11.8%)	20/174 (11.5%)	RR 1.02 (0.57 to 1.83)	2 more per 1,000 (from 49 fewer to 95 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events - gastrointestinal (abdominal pain) -short-term (up to 2 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	16/170 (9.4%)	16/174 (9.2%)	**RR 1.02** (0.53 to 1.98)	**2 more per 1,000** (from 43 fewer to 90 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events - gastrointestinal (constipation) -short-term (up to 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	30/170 (17.6%)	67/174 (38.5%)	**RR 0.46** (0.31 to 0.67)	**208 fewer per 1,000** (from 266 fewer to 127 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events - gastrointestinal (nausea+/or vomiting) -medium-term (2 to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	7/170 (4.1%)	5/174 (2.9%)	**RR 1.43** (0.46 to 4.43)	**12 more per 1,000** (from 16 fewer to 99 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events - gastrointestinal (dyspepsia) -medium-term (2 to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	13/170 (7.6%)	8/174 (4.6%)	**RR 1.66** (0.71 to 3.91)	**30 more per 1,000** (from 13 fewer to 134 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events - gastrointestinal (abdominal pain) -medium-term (2 to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	4/170 (2.4%)	8/174 (4.6%)	**RR 0.51** (0.16 to 1.67)	**23 fewer per 1,000** (from 39 fewer to 31 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
Adverse events - gastrointestinal (constipation) -medium-term (2 to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	9/170 (5.3%)	6/174 (3.4%)	**RR 1.54** (0.56 to 4.22)	**19 more per 1,000** (from 15 fewer to 111 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events - gastrointestinal (diarrhoea) - medium-term (2 to 6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	5/170 (2.9%)	10/174 (5.7%)	**RR 0.51** (0.18 to 1.47)	**28 fewer per 1,000** (from 47 fewer to 27 more)	⊕⊕◯◯ LOW	CRITICAL
Consultation re-attendance for gout during 4-week follow-up - Emergency department – Medium-term (2 to 6 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/170 (0.6%)	1/174 (0.6%)	Peto OR 1.02 (0.06 to 16.23)	0 fewer per 1,000 (from 5 fewer to 80 more)	⊕◯◯◯ VERY LOW	CRITICAL
Consultation re-attendance for gout during 4-week follow-up - GP Medium-term (2 to 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Colchicine subgroup	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26/170 (15.3%)	39/174 (22.4%)	RR 0.68 (0.44 to 1.07)	72 fewer per 1,000 (from 126 fewer to 16 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. Established MIDs VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: joint pain scores: 0.435; joint swelling: 0.98.

Table 21: Clinical evidence profile: IL-1 inhibitors versus corticosteroids

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Il-1 inhibitors	corticosteroids Canakinumab	Relative (95% CI)	Absolute (95% CI)		
Health-related quality of life SF-36 - Physical Component – Short-term (up to 2 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28	57	-	MD 6.4 higher (2.37 higher to 10.43 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 Physical component – long-term (more than 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Il-1 inhibitors	corticosteroids Canakinumab	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28	57	-	MD 5.7 higher (1.88 higher to 9.52 higher)	⊕◯◯◯ VERY LOW	CRITICAL
SF-36 - Mental component - long-term (more than 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28	57	-	MD 4.2 higher (0.22 higher to 8.18 higher)	⊕◯◯◯ VERY LOW	
Pain: 100-mm visual analogue scale – Short-term (up to 2 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	225	229	-	MD 10.56 lower (15.26 lower to 5.87 lower)	⊕⊕◯◯ LOW	CRITICAL
Pain % change 100 mm visual analogue scale short-term (follow up <2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Il-1 inhibitors	corticosteroids Canakinumab	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	very serious [c]	not serious	serious [b]	none	83	111	-	MD 10.32 lower (17.25 lower to 3.38 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Joint swelling – Short-term (up to 2 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-	-	Peto OR 1.58 (1.09 to 2.31)	2 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Joint tenderness – Short-term (up to 2 weeks)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	-	-	Peto OR 2.16 (1.47 to 3.18)	2 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Patient global assessment – Short-term (up to 2 weeks)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	-	-	Peto OR 1.98 (1.39 to 2.83)	2 fewer per 1,000 (from 3 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Il-1 inhibitors	corticosteroids Canakinumab	Relative (95% CI)	Absolute (95% CI)		
Participant global assessment of response to treatment: good or excellent – Short-term (up to 2 weeks) - Canakinumab 150 mg												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	25/27 (92.6%)	31/56 (55.4%)	RR 1.67 (1.29 to 2.17)	371 more per 1,000 (from 161 more to 648 more)	⊕⊕◯◯ LOW	CRITICAL
Any adverse event - short-term (up to 2 weeks)												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	158/253 (62.5%)	145/286 (50.7%)	RR 1.20 (1.03 to 1.39)	101 more per 1,000 (from 15 more to 198 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events- long-term (up to 2 years)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	21/55 (38.2%)	22/54 (40.7%)	RR 0.94 (0.59 to 1.49)	24 fewer per 1,000 (from 167 fewer to 200 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 . Established MIDs for SF-36 physical/mental- 3.75; for VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale; GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: Calculated MIDS for gout flares 1, 2 and 3 were: 9.1, 10.3 and 5.9 (0.5* median of baseline SDs for intervention and control groups)..c. Absolute effect could not be estimated because studies only reported OR and did not report means separately for intervention and control arms. Inverse variance analysis method was used.

