National Institute for Health and Care Excellence

Guideline version (Draft for Consultation)

Gout: Diagnosis and Management

[K] Evidence review for the best serum urate level target to use when treating-to-target in gout?

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.6 to 1.5.7 and research recommendations in the NICE guideline

December 2021

Draft for Consultation

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

Disclaimer

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

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

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ISBN:

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1.1 Review question: What is the best serum urate level target to use when treating-to-target in gout?

1.1.1 Introduction

'Treat-to-target' urate-lowering therapy (ULT) involves starting ULT at low-dose and increasing the dose gradually until serum urate has been lowered below an agreed target level. Monosodium urate crystals form once the level of urate in blood and body tissues exceeds the physiological saturation threshold for urate (approximately 380micromoles/L). National and international rheumatology society guidelines have proposed different targets to ensure urate is lowered to well below this physiological threshold. The British Society for Rheumatology guideline advocates a target below 300micromoles/L (5mg/dL) whereas the European League Against Rheumatism and American College of Rheumatology agree a target below 360micromoles/L (6mg/dL).

In current clinical practice, only one-third of people with gout in primary care are offered urate-lowering therapy and only one-third of these achieve a target serum urate level below 360micromol/L. A national audit of management of gout by UK rheumatologists found that by one year after a new out-patient appointment in rheumatology, only 45% and 25% of patients had achieved target serum urate levels below 360micromol/L and 300micromol/L, respectively.

This evidence review will determine which is the best serum urate level target for 'treat-to-target' ULT.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (18 years and older) with gout taking urate-lowering therapies Strata: • People with CKD (stage 3) • People with CKD (stages 4-5) • People without CKD or people with CKD stages 1-2 • Mixed population (people with CKD and people without CKD) Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
Intervention(s)	Different serum urate target levels, for example: • British Society for Rheumatology recommendation – 300 micromol/L • European and international guidelines recommendation – less than 360 micromol/L
Comparison(s)	• Compared to each other • No serum urate target level
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 • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • 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 • proportion of participants who reach serum urate target level • frequency of flares • 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	RCT Systematic reviews of RCTs If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), 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

No relevant clinical studies comparing different serum urate target levels were identified.

See also the study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

No evidence was identified for this review.

1.1.6 Summary of the effectiveness evidence

No evidence was identified for this review.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

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 Economic model

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

1.1.9 Unit costs

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

Table 2: Unit costs

Resource	Unit costs
Primary care Practice Nurse, cost per hour[(a)]	£42
General Practitioner, cost per 9.22 min consultation[(a)]	£39
Cost of blood test (excluding time to take blood)[(b)]	£3-£4

(a) Source: PSSRU 2020 [1]
(b) Source: NHS reference costs 2019/2020[6]: directly accessed pathology services, haematology and phlebotomy respectively.

1.1.10 Evidence statements

Effectiveness/Qualitative

- No relevant published evidence was identified.

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered the following outcomes as important for decision making health-related quality of life, patient global assessment of treatment success, pain, joint swelling/joint inflammation, joint tenderness, proportion of participants who reach serum urate target level, frequency of flares, tophi, admission (hospital and A&E/urgent care) and GP visits. Proportion of participants who reach serum urate target level, frequency of flares and tophi would have been most important in the committee's decision process if there had been any evidence. Reducing flares and tophi were thought to be highly indicative of the efficacy of achieving the target serum urate level.

The committee decided to combine joint swelling and joint inflammation as they agreed that these outcomes are synonymous for people with gout. The committee also agreed to categorise 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 twelve months).

1.1.11.2 The quality of the evidence

No clinical evidence was identified for the best serum urate level target when treating-to-target in gout.

