National Institute for Health and Care Excellence

Guideline version (Final)

Gout: diagnosis and management

[O] Evidence review for surgical excision of tophi

NICE guideline NG219

Methods and evidence (no recommendation in the NICE guideline)

June 2022

Final

National Institute for Health and Care Excellence

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Contents

1 Surgical excision of tophi

1.1 Review question

What is the clinical and cost effectiveness of surgical excision of tophi (deposits of monosodium urate crystals) in people with gout?

1.1.1 Introduction

Tophaceous gout is characterised by nodular masses of deposited monosodium urate crystals (MSU) due to untreated or partially treated hyperuricaemia with associated chronic inflammation and destructive changes in the surrounding joints and soft tissues. Tophi may be visible under the skin as yellowy/white nodules that are not tender to touch unless there are complications. Complications of tophi include intractable pain due to underlying bone and soft tissue destruction/deformity, compression due to mass effect (for instance, compression of peripheral nerves) and tophi breaching the overlying skin with loss of skin integrity, increased risk of infection of skin, underlying soft tissue, joint space or bone and occasionally chronic skin ulceration.

Urate lowering therapy (ULT) at treat to target dosing can slowly reduce the size of tophi but may take several years in long-standing large tophaceous deposits. It is unknown exactly how prevalent surgical excision of tophi in people with gout is in the UK but is not thought to be commonplace and most likely confined to those patients with complications related to their tophaceous deposits.

This review was carried out to assess the effectiveness of surgical excision of tophi.

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 and tophi 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) CKD 3-5 = more clinically significant and severe CKD 3 = moderate 4= severe Threshold of 60% for population groups (e.g. 60% of study population needs to be stage 3 CKD to be included in the 'people with CKD (stage 3)' strata. Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
Intervention	• Surgery (for example, Debridement, Shaving, Arthroscopic removal, Excision, Debulking)

Comparisons	• Pharmacological - urate lowering drugs e.g. allopurinol and febuxostat (pharmacological therapies not escalated to achieve the target dose) • Treat-to-target (optimum use of pharmacological therapy gradually increased to lower the serum urate to below a target dose) • No treatment/waiting list control • Usual care (where the type of treatment is determined by the Clinicians within the study rather than being a specific comparator as above)

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)
	• 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
	  ○ tophi
	• Surgical complications (wound healing, infection)
	• serum urate levels
	• 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), 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

No relevant clinical studies for surgical excision of tophi were identified.

See also the study selection flow chart in Appendix C.

1.1.4.1 Included studies

No relevant clinical studies for surgical excision of tophi 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

Currency Code	Currency Description	National Average Unit Cost
Knee		
HN24A	Intermediate Knee Procedures for Non-Trauma, 19 years and over, with CC Score 4+	£5,537
HN24B	Intermediate Knee Procedures for Non-Trauma, 19 years and over, with CC Score 2-3	£4,037
HN24C	Intermediate Knee Procedures for Non-Trauma, 19 years and over, with CC Score 0-1	£3,523

Currency Code	Currency Description	National Average Unit Cost
HN25A	Minor Knee Procedures for Non-Trauma, 19 years and over	£2,262
HN26A	Minimal Knee Procedures, 19 years and over	£886
Foot		
HN34A	Intermediate Foot Procedures for Non-Trauma, 19 years and over, with CC Score 4+	£4,854
HN34B	Intermediate Foot Procedures for Non-Trauma, 19 years and over, with CC Score 2-3	£3,920
HN34C	Intermediate Foot Procedures for Non-Trauma, 19 years and over, with CC Score 0-1	£3,448
HN35A	Minor Foot Procedures for Non-Trauma, 19 years and over	£2,531
HN36Z	Minimal Foot Procedures	£1,242
Hand		
HN44A	Intermediate Hand Procedures for Non-Trauma, 19 years and over, with CC Score 2+	£3,488
HN44B	Intermediate Hand Procedures for Non-Trauma, 19 years and over, with CC Score 0-1	£3,195
HN45A	Minor Hand Procedures for Non-Trauma, 19 years and over	£2,052
HN46Z	Minimal Hand Procedures	£763
Elbow		
HN64A	Intermediate Elbow Procedures for Non-Trauma, 19 years and over, with CC Score 2+	£4,064
HN64B	Intermediate Elbow Procedures for Non-Trauma, 19 years and over, with CC Score 0-1	£3,886
HN65Z	Minor Elbow Procedures for Non-Trauma	£2,647
HN66Z	Minimal Elbow Procedures	£522

Source: NHS reference costs 2019/20[3]

1.1.10 Evidence statements

Effectiveness

- 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, pain, patient global assessment of treatment success, cardiovascular, renal and gastrointestinal adverse event, radiographic joint damage, tophi, surgical

complications (wound healing, infection), serum urate levels, admissions (hospital and A&E/urgent care) and GP visits.

