National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[J] Evidence reviews for treat-to-target management

NICE guideline NG219

Evidence reviews underpinning recommendation 1.5.5 in the NICE guideline

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Final

National Institute for Health and Care Excellence

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1.1 Review question: What is the clinical and cost effectiveness of a 'treat-to-target' urate lowering management strategy compared with usual care for gout?

1.1.1 Introduction

Long-term management of gout involves taking urate-lowering therapy (ULT) such as allopurinol or febuxostat to lower serum urate levels, preventing formation of new monosodium urate crystals and dissolving existing crystals. As a result, gout flares cease, tophi reduce in size and eventually disappear, and long-term joint damage can be prevented. 'Treat-to-target' ULT involves starting medication at low-dose and increasing the dose gradually until serum urate has been lowered below an agreed target level.

In clinical practice, only one-third of people with gout receive ULT and most of these remain on a fixed low dose and do not have the dose increased to achieve a target serum urate level. Consequently, many people with gout continue to suffer avoidable gout flares, joint pain, and disability.

This evidence review will compare the clinical and cost effectiveness of a treat-to-target approach to ULT with usual clinical care.

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 • Strata: None • Exclusion: people with calcium pyrophosphate crystal deposition, including pseudogout
Intervention(s)	• Treat-to-target management strategy using urate-lowering therapies (ULT) • Different timing will be combined, e.g. testing every 4 weeks and testing every 8 weeks
Comparison(s)	• Usual care • No ULT • ULT not using treat-to-target approach (fixed dose)
Outcomes	• All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares

	• patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • 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) • adverse events and complications of gout: ○ Radiographic joint damage ○ renal stones ○ tophi ○ admissions (hospital and A&E/urgent care) ○ GP visits ○ Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration.
Study design	• Randomised Controlled Trials (RCTs) • 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 ○ 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

Two RCTs were included in the review.[8, 22] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Both RCTs compared 'treat-to-target' management strategies with usual care for gout.

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

RCTs were the preferred study design but only two RCTs were found, so we also searched for cohort studies to provide more evidence. No cohort studies matched the protocol, so they were excluded.

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
Doherty 20188	Intervention (n=255) Treat to target management plus nurse-led care(first-line treatment was oral allopurinol, started at 100 mg once per day and titrated upwards in 100 mg increments every 3–4 weeks according to serum urate concentrations, to a maximum of 900 mg once per day. As second-line options, oral febuxostat could be started at 80mg and if required increased to the maximum dose of 120 mg once per day or benzbromarone could be started at 50 mg and titrated up in 50 mg increments to a maximum of 200 mg once per day. in addition to the treat-to-target strategy: a nurse-led individualised package of care comprising of a holistic assessment, gout information booklet, individualised education, and engagement of participants by discussion of illness	n=517 Adult patients with diagnosis of gout. Age mean years (SD): Treat to target (Nurse led care) 62.01 (10.81); Usual care 63.69 (11.91) Gender (M/F): Nurse led care (treat to target) 229/26; Usual care 232/30 Ethnicity: not reported UK	Quality of life - SF36 physical component at 1 year; Quality of life - SF36 physical component at 2 years; Quality of life - SF36 mental component at 1 year; Quality of life - SF36 mental component at 2 years; Quality of life - Gout impact scale score (GIS) – gout concern overall at 1 year; Quality of life - Gout impact scale score (GIS) – gout concern overall at 2 years; Quality of life - Gout impact scale score (GIS) – unmet gout treatment need at 1 year; Quality of life - Gout impact scale score (GIS) – unmet gout treatment need at 2 years; Frequency of flares – two or more flares at 1 year; Frequency of flares – two or more flares at 2 years; Adverse events – presence of tophi at 1 year;	CKD stage 3 in treat to target group 53 (23%) and in usual care group 63 24%)

Study	Intervention and comparison	Population	Outcomes	Comments
	perceptions, and shared decision making Taking urate lowering therapy at baseline n (%): 101(40%) (Allopurinol 101(100%)) Prophylaxis – 3 people received Colchicine Comparison (n=262) Usual care - Patients assigned to continue usual GP-led care were given the gout information booklet from Arthritis Research UK. Treatment of flares could be discussed by the research nurse at baseline and at yearly assessments, but if participants enquired about other aspects of management, they were advised to ask their GP. Taking urate lowering therapy at baseline n (%): 102 (39%) (Allopurinol 101 (99%); sulfinpyrazone 1 (1%))		Adverse events – presence of tophi at 2 years.	
Stamp 201722	Intervention (n=90) Treat to target - In the dose escalation (DE) group (Treat to target), allopurinol was increased monthly until SU was <6 mg/dL on three consecutive visits or there were AEs. For example, if SU was <6 mg/dL allopurinol was	n=183 Adult patients with diagnosis of gout. Age: mean years (SD): Dose escalation group (treat-to target): 59.5 (12.1), Control: 60.9 (12.8)	Quality of life – HAQ (health assessment questionnaire); Pain (VAS- change score at 12 months; Joint swelling – swollen joint count at 12 months; Joint tenderness – tender joint count at 12 months;	Population has high prevalence of comorbid conditions, particularly CKD (52% having CrCL< 60mL/min and at least some of these having CKD stage 3 or higher) as well as severe gout (44% with tophi)

Study	Intervention and comparison	Population	Outcomes	Comments
	not escalated but if at the following month urate was >6 mg/dL allopurinol was increased unless there was evidence of poor adherence. The dose was increased by 50 mg/d for those with CrCL <60 mL/min and 100 mg/d in those with CrCL ≥60 mL/min. Baseline Allopurinol dose mg/day n (%): 100 - 200 mg 37 (41.1%) >200 – 300 mg 47(52.2%) >300 mg 7(7.7%) Baseline prophylaxis n (%): Any anti-inflammatory prophylaxis - 51 (57%) Colchicine - 34 (38%) NSAIDs 15 (17%) Prednisolone - 12 (13%) Control group (n=93) Usual care - In the control group, participants continued on the same allopurinol dose throughout the study period. Anti-inflammatory prophylaxis and treatment of gout flares were at the discretion of the investigator. Baseline allopurinol dose mg/day n (%): 100 - 200 mg 31 (33.3%)	Gender (M/F): Dose escalation group (treat-to-target): 82/8, Control: 78/5 Ethnicity: Dose escalation group: NZ European: 41%, Maori: 32%, Pacific island: 21%, Asian: 6%, Other: 0%. Control group: NZ European: 42%, Maori: 24%, Pacific island: 29%, Asian: 4%, Other:1%. New Zealand	Frequency of flares – self reported gout flares at 12 months; Adverse events – cardiovascular at 12 months; Adverse events – renal and urinary disorders at 12 months; Adverse events – gastrointestinal disorders at 12 months; Adverse events – allopurinol-specific at 12 months; Adverse events and complications of gout - complete resolution of tophi at 12 months.	Cardiovascular adverse events included: cardiac disorders, vascular disorders and venous disorders Renal and urinary adverse events included: not specified Gastrointestinal adverse events included: not specified Allopurinol -specific adverse events included: nausea/vomiting and abdominal pain Only the non-laboratory treatment emergent adverse events data were reported. Data on participants with at least one serious adverse event was not reported.

Study	Intervention and comparison	Population	Outcomes	Comments
	>200 – 300 mg 50 (53.4%) >300 mg 12 (12.9%) Baseline prophylaxis n (%): Any anti – inflammatory prophylaxis – 45 (48%) Colchicine – 35 (38%) NSAIDs - 9 (10%) Prednisolone – 12 (13%)			

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Treat-to-target versus usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Treat to target
Quality of life SF-36 Physical component at 1 year (0-100 scale; better indicated by higher score)	517 (1 RCT)	LOW[a,b,e]	-	The mean quality of life SF-36 Physical component at 1 year was 36.54	MD 3.92 higher (1.48 higher to 6.36 higher)
Quality of life SF-36 Physical component at 2 years (0-100 scale; better indicated by higher score)	517 (1 RCT)	LOW[a,b,e]	-	The mean quality of life SF-36 Physical component at 2 years was 37.43	MD 3.58 higher (0.86 higher to 6.3 higher)
Quality of life SF-36 mental component at 1 year (0-100 scale; better indicated by higher score)	517 (1 RCT)	MODERATE[a,e]	-	The mean quality of life SF-36 mental component at 1 year was 54.01	MD 0.55 lower (2.13 lower to 1.03 higher)
Quality of life SF-36 mental component at 2 years (0-100 scale; better indicated by higher score)	517 (1 RCT)	MODERATE[a,e]	-	The mean quality of life SF-36 mental component at 2 years was 54.02	MD 1.1 lower (3.19 lower to 0.99 higher)
Quality of life - Gout impact scale (GIS) - Gout concern overall - at 1 year (0-100 scale; better indicated by lower score)	517 (1 RCT)	LOW[a,b,e]	-	The mean quality of life - Gout impact scale (GIS) - Gout concern overall - at 1 year was 57.79	MD 9.01 lower (13.46 lower to 4.56 lower)
Quality of life - Gout impact scale (GIS) - Gout concern overall - at 2 years (0-100 scale; better indicated by lower score)	517 (1 RCT)	MODERATE[a,e]	-	The mean quality of life - Gout impact scale (GIS) - Gout concern overall - at 2 years was 53.62	MD 16.08 lower (20.56 lower to 11.6 lower)
Quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 1 year (0-100 scale; better indicated by lower score)	517 (1 RCT)	MODERATE[a,e]	-	The mean quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 1 year was 36.29	MD 10.67 lower (13.86 lower to 7.48 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Treat to target
Quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 2 years (0-100 scale; better indicated by lower score)	517 (1 RCT)	MODERATE[a,e]	-	The mean quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 2 years was 33.71	MD 12.68 lower (15.76 lower to 9.6 lower)
Quality of life - health assessment questionnaire (HAQ) at 1 year (0-3 scale; better indicated by lower score)	143 (1 RCT)	MODERATE[a]	-	The mean quality of life - health assessment questionnaire (HAQ) at 1 year was 0.51	MD 0.11 higher (0.14 lower to 0.36 higher)
Pain (VAS) change score at 1 year (0-10 scale; better indicated by lower score)	143 (1 RCT)	MODERATE[a]	-	The mean pain (VAS) change score at 1 year was 2.04	MD 0.11 lower (0.48 lower to 0.26 higher)
Joint swelling - swollen joint count at 1 year (0-3 scale; better indicated by lower score)	143 (1 RCT)	MODERATE[b]	-	The mean joint swelling - swollen joint count at 1 year was 1.58	MD 0.57 lower (0.93 lower to 0.21 lower)
Joint tenderness - tender joint count at 1 year (0-3 scale; better indicated by lower score)	143 (1 RCT)	HIGH	-	The mean joint tenderness - tender joint count at 1 year was 2.07	MD 0.34 lower (0.92 lower to 0.24 higher)
Frequency of flares 1 or more flares at 1 year (better indicated by lower score)	700 (2 RCTs)	VERY LOW[b,c,e]	RR 1.13 (0.77 to 1.66)	448 per 1,000	58 more per 1,000 (103 fewer to 296 more)
Frequency of flares- 2 or more flares at 2 years (better indicated by lower score)	517 (1 RCT)	HIGH[e]	RR 0.32 (0.20 to 0.51)	244 per 1,000	166 fewer per 1,000 (195 fewer to 120 fewer)
Adverse events-cardiovascular disorders[d] at 1 year (better indicated by lower score)	183 (1 RCT)	LOW[b]	RR 0.86 (0.46 to 1.60)	194 per 1,000	27 fewer per 1,000 (105 fewer to 116 more)
Adverse events - renal and urinary disorders at 1 year (better indicated by lower score)	183 (1 RCT)	LOW[b]	Peto OR 7.73	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Treat to target
			(0.48 to 124.51)		
Adverse events - gastrointestinal disorders at 1 year (better indicated by lower score)	183 (1 RCT)	LOW[b]	RR 0.89 (0.51 to 1.55)	226 per 1,000	25 fewer per 1,000 (111 fewer to 124 more)
Adverse events - allopurinol specific disorders at 1 year (better indicated by lower score)	183 (1 RCT)	LOW[b]	RR 0.89 (0.43 to 1.81)	151 per 1,000	17 fewer per 1,000 (86 fewer to 122 more)
Adverse events and complications of gout - presence of tophi at 1 year (better indicated by lower score)	517 (1 RCT)	MODERATE[b,e]	RR 0.68 (0.39 to 1.21)	103 per 1,000	33 fewer per 1,000 (63 fewer to 22 more)
Adverse events and complications of gout - presence of tophi at 2 years (better indicated by lower score)	517 (1 RCT)	HIGH[e]	RR 0.24 (0.11 to 0.54)	115 per 1,000	87 fewer per 1,000 (102 fewer to 53 fewer)
Adverse events - resolution of measurable tophi at 1 year (better indicated by lower score)	75 (1 RCT)	LOW[a]	RR 1.01 (0.39 to 2.62)	186 per 1,000	2 more per 1,000 (113 fewer to 301 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; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ – 0.22; Pain (VAS) was improvement 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. For continuous outcomes 0.5 x baseline SD for continuous outcomes. For joint swelling the MID was 0.655, for joint tenderness the MID was 0.96. Clinical benefit or harm MCIDs: frequency of flares: 100 fewer per 1,000 patients = clinical benefit of intervention; Adverse events: 50 more per 1,000 patients = clinical harm of intervention; Renal stones: 50 more per 1,000 patients = clinical harm of intervention; tophi: 50 fewer per 1,000 patients = clinical benefit of intervention; admission: 100 fewer per 1,000 patients = clinical benefit of intervention; GP visits: 100 fewer per 1,000 patients = clinical benefit of intervention.