1.1.11.3 Benefits and harms

The committee discussed that currently there are different national and international recommendations for the serum urate target level. The British Society of Rheumatology recommendation is <300µmol/L (5mg/dl) and the European League Against Rheumatism (EULAR) guidelines recommend <360µmol/L (6 mg/dl). The committee agreed that a serum urate level of <360µmol/L (6mg/dl) would be more appropriate as it is more attainable and requires lower doses of ULT, which may improve patient adherence. The committee also acknowledged aiming for a target of below 360µmol/L reflected practice within primary care. However, the committee also noted that to assist faster dissolution of crystal deposits a lower serum urate level should be recommended if the person has tophi or chronic gouty arthritis or continues to have ongoing frequent flares despite achieving a target level below 6mg/dL (360µmol/L). People with tophi, chronic gouty arthritis or frequent flares are likely to have a higher burden of crystal deposition, meaning that treatment response would take longer. Hence, a lower target level is likely to bring about more rapid response to treatment. The committee suggested that the target serum urate levels should be the same in people with CKD.

The committee agreed a discussion with the patient should take place to explain the benefits of lowering serum urate levels to a target level. While the aim would usually be to titrate the dose to achieve 360µmol/L, a personalised approach should be taken according to the person's symptoms and tolerability to ULT. Given the lack of evidence the committee made a strong consensus recommendation in line with current practice and a weaker consider recommendation for the lower serum urate target. The committee agreed a research

recommendation should be made on the best serum urate level target to use when treating to target.

1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question. Unit costs were presented to aid to committee consideration of cost effectiveness.

The committee discussed the clinical benefits and costs associated with the two target serum levels being compared (less than 300µmol/L and less than 360µmol/L). The committee noted that for the majority of people there is no clinical difference between the two target serum urate levels because the number of flares people experience will likely be the same irrespective of the target serum urate level people achieve (300µmol/L or 360µmol/L). In addition, the cost of achieving a target serum urate level of less than 360µmol/L will likely be cheaper than the cost of achieving a target serum urate level of less than 300µmol/. This is due to the fact that achieving a lower target serum urate level is likely to be associated with more appointment costs and blood tests when a treat-to-target management strategy is employed.

The committee did however note that in people with more severe gout (for example, those still experiencing gout flares at a target level of 360 µmol/L and people with tophi) a target level of less than 300µmol/L may be more applicable. The committee acknowledged that in these instances, the additional costs of employing a target serum urate level of less than 300µmol/L would be offset by the cost savings observed from people not experiencing gout flares in the form of fewer GP appointments and medications prescribed for treatment of a gout flare. Subsequently the committee made a consensus recommendation for people with gout receiving ULT to obtain a target serum urate level of 360µmol/L, stipulating that in some instances a target level of 300µmol/L may be more appropriate.

This recommendation is largely reflective of current practice and therefore not expected to result in a substantial resource impact.

1.1.11.5 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.6 to 1.5.7 and the research recommendation on, what is the best target serum urate level when using a treat-to-target strategy to treat gout.

1.1.12 References

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Appendices

Appendix A – Review protocols

Review protocol for the best serum urate level target to use when treating-to-target in gout

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	The best serum urate level target to use when treating-to-target in gout?
2.	Review question	What is the best serum urate level target to use when treating-to-target in gout?
3.	Objective	To determine what is the best serum urate level target to use when treating-to-target in 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 taking urate-lowering therapies Strata: • People with CKD (stage 3) • People with CKD (stages 4-5) • People without CKD or people with CKD stages 1-2 • Mixed population (people with CKD and people without CKD) Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
7.	Intervention/Exposure/Test	Different serum urate target levels, for example: • British Society for Rheumatology recommendation – 300 micromol/L • European and international guidelines recommendation – less than 360 micromol/L
8.	Comparator/Reference standard/Confounding factors	• Compared to each other • No serum urate target level
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), 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	In order to 'treat-to-target' a target serum urate level is required and currently an agreed target does not exist. This question will compare

		different serum urate level targets (or to no target) to establish the most beneficial target.
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 • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • 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 • proportion of participants who reach serum urate target level • frequency of flares • 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.
13.	Secondary outcomes (important outcomes)	N/A
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Evibase will be used for data extraction. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data