The timepoints were separated by short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months) duration.

1.1.11.2 The quality of the evidence

No clinical or cost-effectiveness evidence was identified for the surgical excision of tophi. The committee decided to make a consensus recommendation based on their clinical experience.

1.1.11.3 Benefits and harms

The committee agreed surgical excision of tophi is an uncommon procedure, and surgery is only offered to people with gout who have symptomatic tophi adversely affecting their quality of life due to pain and/or restriction of movement. The committee discussed that tophi develop very slowly over many years and typically occur in the toe, fingers, attachment of the Achilles tendon to the heel or the elbow, in people with high urate or long-standing under-treated gout.

The committee noted surgical excision is not without complications, including damage to tendons and blood vessels, infection, and reduced wound-healings. Nerve entrapment can also make removal of tophi more complicated. The committee discussed that development of tophi is seen in people with uncontrolled gout and tends to be in an older population. They agreed that treat-to-target ULT will reduce serum urate levels and shrink tophi over time. In their experience, referral to orthopaedic surgery would be rarely required.

The committee decided not to make a recommendation as there was no clinical or cost-effectiveness evidence and they did not think a consensus recommendation was appropriate because in their experience a decision to refer for consideration for surgery is rare and would only be made on an individual patient and clinician preference.

The committee discussed whether a research recommendation was required but agreed it would be very difficult to conduct research in this area due to the limited number of people that have the operation, and concluded it was not feasible and also of low priority given the few people who undergo surgery. The committee also noted that the recommendations made in this guideline, regarding urate-lowering therapy, should result in more people receiving and benefitting from effective treat-to-target ULT. This would result in fewer people being referred for surgical excision.

1.1.11.4 Cost effectiveness and resource use

No health economic studies were identified for this review. Unit costs were sought to aid consideration of cost effectiveness.

Overall, due to a lack of clinical and cost effectiveness evidence the committee did not make a recommendation for this review question. Subsequently there is not expected to be a substantial resource impact.

1.1.12 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

1.1.13 References

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10. Wang X, Wanyan P, Wang JM, Tian JH, Hu L, Shen XP et al. A randomized, controlled trial to assess the efficacy of arthroscopic debridement in combination with oral medication versus oral medication in patients with gouty knee arthritis. Indian Journal of Surgery. 2015; 77(Suppl 2):628-634

Appendices

Appendix A – Review protocols

Review protocol for surgical excision of tophi

ID	Field	Content
0.	PROSPERO registration number	CRD42021243749
1.	Review title	The clinical and cost effectiveness of surgical excision of tophi (deposits of monosodium urate crystals) in people with gout?
2.	Review question	What is the clinical and cost effectiveness of surgical excision of tophi (deposits of monosodium urate crystals) in people with gout?
3.	Objective	To determine whether surgical excision of tophi is clinically and cost-effective in people with 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 and tophi 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) CKD 3-5 = more clinically significant and severe CKD 3 = moderate 4= severe Threshold of 60% for population groups (e.g. 60% of study population needs to be stage 3 CKD to be included in the 'people with CKD (stage 3)' strata. Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
7.	Intervention/Exposure/Test	Surgery (for example, Debridement, Shaving, Arthroscopic removal, Excision, Debulking)
8.	Comparator/Reference standard/Confounding factors	• Pharmacological - urate lowering drugs e.g. allopurinal and febuxostat (pharmacological therapies not escalated to achieve the target dose) • Treat-to-target (optimum use of pharmacological therapy gradually increased to lower the serum urate to below a target dose) • No treatment /waiting list control • Usual care (where the type of treatment is determined by the Clinicians within the study rather than being a specific comparator as above)
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	Most people with gout use pharmacological and non-pharmacological interventions. In clinical practice, surgical excision of tophi is sometimes performed. This review focuses on the benefits and harms of any type of surgery for tophi in comparison to other interventions.
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) • 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: o radiographic joint damage o tophi • Surgical complications (wound healing, infection) • serum urate levels • 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. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Type of surgery
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	14th January 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] Julie Neilson [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).[2] **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 surgical excision of tophi (deposits of monosodium urate crystals) in people with gout?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[2]

