National Institute for Health and Care Excellence

1

Guideline version (Draft for Consultation)

Gout: Diagnosis and Management

[M] Evidence review for follow-up for people with gout after a gout flare

NICE guideline <number>

Evidence reviews underpinning recommendation 1.3.6 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

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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.

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ISBN:

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1.1 Review question: What follow-up should be offered to people with gout after a gout flare?

1.1.1 Introduction

Gout flares are characterised by rapid onset of severe pain, joint swelling and erythema. A flare can be an indication that current treatment is ineffective, and each flare exposes the patient to painful, debilitating symptoms. Importantly, gout continues to affect patients insidiously between flares.

Reviewing a person following a flare provides an opportunity to re-evaluate their treatment, lifestyle, and their understanding of the condition. Currently there is no standardisation in practice regarding when or if a follow-up review should occur or what it should comprise of. This evidence review aims to determine what follow-up should be offered to people after a gout flare.

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 who have had gout flare(s) • Strata: None • Exclusion: people with calcium pyrophosphate crystal deposition, including pseudogout
Interventions	• Follow-up care strategies, including: • Specific frequencies and durations • Led by specific healthcare professionals • Settings (community versus secondary/hospital-based care) • Patient- tailored
Comparisons	• Within-type comparisons (e.g. community versus secondary/hospital-based care) • Compared to each other • Standard/usual care • Control (no follow-up)
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 ○ frequency of flares ○ patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) ○ proportion of people with gout using ULT ○ patient awareness of their condition/treatment ○ 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

1.1.4.1 Included studies

No relevant clinical studies comparing follow-up care strategies 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 (Band 5), cost per hour[a]	£42
General Practitioner, cost per consultation (9.22 minutes)[a]	£37
Cost of blood test (excluding time to take blood)[b]	£3-£4

1. *Source: PSSRU 2020[2]; Including qualification costs but excluding individual and productivity costs*
2. *Source: NHS reference costs 2019/2020[8]: directly accessed pathology services, haematology and phlebotomy respectively.*

1.1.10 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered the following outcomes as important for decision making: health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures, frequency of flares, patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)), proportion of people with gout using ULT, patient awareness of their condition/treatment, serum urate levels, admissions (hospital and A&E/urgent care) and GP visits.

The committee considered the impact on the patient's health-related quality of life to be particularly important for this question because the aim of providing follow-up is to improve quality of care for the patient by increasing awareness of their condition and treatments available to prevent another flare in the future. Outcomes reporting whether follow-up would improve the person's serum urate levels or made any impact on admissions or frequency of G.P appointments after flares would also aid the committee's decision making.

To help guide recommendations the committee were interested in the frequency and duration of follow-up reported and decided to categorise time-points reported in the included studies by short-term (less than three months), medium-term (three to 12 months) and long-term (more than 12 months).

1.1.11.2 The quality of the evidence

No evidence was identified for this question. The committee were particularly interested in evidence that addressed different forms of follow-up strategies, including the frequency and duration of follow-up, who should provide it and in which setting. The committee therefore agreed to make a consensus recommendation based on their clinical experience.

Given the lack of evidence and the importance of this area of practice the committee agreed to make a research recommendation on what is the clinical and cost-effectiveness and acceptability of different approaches of follow-up after a gout flare including provision of information? The committee acknowledged provision of information on self-management and prevention of flares was variable, and further research would facilitate the optimum timing and delivery of information.

1.1.11.3 Benefits and harms

The committee discussed that in current practice offering a follow-up appointment to people after a gout flare is variable and it would be more typical for any follow-up to be initiated by the patient themselves. The committee agreed that whether a follow-up appointment was offered or not was often dependent on the health care practitioner's knowledge of gout and gout flares. The committee considered that making a specific recommendation for follow up following a gout flare was helpful as this will promote practitioners and patients understanding of the long-term nature of gout and the need for proper evaluation of a patient who presents with a gout flare. A gout flare can be very painful and distressing and the immediate requirement is for appropriate pain relief. A follow up appointment allows an opportunity to provide information, make a more comprehensive assessment of the person's co-morbidities and explore the person's concerns and expectations. The committee considered these advantages would outweigh any costs associated with follow up. Many people also self-manage gout and consult infrequently so presentation with a flare is an opportunity to review understanding and optimise care.