[c]. Downgraded by 2 increments because the point estimate varies widely across studies and I^2=83%, subgroup analysis could not be performed as only 2 studies included in the analysisso a random effects model was used.

[d] The study reported cardiac disorders, vascular disorders and venous disorders, which were combined for the analysis.

[e] One study was treat-to-target plus nurse-led individualised care package compared to usual care (GP care).

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with the relevant comparison was included in this review[8]. This is summarised in the health economic evidence profile below (Table 4) and the health economic evidence table in Appendix H.

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 4: Health economic evidence profile: Target-to-treat management versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Doherty 2018[8]([UK])	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Within-RCT analysis (Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial / Doherty 2018[8]) • Cost-utility analysis (QALYs) • Population: Adults with gout • Comparators: Treat-to-target versus usual care • ULTs in the treat-to-target arm: 84% allopurinol, 14% febuxostat, 2% other. ULTs in the usual care arm: 96% allopurinol, 3% febuxostat, 1% other • Time horizon: 24 months (within-trial analysis), data extrapolation used to calculate outcomes at 3, 5, and 10 years	24 months: £84[(c)] 3 years: £10[(c)] 5 years: -£126[(c)] 10 years: -£412[(c)]	24 months: 0.0165 QALYs 3 years: 0.036 QALYs 5 years: 0.073 QALYs 10 years: 0.148 QALYs	24 months: £5,066 per QALY gained 3 years: £285 per QALY gained 5 years: Dominant 10 years: Dominant	Probability treat-to-target cost effective (£20/£30K threshold): NR Sensitivity analyses were conducted: decreasing the cost of a gout flare, increasing nurse-time in the treat-to-target strategy, and decreasing the efficacy of the intervention. At time points 3,5, and 10 years treat-to-target was still cost effective at NICEs £20,000 threshold. The largest cost per QALY observed in these scenario analyses was at 3 years when the cost of a gout flare was decreased to £50 per flare resulting in cost per QALY of £6,144.

Abbreviations: 95% CI= 95% confidence interval; CUA= cost-utility analysis; ICER= incremental cost-effectiveness ratio; NA= not applicable; NR= not reported; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Baseline health state utilities obtained by mapping SF-36 data from the current trial

(b) Method of eliciting disutility values for flares was unclear. This study was based on one single centre RCT. Unit costs were obtained from a NICE TA conducted several years ago; it is unclear what the primary sources for this analysis were and the cost of a gout flare is significantly higher compared to the estimated costs in Evidence review G (£295 compared to £27.19 - £55.60). Assumed flares observed in months 13 to 24 were applicable to the remainder of the modelling period. Minimal interpretation is provided for the rate of flares per serum urate level band. Total costs and QALYs not reported, only incremental values. No probabilistic analysis undertaken.

(c) 2015/16 UK pounds. Cost components incorporated: drug costs, appointment costs, cost of a gout flare, nurse training, face-to-face nurse-led appointments, laboratory tests serum urate level, glomerular filtration rate, tophi..

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 5: Urate-lowering therapy costs

Resource	Cost per unit	Dosage
Allopurinol 100mg tablet	£0.04	100mg – 900mg per day
Allopurinol 300mg tablet	£0.05	
Febuxostat 80mg tablet	£0.09	80mg – 120mg per day
Febuxostat 120mg tablet	£0.87	

Source: British National Formulary, February 2022[6]

Table 6: Staff costs

Resource	Unit costs
Primary care Practice Nurse (Band 5), cost per hour[(a)]	£42
General Practitioner, cost per consultation (9.22 minutes)[(a)]	£37

Source: PSSRU 2020[5]
(a) Including qualification costs but excluding individual and productivity costs.

1.1.11 Evidence statements

Economic

- One cost–utility analysis found that treat-to-target was cost effective compared to usual care for treating gout (ICER: £5,066 per QALY gained at 2 years, £285 per QALY gained at 3 years, and dominant [less costly and more effective] at 5 and 10 years). This analysis was assessed as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

In this review the committee considered the following outcomes as critical for decision-making: health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, frequency of flares, patient global assessment of treatment success, adverse events (cardiovascular, renal and gastrointestinal), adverse events (renal stones, tophi), admission (hospital and A&E/urgent care) and GP visits. The committee considered outcomes for health related quality of life, joint swelling and tenderness, pain and adverse events to be the most informative, in terms of the impact of a treat to target approach.

The committee agreed to combine joint swelling and joint inflammation as these outcomes are synonymous for people with gout. The committee also agreed to categorise time-points reported in the included studies by short-term (less than three months), medium-term (three to twelve months) and long-term (more than 12 months). A timepoint of less than 3 months was considered less useful because starting ULT can trigger flares and an increase in the number of flares in the first year of ULT would not be unusual, therefore the committee

agreed outcomes reported at longer time-points were more useful in terms of decision making.

No clinical evidence was identified for the following outcomes: adverse events (radiographic joint damage and renal stones), admissions (hospital and A&E/urgent care) and GP visits. There were no short-term or medium-term outcomes reported, all studies were long-term (1 or 2 years).

1.1.12.2 The quality of the evidence

Two randomised controlled trials (RCTs), evaluating treat-to-target management strategies using urate-lowering therapies (ULT) compared to usual care, were included in this review. Usual care in the included studies could be any available option, chosen by the health care provider, such as continuing their current dose of allopurinol, febuxostat or no treatment. The committee noted that in one study the usual arm was not clearly reported so it was unknown whether or how many people in the usual care arm were following the treat-to-target approach (dependent on the G.P. and their usual care). This study could be comparing treat-to target with itself which could potentially skew the results. However, the authors noted that this group had low levels of ULT use at baseline, typical of usual care in the UK, which is generally considered to have low treat-to-target use.

The quality of evidence for all outcomes included in this review ranged from very low to high, but mostly moderate to low. The main reasons for downgrading were risk of bias and imprecision. There was a lack of blinding in the studies, due to the nature of the interventions. The intervention was delivered by a study healthcare practitioner and titration to a certain serum urate level would be obvious to both patient and practitioner, which led to a high risk of bias for many outcomes. Furthermore, the treat-to-target group maximum dosage of allopurinol was 900mg, which is not typical of current clinical practice in the UK, and this was unlikely to be the dosage in the GP-led arm. However, this is part of the study's treat-to-target strategy and is testing what may be done to improve outcomes. Only one outcome could be meta-analysed (frequency of flares at 1 year) and this had a high degree of heterogeneity, which could not be resolved by subgroup analysis as there were only two studies included. However, it should be noted that one study reported 1 or more flares at one year and the other 2 or more flares at one year which may have caused a difference. This outcome was downgraded for inconsistency.

The treat-to-target arm in one of the trials included a nurse-led individualised package of care (gout information booklet, individualised education, and engagement of participants) in addition to the treat-to-target strategy. The comparison group was provided with a gout information booklet and was GP-led. The committee discussed whether it was the whole package of care that improves outcomes rather than the titration of ULT to achieve a target. However, the committee also acknowledged elements of the package of care, such as explaining the treat to target approach and discussing the benefits with the person would reflect current good practice and could be considered part of a treat-to-target strategy. The committee therefore did not think this to be a source of bias and had confidence in the results. It was also noted that there was a protocol adjustment for the usual care group and patients were given a financial incentive to complete the questionnaire and assessment to the 2 years.

The committee noted the second line treatment option in one of the studies was the use of either febuxostat or benzbromarone, with febuxostat being taken by more patients in the nurse-led group than in the usual care group at 2 years (14% compared to 3%). Four patients in the nurse-led group and 1 in the usual-care group received uricosurics (benzbromarone) at 2 years. This Benzbromarone is a uricosuric drug not available in the UK, unless under special arrangement for use as a urate-lowering therapy in people who are resistant to or are intolerant of allopurinol of febuxostat. The committee noted the choice of

drug may be based on the clinical practice of the investigators. The committee was unclear whether this would introduce bias for the intervention arm.

1.1.12.3 Benefits and harms

The evidence showed a clinically important difference in favour of a treat-to-target management approach when compared to usual care for quality of life (SF-36 physical component at 1 year, GIS gout concern overall and unmet gout treatment need components at 1 and 2 years), frequency of flares (2 or more flares) and complications of gout (presence of tophi) at 2 years. The committee noted that there was some uncertainty around the effect size for the quality of life measures (SF-36 physical component at 1 year and GIS – gout concern overall at 1 year). There was no uncertainty found for other quality of life outcomes that showed clinical benefit.

The evidence showed a clinical harm for treat-to-target management, when compared to usual care, for frequency of flares at 1 year, however frequency of flares at 2 years showed a clinically important benefit for the treat-to-target management approach. It should be noted that the year one data included 2 studies, and at 2 years was just 1 study. The committee noted that there was some uncertainty around the effect size as the confidence interval crossed the MID threshold and there was inconsistency. The committee discussed the reasons for clinical harm at one year compared to a clinical benefit of two years. It was agreed that any increase in dosage could set off a flare so lowering serum urate can increase flares initially (the first year) but by the second year the dose would be stabilised, and the number of flares would reduce. This was particularly relevant to one study in which very few participants were given prophylaxis. The committee agreed this could have contributed to the frequency of flares in the first year. There was no evidence in the short or medium-term to assess flares at shorter time frames.

The higher number of people on second line Febuxostat (80mg up to 120mg once daily) in one study was also noted as not reflecting current practice. However, if treating to target with higher doses of allopurinol (maximum allowed dosage was 900mg) there is likely to be a higher incidence of adverse events which may lead to an increased use of Febuxostat. The committee noted that frequency of flares may be of less importance to a patient than the severity of the flare as this could have a greater impact on the person’s quality of life than someone who has mild flares, however this is difficult to quantify in a study.

The evidence suggested that there was no clinically important difference for the SF-36 physical component at 2 years (although this was very close to being clinically important) and for the SF-36 mental component at 1 year and 2 years. However, SF-36 was thought to be insensitive for musculoskeletal conditions. There were no clinically important differences at 1 year for the health assessment questionnaire (HAQ), the pain (VAS) change score, joint swelling, joint tenderness, cardiovascular adverse events, renal and urinary adverse events, gastrointestinal adverse events, allopurinol specific adverse events and adverse events. Complications of gout (presence of tophi) and resolution of measurable tophi showed no difference at 1 year; however, the treat-to-target strategy showed clinically significant less presence of tophi at 2 years. The committee noted that it is possible to see an improvement in tophi in the first year of treatment, but it may be longer for crystals to have dissolved enough for tophi to noticeably reduce in size. The committee acknowledged the similar finding for frequency of flares at 2 years, indicating the long-term effect of a treat-to-target strategy. The committee also noted one of the studies included a population with a particularly high prevalence (52%) of stage 3 CKD or greater, providing evidence of the safety and efficacy of a treat-to-target strategy in people with CKD.

Overall, the committee agreed, based on the benefits shown for quality of life outcomes and frequency of flares in the longer term, that the evidence and the consensus of the group supported a treat-to target approach.

Treatment options

The committee discussed the two different delivery methods for treat-to-target management described in the studies. One study included nurse-led care in the intervention arm and usual GP care in the comparator arm and another study used Rheumatologist-led care. The committee pointed out that in current UK practice treat-to-target is usually delivered by GPs however the committee acknowledged a treat to target management approach is uncommonly used in primary care. The nurse-led service was shown to be effective, and the committee discussed that this method of delivery could improve care for gout patients and be more efficient, because appointment times could be longer than a GP consultation allowing more time for the patient to ask questions and the nurse to provide advice and information. The committee discussed that the individualised package of care delivered by a nurse was very comprehensive, including a holistic assessment, discussion and information on gout as well as follow-up assessments and telephone contact between appointments if wanted. The committee agreed that elements of what is included in the nurse-led group, such as assessment, discussion and information about gout reflected current best practice, and it was appropriate to draw upon this evidence when considering recommendations.

