National Institute for Health and Care Excellence

Guideline version (Draft for Consultation)

# Gout: Diagnosis and Management

## [E] Evidence reviews for which people with gout should be offered a urate-lowering therapy

*NICE guideline <number>*

*Evidence reviews underpinning recommendations 1.5.1 to 1.5.3 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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ISBN:

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# 1 Which people with gout should be offered a urate-lowering therapy?

## 1.1 Review question: Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?

### 1.1.1 Introduction

The main aim of treating gout is to minimize the likelihood of gout flares reoccurring. Urate-lowering therapy works by reducing the production of serum urate or increasing the excretion of serum urate. If gout is not treated this can result in more gout attacks causing severe pain, joint inflammation, the possibility of joint destruction, and negatively impact on physical, psychological and social function.

Urate-lowering therapy includes xanthine oxidase inhibitors, uricosuric and uricase medications. The use of urate-lowering therapy in current practice is not standardised.

This aim of this review is to identify which groups of people with gout are at higher risk of having flares or disabilities and more likely to benefit from taking urate-lowering therapy.

### 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<br><br>Strata: None<br><br>Exclusion: people with calcium pyrophosphate crystal deposition, including pseudogout |
| **Prognostic variables under consideration** | Patient risk factors:<br>• Flare frequency<br>• Presence of tophi<br>• Chronic gouty arthritis<br>• Presence of any joint damage<br>• Renal impairment (eGFR less than 60 ml/min)<br>• history of urinary stones<br>• Diuretic use<br>• Young age of onset of primary gout<br>• or a combination of the above |
| **Confounding factors** | Confounding factors that may be independently associated with prognostic variable: |

| | |
|---|---|
| | • Age<br>• Gender<br><br>Multivariate studies need to have adjusted for both of these prognostic variables. |
| **Outcomes** | All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• Frequency of flares<br>• 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 |
| **Study design** | • Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analysis. |

### 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

Three cohort studies included in this review[27-29] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 to Table 7).

### 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

**Table 2: Summary of studies included in the evidence review**

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| Rashid 2015[27]<br>Retrospective cohort study | n=8828<br><br>Patients were included if they received a prescription for a urate-lowering therapy (ULT) - allopurinol, febuxostat, or probenecid, during the study time period (January 2007–December 2010); the index date was defined as the patient's first ULT prescription identified during | Multivariable logistic regression models | Risk factor<br>Diuretic use at baseline:<br>1-2 flares group: 2345 (48.5%),<br>≥3 flares group: 701 (55.1%)<br>No flares group: 1331 (47.6%)<br><br>Comparison<br>No diuretic use at baseline:<br>1-2 flares group: 2453 (51.5%),<br>≥3 flares group: 549 (44.9%) | Confounders adjusted for: sex, age, race, Serum Uric Acid (sUA) levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber | Frequency of flares - patients with 1-2 flares during 12 months post index<br><br>Frequency of flares - patients with ≥3 flares during 12 months post index<br><br>Frequency of flares - patients with no flares during 12 months post index | None |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| | the study time period. Patients had to be ≥18 years of age at time of index date and were required to have at least 12 months of Kaiser Permanente Southern California (SPSC) membership eligibility including drug benefits prior to their index date, index date, and 12 months post-index.<br><br>Age –<br>1-2 flares group:<br><55 years old – 41%<br>55-64 years old – 28.5%<br>≥65 years old – 35.5%<br><br>≥3 flares group:<br><55 years old – 30.5%<br>55-64 years old – 22.2%<br>≥65 years old – 47.3 | | No flares group: 1449 (52.4%) | | | |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| | no gout flares group:<br><55 years old – 34.2%<br>55-64 years old – 28.4%<br>≥65 years old – 37.2%<br><br>Gender (M/F) – 7045/1783<br><br>Ethnicity: 1-2 flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific Islander 23.4 %, Other 0.5%<br><br>≥3 flares group, Caucasian 42.7%, African-American 14.1% , Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5%<br><br>no gout flares group: Caucasian | | | | | |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| | 42.7%, African-American 14.1% , Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5%<br><br>USA | | | | | |
| Rothenbacher 2011[28]<br>Prospective cohort study | n=23857<br><br>Single cohort of patients aged 20-89 years diagnosed with incident gout between the years 2000 and 2007. Subjects with any prescription of anti-gout treatment or any Read code suggesting gout before the start date were subsequently excluded from the cohort and considered as prevalent patients. All patients with cancer before the start date were also | Multivariate analysis using Cox proportional hazard model | Risk factor:<br>History of chronic kidney failure (n=880 (3.7%))<br><br>Comparison:<br>No history of chronic kidney failure (n=22977 (96.3%) | HR adjusted for sex, age (at start date of follow-up), GP visits (1 year before first-ever diagnosis of gout), smoking, alcohol, BMI, IHD, hypertension, hyperlipidaemia, renal failure and diabetes.<br><br>before first-ever diagnosis of gout). | Frequency of flares – 1 or more flares (mean follow-up 3.8 years) | None |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| | excluded.<br><br>Age – n (%):<br>20-49 years – 5211 (21.8%)<br>50-59 years – 4761 (20.1%)<br>60-69 years -5547 (23.3%)<br>70-79 years – 5533 (23.2%<br>80-89 years – 2805 (11.8%)<br><br>Gender (M/F): 17358/7499<br><br>Ethnicity: not reported<br><br>UK | | | | | |
| Scire 2013[29]<br><br>Retrospective cohort study | N=446<br>Patients with a clinical diagnosis of<br>gout from 30 rheumatology centres in Italy<br><br>Age – mean years (SD): 63.9 (11.6) | Multivariate linear regression model | Risk factors 1<br>Presence of tophi (n=87)<br><br>Comparison 1<br>No tophi (n=359)<br><br>Risk factors 2<br>number of swollen joints (n=not reported)<br>Median (IQR) 0 (0 to1) | Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment | SF36 physical component at 6 months;<br><br>SF36 mental component at 6 months;<br><br>HAQ-DI at 6 months. | None |