		• a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. If sufficient data is available and it is methodologically appropriate, network meta-analysis (NMA) will conducted. NMA will be prioritised for the following outcomes, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence: • Frequency of flares • Tophi • GRADEpro will be used to assess the quality of evidence for each outcome, taking into

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

• Setting (primary/community vs hospital/secondary)

• Presence of tophi</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td><table>
<tr><td>☒</td><td>Intervention</td></tr>
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<tr><td>21.</td><td>Anticipated or actual start date</td><td>4th December 2020</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td>13th June 2022</td></tr>
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<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
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		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team		
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] Sedina Lewis [Senior systematic reviewer] Audrius Stonkus [Systematic reviewer] Alexandra Bonnon [Health economist] Amber Hernaman [Project manager] Joseph Runicles [Information specialist]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the		

		minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details	[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	

1

1 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).[5] **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 best serum urate level target to use when treating-to-target in gout?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[5]

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 3: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp Gout/
2.	gout*.ti,ab.
3.	toph*.ti,ab.
4.	podagra.ti,ab.
5.	pseudogout.ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/

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

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

1 **Embase (Ovid) search terms**

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

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

1 **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 4: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

1 **Embase (Ovid) search terms**

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

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

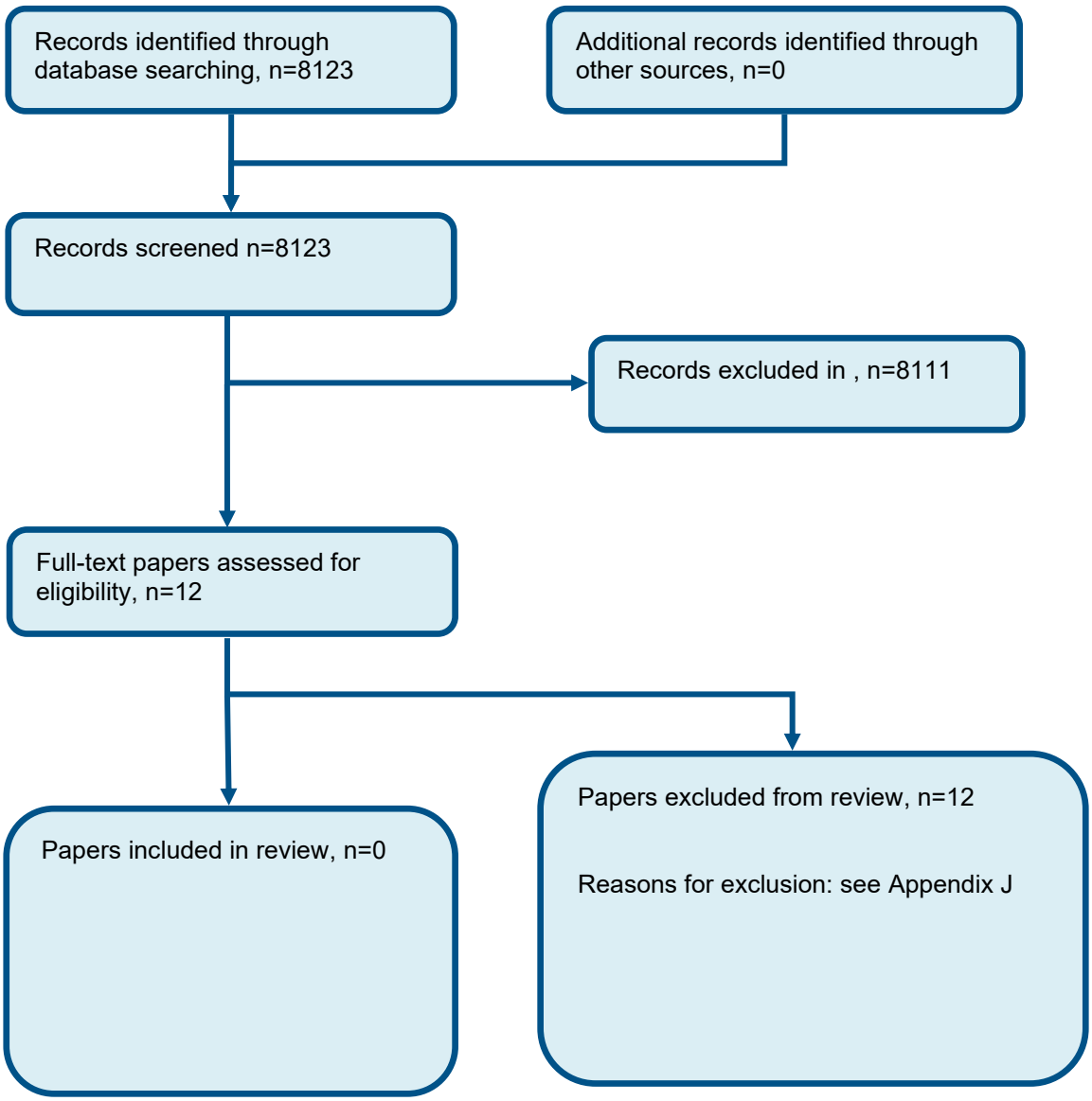
1 **NHS EED and HTA (CRD) search terms**