Although the nurse-led delivery approach was of interest to the committee they agreed people with gout often have co-morbidities and their treatment can be more complex and would often require management by a GP.

The committee agreed a starting dose of 100mg of allopurinol is accepted practice. For people with severe CKD, usual practice would be to start at a lower dose and titration would be with smaller increments up to same serum urate target as in people without CKD. This allows the clinician to monitor for any adverse events.

The committee agreed to recommend a treat-to-target approach for patients choosing to take urate lowering therapy as the evidence and their consensus supported a treat to target approach with better outcomes for people treated in this way. When considering the recommendation the committee drew upon the body of evidence they had considered for ULT, including evidence review G on ULT for long-term management of gout and the health economic evidence analysis demonstrating cost-effectiveness. Overall, because the committee considered the strategies described within the studies broadly reflected best practice and was shown to be effective, further research evaluating different strategies was not a priority and they decided a research recommendation was not necessary.

The committee also decided to specify that treat-to-target should involve starting serum urate lowering therapy at a low dose and up-titrating according to serum urate level at monthly intervals with the aim of achieving target serum urate level. The committee based the recommendation for monitoring serum urate monthly on their clinical experience and agreed this reflected usual practice. They also noted both studies reported increasing ULT at 3-4 week intervals according to serum urate levels which indicated making a recommendation to monitor monthly was a reasonable frequency.

1.1.12.4 Cost effectiveness and resource use

One cost-utility analysis comparing a treat-to-target management strategy with usual care from an NHS and PSS perspective was identified for this review. This cost-utility analysis comprised of a within-trial cost effectiveness analysis up to the timepoint of 2 years and results were extrapolated for years 3, 5, and 10.

The within-trial cost effectiveness analysis was based on one of the two studies included in the clinical review (Doherty 2018) and demonstrated that treat-to-target was cost effective compared to usual care with an ICER of £5,066 per QALY. In addition, when the results were extrapolated, an ICER of £285 per QALY was observed at year 3. At years 5 and 10 treat-to-target was the dominant strategy (less costly and more effective).

The committee discussed the potential limitations with the study but concluded the data inputs used in the model were reasonable and of the best available evidence. Of note, the committee also acknowledged the high cost of a gout flare used in the analysis but noted when the cost of a gout flare was decreased to £50 the cost per QALY was £6,144, and therefore a treat-to-target management strategy was still cost effective.

The committee discussed the appropriateness of the comparators in the study noting the treat-to-target arm was representative of how a treat-to-target management strategy should be conducted in clinical practice – people should be up titrated at monthly intervals and provided information on the benefits of a treat-to-target management strategy. The committee noted that current practice varies and acknowledged care is sub-optimal, whereby the majority of people are likely to receive usual care (a non-treat-to-target management strategy). In current practice usual care consists of people being prescribed an initial dose of 100mg allopurinol, with the dose not being escalated further, or conversely, the dose is escalated beyond the starting dose, but is not sufficient to achieve target serum urate levels. Overall, based on the proportion of people receiving different doses of allopurinol and achieving target serum urate levels in the Doherty trial, the committee concluded the usual care arm was representative of current practice.

The committee also discussed the evidence presented for the treat-to-target review alongside the evidence presented in Evidence review G. Evidence review G illustrated a fixed dose of 300mg allopurinol was cost effective compared to no treatment. As detailed above, the committee concluded a comparator of 300mg is not representative of what is observed in clinical practice. However, the committee acknowledged that Evidence review G provides additional merit illustrating a treat-to-target management strategy is cost effective.

The committee acknowledged the Doherty trial did not compare a fixed dose of allopurinol to a treat-to-target management strategy. Over the study duration of the Doherty trial increasing numbers of people initiated ULT in the usual care arm (at baseline 38.93% of people were receiving ULT, at one year 46.83% of people were receiving ULT, and at two years 56.13% of people were receiving ULT). The committee acknowledged these proportions are what would be expected in clinical practice because a number of people not receiving treatment will start to experience more frequent or troublesome flares and therefore wish to initiate ULT. The committee discussed that in Doherty the proportion of people receiving each dose of allopurinol remained relatively constant over the two-year time horizon of the study. The proportion of people receiving 100mg of allopurinol was 31% at baseline and 33% in year two, the proportion of people receiving 200mg was 19% at baseline and 16% in year two, the proportion of people receiving 300mg 42% at baseline and 41% in year two, the proportion of people receiving 400mg was 7% at baseline and 8% in year two, and the proportion of people receiving ≥500mg was 1% at baseline and 2% in year two. Although the Doherty trial did not compare a specific fixed dose of allopurinol, the committee noted this is reflective of current practice – noting usual care is predominately a fixed dose strategy because the proportion of people receiving different doses of allopurinol does not change significantly. The committee concluded this demonstrated a treat-to-target management strategy was cost effective compared to no treatment because the doses were relatively constant over time.

Based on the clinical and health economic evidence presented the committee made a recommendation to treat people receiving ULT with a treat-to-target management strategy.

Due to the increased amount of people receiving a treat-to-target management strategy as a result of this recommendation there is expected to be an initial substantial resource impact. Increase in resources will be seen as a result of additional staff time required in the form of appointments for up titration and measuring of serum urate levels. Additional money will be spent because a higher proportion of people will be receiving higher doses of allopurinol and subsequently receive prophylaxis for a greater period of time. The committee did however note the benefits of a treat-to-target management strategy will likely offset the additional costs in the form of reduced flares in the long-term due to a greater proportion of people

achieving target serum urate levels. The committee also acknowledged that fewer flares results in a better quality of life for people because gout flares are extremely painful and debilitating.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.5.

1.1.14 References

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Appendices

Appendix A – Review protocols

Review protocol for treat-to-target management

ID	Field	Content
0.	PROSPERO registration number	CRD42021238070
1.	Review title	The clinical and cost effectiveness of a 'treat-to-target' management strategy compared with usual care for gout
2.	Review question	What is the clinical and cost effectiveness of a 'treat-to-target' urate lowering management strategy compared with usual care for gout?
3.	Objective	To determine if 'treat-to-target' management strategies are more clinically and cost-effective than usual care for gout
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 Strata: None Exclusion: People with calcium pyrophosphate crystal deposition (CPPD), also known as pseudogout
7.	Intervention/Exposure/Test	• Treat-to-target management strategy using urate-lowering therapies (ULT) Different timing will be combined, e.g. testing every 4 weeks and testing every 8 weeks
8.	Comparator/Reference standard/Confounding factors	• Usual care • ULT not using treat-to-target approach (fixed dose)
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 Published NMAs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available
11.	Context	People with gout who use urate-lowering therapy (ULT) to manage their condition can have their urate-lowering therapy administered in a treat-to-target approach. The treat-to-target approach involves using a starting ULT dose and escalating the dose gradually target serum urate level has been reached.

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater) • joint swelling/joint inflammation • joint tenderness • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • 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) (cardiovascular events can include stroke and coronary artery disease) • adverse events and complications of gout: o radiographic joint damage o renal stones o tophi • admissions (hospital and A&E/urgent care) • GP visits Timepoints: short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Evibase will be used for data extraction.

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

		NMA will be prioritised for the following outcome, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence: • Frequency of flares • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Serum urate target (300 micrmol/L versus 360 micromol/L versus other targets) • Choice of ULT • Age (over 65 years vs under 65 years) • CKD (CKD versus no CKD)	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	

21.	Anticipated or actual start date	30th October 2020		
22.	Anticipated completion date	13th June 2022		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
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	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]
32.	Keywords	[Give words or phrases that best describe the review.]
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it

		needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Review question	All questions – health economic evidence
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 – see appendix B below.
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 (2014).[15] **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 make a decision 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 on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

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

Appendix B – Literature search strategies

- What is the clinical and cost effectiveness of a 'treat-to-target' urate lowering management strategy compared with usual care for gout?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[15]

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 7: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

Embase (Ovid) search terms

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

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

Cochrane Library (Wiley) search terms

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

#6.	(or #1-#5)

B.2 Health Economics literature search strategy

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

Table 8: Database date parameters and filters used

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

Medline (Ovid) search terms

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

14.	exp historical article/
15.	Anecdotes as Topic/
16.	comment/
17.	case report/
18.	(letter or comment*).ti.
19.	or/11-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	10 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	quality-adjusted life years/
49.	sickness impact profile/
50.	(quality adj2 (wellbeing or well being)).ti,ab.
51.	sickness impact profile.ti,ab.
52.	disability adjusted life.ti,ab.
53.	(qal* or qtime* or qwb* or daly*).ti,ab.
54.	(euroqol* or eq5d* or eq 5*).ti,ab.

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

Embase (Ovid) search terms

1.	exp gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	exp uric acid/
5.	uric acid*.ti,ab.
6.	(urate adj (crystal* or sodium or mono sodium)).ti,ab.
7.	exp hyperuricemia/
8.	(hyperuric* or hyper uric*).ti,ab.
9.	podagra.ti,ab.
10.	or/1-9
11.	letter.pt. or letter/
12.	note.pt.
13.	editorial.pt.
14.	Case report/ or Case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26

28.	limit 27 to English language
29.	health economics/
30.	exp economic evaluation/
31.	exp health care cost/
32.	exp fee/
33.	budget/
34.	funding/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/29-41
43.	quality adjusted life year/
44.	"quality of life index"/
45.	short form 12/ or short form 20/ or short form 36/ or short form 8/
46.	sickness impact profile/
47.	(quality adj2 (wellbeing or well being)).ti,ab.
48.	sickness impact profile.ti,ab.
49.	disability adjusted life.ti,ab.
50.	(qal* or qtime* or qwb* or daly*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
53.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
54.	(hui or hui1 or hui2 or hui3).ti,ab.
55.	(health* year* equivalent* or hye or hyes).ti,ab.
56.	discrete choice*.ti,ab.
57.	rosser.ti,ab.
58.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
59.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
60.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
61.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
62.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
63.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
64.	or/43-63
65.	28 and (42 or 64)

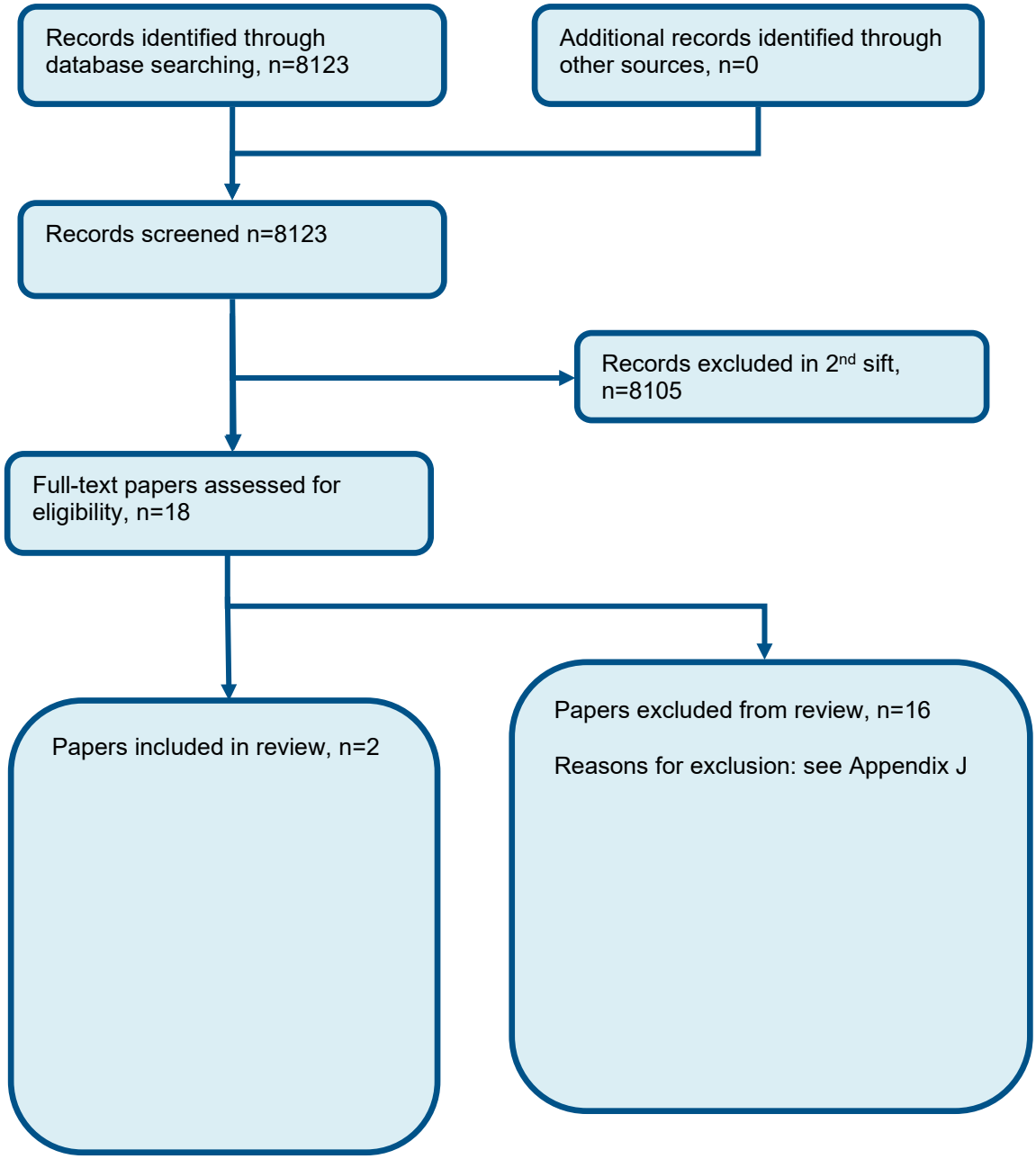
NHS EED and HTA (CRD) search terms

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

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

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of treat-to-target versus usual care