d. I^2=79%, p=0.03

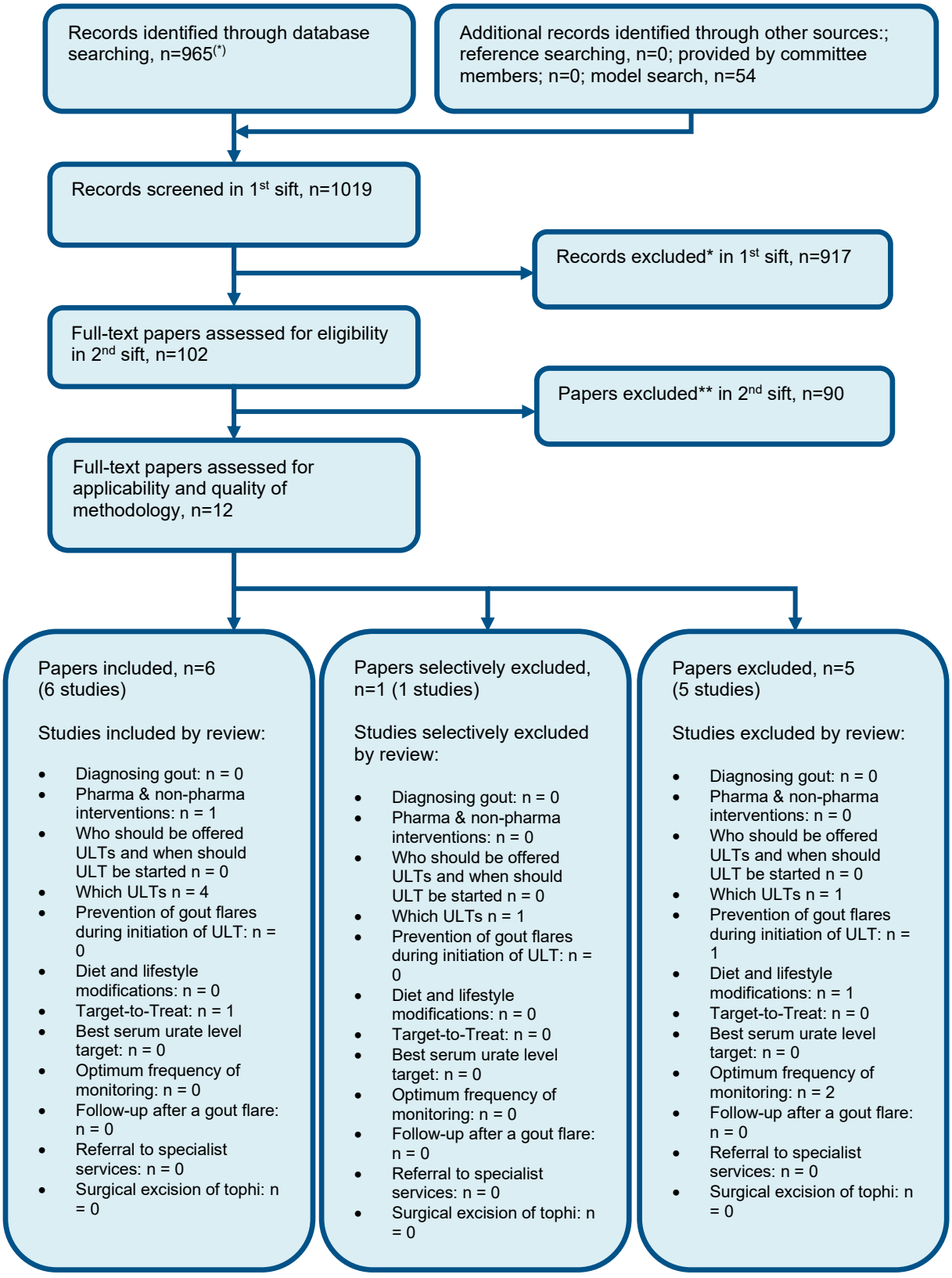
Table 22: Clinical evidence profile: ice plus prednisone and colchicine versus prednisone and colchicine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ice+corticosteroids+colchicine	corticosteroids+colchicine	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-10) -Short-term (up to 2 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	10	9	-	MD **3.94 lower** (6.02 lower to 1.86 lower)	⊕⊕◯◯ LOW	CRITICAL
Joint circumference (joint swelling) (cm) – Short-term (up to 2 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	10	9	-	MD **0.9 lower** (9.45 lower to 7.65 higher)	⊕◯◯◯ 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. Established MIDs VAS continuous scale - improvements of ≥ 10 points on a 1-100 scale. GRADE default MIDs used for all other outcomes. For dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25. For continuous outcomes 0.5 x baseline SD was calculated: joint circumference no baseline values reported so the control group SD was used: 5.13.