The committee considered that a follow-up appointment would enable the clinician to provide the person with information about gout and how to reduce the risk of future flares. This could include a discussion about lifestyle factors such as diet and exercise and how people can self-manage flares if they occur again using pharmacological and non-pharmacological methods. The committee noted it would be an optimum time for a serum urate level measurement to be taken, and a review of medication including discussion of the possible benefits of long-term urate lowering therapy (ULT). This is currently under-prescribed (31.8% of people with gout are currently prescribed ULT)[6] and committee experience is that people have many pre-conceptions about gout so a recent flare is a good opportunity to provide information about short and long term issues including the potential use of ULT. Assessment of co-morbidities is particularly important both to assess any comorbidities that could impact on gout and how it is treated, such as cardiovascular risk factors or renal function. The committee noted CKD as a significant risk factor as the prevalence of CKD is recognised to be higher in people with gout. The committee agreed all these elements should be considered by the health professional when following up a person who has had a flare and included these in the recommendation.

The committee discussed when a follow-up appointment should take place and agreed that when a person is in pain it is hard to take in any information, therefore the optimum time would be after the flare has resolved. The committee discussed the time-efficiency of arranging testing of serum urate levels before a follow-up appointment took place, because having the results at the time of the appointment would provide an opportunity to discuss with the person about their serum urate level, treatments and self-managing the condition. The committee concluded the logistics of arranging this would not be practical but agreed the appointment should take place after a person's flare has settled and included this within the recommendation.

The review question was not only looking at whether follow-up was clinically and cost-effective but also specifically which follow-up strategies would be most effective, including which frequency and duration of follow-up, which healthcare professionals should lead the follow-up and in what settings (community versus secondary/hospital-based care). As no evidence was found, the committee decided to include a research recommendation to investigate the clinical and cost-effectiveness and acceptability of different approaches of follow-up for gout flares.

Overall, the committee agreed that there were no harms in following-up a person who has had an acute gout flare. Based on their clinical experience they agreed there were substantial benefits to be gained if these measures were put in place to ensure people were receiving optimum medication and provided with information on how best to self-manage their gout, which would lead to improvements in the overall health of the person and help prevent further flares. In the long-term this could also reduce the number of GP appointments made. How follow up is organised could be negotiated with individual people so that some follow up could happen by telephone or in person.

1.1.11.4 Cost effectiveness and resource use

No published health economic evidence was identified for this review question. Unit costs associated with follow-up appointments following a gout flare were presented to the committee to aid consideration of cost-effectiveness. The unit cost of a primary care practice nurse was £42 per hour and the cost per 9.22 min consultation with a GP was £37. In addition, the costs of blood tests (excluding the time to take the blood) were presented and estimated to be between £3 and £4.

In current practice, generally little-to-no follow-up is offered to people after a gout flare. However, the committee noted that follow-up after an initial gout flare provides an opportunity for health care professionals to assess and review a person's medication or initiate ULT. In addition, follow-up appointments provide clinicians the opportunity to provide a person with

gout additional information such as, diet and lifestyle advice and information on how to reduce the risk of future flares. Although no clinical or health economic evidence was identified for this review question the committee concluded follow-up appointments after an initial flare would likely result in people experiencing a higher health-related quality of life in the long-term as people would likely initiate ULT sooner compared to what is currently observed in clinical practice. Therefore, ultimately people would experience fewer flares by achieving target serum urate levels sooner as a result of initiating ULT.

The committee acknowledged it may not be appropriate for all people to initiate ULT after an initial gout flare but providing people information about gout and the best course of treatment dependent on the severity of a person's gout would result in better health outcomes for people. The committee noted that in current practice a high proportion of people with gout may only ever seek treatment with a GP once because they are not fully informed of the treatment options available to them. As a result of follow-up appointments people with gout will be better equipped to manage their gout flares as they will have been provided information on the preventative measures people can take to minimise their chances or recurrent gout flares.

Overall, the committee discussed that the benefits and downstream cost savings associated with follow-up appointments would outweigh the costs of follow-up appointments. The committee acknowledged that one follow-up appointment would cost between £10.50 (assuming 15 minutes of nurse time) and £37 dependent on the health care professional conducting the appointment. The cost of a gout flare is estimated to be £27.19 - £55.60 (See Evidence review G: Which ULTs). Based on their clinical experience, the committee concluded the care and information provided to people in a follow-up appointment after a gout flare could prevent two flares, on average, over a person's lifetime and therefore be cost saving. To put this into context a trial by Doherty et al 2018[3] found that in the usual care arm, which is considered by the committee to be a conservative representation of people with gout in current practice, 80% and 35% had two or more and four or more flares in the past year respectively. People will also experience improved quality of life from experiencing fewer flares which the committee noted are very painful and can sometimes be debilitating. Overall, as no clinical or health economic evidence was identified for this review question, the committee made a consensus recommendation to consider follow-up after a gout flare.