Appendix D – Effectiveness evidence

Study	Doherty 2018[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=517)
Countries and setting	Conducted in United Kingdom; Setting: 56 East Midlands general practices that represented urban and rural settings around the Nottingham area.
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Each practice sent a questionnaire to adults (age >21 years) on their database who had a diagnosis of gout. Respondents who reported at least one gout flare in the previous 12 months and indicated willingness for further contact were sent information on the study which explained that nurses successfully manage many long-term conditions in primary care and that the aim of the trial was to assess how well gout would be managed over a 2-year period by specially trained nurses compared with GPs. Patients who were interested in participating returned a reply slip and were telephoned to ensure they fulfilled 1977 American College of Rheumatology gout classification criteria. Eligible patients were assessed in their GP surgery by a research nurse. Placement of a study advertisement in two Nottinghamshire newspapers was added to the study protocol as a further recruitment approach. People who responded to these advertisements were sent the questionnaire and those willing to participate underwent telephone screening and assessment in their homes.
Exclusion criteria	Exclusion criteria were not meeting the 1977 American College of Rheumatology gout classification criteria, inability to consent, and terminal or severe illness. After a protocol amendment, financial incentives were offered to unresponsive patients in the usual-care group in return for completing the questionnaire and attending the assessment at the end of year 2.
Recruitment/selection of patients	Consecutive

Age, gender and ethnicity	Age - Mean (SD): Nurse led care (treat to target) 62.01(10.81); Usual care 63.69(11.91). Gender (M:F): Nurse led care(treat to target) 229/26; Usual care 232/30. Ethnicity: Not reported
Further population details	1. Age: Less than 65 years old Nurse led care (treat to target) 62.01(10.81; Usual care 63.69). 2. CKD (CKD versus no CKD): CKD (CKD stage 3: Nurse led care (treat to target) - 53(23%); Usual care 63(24%)).
Indirectness of population	No indirectness
Interventions	(n=255) Intervention 1: Treat-to-target management using urate lowering therapies (ULT). Nurse-led care: first-line treatment was oral allopurinol, started at 100 mg once per day and titrated upwards in 100 mg increments every 3–4 weeks according to serum urate concentrations, to a maximum of 900 mg once per day. As second-line options, oral febuxostat could be started at 80 mg and if required increased to the maximum dose of 120 mg once per day or benzbromarone could be started at 50 mg and titrated up in 50 mg increments to a maximum of 200 mg once per day. Combination urate-lowering therapy (xanthine oxidase inhibitor plus uricosuric) could be used as the final treatment option. Colchicine as prophylaxis against gout flares could be considered. If the nurses had questions about gout management, they could seek advice from a study rheumatologist (MD, FR, or AA). All contacts with participants were logged. As part of an individualised package of care, the nurses provided patients with holistic assessment, discussion of illness perceptions, and full information on gout (nature, causes, associations, consequences, and treatment options), and encouraged them to share in decision making. Patients were given the Arthritis Research UK gout information booklet. Follow-up assessments and measurement of serum urate concentrations were done as often as required by the nurse. Telephone contact (e.g to review serum urate results) could be substituted for face-to-face visits, and home visits were permitted (e.g for older patients). Duration 2 years. Concurrent medication/care: Out of 255 patients 101(40%) took urate lowering therapy (Allopurinol) at baseline. Further details: 1. Choice of ULT: Allopurinol as a first line, febuxostat and benzbromarone as a second line, combination urate-lowering therapy (xantine oxidase inhibitor plus uricosuric) Colchicine as prophylaxis against gout flares could be considered.). 2. Serum urate target (300 micromol/L versus 360 micromol/L versus other targets): Serum urate target 360 micromol/L (<360µmol/L). (n=262) Intervention 2: Usual care. Patients assigned to continue usual GP-led care were given the gout information booklet from Arthritis Research UK. Treatment of flares could be discussed by the research nurse at baseline and at yearly assessments, but if participants enquired about other aspects of management they were advised to ask their GP. Duration 2 years. Concurrent medication/care: out of 262 patients 102(39%) took urate lowering therapy at baseline (101 Allopurinol and 1 Suffinpyrazone). Indirectness: No indirectness Further details: 1. Choice of ULT: Not stated / Unclear (unclear). 2. Serum urate target (300 micromol/L versus 360 micromol/L versus other targets): Not applicable (not treat-to-target).

Funding	Academic or government funding (Arthritis Research UK.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET MANAGEMENT USING URATE LOWERING THERAPIES (ULT) versus USUAL CARE

Protocol outcome 1: Quality of life medium-term (3 to 12 months)
- Actual outcome: SF 36 Physical component at 1 year; Group 1: mean 40.46 (SD 14.1); n=255, Group 2: mean 36.54 (SD 14.21); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 16 ; Group 2 Number missing: 19
- Actual outcome: SF 36 Mental component at 1 year; Group 1: mean 53.46 (SD 8.99); n=255, Group 2: mean 54.01 (SD 9.33); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 16; Group 2 Number missing: 19
- Actual outcome: Gout impact scale score (GIS) - Gout concern overall at 1 year; Group 1: mean 48.78 (SD 25.05); n=255, Group 2: mean 57.79 (SD 26.53); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 16; Group 2 Number missing: 19
- Actual outcome: Gout impact scale score (GIS) - Unmet gout treatment need at 1 year; Group 1: mean 25.62 (SD 18.16); n=255, Group 2: mean 36.29 (SD 18.81); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 16; Group 2 Number missing: 19

Protocol outcome 2: Quality of life Long-term (more than 12 months)
- Actual outcome: SF 36 Physical component at 2 years; Group 1: mean 41.01 (SD 16.71); n=255, Group 2: mean 37.43 (SD 14.8); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 54
- Actual outcome: SF 36 Mental component at 2 years; Group 1: mean 52.92 (SD 14.34); n=255, Group 2: mean 54.02 (SD 9.26); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 54
- Actual outcome: Gout impact scale score (GIS) - Gout concern overall at 2 years; Group 1: mean 37.54 (SD 24.97); n=255, Group 2: mean 53.62 (SD 27.02); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 54
- Actual outcome: Gout impact scale score (GIS) - Unmet gout treatment need at 2 years; Group 1: mean 21.03 (SD 15.93); n=255, Group 2: mean 33.71 (SD 19.67); n=262
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 54

Protocol outcome 3: Frequency of flares medium-term (3 to 12 months)
- Actual outcome: Two or more flares at 1 year; Group 1: 138/255, Group 2: 104/262; Comments: Number of patients calculated by NGC as paper provided percentages Nurse led care 53.99%, Usual care 39.82%

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: 16; Group 2 Number missing: 19 Protocol outcome 4: Frequency of flares long-term (more than 12 months) - Actual outcome: Two or more flares at 2 years; Group 1: 20/255, Group 2: 64/262; Comments: Number of patients calculated by NGC as paper provided percentages Nurse led care 8.00%, Usual care 24.29% 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: 22; Group 2 Number missing: 54 Protocol outcome 5: Adverse events and complications of gout (renal stones, tophi) medium-term (3 to 12 months) - Actual outcome: Presence of tophi at 1 year; Group 1: 18/255, Group 2: 27/262; Comments: Number of patients calculated by NGC as paper provided percentages Nurse led care 7.06%, Usual care 10.15% 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: 16; Group 2 Number missing: 19 Protocol outcome 6: Adverse events and complications of gout (renal stones, tophi) long-term (more than 12 months) - Actual outcome: Presence of tophi at 2 years; Group 1: 7/255, Group 2: 30/262; Comments: Number of patients calculated by NGC as paper provided percentages Nurse led care 2.85%, Usual care 11.29% 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:22; Group 2 Number missing: 54	
Protocol outcomes not reported by the study	Quality of life short-term (less than three months); Pain short-term (less than 3 months); Pain short-term medium-term (3 to 12 months); Pain short-term Long-term (more than 12 months); Joint swelling/inflammation short-term (less than 3 months); Joint swelling/inflammation medium-term (3 to 12 months); Joint swelling/inflammation long-term (more than 12 months); Joint tenderness short-term (less than 3 months); Joint tenderness medium-term (3 to 12 months); Joint tenderness long-term (more than 12 months); Frequency of flares short-term (less than 3 months); Patient global assessment of treatment success short-term (less than three months); Patient global assessment of treatment success medium-term (3 to 12 months); Patient global assessment of treatment success long-term (more than 12 months); Adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) short-term (less than 3 months); Adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) short-term medium-term (3 to 12 months); Adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) long-term (more than 12 months); Adverse events and complications of gout (renal stones, tophi) short-term (less than 3 months); Admissions (hospital and A&E/urgent care) short-term (less than 3 months); Admissions (hospital and A&E/urgent care) medium-term (3 to 12

	months); Admissions (hospital and A&E/urgent care) long-term (more than 12 months); GP visits short-term (less than 3 months); GP visits medium-term (3 to 12 months); GP visits long-term (more than 12 months)

Study	**Stamp 2017[22]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=183)
Countries and setting	Conducted in New Zealand; Setting: two sites in New Zealand. Participants were recruited from primary and secondary care.
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with gout defined by the American Rheumatism Association 1977 preliminary classification criteria for gout receiving at least CrCL-based dose of allopurinol for ≥1 month and with SU ≥6 mg/dL at screening were recruited.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with gout defined by the American Rheumatism Association 1977 preliminary classification criteria for gout receiving at least CrCL-based dose of allopurinol for ≥1 month and with SU ≥6 mg/dL at screening were recruited.
Exclusion criteria	People with a history of intolerance to allopurinol and those receiving azathioprine were excluded. CKD was not an exclusion criterion.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Dose escalation group: 59.5(12.1), Control: 60.9(12.8). Gender (M:F): Dose escalation group: 82/8, Control: 78/5. Ethnicity: Ethnicity: Dose escalation group: NZ European: 41%, Maori: 32%, Pacific island: 21%, Asian: 6%, Other: 0%. Control group: NZ European: 42%, Maori: 24%, Pacific island: 29%, Asian: 4%, Other:1%.
Further population details	1. Age: Less than 65 years old (Dose escalation group: 59.5(12.1), Control: 60.9(12.8)). 2. CKD (CKD versus no CKD): Not stated / Unclear (unclear).
Indirectness of population	No indirectness

Interventions	(n=90) Intervention 1: Treat-to-target management using urate lowering therapies (ULT). In the DE group (Treat to target), allopurinol was increased monthly until SU was <6 mg/dL on three consecutive visits or there were AEs. For example, if SU was <6 mg/dL allopurinol was not escalated but if at the following month urate was >6 mg/dL allopurinol was increased unless there was evidence of poor adherence. The dose was increased by 50 mg/d for those with CrCL <60 mL/min and 100 mg/d in those with CrCL ≥60 mL/min. Duration 12 months. Concurrent medication/care: Anti-inflammatory prophylaxis and treatment of gout flares were at the discretion of the investigator. AT BASELINE Allopurinol (mean dose) - 261.9 (100-200 mg/day - 37; >200-200 - 47; >300 - 7) Concurrent medications: Diuretic - 38, Aspirin - 40. Colchicine - 34, NSAIDs - 15, Prednisolone - 12, any anti-inflammatory prophylaxis 51. Indirectness: No indirectness Further details: 1. Choice of ULT: Allopurinol - In the DE group, allopurinol was increased monthly until SU was <6 mg/dL on three consecutive visits or there were AEs). 2. Serum urate target (300 micromol/L versus 360 micromol/L versus other targets): Serum urate target other targets (<6 mg/dL). (n=93) Intervention 2: Usual care. In the control group, participants continued on the same allopurinol dose throughout the study period. Anti-inflammatory prophylaxis and treatment of gout flares were at the discretion of the investigator. Duration 12 months. Concurrent medication/care: Anti-inflammatory prophylaxis and treatment of gout flares were at the discretion of the investigator. AT BASELINE Allopurinol (mean dose) - 275.8 (100-200 mg/day - 31; >200-200 - 50; >300 - 12) Concurrent medications: Diuretic - 43, Aspirin - 41. Prophylaxis Colchicine - 35, NSAIDs - 9, Prednisolone - 12, any anti-inflammatory prophylaxis 45. Indirectness: No indirectness Further details: 1. Choice of ULT: Allopurinol "same dose throughout the study". 2. Serum urate target (300 micrmol/L versus 360 micromol/L versus other targets): Not applicable (Not treat to target).
Funding	Academic or government funding (this study was funded by the Health Research Council of New Zealand)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TREAT-TO-TARGET MANAGEMENT USING URATE LOWERING THERAPIES (ULT) versus USUAL CARE