Appendix G – Economic evidence study selection



* excludes conference abstracts (n=280)

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

Appendix H – Economic evidence tables

Study	**Roddy 2020[47]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level resource use, with unit costs applied. QALYs calculated adjusted for baseline EQ-5D values. **Perspective:** UK NHS **Follow-up**: 4 weeks **Treatment effect duration:**[(a)] 4 weeks **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People 18 years and over consulting for a current gout flare. **Patient characteristics:** N = 399 Mean age: 59.35 Male: 86.95% **Intervention 1:** Low-dose colchicine, 500mcg three times per day for 4 days. **Intervention 2:** Naproxen, 750mg immediately then 250mg every 8 hours for 7 days.	**Total costs (mean per patient):** Intervention 1: £23.31 Intervention 2: £17.57 Incremental (2−1): saves £5.74 (95% CI:-10.03 to -1.64 ; p=NR) **Currency & cost year:** 2015/16 UK pounds. **Cost components incorporated:** Drug costs, GP costs, nurse costs, Emergency GP costs, A&E costs, intervention costs.	**QALYs (mean per patient):** Intervention 1: 0.0658[(b)] Intervention 2: 0.0662[(b)] Incremental (2−1): 0.0004 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Naproxen dominates (less costly and more effective) Probability Intervention 2 cost effective (£20K threshold): 80% **Analysis of uncertainty:** Five thousand pairs of mean cost and QALY differences were estimated by non-parametric bootstrapping and presented on a cost-effectiveness plane. Cost-effectiveness acceptability curve plotted to determine the probability that naproxen was cost-effective at NICE's £20,000 threshold.
Data sources				

Health outcomes: This RCT was 1 of 12 studies identified in the systematic review of the evidence – this was the only RCT comparing naproxen and low-dose colchicine. The results of this RCT are similar to the one other additional study included in the clinical review (Lui 2019) assessing the effectiveness of NSAIDs and colchicine which compared colchicine and etoricoxib. **Quality-of-life weights:** EQ-5D-5L UK tariff. **Cost sources:** NR
Comments
Source of funding: National Institute for Health Research School for Primary Care Research. **Limitations:** The analysis uses EQ-5D-5L and so is not in line with the NICE reference case with preference for the EQ-5D-3L. Unit costs taken from 'standard UK sources' but no references provided cost of PPIs not included for naproxen, short time horizon. **Other:** n/a
Overall applicability:[c] Partially applicable **Overall quality:**[d] Minor limitations

Abbreviations: A&E= Accident and Emergency; 95% CI= 95% confidence interval; CUA= cost–utility analysis;; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GP= general practitioner;; ICER= incremental cost-effectiveness ratio; mcg= micrograms; mg= milligrams; NR= not reported;; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) QALYs adjusted for baseline values (both 'QALYs' and 'QALYs adjusted for baseline values' were reported in the study).