| Study | Population | Analysis | Prognostic variables | Confounders | Outcomes | Limitations |
|---|---|---|---|---|---|---|
| | Gender (M/F): 403/43<br><br>Ethnicity: not reported<br><br>Italy | | Comparison 2<br>number of swollen joints (n=not reported)<br><br>Risk factors 2<br>number of tender joints (n=not reported) Median (IQR) 1 (0 to 3)<br><br>Comparison 2<br>number of tender joints (n=not reported) | | | |

1 See Appendix D for full evidence tables.

2 **1.1.6 Summary of the prognostic evidence**

3 **Table 3: Clinical evidence summary: renal impairment - history of chronic renal failure**

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| Frequency of flares (1 or more flares) | n=23857 | HIGHa | Adjusted HR 1.33 (1.20 to 1.47)b |
| a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years); number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30). | | | |

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. | | | |

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2 **Table 4: Clinical evidence summary: diuretics use**

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| One to two flares | n=8828 | HIGHa | Adjusted OR 1.19 (1.05 to 1.35)b |
| Over or equal to 3 flares | n=8828 | HIGHa | Adjusted OR 1.23 (1.01 to 1.50)b |
| a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30);<br>b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. | | | |

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4 **Table 5: Clinical evidence summary: presence of tophi**

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| SF-36 physical component (presence of tophi) (higher is better) | N=446 | HIGHa | Adjusted MD 3.2 lower (5.41 lower to 0.99 lower)c |
| SF-36 mental component (presence of tophi) (higher is better) | N=446 | MODERATEa,b | Adjusted MD 1.26 higher (0.88 lower to 3.4 higher)c |

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| | | | |
| HAQ-DI (presence of tophi) (lower is better) | N=446 | HIGHa | Adjusted OR 1.92 (1.07 to 3.45)c |

a Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis: Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

b Downgraded by 1 increment because the confidence interval crossed the null line

c. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

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2 **Table 6: Clinical evidence summary: presence of any joint damage – number of swollen joints**

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| SF-36 physical component (presence of any joint damage – number of swollen joints) (higher is better) | N=446 | HIGHa | Adjusted MD 0.54 lower (0.79 lower to 0.29 lower)c |
| SF-36 mental component (presence of any joint damage – number of swollen joints) (higher is better) | N=446 | MODERATEa,b | Adjusted MD 0.2 lower (0.45 lower to 0.05 higher)c |
| HAQ-DI (presence of any joint damage – number of swollen joints) (lower is better) | N=446 | HIGHa | Adjusted OR 1.23 (1.13 to 1.34)c |

a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Method: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

b. Downgraded by 1 increment because the confidence interval crossed the null line.