Protocol outcome 1: Pain short-term medium-term (3 to 12 months)
- Actual outcome: Pain (VAS) at 12 months; Group 1: mean 1.93 (SD 1.09); n=70, Group 2: mean 2.04 (SD 1.14); n=73; Comments: Outcome reported as mean and (SE)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 22
- Actual outcome: Quality of life - HAQ (health assessment questionnaire) at 12 months; Group 1: mean 0.62 (SD 0.75); n=70, Group 2: mean 0.51 (SD 0.77); n=73;

Comments: Outcome reported as mean and (SE)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 22; Group 2 Number missing: 22

Protocol outcome 2: Joint swelling/inflammation medium-term (3 to 12 months)
- Actual outcome: Joint swelling - swollen joint count at 12 months; Group 1: mean 1.01 (SD 0.85); n=70, Group 2: mean 1.58 (SD 1.31); n=73; Comments: Outcome reported as mean (se) - standard deviation calculated by NGC
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: 22; Group 2 Number missing: 22

Protocol outcome 3: Joint tenderness medium-term (3 to 12 months)
- Actual outcome: Joint tenderness - tender joint count at 12 months; Group 1: mean 1.73 (SD 1.6); n=70, Group 2: mean 2.07 (SD 1.92); n=73; Comments: Outcome reported as mean (se) - standard deviation calculated by NGC
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: 22; Group 2 Number missing: 22

Protocol outcome 4: Frequency of flares medium-term (3 to 12 months)
- Actual outcome: Self-reported gout flare at 12 months; Group 1: 49/90, Group 2: 55/93; Comments: 54 % (48.6 patients)in the DE group and 59% (54.87 patients) in the control group reported gout flares
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:22; Group 2 Number missing: 22

Protocol outcome 5: Adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) short-term medium-term (3 to 12 months)
- Actual outcome: Adverse events - Gastrointestinal disorders at 12 months; Group 1: 18/90, Group 2: 21/93
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: 22; Group 2 Number missing: 22
- Actual outcome: Adverse events - Renal and urinary disorders at 12 months; Group 1: 2/90, Group 2: 0/93
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: 22; Group 2 Number missing: 22
- Actual outcome: Adverse events - Cardiovascular at 12 months; Group 1: 15/90, Group 2: 18/93; Comments: Cardiovascular events included: Vascular, venous and cardiac events (which we combined for the analysis).
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: 22; Group 2 Number missing: 22- Actual outcome: Adverse events - Allopurinol specific at 12 months; Group 1: 12/90, Group 2: 14/93; Comments: Allopurinol specific included: Nausea/vomiting, abdominal pain
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: 22; Group 2 Number missing: 22

- Actual outcome: Adverse events - Resolution of measurable tophi at 12 months; Group 1: 6/32, Group 2: 8/43; Comments: those with measurable tophi were analysed 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: 58, Reason: people without tophi; Group 2 Number missing: 50, Reason: people without tophi For all adverse events only the non-laboratory treatment emergent adverse events data were reported. Data on participants with at least one serious adverse event was not reported. Treatment-emergent AEs were defined as any AE occurring after entry into the study until the end of month 12.	
Protocol outcomes not reported by the study	Quality of life short-term (less than three months); Quality of life medium-term (3 to 12 months); Quality of life Long-term (more than 12 months); Pain short-term (less than 3 months) ; Pain short-term Long-term (more than 12 months); Joint swelling/inflammation short-term (less than 3 months); Joint swelling/inflammation long-term (more than 12 months); Joint tenderness short-term (less than 3 months); Joint tenderness long-term (more than 12 months); Frequency of flares short-term (less than 3 months); Frequency of flares long-term (more than 12 months); Patient global assessment of treatment success short-term (less than three months); Patient global assessment of treatment success medium-term (3 to 12 months); Patient global assessment of treatment success long-term (more than 12 months); Adverse events – (1) cardiovascular, (2) renal and (3) gastrointestinal (e.g. diarrhoea) short-term (less than 3 months); Adverse events and complications of gout (renal stones, tophi) short-term (less than 3 months); Adverse events and complications of gout (renal stones, tophi) medium-term (3 to 12 months); Adverse events and complications of gout (renal stones, tophi) long-term (more than 12 months); Admissions (hospital and A&E/urgent care) short-term (less than 3 months); Admissions (hospital and A&E/urgent care) medium-term (3 to 12 months); Admissions (hospital and A&E/urgent care) long-term (more than 12 months); GP visits short-term (less than 3 months); GP visits medium-term (3 to 12 months); GP visits long-term (more than 12 months)

Appendix E – Forest plots

E.1 Treat-to-target versus usual care

Figure 2: Quality of life SF36 physical component at 1 year (0-100 scale; better indicated by higher score)

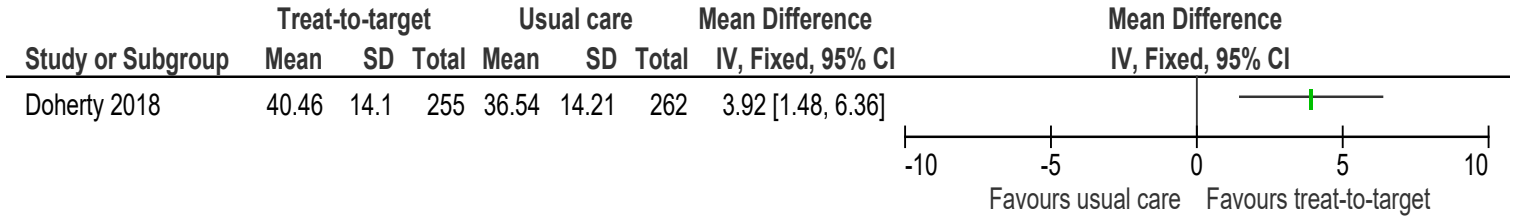


Figure 3: Quality of life SF36 physical component at 2 years (0-100 scale; better indicated by higher score)

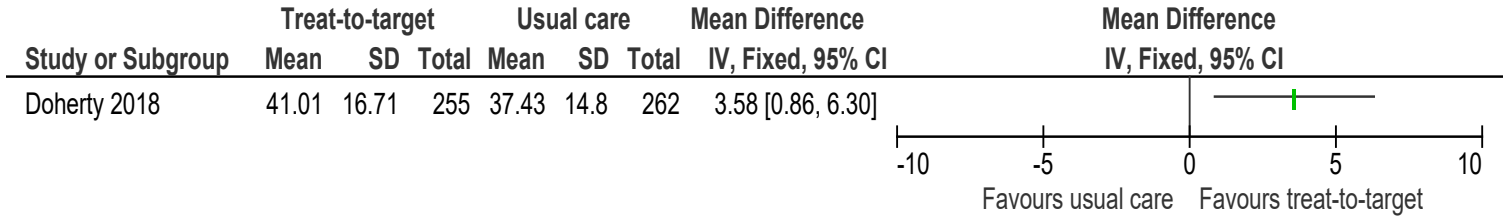


Figure 4: Quality of life SF36 mental component at 1 year (0-100 scale, better indicated by higher score)

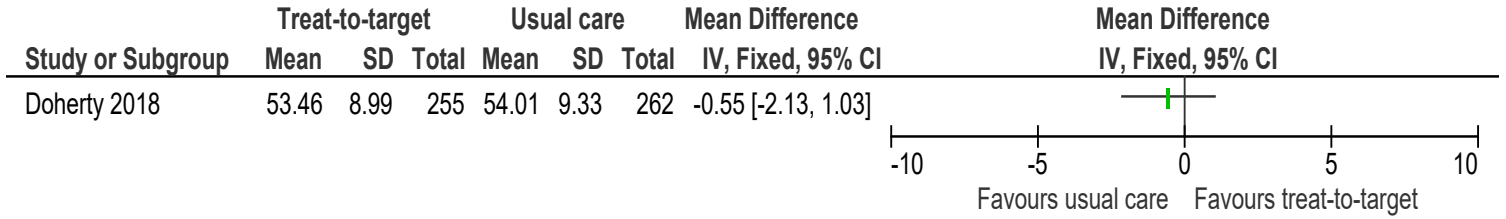


Figure 5: Quality of life SF36 mental component at 2 years (0-100 scale; better indicated by higher score)

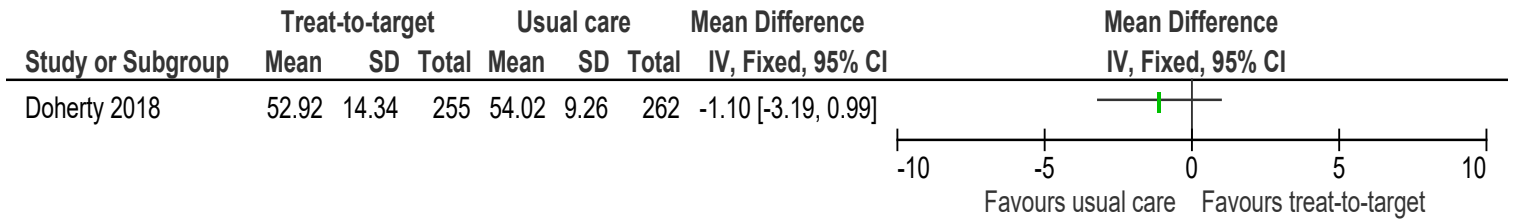


Figure 6: Quality of life – gout impact scale (GIS) - gout concern overall at 1 year (0-100 scale; better indicated by lower score)

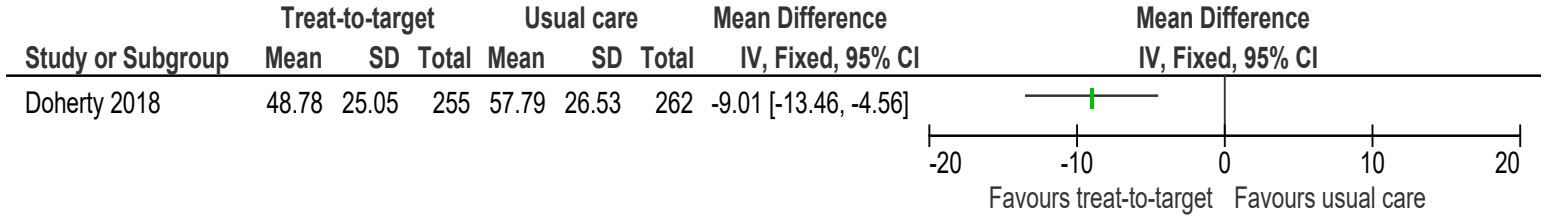


Figure 7: Quality of life – gout impact scale (GIS) - gout concern overall at 2 years (0-100 scale; better indicated by lower score)

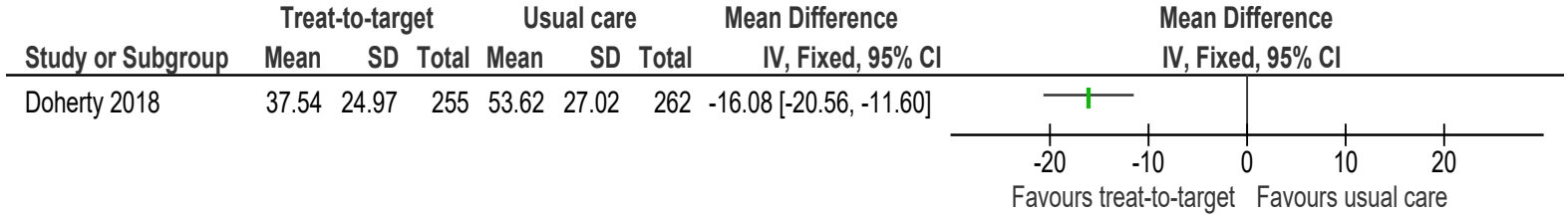


Figure 8: Quality of life – gout impact scale (GIS) – unmet gout treatment need at 1 year (better indicated by lower score)