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

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

Appendix J – Excluded studies

Clinical studies

Table 23: Studies excluded from the clinical review

Study	Exclusion reason
Ahern 1987[1]	Incorrect intervention - very high dose of colchicine, 6.7 mg
Alloway 1993[2]	Incorrect study design - not all patients included in the analysis were randomised, "Patients with renal insufficiency, a history of GI side effects to NSAID, peptic ulcer disease or gastritis; or any other contraindication to indomethacin were treated with triamcinolone acetonide, but all other patients were randomly assigned."
Altman 1988[3]	Incorrect intervention - ketoprofen compared to indomethacin
Anonymous 2002[4]	Incorrect study design - article
Anonymous 2008[5]	Incorrect study design - article
Araujo 2015[6]	Systematic review - references checked
Balasubramaniam 2017[7]	Incorrect study design - study protocol
Billy 2018[8]	systematic review - references checked
Bruce 2006[10]	Systematic review - references checked
Butler 1985[11]	Incorrect intervention - flurbiprofen vs phenylbutazone
Cheng 2004[12]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Daoussis 2018[13]	Incorrect study design - study description/study protocol
Denman 2016[14]	Incorrect study design - abstract only
Dumusc 2015[15]	Systematic review - references checked
Fravel 2011[16]	Systematic review - references checked
Guillot 2019[17]	Incorrect population - only 17 out of 47 patients included had gout, 11 calcium pyrophosphate diseases, 13 rheumatoid arthritis, 6 spondylarthritis
Hay 2021[18]	Systematic review - references checked
Hu 2020[19]	Systematic review - references checked
Huizinga 2010[21]	Incorrect study design-commentary
Huizinga 2011[20]	Incorrect study design - commentary
Janssen 2019[23]	Incorrect comparison - anakinra versus usual care (either colchicine 18 patients, naproxen 13 patients or prednisolone 14)
Janssen 2019[22]	Incorrect comparison - Anakinra compared to standard care which included either colchicine, NSAID or corticosteroids)
Janssens 2008[24]	Cochrane review - was excluded because two out of three included studies were not relevant, one of them had no pairwise analysis and another one included inappropriate comparison

Study	Exclusion reason
	(adrenocorticotropic hormone vs triamcinolone). References checked for inclusion.
Janssens 2009[26]	Not in English
Jomori 2015[27]	Incorrect intervention - topiroxostat vs placebo
Khanna 2014[28]	Systematic review - references checked
Lederman 1990[29]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Li,2013[30]	Incorrect intervention - Rilonacept compared to indomethacin
Lin 2019[31]	Systematic review - references checked
Liu 2015[34]	Incorrect comparison - colchicine with dexamethasone vs colchicine large dose
Liu 2017[33]	Systematic review - references checked
Lundberg 2008[35]	Incorrect study design - video presentation
Maccagno 1991[36]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Martina 2005[38]	Systematic review - references checked
Moon 2011[39]	Incorrect study design - Abstract only
Navarra 2007[42]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Parperis 2019[44]	Incorrect study design - response letter
Perez-Ruiz 1999[45]	Incorrect e population/incorrect intervention - people with chronic gout, benzbromarone vs allopurinol
Roddy 2019[48]	Incorrect study design - response letter
Rubin 2004[49]	Incorrect e comparison - intraclass comparison, NSAIDS compared to NSAIDS
Schlesinger 2009[55]	Incorrect study design – sub-study of two studies comparing Etoricoxib vs Indomethacin (both NSAIDs)
Schlesinger 2011[54]	Incorrect population - study assessed risk of acute gouty arthritis flares during initiation of Allopurinol
Schumacher 2002[57]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Schumacher 2012[56]	Incorrect comparison - intraclass comparison, NSAIDS compared to NSAIDS
Seth 2014[58]	Systematic reviews - references checked
Sharma 2019[59]	Incorrect study design - not RCT, retrospective case control study
Shekelle 2017[60]	Systematic review - references checked
Shrestha 1995[61]	Incorrect intervention – intramuscular ketorolac plus oral placebo vs oral indomethacin plus intramuscular placebo
Sivera 2014[62]	Cochrane review - was excluded because one of the included studies had inappropriate intervention (Rilonacept vs indomethacin) and for other three studies outcomes were extracted at different time points (at 72 hours) and we