If implemented, this recommendation is likely to be a change in practice for many and will affect a large proportion of the gout population. However, the committee agreed that it is likely that this recommendation would be cost saving or at least cost neutral in terms of resource impact, as a follow up appointment may prevent up to two flares over a lifetime.

1.1.11.5 Other factors the committee took into account

The committee agreed that it would be appropriate to cross refer to the NICE guideline Medicines adherence (CG76) and Shared decision making (ng197) when reviewing a person's medication for gout and having a discussion with the person about considering urate lowering therapies and the possibility of flares when initiating treatment.

The committee agreed cross reference should also be made to the Chronic kidney disease in adults (CG182) and Cardiovascular disease risk assessment (CG 181) for recommendations on risk assessment and managing medicines in these populations.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.6 and the research recommendation on the effectiveness and patient acceptability of different approaches of follow-up, including provision of patient information and for managing gout flares?

1.1.13 References

1. Barber C, Thompson K, Hanly JG. Impact of a rheumatology consultation service on the diagnostic accuracy and management of gout in hospitalized patients. Journal of Rheumatology. 2009; 36(8):1699-1704

2. Beecham J, Curtis L. Unit costs of health and social care 2020. Canterbury. Personal Social Services Research Unit University of Kent, 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/

3. Doherty M, Jenkins W, Richardson H, Sarmanova A, Abhishek A, Ashton D et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet. 2018; 392(10156):1403-1412

4. Fautrel B, Belhassen M, Hudry C, Woronoff-Lemsi MC, Levy-Bachelot L, Van Ganse E et al. Predictive factors of tumour necrosis inhibitor treatment persistence for rheumatoid arthritis: An observational study in 8052 patients. Joint, Bone, Spine: Revue du Rhumatisme. 2020; 87(2):137-139

5. Goossens J, Lancrenon S, Lanz S, Ea HK, Lambert C, Guggenbuhl P et al. GOSPEL 3: Management of gout by primary-care physicians and office-based rheumatologists in France in the early 21st century - comparison with 2006 EULAR Recommendations. Joint, Bone, Spine: Revue du Rhumatisme. 2017; 84(4):447-453

6. Guthrie B. Multimorbidity and clinical guidelines: using epidemiology to quantify the applicability of trial evidence to inform guideline development [unpublished]. University of Edinburgh.

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

8. NHS England and NHS Improvement. National Cost Collection Data Publication 2019-2020. London. 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/06/National-Cost-Collection-2019-20-Report-FINAL.pdf

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for follow-up for people with gout after a gout flare

ID	Field	Content
0.	PROSPERO registration number	CRD42021230918
1.	Review title	Follow-up for people with gout after a gout flare
2.	Review question	What follow-up should be offered to people with gout after a gout flare?
3.	Objective	To determine which follow-up strategy should be offered to people with gout after a gout flare
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 who have had gout flare(s) Strata: None

		Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout
7.	Intervention/Exposure/Test	Follow-up care strategies, including: • Specific frequencies and durations • Led by specific healthcare professionals • Settings (community versus secondary/hospital-based care) • Patient- tailored
8.	Comparator/Reference standard/Confounding factors	• Within-type comparisons (e.g. community versus secondary/hospital-based care) • Compared to each other • Standard/usual care • Control (no follow-up)
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	There is currently variation in follow-up offered to people with gout after a flare. Standardisation of follow-up care is essential for patient care.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • health-related quality of life (e.g. as described by SF-36, Gout Assessment

		Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures • frequency of flares • patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS)) • proportion of people with gout using ULT • patient awareness of their condition/treatment • 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.
13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EPPI-5 reviewer 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: • Serum urate levels • Frequency of flares • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of

		Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	30th October 2020	
22.	Anticipated completion date	13th June 2022	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact	

		National Guideline Centre 5b Named contact e-mail managementofgout@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
25.	Review team members	From the National Guideline Centre: Gill Ritchie [Guideline lead] 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	N/A	
36.	Details of final publication	www.nice.org.uk	

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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).[7] **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.