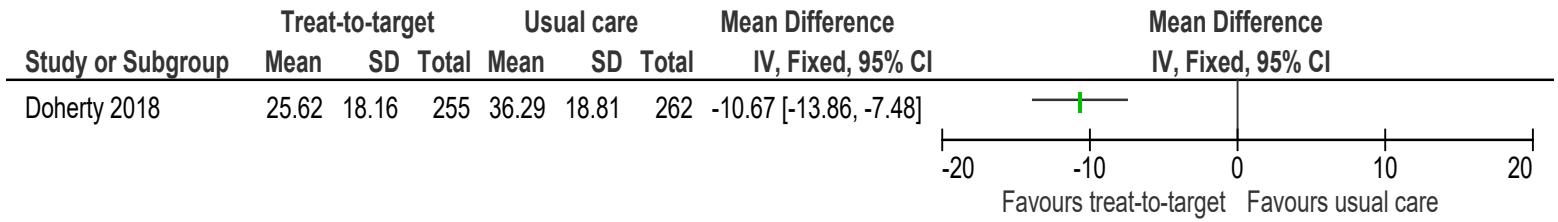


Figure 9: Quality of life – gout impact scale (GIS) – unmet gout treatment need at 2 years (0-100 scale; better indicated by lower score)

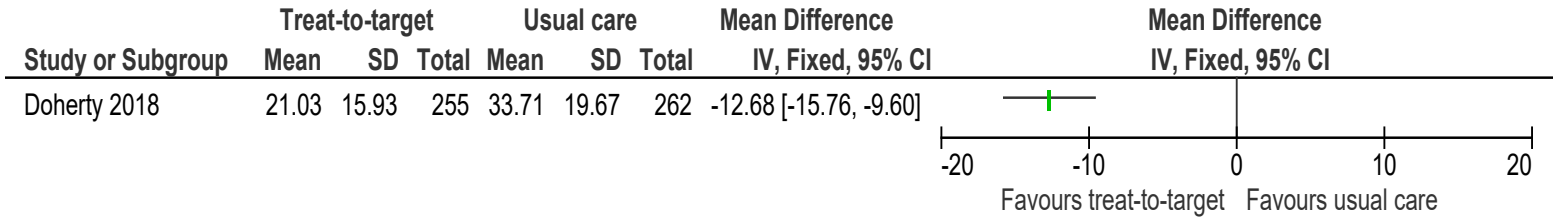


Figure 10: Quality of life – health assessment questionnaire (HAQ) at 1 year (0-3 scale; better indicated by lower score)

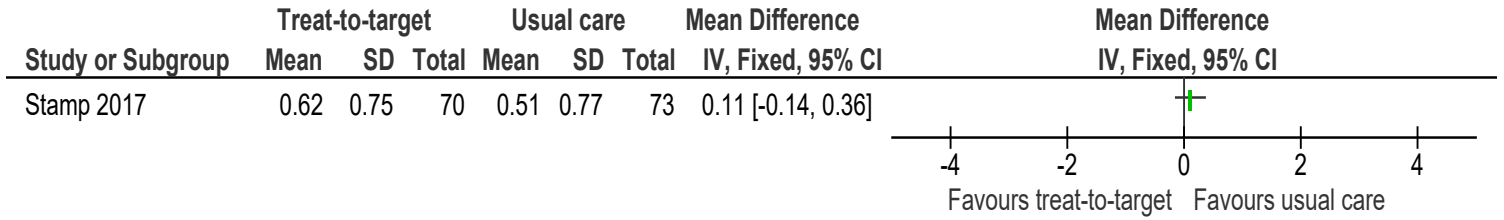


Figure 11: Pain (VAS) at 1 year (better indicated by lower score)

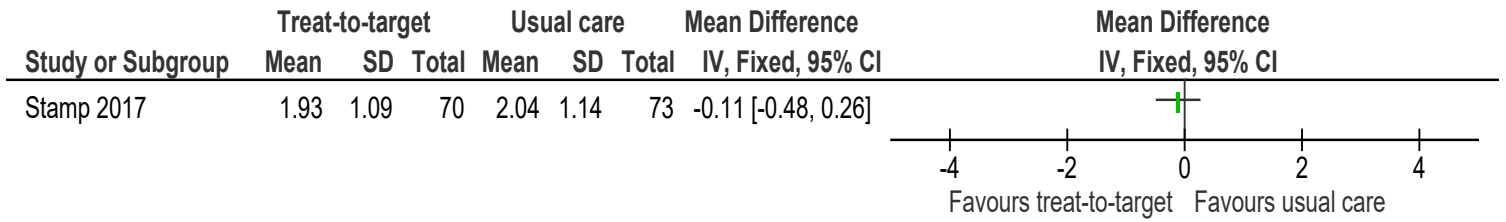


Figure 12: Joint swelling – swollen joint count at 1 year (0-3 scale; better indicated by lower score)

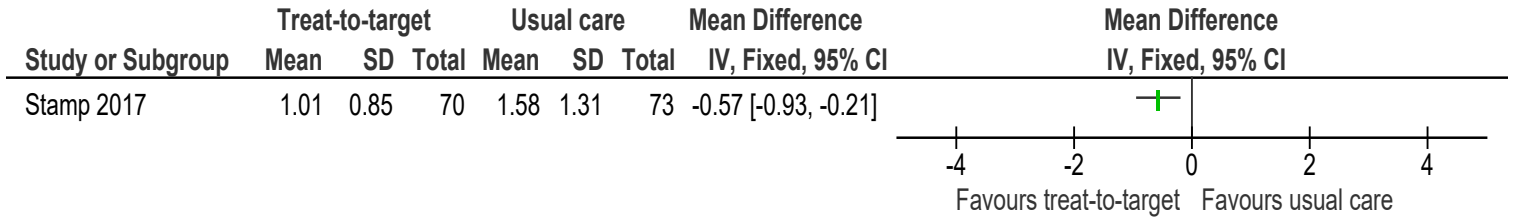


Figure 13: Joint tenderness – tender joint count at 1 year (0-3 scale; better indicated by lower score)

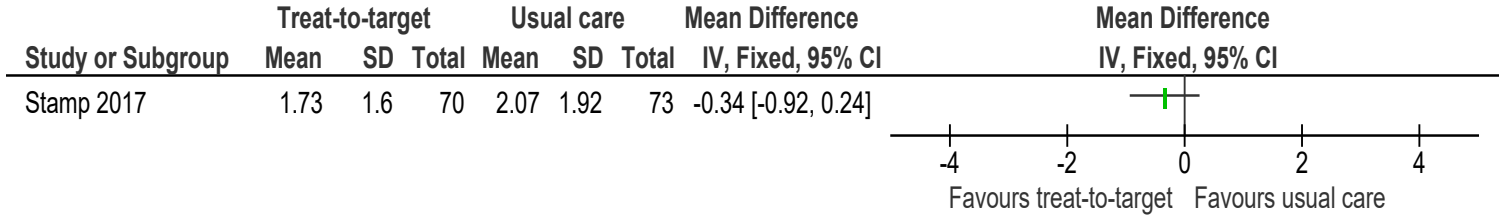


Figure 14: Frequency of flares – 1 or more flares at 1 year (better indicated by lower score)

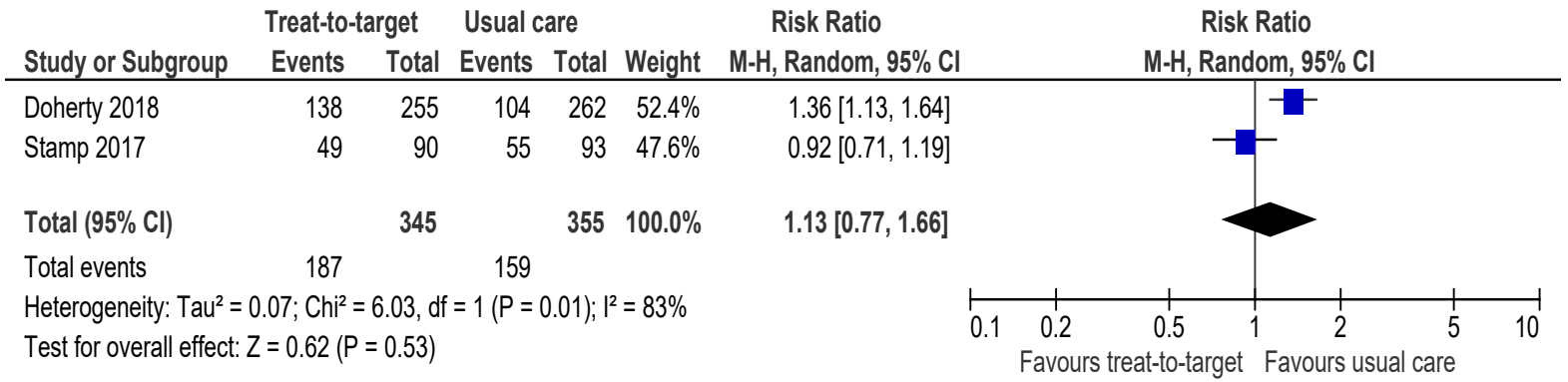


Figure 15: Frequency of flares 2 or more flares at 2 years (better indicated by lower score)

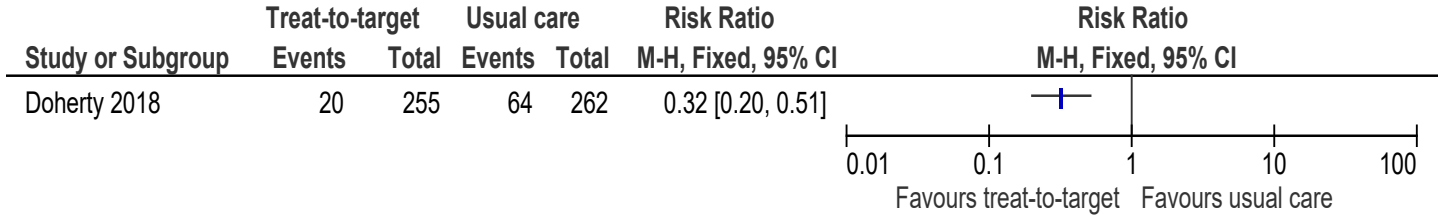
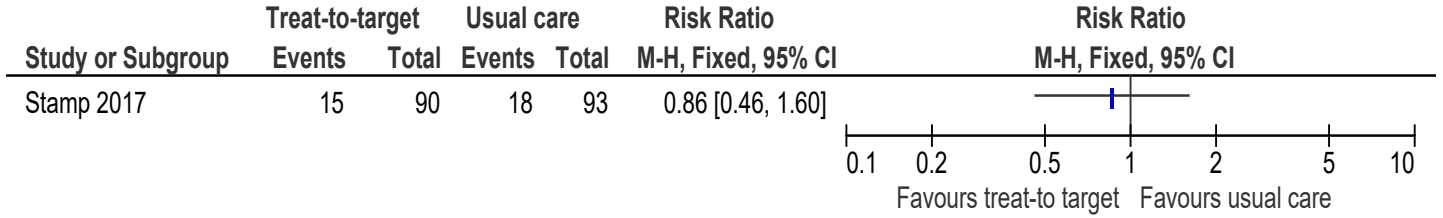
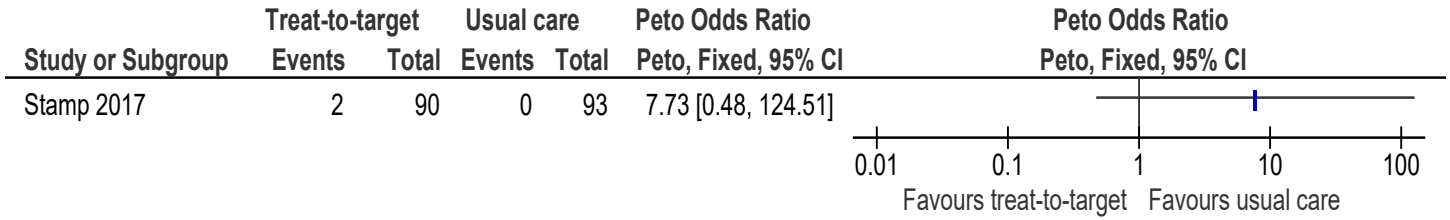


Figure 16: Adverse events - Cardiovascular disorders[a] at 1 year (better indicated by lower score)



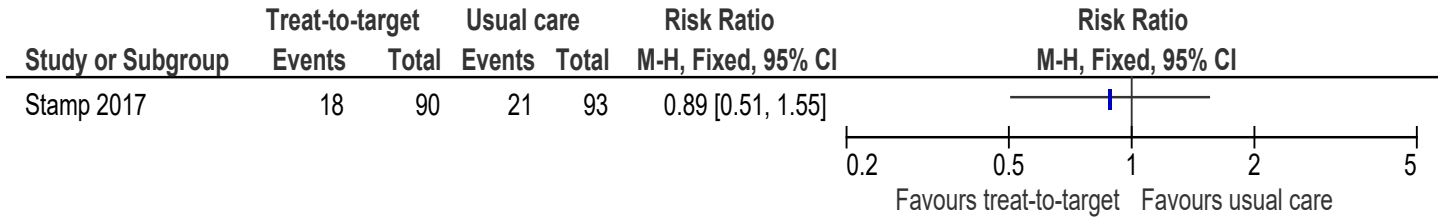
[a] The study reported cardiac disorders, vascular disorders and venous disorders, which were combined for the analysis. Only the non-laboratory treatment emergent adverse events data were analysed.