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| c. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. | | | |

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2 **Table 7: Clinical evidence summary: presence of any joint damage – number of tender joints**

| Risk factor and outcome (population) | Number of participants (studies) Follow up | Quality of the evidence (GRADE) | Effect (95% CI) |
|---|---|---|---|
| SF-36 physical component (presence of any joint damage – number of tender joints) (higher is better) | N=446 | HIGHa | Adjusted MD 0.39 lower (0.55 lower to 0.23 lower)b |
| SF-36 mental component (presence of any joint damage – number of tender joints) (higher is better) | N=446 | HIGHa | Adjusted MD 0.24 lower (0.39 lower to 0.09 lower)b |
| HAQ-DI (presence of any joint damage – number of tender joints) (lower is better) | N=446 | HIGHa | Adjusted OR 1.10 (1.06 to 1.14)b |
| a. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.<br>b. Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes. | | | |

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4 See Appendix F for full GRADE

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## 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 8: Urate-lowering therapy costs**

| Resource | Cost per unit | Dosage |
|---|---|---|
| Allopurinol 100mg tablet | £0.04 | 100mg – 900mg per day |
| Allopurinol 300mg tablet | £0.06 | |
| Febuxostat 80mg tablet | £0.10 | 80mg – 120mg per day |
| Febuxostat 120mg tablet | £0.87 | |

*Source: British National Formulary, September 2021*[5]

## 1.1.10 Evidence statements

**Economic**

- No relevant economic evaluations were identified.

## 1.1.11 The committee's discussion and interpretation of the evidence

The effectiveness of ULTs is addressed in Evidence Review G and recommendations have been made on prescribing ULTs.

### 1.1.11.1. The outcomes that matter most

The committee considered frequency of flares and health-related quality of life as the two most important outcomes for decision-making. The committee agreed that highlighting specific groups as being at higher risk of having flares or lower quality of life would help clinicians to identify people more likely to benefit from taking urate-lowering therapy.

### 1.1.11.2 The quality of the evidence

Three cohort studies evaluating which patient risk factors are associated with worse outcomes in terms of quality of life or frequency of flares were included in this review.

One cohort study evaluated the association between history of chronic renal failure and frequency of flares outcome. The quality of evidence was graded high. Another cohort study

evaluated the association between diuretic use and frequency of flares (1 - 2 flares and ≥3 flares). The quality of evidence was high. One cohort study evaluated the association between presence of tophi, number of swollen joints, number of tender joints and quality of life outcomes: SF-36 (physical and mental components) and HAQ-DI. The quality of evidence ranged from moderate to high, the mental component of the SF-36 was downgraded due to imprecision. This was a very small study, with a short follow-up time (6 months) in comparison to the other studies (12 months and 3.8 years).

#### 1.1.11.3 Benefits and harms

The committee agreed that although the quality ranged from moderate to high, the evidence was limited by the lack of studies and lack of clinical benefits for health-related quality of life. The evidence showed no clinical difference for SF-36 physical and mental components in relation to tophi, swollen joints, and presence of tender joints but the SF-36 is thought to be not particularly sensitive to change in musculoskeletal conditions, therefore the committee had less confidence in these results.

The evidence showed that gout flares are more likely in patients with a history of chronic renal failure (one or more flares) or in patients using diuretics (one to three or more flares). Furthermore, the evidence showed that presence of tophi, swollen joints and tender joints were associated with higher HAQ-DI score (more disability). The committee discussed that within current practice gout is not well managed and the people to whom ULT is offered is very variable. However, the committee agreed that the groups studied reflected the people who in their experience would be identified as benefiting from ULT.

People on diuretics are prone to significant hyperuricaemia and frequent flares owing to the effect of diuretics in reducing renal urate excretion. The committee noted people with CKD or on diuretics tend to have more flares than people with normal renal function due to reduced urate excretion leading to more severe hyperuricaemia and greater monosodium urate crystal formation. They agreed that people with multiple or troublesome flares with painful swollen joints are harder to treat. The committee discussed the debilitating effects that tophi and swollen joints can have and the major impact on quality of life. They noted that chronic gouty arthritis can lead to permanent joint damage and loss of range of motion in the joints. Overall, the committee agreed gout can lead to significant harms and therefore agreed ULT should be offered to people with multiple or troublesome flares, CKD stages 3 - 5, diuretic use, tophi and/or chronic gouty arthritis.