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Appendix B – Literature search strategies

- What follow-up should be offered to people with gout after a gout flare?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[7]

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

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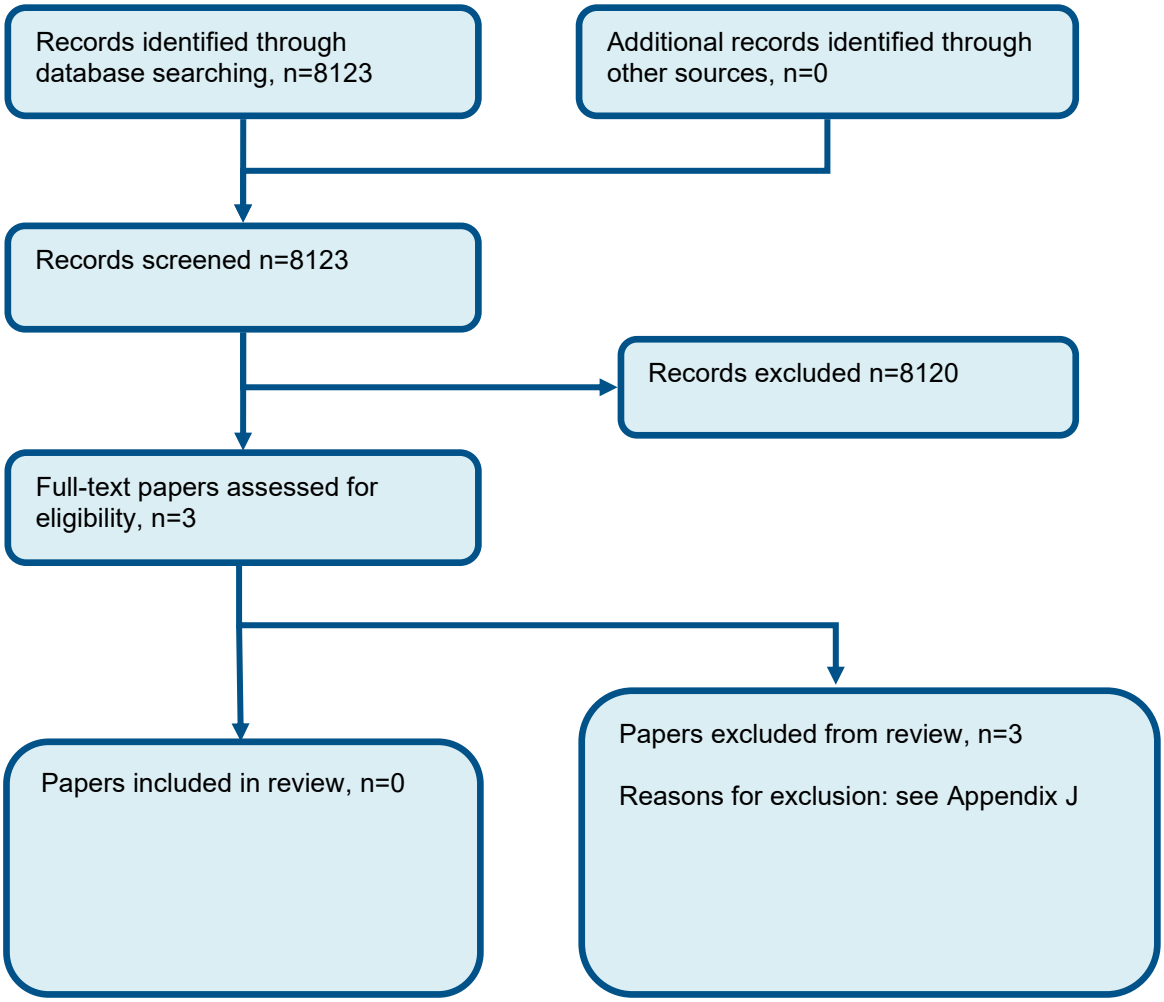
Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

No studies were included.