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

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

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of the best serum urate level target to use when monitoring disease activity in gout



Appendix D – Effectiveness evidence

No studies were included

Appendix E – Forest plots

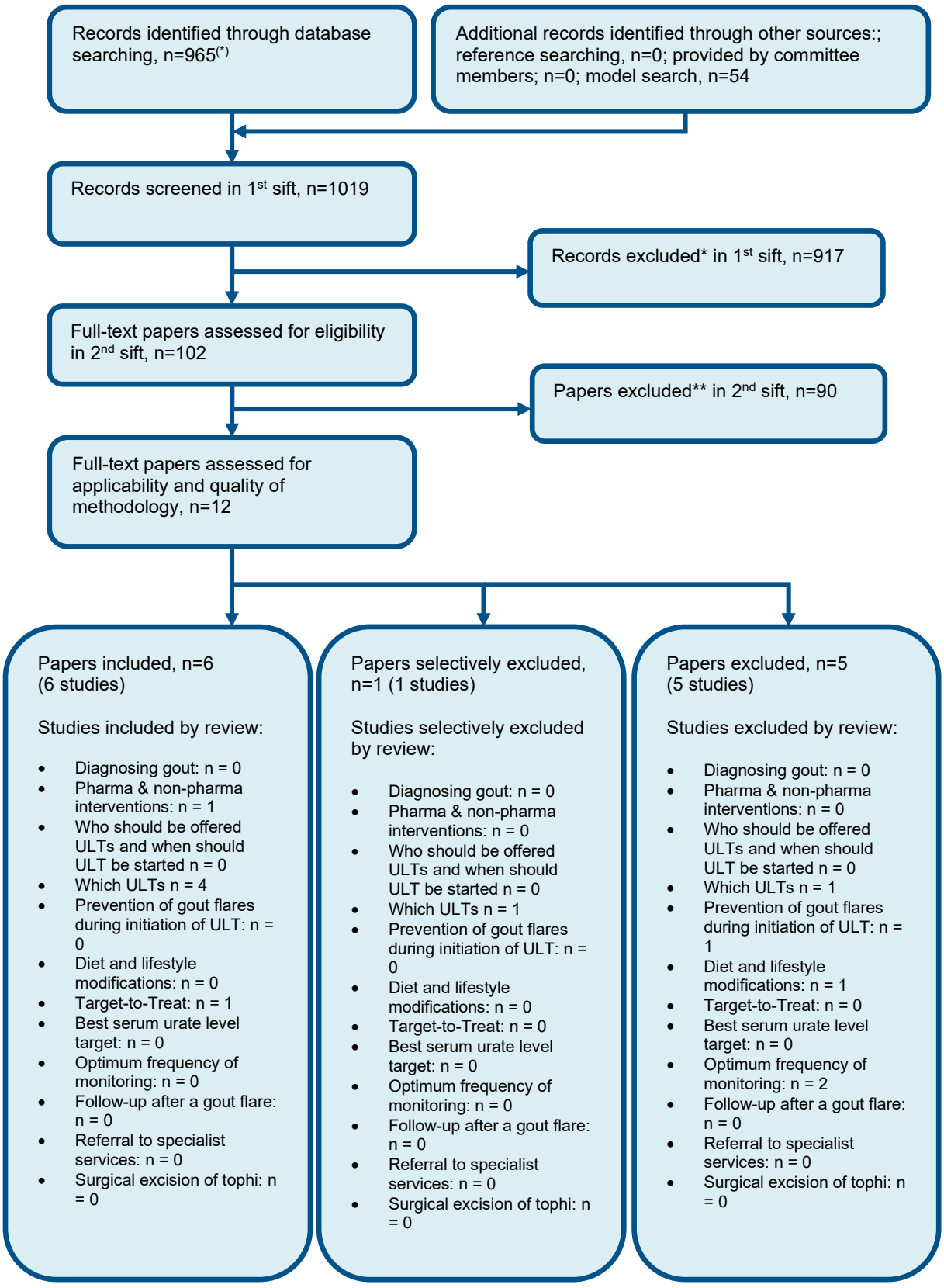
No studies were included

Appendix F – GRADE tables

No studies were included

Appendix G – Economic evidence study selection

Figure 2: Flow chart of health economic study selection for the guideline



* excludes conference abstracts (n=280)

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

Appendix H – Economic evidence tables

None

Appendix I – Health economic model

No original economic modelling was undertaken for this review question.

Appendix J – Excluded studies

Clinical studies

Table 5: Studies excluded from the clinical review

Study	Exclusion reason
Mak 2009[4]	Incorrect analysis/incorrect comparison - risk factors (such as age, gender, comorbidities etc) predictive of gout flares were studied using regression models
Gamala 2020[2]	Incorrect population/incorrect analysis - patients with acute, unclassified mono or oligoarthritic, study aimed to establish performance of 2015 ACR/EULAR gout classification criteria in patients with unclassified arthritis, sensitivity and specificity of dual-energy CT was analysed
Li-Yu 2001[3]	Incorrect analysis/incorrect comparison - study compared patients with SUA >6mg/dl vs patients with SUA =< 6 mg/dl, study aimed to determine if lowering serum uric acid will result in depletion of urate crystals from the knee joints