CPRD data provided by Guthrie et al.[14] found that only 31.8% of people with gout are being treated with ULT. The committee noted that there may be missed opportunities of not offering ULTs to people with gout early in their disease but acknowledged that there was a lack of evidence for this. However, they agreed as uptake of ULT was low it was important to take the opportunity to discuss the option of starting ULT with all people experiencing a first or subsequent gout flare. As part of the discussion, the committee agreed it was important to ensure that people understood ULT is a long-term treatment and would usually continue even when the target serum urate level is reached. Based on the evidence and their experience the committee agreed that urate-lowering therapy should be discussed and considered with all people experiencing a first or subsequent gout flare.

#### 1.1.11.4 Cost effectiveness and resource use

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

A number of specific groups of patients were identified in the clinical evidence as being more likely to have flares or disability and therefore more likely to benefit from ULTs. In addition, the committee noted that the clinical benefit for quality of life may not be fully captured in the included studies due to short follow up.

The committee discussed that people who do not receive ULT for their gout will experience more flares and are highly unlikely to achieve target serum urate levels compared to those people who receive ULT (evidence of this can be found in Evidence review G). Also, when employing a treat-to-target management strategy for treatment with ULT (as recommended as part of this guideline) more people achieve target serum urate levels and fewer flares are observed compared to usual care (evidence of this can be found in Evidence review J).

Evidence review G also illustrated that ULTs are cost effective compared to no treatment. Of note, the price of 80mg febuxostat has decreased since the previous TA [15, 22, 31, 32](£0.10 compared to £0.87) and the price of allopurinol has marginally increased (£0.060 compared to £0.047). Therefore, febuxostat will be more cost effective than the economic evidence presented in evidence review G suggests and allopurinol will be marginally less cost effective compared to no treatment with ULTs. In addition, Evidence review J demonstrated a treat-to-target management strategy was cost effective compared to usual care. In the included health economic study, a large proportion of people in the usual care arm did not receive treatment with ULTs (43.87% at two years compared to 3.9% of people in the treat-to-target arm), again strengthening the case that treatment with ULT is more cost effective than no treatment.

The committee discussed current practice regarding the prescription of ULTs, noting current practice is highly variable and uptake of ULTs is poor. Current best practice is to offer ULT for people who experience multiple flares, have CKD (stage 3 to 5), are receiving diuretic therapy, have tophi, or have chronic gouty arthritis. In addition, the committee also noted current best practice is to consider the option of ULT with a treat-to-target management strategy for people experiencing a first or subsequent flare. Overall, the committee made an offer and a consider recommendation which are reflective of current best practice.

CPRD data analysed by Guthrie et al.[14] found that currently only 31.8% of people with gout are treated with ULT. However, the recommendations made as a result of this review question are likely to result in an increase in uptake of ULT. The committee noted it was difficult to accurately estimate what proportion of people will receive ULT as a result of the recommendations made. However, they noted it was unlikely more than 60%-70% of people with gout would be treated with ULT. This is because it may be a number of years until a person experiences a subsequent flare, and therefore the benefits of ULT may not outweigh the costs if ULT is initiated after an acute gout flare. In general, the decision to initiate ULT will be made by the person with gout and with help of a clinician to explain the benefits and harms of initiating ULT and assessing individual risks factors for subsequent flares and how frequent these may be.

Although the recommendations made as part of this review question will result in an uptake of people receiving ULT, the committee noted gout flares are costly to the NHS and have a significant impact on a person's quality of life. People experiencing gout flares may require a GP appointment to help manage their pain or seek help and advice. In addition, all people experiencing a gout flare will likely require a repeat prescription for their medication which will involve GP time and the cost of drugs prescribed (for example, NSAIDs, colchicine, and oral corticosteroids).