Appendix E – Forest plots

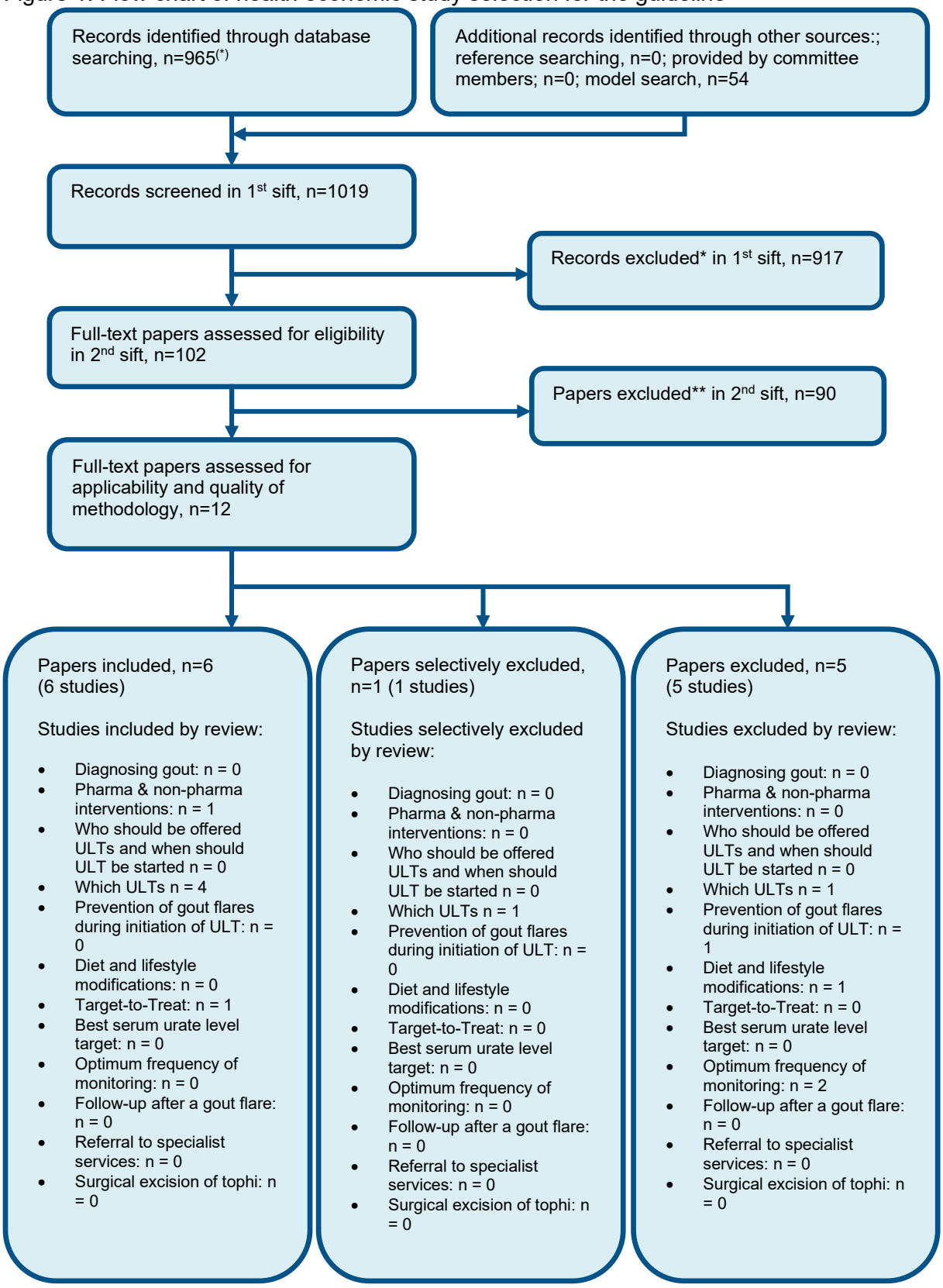
No studies were included.

Appendix F – GRADE and/or GRADE-CERQual tables

No studies were included

Appendix G – Economic evidence study selection

Figure 1: 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
Goossens, 2017[5]	Incorrect study design – descriptive study of management of gout by primary care physicians and office-based rheumatologists compared with 2006 EULAR recommendations.
Barber, 2009[1]	Incorrect study design/outcomes/population - retrospective case-control study. Outcomes were diagnostic accuracy and adherence to established guidelines. Not related to gout flares.
Fautrel, 2020[4]	Incorrect study design: prognostic study of predictive risk factors.

Health Economic studies

Appendix K None.

Appendix K– Research recommendations – full details

K.1 Research recommendation

What is the clinical and cost effectiveness and patient acceptability of different approaches to follow-up, including provision of patient information and managing gout flares?