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)

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 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)

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)

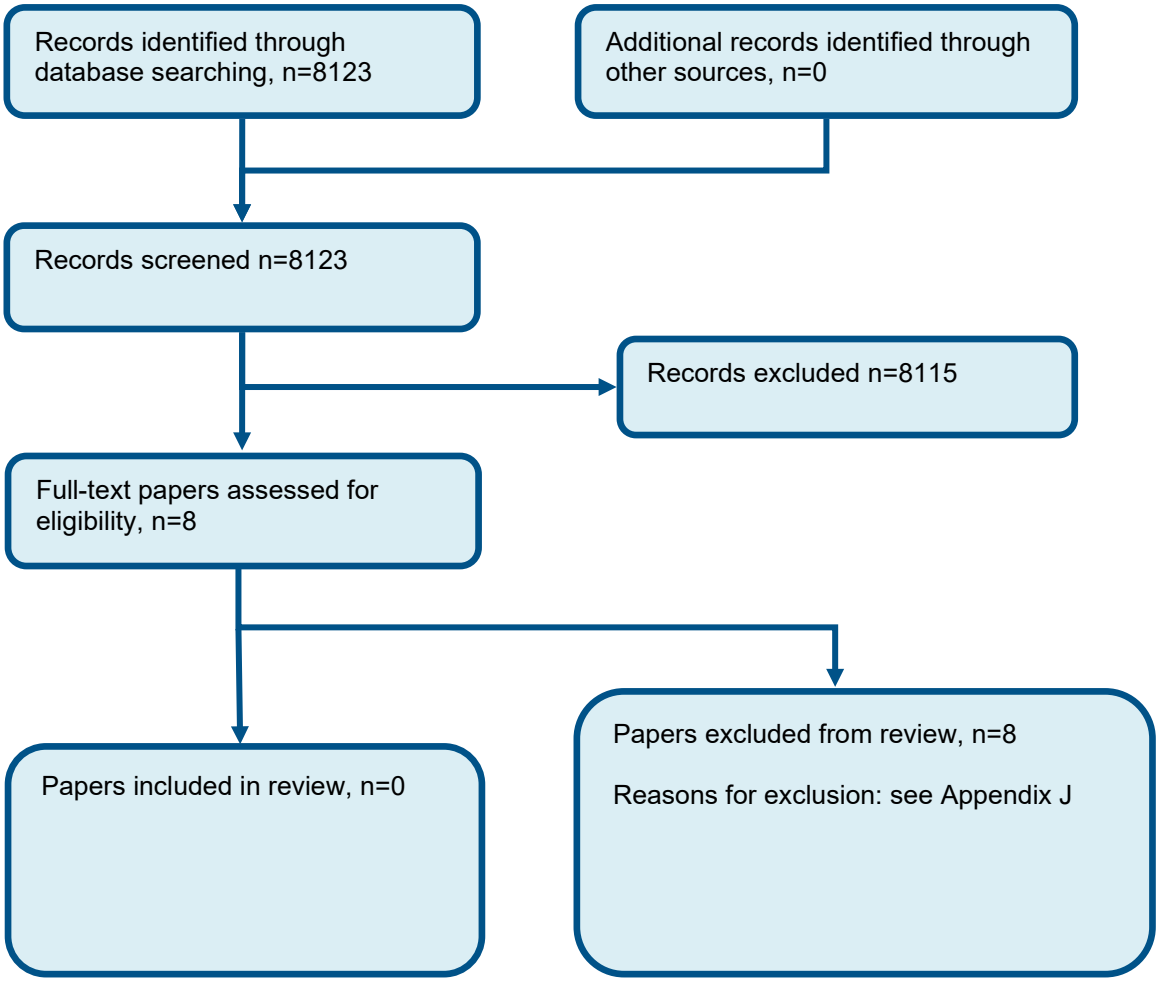
NHS EED and HTA (CRD) search terms

#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 surgical excision of tophi



Appendix D – Effectiveness evidence

No studies were included.