The estimated cost of a gout flare (as can be found in evidence review G) ranged from £27.19 - £55.60. The committee noted the majority of people will achieve target serum urate levels on 80mg of febuxostat or by the time they have been up titrated to 400mg allopurinol. Therefore, assuming only the cost of ULT for febuxostat 80mg and allopurinol 400mg, one year of treatment costs £36.50 per year (£0.10*365 for 80mg febuxostat and ([£0.06+£0.04]*365 for 400mg allopurinol). In the Doherty trial 79.92% of the 255 people in the nurse led arm experienced two or more flares at baseline and 8% of people experienced flares at two years. 38.04% of people experienced four or more flares at baseline and 1.15% of people experienced four or more flares at two years. This equates to 204 people experiencing two or more flares at baseline, 20 people experiencing two or more flares at 2

years, 97 people experiencing four or more flares at baseline, and 3 people experiencing four or more flares at two years. Assuming at baseline, 204 people experience two flares, and 97 people experience four flares – overall 796 flares are observed at baseline. Assuming at two years, 20 people experience two flares, and 3 people experience four flares – 23 flares are observed at year two. If it is assumed baseline equates to no treatment – no treatment results in 3.12 (796/255) flares per person. After two years of treatment 0.09 (23/255) flares are observed per person.

Employing the lowest cost of a gout flare (£27.19), as calculated in Evidence review G, the cost of flares for no treatment (baseline) is £84.83 (£27.19*3.12). Therefore, assuming only the cost of ULT (£36.50), treatment with ULT is cheaper than the cost of treating gout flares (£84.83) which would be observed as a result of no treatment. Treatment is also cheaper when the highest cost of a gout flare is used, £36.50 compared to £173.47 (£55.60*3.12) for no treatment. The committee acknowledged there would be additional costs associated with ULT in the first year of treatment. For example, the cost of prophylaxis used when initiating and up titrating ULT, up titration costs in the form of GP and nurse time, and the cost of flares associated with the flare triggering effect which is observed when initiating and up titrating ULT. In addition, some people may still experience flares once they have achieved target serum urate levels. The committee concluded the overall cost of treatment in the first year may be slightly higher than the cost of flares avoided initially but noted after two years of treatment the only costs associated with ULT would be the drug costs and cost of any additional monitoring of serum urate levels, if conducted. The committee acknowledged that in the long term the number of flares avoided was significant at 3.03 per person (3.12 – 0.09), saving the NHS £82.39 - £168.47 per person per year, and the committee concluded the average number of flares at 2 years was likely be similar to those observed in the long term. Although, the number of flares people experience in the long term may increase if people do not adhere to their medication.

Based on data in the Doherty trial, the long-term cost of ULT plus the number of flares people experience ranges from £38.95 (£36.50 + [£27.19*0.09]) to £41.50 (£36.50 + [£55.60*0.9]). Including a cost of £34.14 for annual monitoring (see Evidence review L) treatment with ULT is still cheaper than no treatment. The estimated cost of treatment ranges from £73.09 - £75.64 (compared to £84.83 - £173.47 for no treatment). The committee also reiterated the quality-of-life improvements for people not experiencing such severe and frequent flares.

The committee also noted that if gout goes untreated without ULT for a long period of time people are at greater risk of experiencing tophi and long-term joint damage. If a person with gout develops tophi more aggressive and costly treatment with ULT is required to dissolve the tophi and obtain target serum urate levels, in turn costing the NHS more money. Long-term joint damage will likely be highly costly for the NHS and have a severe negative impact on a person’s quality of life. The committee also noted gout flares can be very painful and debilitating, noting it is unlikely someone experiencing a severe gout flare will be able to participate in their usual daily activities.

The recommendations made as a result of this review question are likely to result in a significant resource impact given the prevalence of gout and the current poor uptake of ULTs. However, the committee concluded these recommendations were important in improving the standards of care for the gout population. As a result of the recommendations made, treatment will become standardised whereby all people with gout will have the option to receive ULT if they wish to do so. In addition, the committee emphasised treatment with ULT is highly likely to be cost effective and improve people’s quality of life with gout.