K.2 Why this is important

Gout is the most common type of inflammatory arthritis, causing both painful inflammatory gout flares and more insidious inflammation between flares. Most patients and healthcare professionals consider flares to be the only effect of gout. Prevalence and severity of gout are both associated with lower levels of education and lower socio-economic status whilst more frequent flares are associated with work absenteeism. Coupled with persisting and incorrect societal beliefs that gout is a self-inflicted lifestyle disease, these misconceptions often prevent gout patients receiving timely follow-up for their gout flares and explanation of the long-term effects of gout and available treatment which would help them manage their condition. There is a need for better provision of patient information and understanding of how this information should be provided, by whom and when to ensure that this provision of information is acceptable to and understood by the patient. This would facilitate the provision of clinically and cost-effective patient information and advice and reduce inequalities and variation in care.

K.3 Rationale for research recommendation

Importance to 'patients' or the population	People with gout would receive timely and effective patient centric education about their gout including the causes of gout, its long-term effects and why it is important to consider long-term treatment in a way that they can understand. Patients would have the opportunity to engage in shared decision making and discuss any concerns regarding starting on long - term medication. This would improve patient engagement with starting long-term treatment for gout in a timely and systematic manner, improve adherence with treatment, improve patient outcomes, reduce the number of gout flares, reduce risks of developing/worsening comorbidities (e.g. chronic kidney disease) and improve quality of life.
Relevance to NICE guidance	Peoples lack of understanding about the long-term consequences of gout and patient perceptions as to why they have gout have been raised by the NICE Gout Guideline Committee as perceived barriers to treatment and a cause of lack of adherence to medication. The majority of gout patients are diagnosed and treated in primary care. There is no study that assesses these information barriers in primary care including the type and style of patient information which is patient-centric, when best to

	deliver this information, and best modes of information delivery including timing and by whom. There is the risk of inequalities of treatment between patients well informed about gout and those that are not.
Relevance to the NHS	There are important cost and resource implications of under provision of information in primary care including more frequent flares with resulting patient contact and pain medication usage, time off work, long-term adverse consequences including development of new/worsening of existing comorbidities and resource impact, and risk of inequalities of treatment between patients well informed about gout and those that are not. Over the medium and long-term, application of an evidence-based strategy of the most clinically and cost-effective ways of delivering patient-centric information on gout including why long-term treatment is advised should positively reduce resource use and improve the overall gout patient population's health with resultant cost-savings for NHSE.
National priorities	High- gout is an area of concern identified by NICE as having high variability and needing guidance to improve patient outcomes and standards of care. These aspects have relevance to NHSE 10 Year Plan, the Best MSK Health Initiative and the 2019 MSK Health 5 Year Strategy aims of removing inequalities and variation in care and improved outcomes in patients' self-care, especially in Rheumatology and Musculoskeletal Medicine.
Current evidence base	No evidence was identified
Equality considerations	Prevalence and severity of gout are associated with lower levels of education and lower socio-economic status whilst more frequent flares are associated with higher levels of work absenteeism. Given the evidence that there is an existing relationship between gout and individual deprivation, we need to ensure that the current approach to helping patients manage the condition isn't exacerbating this inequality.

K.12.4 Modified PICO table

Population	People presenting in primary care with gout flares (including people with gout and CKD) who are not on long-term gout treatment. This includes people who present with their first flare of gout and those who are presenting with their second or subsequent flares of gout but not currently on long-term treatment for gout.

Intervention	Provision of patient information looking at the type and style of patient information that is patient-centric, when best to deliver this information, and best modes of information delivery including timing and by whom.
Comparator	Current standard of care
Outcome	Percentage of patients starting on long-term treatment for gout, adherence of long-term treatment once started, drop-out rates from long-term treatment, rates of gout flare over 1, 2, 3 and 5 years, patient understanding of gout, health related quality of life measures (Gout assessment questionnaire and the Gout impact scale), pain (VAS), frequency of flares, joint swelling, patient global assessment of treatment success (VAS), adverse events (cardiovascular, renal, GI), admissions (hospital, A&E, urgent care) and GP visits.
Study design	RCT unblinded study design
Timeframe	Short and medium term
Additional information	High: the research is important in analysing the causes of and finding pragmatic ways to reduce inequalities and variation in care, and essential to inform future updates of key recommendations in the guideline.

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