Study	Exclusion reason
	have used last available timepoint (7 days) for the review. References checked for inclusion.
So 2011[64]	Inappropriate study design - Abstract only
Solomon 2018[65]	Incorrect population - patients who had myocardial infarction
Stewart 2020[66]	Systematic review - references checked
Stubbs 1989[67]	Systematic review references checked
Sturge 1977[68]	Incorrect intervention - Naproxen versus phenylbutazone
Terkeltaub 2013[70]	Incorrect intervention - Rilonacept compared to indomethacin
Underwood 2015[71]	Systematic review references checked
Valdes 1987[72]	Incorrect intervention/inappropriate comparison - Tenoxicam 20 mg versus tenoxicam 40 mg
van 2014[73]	Cochrane review - excluded as only three out of twenty-three included studies were relevant, studies were excluded due to inappropriate intervention, inappropriate comparison or were not available, references checked for inclusion
van Echteld 2014[75]	Systematic review - references checked
van Echteld 2014[74]	Systematic review - references checked
Wechalekar 2013[77]	Cochrane review - was excluded because this review had no included studies.
Wechalekar 2014[76]	Systematic review - references checked
Weiner 1979[78]	Incorrect intervention/ Inappropriate comparison - fenoprofen compared to phenylbutazone
Willburger 2007[79]	Incorrect intervention - lumiracoxib versus indomethacin
Xu 2015[81]	Incorrect intervention - celecoxib compared to methylprednisolone
Yu 2018[83]	Inappropriate study design - protocol for systematic review
Yu 2018[82]	Systematic review - references checked
Zeng 2020 [84]	Network meta-analysis – methods not clearly reported, not suitable for inclusion
Zhang 2014[86]	Incorrect intervention - betamethasone
Zhang 2016[85]	Systematic review - references checked

Appendix K– Research recommendation – 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 colchicine compared with corticosteroids for managing gout flares?

J.1.2 Why this is important

Gout flares are excruciatingly painful and require rapid treatment with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids. Flares are most frequently treated with NSAIDs, although many people with gout have contraindications to NSAIDs, e.g. chronic kidney disease or cardiovascular disease. RCTs show that NSAIDs have similar effectiveness for flares to colchicine and corticosteroids, however, there has never been a direct comparison of the effectiveness and safety of colchicine and corticosteroids.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	People with gout experiencing a gout flare want treatment that will rapidly alleviate their severe pain and joint inflammation. Although NSAIDs are the most common treatments for gout flares, many people with gout have contraindications to NSAIDs and it is not known whether corticosteroids or colchicine is more effective or better tolerated. Evidence will be provided for comparative effectiveness of corticosteroids and colchicine, allowing patients and practitioners to reach informed treatment decisions, particularly in people who have contraindications to NSAIDs.
Relevance to NICE guidance	The guideline recommends offering NSAIDs, colchicine, or corticosteroids as first-line treatment of a gout flare, taking into account patient comorbidities, co-prescribing and patient preferences. The evidence review included RCTs which compared NSAIDs with corticosteroids and NSAIDs with colchicine, but there were no relevant RCTs which compared corticosteroids with colchicine. Evidence provided by this RCT would allow a more informed recommendation concerning the effectiveness and safety of these options for flare management.
Relevance to the NHS	Gout is the most common inflammatory arthritis and places a significant burden on healthcare resources. It is exceedingly painful, leading patients to frequently seek care for gout flares. Although it is predominantly managed in primary care, hospital admissions for gout in England rose by 59% from 2006 to 2017 and gout has overtaken rheumatoid arthritis as the

	commonest rheumatological cause for hospitalisation in the UK. The outcome would provide much needed evidence for the effectiveness of interventions for gout flares provided by the NHS, which will inform clinical decision-making and allow patients to receive the most effective treatment to reduce the severe pain associated with gout flares and potentially reduce the need for hospital admission.
National priorities	None
Current evidence base	The evidence review identified 12 RCTs evaluating interventions for flare management. There were no RCTs directly comparing corticosteroids and colchicine for gout flares.
Equality considerations	None known

J.1.4 Modified PICO table

Population	People with a gout flare
Intervention	Oral corticosteroids
Comparator	Oral colchicine
Outcome	Pain, quality of life, adverse events, analgesic use, treatment adherence, flare relapse/recurrence, treatment satisfaction, healthcare utilisation, work/education absence.
Study design	Randomised controlled trial
Timeframe	Short term (e.g. 4 weeks)
Additional information	None