### 1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.3.

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# 1 Appendices

## 2 Appendix A – Review protocol

3 Review protocol for which patients should be selected for urate-lowering therapy

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42021249992 |
| 1. | Review title | Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase? |
| 2. | Review question | Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase? |
| 3. | Objective | To determine which patient risk factors predict worse outcome in terms of quality of life or frequency of flares to inform who should be offered ULT |
| 4. | Searches | The following databases (from inception) will be searched:<br>• Embase<br>• MEDLINE<br><br>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details)<br><br>Searches will be restricted by:<br>• English language studies<br>• Human studies<br><br>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.<br><br>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<br><br>Strata: None<br><br>Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout |

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|---|---|---|
| 7. | Intervention/Exposure/Test | Patient risk factors:<br>• Flare frequency<br>• Presence of tophi<br>• Chronic gouty arthritis<br>• Presence of any joint damage<br>• Renal impairment (eGFR less than 60 ml/min)<br>• A history of urinary stones<br>• Diuretic use<br>• Young age of onset of primary gout<br>• or a combination of the above |
| 8. | Comparator/Reference standard/Confounding factors | Confounding factors that may be independently associated with prognostic variable:<br>• Age<br>• Gender<br>Multivariate studies need to have adjusted for both of these prognostic variables. |
| 9. | Types of study to be included | • Prospective and retrospective cohort studies if all the key confounders have been accounted for in a multivariate analysis.<br>• |
| 10. | Other exclusion criteria | • Non-English language studies.<br>• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.<br>• Studies that do not adjust for the above confounding factors.<br>• Studies with fewer than 10 participants per confounder |
| 11. | Context | It is unknown whether all patients should receive ULT or not. To find out who will benefit most from ULT we need to establish which risk factors predict poor outcomes for the most important long-term patient outcomes, which was identified by the GC as quality of life and frequency of flares. |
| 12. | Primary outcomes (critical outcomes) | All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• Frequency of flares<br>• 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 |
| 13. | Secondary outcomes (important outcomes) | None |
| 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.<br><br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).<br><br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br><br>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.<br><br>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. The appropriate checklist for this review is Quality in Prognostic Studies (QUIPS) tool |
| 16. | Strategy for data synthesis | • Pairwise meta-analyses will be conducted if the studies significantly match the protocol and adjust for relevant confounders, otherwise each study will be analysed separately. If used, 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.<br><br>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. |

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| | | • A modified GRADEpro will be used to assess the quality of evidence for each risk factors, 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.<br>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/<br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. |
| 17. | Analysis of sub-groups | Subgroups that will be investigated if heterogeneity is present:<br>• None. |
| 18. | Type and method of review | ☐ Intervention<br>☐ Diagnostic<br>☒ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) |
| 19. | Language | English |
| 20. | Country | England |
| 21. | Anticipated or actual start date | 4th December 2020 |
| 22. | Anticipated completion date | 13th June 2022 |
| 23. | Stage of review at time of this submission | Review stage / Started / Completed<br>Preliminary searches: ☑ / ☑<br>Piloting of the study selection process: ☐ / ☐<br>Formal screening of search results against eligibility criteria: ☐ / ☐<br>Data extraction: ☐ / ☐ |

| | | | | |
|---|---|---|---|---|
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>managementofgout@nice.org.uk<br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>Gill Ritchie [Guideline lead]<br>Julie Neilson [Senior systematic reviewer]<br>Audrius Stonkus [Systematic reviewer]<br>Alexandra Bonnon [Health economist]<br>Amber Hernaman [Project manager]<br>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 | N/A | | |
| 30. | Reference/URL for published protocol | N/A | | |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: | | |

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|---|---|---|---|
| | | • notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. | |
| 32. | Keywords | | |
| 33. | Details of existing review of same topic by same authors | N/A | |
| 34. | Current review status | ☒ | Ongoing |
| | | ☒ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 35.. | Additional information | None | |
| 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.<br>• 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).<br>• 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.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• 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.<br>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).[23]<br><br>**Inclusion and exclusion criteria**<br>• 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.<br>• 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.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>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.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). |

| | |
|---|---|
| | • OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• 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'.<br>• Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• 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

- Which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[23]

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 one or more of the following approaches:

- Population AND Study filter(s)

**Table 9: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 06 July 2021 | Observational studies<br>Prognostic studies<br><br>Exclusions (animal studies, letters, comments) |
| Embase (OVID) | 1974 – 06 July 2021 | Observational studies<br>Prognostic studies<br><br>Exclusions (animal studies, letters, comments) |