Figure 17: Adverse events – renal and urinary disorders[a] at 1 year (better indicated by lower score)



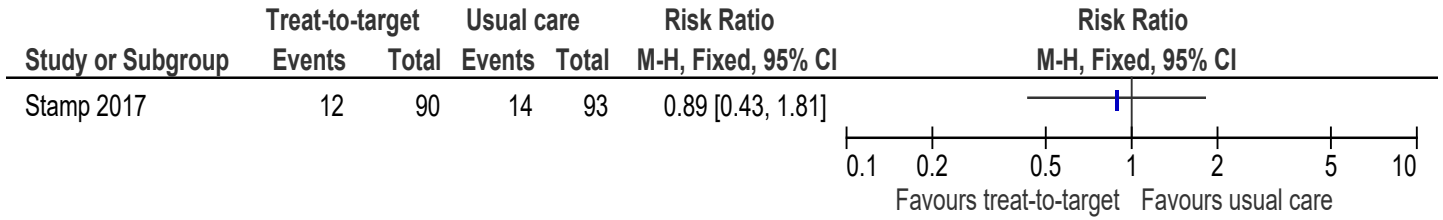
[a] Only the non-laboratory treatment emergent adverse events data were analysed.

Figure 18: Adverse events – gastrointestinal disorders[a] at 1 year (better indicated by lower score)



[a] Only the non-laboratory treatment emergent adverse events data were analysed.

Figure 19: Adverse events allopurinol-specific adverse events[a] at 1 year (better indicated by lower score)



[a] Nausea/vomiting and abdominal pain were combined for the analysis. Only the non-laboratory treatment emergent adverse events data were analysed.

Figure 20: Adverse events and complications of gout – presence of tophi at 1 year (better indicated by lower score)

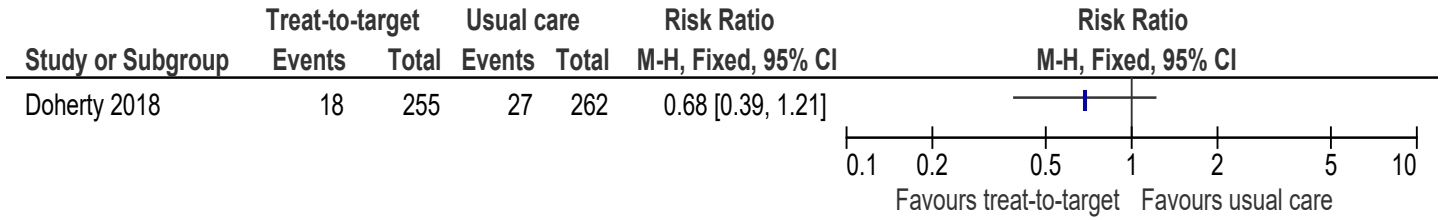


Figure 21: Adverse events and complications of gout – presence of tophi at 2 years (better indicated by lower score)

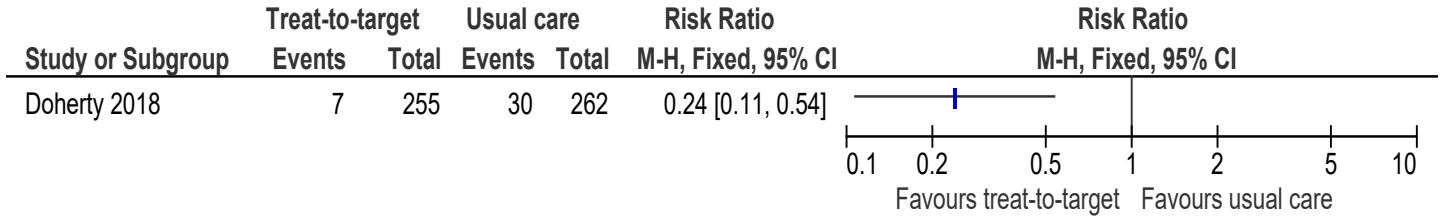
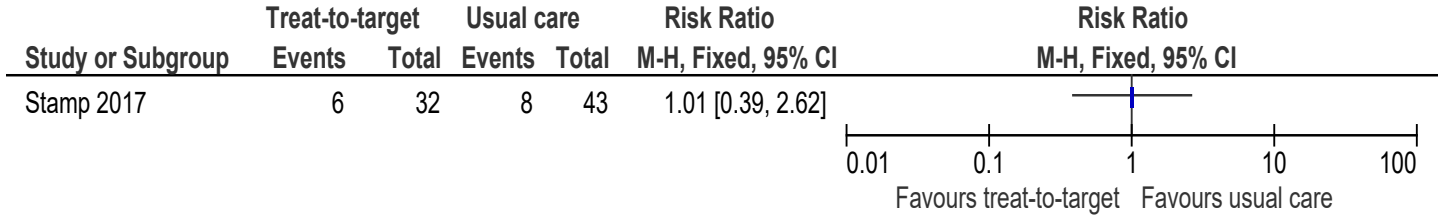


Figure 22: Adverse events – and complications of gout – resolution of measurable tophi at 1 year (better indicated by lower score)



Appendix F – GRADE tables

Table 9: Clinical evidence profile: treat-to-target versus usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life SF-36 Physical component at 1 year												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	255	262	-	MD **3.92 higher** (1.48 higher to 6.36 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life SF-36 Physical component at 2 years												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	255	262	-	MD **3.58 higher** (0.86 higher to 6.3 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life SF-36 mental component at 1 year												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	255	262	-	MD **0.55 lower** (2.13 lower to 1.03 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality of life SF-36 mental component at 2 years

1	randomised trials	serious [a]	not serious	not serious	not serious	none	255	262	-	MD **1.1 lower** (3.19 lower to 0.99 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality of life - Gout impact scale (GIS) - Gout concern overall - at 1 year

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	255	262	-	MD **9.01 lower** (13.46 lower to 4.56 lower)	⊕⊕◯◯ LOW	CRITICAL

Quality of life - Gout impact scale (GIS) - Gout concern overall - at 2 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	255	262	-	MD **16.08 lower** (20.56 lower to 11.6 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 1 year

1	randomised trials	serious [a]	not serious	not serious	not serious	none	255	262	-	MD **10.67 lower** (13.86 lower to 7.48 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality of life - Gout impact scale (GIS) - unmet gout treatment need - at 2 years

1	randomised trials	serious [a]	not serious	not serious	not serious	none	255	262	-	MD **12.68 lower** (15.76 lower to 9.6 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Quality of life - health assessment questionnaire (HAQ) at 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [b]	none	70	73	-	MD **0.11 higher** (0.14 lower to 0.36 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Pain (VAS) change score at 1 year

1	randomised trials	serious [a]	not serious	not serious	serious[b]	none	70	73	-	MD **0.11 lower** (0.48 lower to 0.26 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Joint swelling - swollen joint count at 1 year

1	randomised trials	not serious	not serious	not serious	serious [b]	none	70	73	-	MD **0.57 lower** (0.93 lower to 0.21 lower)	⊕⊕⊕◯ MODERATE	CRITICAL

Joint tenderness - tender joint count at 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	70	73	-	MD **0.34 lower** (0.92 lower to 0.24 higher)	⨁⨁⨁⨁ HIGH	CRITICAL

Frequency of flares 1 or more flares at 1 year

2	randomised trials	not serious	very serious c	not serious	very serious [b]	none	187/345 (54.2%)	159/355 (44.8%)	**RR 1.13** (0.77 to 1.66)	**58 more per 1,000** (from 195 fewer to 184 more)	⨁◯◯◯ VERY LOW	CRITICAL

Frequency of flares- 2 or more flares at 2 years

1	randomised trials	not serious	not serious	not serious	not serious	none	20/255 (7.8%)	64/262 (24.4%)	**RR 0.32** (0.20 to 0.51)	**166 fewer per 1,000** (from 195 fewer to 120 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Adverse events-cardiovascular disorders at 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	15/90 (16.7%)	18/93 (19.4%)	**RR 0.86** (0.46 to 1.60)	**27 fewer per 1,000** (from 105 fewer to 116 more)	⨁⨁◯◯ LOW	CRITICAL

Adverse events - renal and urinary disorders at 1 year

1	randomised trials	not serious	not serious	not serious	very serious [b]	none	2/90 (2.2%)	0/93 (0.0%)	**Peto OR 7.73** (0.48 to 124.51)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

Adverse events - gastrointestinal disorders at 1 year

1	randomised trials	not serious	not serious	not serious	very serious [b]	none	18/90 (20.0%)	21/93 (22.6%)	**RR 0.89** (0.51 to 1.55)	**25 fewer per 1,000** (from 111 fewer to 124 more)	⨁⨁◯◯ LOW	CRITICAL

Adverse events - allopurinol specific disorders at 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	12/90 (13.3%)	14/93 (15.1%)	**RR 0.89** (0.43 to 1.81)	**17 fewer per 1,000** (from 86 fewer to 122 more)	⨁⨁◯◯ LOW	CRITICAL

Adverse events and complications of gout - presence of tophi at 1 year

1	randomised trials	not serious	not serious	not serious	serious [b]	none	18/255 (7.1%)	27/262 (10.3%)	**RR 0.68** (0.39 to 1.21)	**33 fewer per 1,000** (from 63 fewer to 22 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Adverse events and complications of gout - presence of tophi at 2 years

1	randomised trials	not serious	not serious	not serious	not serious	none	7/255 (2.7%)	30/262 (11.5%)	**RR 0.24** (0.11 to 0.54)	**87 fewer per 1,000** (from 102 fewer to 53 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Adverse events - resolution of measurable tophi at 1 year

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treat to target	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	6/32 (18.8%)	8/43 (18.6%)	**RR 1.01** (0.39 to 2.62)	**2 more per 1,000** (from 113 fewer to 301 more)	⨁⨁◯◯ LOW	CRITICAL

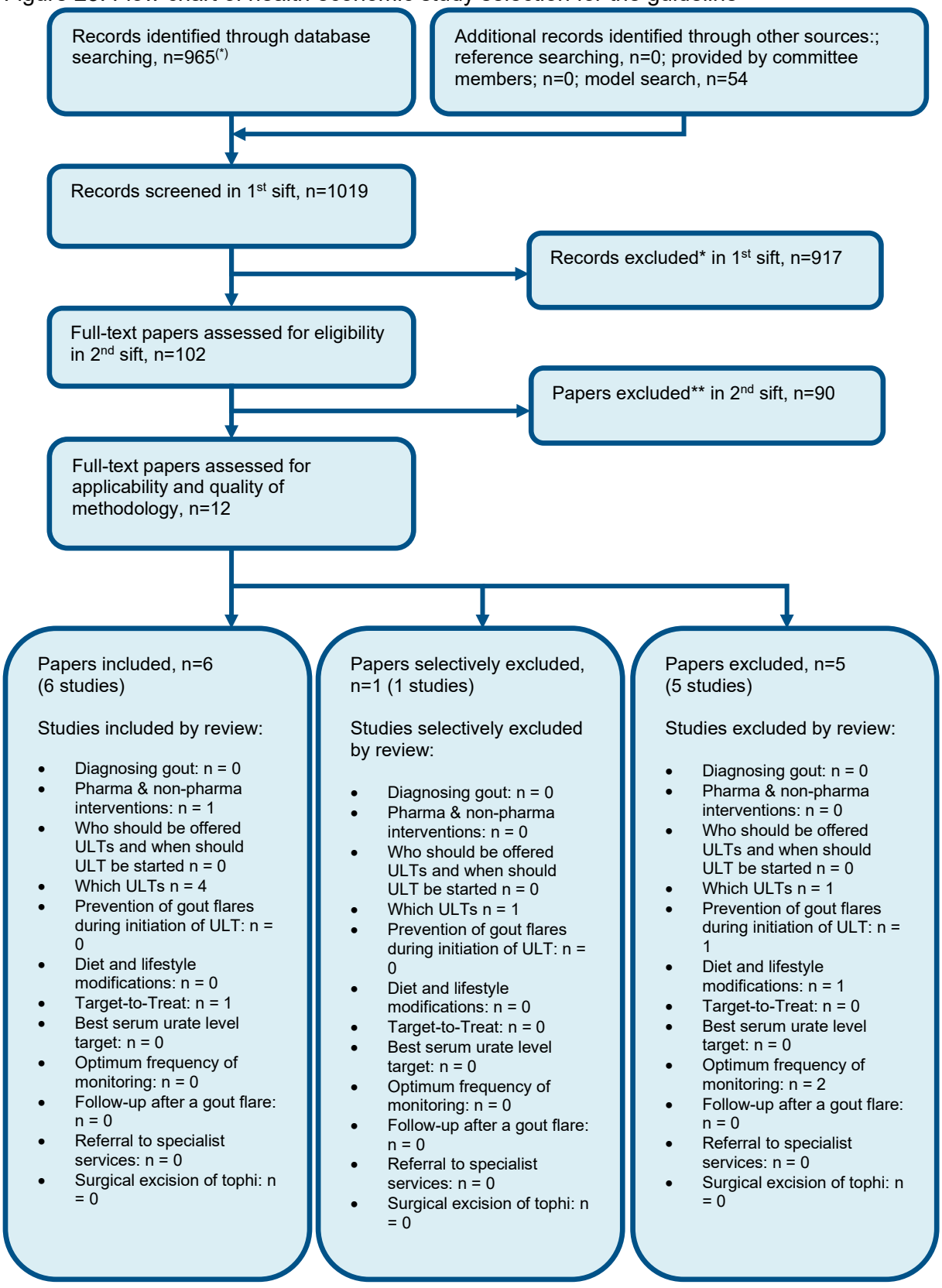
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