Perez Ruiz 2019[8]	Incorrect analysis/incorrect comparison - study aimed to determine impact of achieving serum uric acid of <0.36mmol/L on overall and cardiovascular mortality in patients with gout
Perez-Ruiz 2002[7]	Incorrect intervention/incorrect comparison - study evaluated the relationship between serum urate lowering therapy (allopurinol vs benzbromarone vs allopurinol plus benzbromarone) and velocity of reduction of tophi, no multivariate analysis. Mean serum urate levels were compared during follow-up in three treatment groups
Sheer 2017[9]	Incorrect analysis - study assessed impact of predictor variables on achieving serum urate level (<6 mg/dL)
Shoji 2004[10]	Incorrect analysis/incorrect comparison - linear regression model of average serum urate level and recurrent gout attacks, no multivariate analysis
Te Kampe 2020[11]	Incorrect comparison- intervention group was aiming for a serum urate level of <0.3mmol/L, and the majority of the comparator group (60.5%) was aiming for the same level due to having tophi. Results for the remainder of the group who were aiming for <0.36mmol/L were not reported separately therefore the comparison reported for the study was the centre/ mode of monitoring rather than serum urate level.
Trontzas 1998[12]	Incorrect analysis/incorrect comparison - serum and synovial fluid interleukin-11 levels were measured and Spearman correlation coefficient was calculated in patients with RA (31 people),