**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. | Epidemiologic studies/ |
| 28. | Observational study/ |
| 29. | exp Cohort studies/ |
| 30. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 31. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 32. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 33. | Controlled Before-After Studies/ |
| 34. | Historically Controlled Study/ |
| 35. | Interrupted Time Series Analysis/ |
| 36. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 37. | exp case control studies/ |
| 38. | case control*.ti,ab. |
| 39. | Cross-sectional studies/ |
| 40. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 41. | or/27-40 |
| 42. | predict.ti. |
| 43. | (validat* or rule*).ti,ab. |
| 44. | (predict* and (outcome* or risk* or model*)).ti,ab. |
| 45. | ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. |
| 46. | decision*.ti,ab. and Logistic models/ |
| 47. | (decision* and (model* or clinical*)).ti,ab. |
| 48. | (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. |
| 49. | (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab. |
| 50. | ROC curve/ |
| 51. | or/42-50 |
| 52. | 26 and (41 or 51) |

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. | Clinical study/ |
| 26. | Observational study/ |
| 27. | family study/ |
| 28. | longitudinal study/ |
| 29. | retrospective study/ |
| 30. | prospective study/ |
| 31. | cohort analysis/ |
| 32. | follow-up/ |
| 33. | cohort*.ti,ab. |
| 34. | 32 and 33 |
| 35. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 36. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 37. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 38. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 39. | exp case control study/ |
| 40. | case control*.ti,ab. |
| 41. | cross-sectional study/ |
| 42. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 43. | or/25-31,34-42 |
| 44. | predict.ti. |
| 45. | (validat* or rule*).ti,ab. |
| 46. | (predict* and (outcome* or risk* or model*)).ti,ab. |
| 47. | ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. |

| | |
|---|---|
| 48. | decision*.ti,ab. and Statistical model/ |
| 49. | (decision* and (model* or clinical*)).ti,ab. |
| 50. | (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. |
| 51. | (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab. |
| 52. | Receiver operating characteristic/ |
| 53. | or/44-52 |
| 54. | 24 and (43 or 53) |

# 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 10: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | Health Economics<br>1 January 2014 – 14 June 2021<br>Quality of Life<br>1946 – 14 June 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments) |
| Embase | Health Economics<br>1 January 2014 – 14 June 2021<br>Quality of Life<br>1974 – 14 June 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments) |
| Centre for Research and Dissemination (CRD) | HTA - Inception – 31 March 2018<br>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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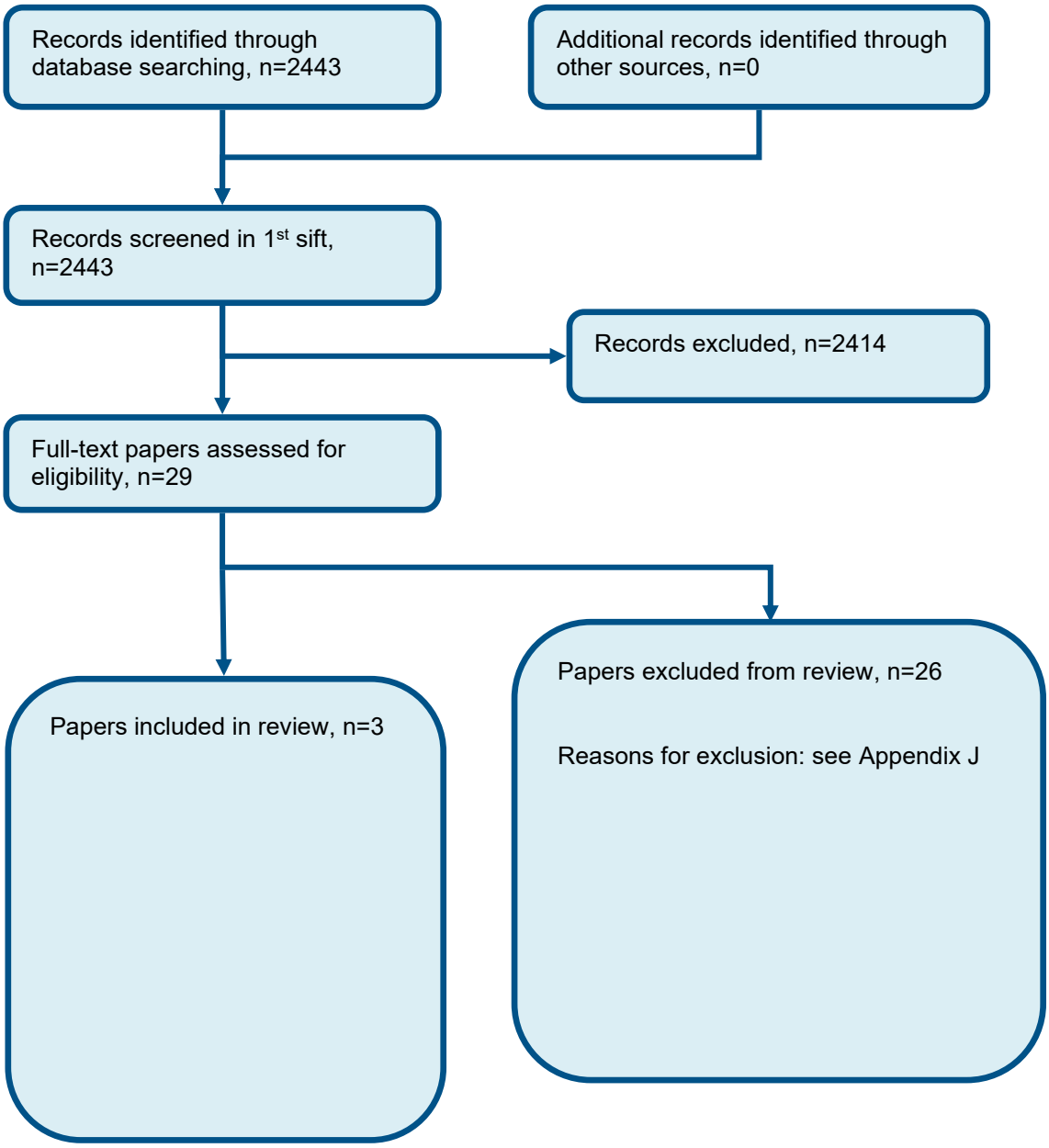
# Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of which people with gout should be offered a urate-lowering therapy such as a xanthine oxidase inhibitor, a uricosuric or a uricase?