Appendix E – Forest plots

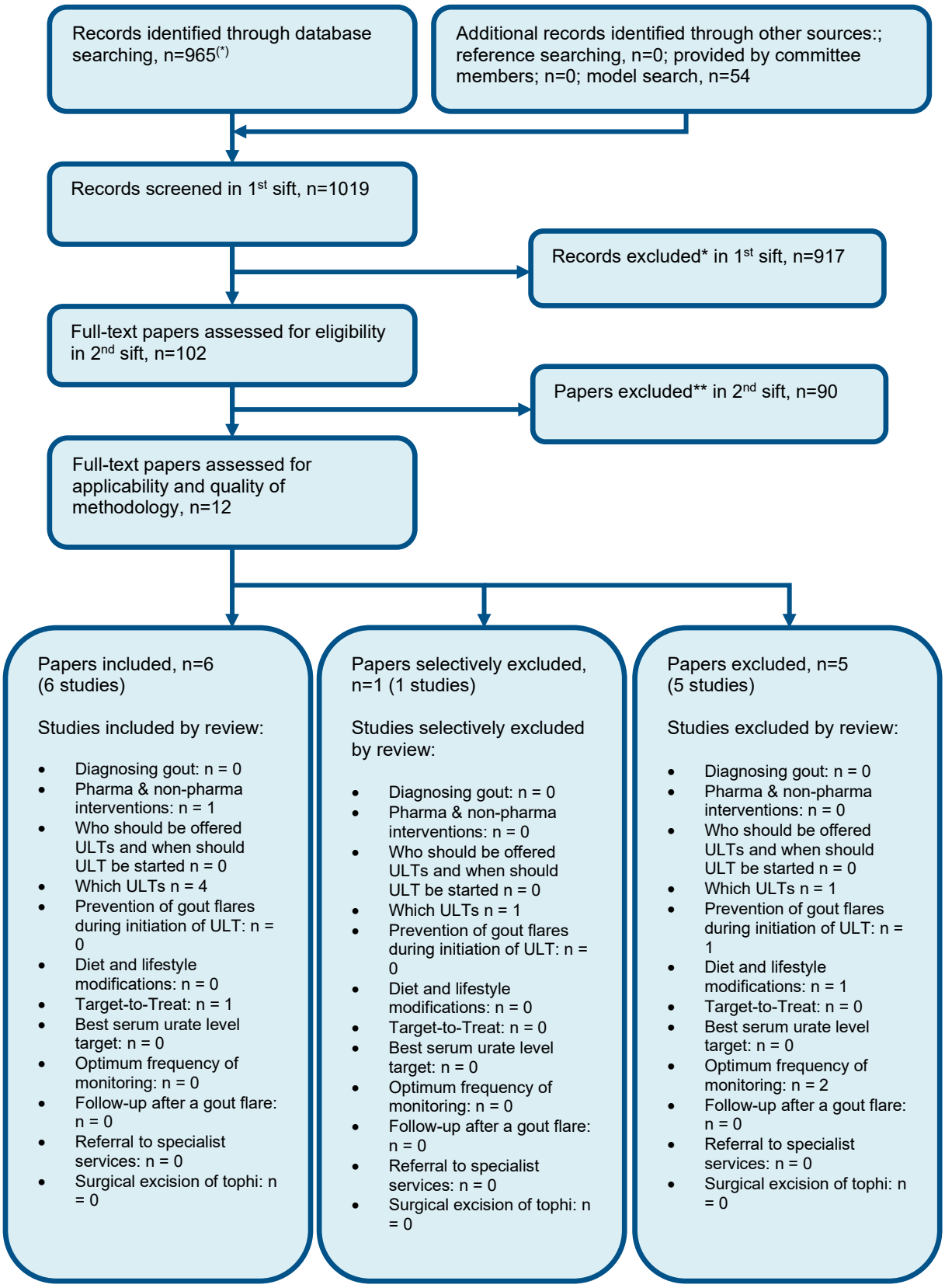
No studies were included.

Appendix F – GRADE and/or GRADE-CERQual 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
Kasper, 2016[1]	Incorrect study design: review of surgical case series
Poratt, 2016[4]	Incorrect study design: systematic review of case series
Sriranganathan, 2014[5]	Incorrect study design: this was a Cochrane review but none of the surgical studies involved the correct study design (case series/reports).
Sriranganathan, 2014[6]	Incorrect study design: this was a Cochrane review but none of the surgical studies involved the correct study design (case series/reports).
Tang, 2011[7]	Incorrect study design: literature review
Wang, 2009[8]	Incorrect study design: case-series
Wang, 2008[9]	Order cancelled: Non-English language publication
Wang, 2015[10]	Incorrect population and intervention: the study includes people with gouty arthritis and does not mention tophi. The intervention involves surgical debridement and oral medication compared to oral medication.

Health Economic studies

None.