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; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ– 0.22; Pain (VAS) was improvement 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. For continuous outcomes 0.5 x baseline SD for continuous outcomes. For joint swelling the MID was 0.655, for joint tenderness the MID was 0.96. Clinical benefit or harm MCIDs: frequency of flares: 100 fewer per 1,000 patients = clinical benefit of intervention; Adverse events: 50 more per 1,000 patients = clinical harm of intervention; Renal stones: 50 more per 1,000 patients = clinical harm of intervention; tophi: 50 fewer per 1,000 patients = clinical benefit of intervention; admission: 100 fewer per 1,000 patients = clinical benefit of intervention; GP visits: 100 fewer per 1,000 patients = clinical benefit of intervention.

c. Downgraded by 2 increments because the point estimate varies widely across studies and I^2=83%, subgroup analysis could not be performed as only 2 studies included in the analysis so random effects model used.

Appendix G – Economic evidence study selection

Figure 23: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

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

Appendix H – Economic evidence tables

Study	Doherty 2018[8]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Economic analysis within-trial RCT **Approach to analysis:** A state transition model was constructed based on four serum urate concentration ranges (<360 µmol/L, ≥360 to <480 µmol/L, ≥480 to <600 µmol/L, and ≥600 µmol/L) and the rate of gout flares observed over the course of the RCT. The model was extrapolated beyond the RCT study period assuming flare rates per range of serum urate concentration were independent of initial management.	**Population:** Adults with gout **Cohort settings:** Median age: 63 years Male: 90% N = 517 **Intervention 1:** Usual care (Nurses provided patients with the gout information booklet from Arthritis Research UK. Treatment of flares could be discussed by the research nurse at baseline and at yearly assessments, but if participants enquired about other aspects of management, they were advised to ask their GP) **Intervention 2:** Treat-to-target ULT (Nurses provided patients with holistic assessment, discussion of illness perceptions, and full information on gout (nature, causes,	**Total costs (mean per patient):** 24 months: Intervention 1: NR Intervention 2: NR Incremental (2−1): £84 (95% CI: NR; p=NR) 3 years Intervention 1: NR Intervention 2: NR Incremental (2−1): £10 (95% CI: NR; p=NR) 5 years Intervention 1: NR Intervention 2: NR Incremental (2−1): -£126 (95% CI: NR; p=NR) 10 years Intervention 1: NR Intervention 2: NR Incremental (2−1): -£412 (95% CI: NR; p=NR) **Currency & cost year:**	**QALYs (mean per patient):** 24 months: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.017 (95% CI: NR; p=NR) 3 years Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.036 (95% CI: NR; p=NR) 5 years Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.073 (95% CI: NR; p=NR) 10 years Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.148 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** 24 months: £5,066 per QALY gained 3 years: £285 per QALY gained 5 years: Dominant 10 years: Dominant 95% CI: NR Probability that Intervention 2 was cost effective (£20k/30k threshold): NA Nurse-led treat-to-target ULT was cost effective at every time point and increasingly so over time given that at the end of the study the patients had lower serum urate levels in the nurse-led approach than the patients in the usual care arm. **Analysis of uncertainty:** Reducing the cost per flare (from £341 to £50) resulted in an ICER of £6,144 at 3 years, £3,578 at 5 years, and £2,425 at 10 years Adding nurse time for reviewing patients (an extra 30 min per 6 months) in years 3 and 4 (appendix) resulted in an ICER of £806 in year 3.

Perspective: UK NHS and PSS **Time horizon:** 24 months, 3, 5, 10 years **Treatment effect duration:**[(a)] NA **Discounting:** Costs: 3.5% Outcomes: 3.5%	associations, consequences, and treatment options), and encouraged them to share in decision making. Patients were provided with the gout information booklet from Arthritis Research UK. Follow-up assessments and measurement of serum urate concentrations were done as often as required by the nurse. Telephone contact (eg to review serum urate results) could be substituted for face-to-face visits, and home visits were permitted (eg for older patients). ULT was obtained from a hospital pharmacy.	2015/16 UK pounds **Cost components incorporated:** Nurse training, face-to-face nurse-led appointments, laboratory tests serum urate level, glomerular filtration rate, tophi and ULT medications.		Increasing flare rates by 20% in the first 2 years and the split of patients across the serum urate concentration ranges at the end of year 2 resulted in an ICER of £5,011 at 3 years and £648 at 5 years. Adding nurse time for reviewing patients' years 3 and 4 resulted in years 5 and 10 being a dominant strategy. In addition, increasing flare rates by 20% in the first 2 years and the split of patients across the serum urate concentration ranges at the end of year 2 resulted in a dominant strategy for year 10.
Data sources				
Health outcomes: Age, sex, gout history (age at onset and flare frequency in the previous 12 months), medications, comorbidities, body-mass index and subcutaneous tophi (number, sites, and maximum diameter of the largest tophus measured with a Vernier caliper), serum urate concentration and creatinine concentration to estimate glomerular filtration rate were assessed at baseline in the current study. Patients in both study groups were given diaries in which to record flares. Participants were classified according to four serum urate concentration ranges (<360 µmol/L, ≥360 to <480 µmol/L, ≥480 to <600 µmol/L, and ≥600 µmol/L). Flare rates were calculated as the number of flares divided by the number of patient-months of follow-up during a period. It was assumed that flare rates were constant within each 0–6 month, 7–12 month, and 13–24 month follow-up period. Flare rates reported by participants at each serum urate level were used to inform the model over the 24-month horizon. Beyond 24 months we assumed that the flare rates per range of serum urate concentration would be independent of initial management and set the values to the average nurse-led and usual-care values between 12 and 24 months. In the extrapolation period it was assumed that the rates observed in months 13 to 24 were applicable for the remainder of the modelling period. The nurse-led arm provoked a higher rate of flares across all serum urate bands in the initial six months as would be clinically expected, especially since uptake of prophylaxis was low. There was no such pattern for the usual care arm and thus a constant rate was used across all time periods. For the extrapolation period, a simple average of the rates between the nurse-led and the usual care arm was used. Mortality rates observed within the study were used for the initial 24 months. Beyond this time point the death rate was assumed to be that reported in UK life tables (Office for				

National Statistics 2018). **Quality-of-life weights:** Patients in the current RCT completed an SF-36 questionnaire at baseline,12-months and 24-months. SF-36 scores were mapped to SF-6D values using the approach recommended by Brazier 2002. Chronic utility was assumed not to differ between serum urate concentration ranges. Gout flares were assumed to decrease quality of life and disutilites were obtained from the NICE Technology Appraisal of Pegloticase (TA291; 2013). In the model extrapolation, chronic utility was age-adjusted based on the formula presented in Ara and Brazier 2010; patients were assumed to be 63 years of age in line with the age of the population of the current RCT. **Cost sources:** The unit costs of treating gout flares were obtained from the NICE Technology Appraisal for Pegloticase and inflated to 2015/16 prices (TA291; 2013). Resource use was based on the current RCT and included face to face appointment in the first month with a nurse to assess SU level, Glomerular Filtration Rate and tophi. All participants also received further face to face nurse appointments at month 12 and month 24. The type of ULT and dosage for all participants was recorded at baseline, and at each appointment with a nurse, which was at month 12 and month 24 in the usual care arm but could be more frequent in the nurse-led arm. It was assumed that the type and dosage of ULT was constant between appointments. The costs of ULTs were taken from the British National Formulary. There were five participants in the trial receiving benzbromarone or sulfinpyrazone, and as prices for these medications were not provided in the British National Formulary, they were assumed to cost the same as allopurinol. The nurse-led arm had additional costs compared with the usual care approach. These consisted of training the seven research nurses (and trainer) within the trial, assuming 25 hours of training and a cost per hour for a band 6 community nurse (Curtis 2017) and additional appointments with a nurse if a patient in the nurse-led arm had an SU level ≥ 360µmol/L, where a blood test was taken and the serum urate level was assessed. Once the results were known the nurse would phone the patient to advise if the dose of their ULT needed to be changed or another ULT prescribed instead. Both types of costs were included within the analyses.

Comments

Source of funding: Arthritis Research UK **Limitations:** Baseline health state utilities obtained by mapping SF-36 data from the current trial. Method of eliciting disutility values for flares was unclear. This study was based on one single centre RCT. Unit costs were obtained from a NICE TA conducted several years ago; it is unclear what the primary sources for this analysis were and the cost of a gout flare was significantly higher compared to the estimated cost of a gout flare in Evidence review G (£295 compared to £27.19 - £55.60). Assumed flares observed in months 13 to 24 were applicable to the remaining modelling period. Minimal interpretation is provided for the rate of flares per serum urate band. Total costs and QALYs not reported, only incremental values. No probabilistic sensitivity analysis conducted. **Other:** NA

Overall applicability:[c] Directly applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost utility analysis; ICER= incremental cost-effectiveness ratio; NA = not applicable; NR= not reported; QALYs= quality-adjusted life years; RCT = randomized controlled trial; ULT = urate lowering therapy.

(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) Converted using 2018/19 purchasing power parities[17]

(c) Directly applicable / Partially applicable / Not applicable

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

Appendix I – Health economic model

No original economic modelling was undertaken for this review question.

Appendix J – Excluded studies

Clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Andres 2014[1]	Systematic review - references checked
Arroll 2009[2]	Incorrect study design – non-randomised study, before and after study. No relevant outcomes
Bai 2021[3]	Incorrect study design – non-randomised study, retrospective observational study. No relevant outcomes
Baker 2007[4]	Incorrect study design – non-randomised study, cohort study, study assessed uric acid level and risk of peripheral arterial disease
Dalbeth 2019[7]	No relevant outcomes - imaging data analysis
Goldfien 2016[9]	No relevant outcomes – study reported serum urate and creatinine level change
Kannangara 2017[10]	Incorrect study design – non-randomised study, cohort study, published and unpublished data was used
Kim 2019[11]	Incorrect study design – non-randomised study, cohort study. No relevant outcomes
Lim 2012[12]	Incorrect study design – non-randomised study, prospective cohort study
Machado 2019[13]	Incorrect study design - literature review
Muller 1993[14]	Incorrect study design - not treat to target study, study compared allomaron versus Zyloprim
Novella-Navarro 2020[16]	Incorrect study design – non-randomised study, retrospective observational study. No relevant outcomes
Stamp 2017[21]	Incorrect comparison - study compared control group (first 12 months) plus dose escalation group versus (for another 12 months) versus dose escalation group (24 months). Patients were grouped according to kidney function at baseline, none/mild, moderate and severe.
Stamp 2017[19]	Incorrect comparison - study compared control group (first 12 months) plus dose escalation group versus (for another 12 months) versus dose escalation group (24 months). Patients were grouped according to kidney function at baseline, none/mild, moderate and severe.
Stamp 2018[18]	Systematic review - references checked
Stamp 2018[20]	Incorrect comparison - study compared only patients undergoing Allopurinol dose escalation by response level to treatment: Complete response vs partial response vs inadequate response

Health Economic studies

None.