Study	Exclusion reason
	seronegative spondylarthritis (20 people), gout (14 people), osteoarthritis (20 people)
Wasserman 2010[13]	Incorrect population - only 2% of included patients in this study had gout
Yamanaka 1998[14]	Incorrect analysis - study assessed risk of gout attack within the serum urate level (4.6-6.6 mg/l) as opposed to outside this level
Yokose 2020[15]	Incorrect analysis/incorrect comparison - patients enrolled in the gout E-visit program were compared to historical controls. The primary outcome was proportion of patients achieving SU target of less than 6mg/dL at six months

1

2 **Health Economic studies**

3 **None.**

Appendix K– Research recommendations – full details

J.1 Research recommendation

What is the best target serum urate level when using a treat-to-target strategy to treat gout, including in people with chronic kidney disease?

J.2 Why this is important

Gout is frequently under-treated with only a minority of patients receiving definitive treat-to-target urate-lowering therapy to lower the serum urate level below a target level. Treatment-to-target has been shown to prevent gout flares, shrink tophi and improve quality of life. Only 30-40% of people with gout in primary care are offered urate-lowering therapy and only one-third of these achieve a target serum urate level below 360micromol/L. A national audit of management of gout by UK rheumatologists found that by one year after a new out-patient appointment in rheumatology, only 45% and 25% of patients had achieved target serum urate levels below 360micromol/L and 300micromol/L, respectively.

Possible explanations for under-treatment are uncertainty about what the optimum target level should be and disagreement between specialist society guidelines. The British Society for Rheumatology guideline recommends reducing the serum urate level to below 300micromol/L whereas the American College of Rheumatology and European League Against Rheumatism guidelines advocate a target level below 360micromol/L. A lower serum urate target requires higher drug doses and greater healthcare resource to achieve the target. In the review of evidence for the best serum urate target level, the committee found no relevant studies comparing different target serum urate levels. A better understanding of the optimum target serum urate level would provide certainty for patients and clinicians, guiding more frequent uptake of treat-to-target urate-lowering therapy and reducing frequent pain and disability associated with under-treated gout.

J.3 Rationale for research recommendation

Importance to ‘patients’ or the population	Gout is frequently under-treated, resulting in unnecessary gout flares, pain and disability. Better understanding of which target serum urate level best prevents flares would help reduce the suffering caused by under-treated gout.
Relevance to NICE guidance	There is a lack of evidence on the most appropriate target urate level when treating people with gout with urate-lowering therapy. This guideline recommends treating gout using treat-to-target urate-lowering therapy to lower serum urate levels below a target level of 360 micromol/L. This level is based on the physiological saturation threshold of urate in body tissues at which monosodium urate crystals begin to form (approximately 380micromol/L), rather than clinical evidence.
Relevance to the NHS	The outcome would determine which serum urate level treat-to-target urate-lowering therapy

	should aim to achieve. As well as reducing the suffering that gout causes patients, this has the potential to reduce the considerable burden which gout places on NHS resources. It will also balance the additional resource implications (higher drug doses, clinician time) required to achieve a lower target level against its possible clinical benefits.
National priorities	None
Current evidence base	In the guideline review, no relevant clinical studies comparing different serum urate target levels were identified.
Equality considerations	None known

1

J.124 Modified PICO table

3

Population	People with gout commencing treat-to-target urate-lowering therapy
Intervention	Treat-to-target dose escalation protocol with a target serum urate level <300micromoles/litre
Comparator	Treat-to-target dose escalation protocol with a target serum urate level <360micromoles/litre
Outcome	Secondary outcomes: gout flare severity and duration; quality of life; tophi; serum urate level; comorbidities (CKD, cardiovascular disease, neurological); adverse events; healthcare utilisation including hospitalisation for gout
Study design	Randomised controlled trial
Timeframe	Long-term (e.g 2-3 years)
Additional information	None

4

5