# Appendix D – Effectiveness evidence

| **Study** | Rashid 2015[27] |
|---|---|
| Study type | Retrospective cohort study |
| Number of studies (number of participants) | 1 (n=8828) |
| Countries and setting | Conducted in USA; Setting: 14 hospitals, 202 outpatient facilities, and a centralized laboratory |
| Line of therapy | Not applicable |
| Duration of study | January 1, 2007–December 31, 2010: 4 years |
| Method of assessment of guideline condition | Eligible patients were required to have two outpatient gout diagnoses [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 274.xx] ≥30 days apart or one inpatient gout diagnosis code in any position anytime during the study time period. |
| Stratum | Not applicable |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Patients were included if they received a prescription for a ULT (allopurinol, febuxostat, or probenecid) during the study time period; the index date was defined as the patient's first ULT prescription identified during the study time period. Patients had to be ≥18 years of age at time of index date and were required to have at least 12 months of KPSC membership eligibility including drug benefits prior to their index date, index date, and 12 months post-index |
| Exclusion criteria | Patients were excluded if they had history of human immunodeficiency virus (HIV), a diagnosis code for chronic kidney disease (CKD) stage 5 or an estimated glomerular filtration rate (GFR) <15 ml/min/1.73 m2, history of dialysis, active cancer, current chemotherapy, or kidney stones/nephrolithiasis |
| Recruitment/selection of patients | Consecutive |

| | |
|---|---|
| Age, gender and ethnicity | Age: 1-2 flares group: <55 years old – 41%; 55-64 years old – 28.5%; ≥65 years old – 35.5%<br>≥3 flares group: <55 years old – 30.5%; 55-64 years old – 22.2%; ≥65 years old – 47.3.<br>no gout flares group: <55 years old – 34.2%; 55-64 years old – 28.4%; ≥65 years old – 37.2%<br><br>Ethnicity: 1-2 flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific Islander 23.4 %, Other 0.5%<br><br>≥3 flares group, Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5%<br><br>no gout flares group: Caucasian 42.7%, African-American 14.1%, Hispanic 19.3%, Asian/Pacific islander 23.4 %, Other 0.5% |
| Further population details | Previous treatment: At baseline - 1-2 flares group: NSAIDS 66.7%, Corticosteroids 30.1%, colchicine 52%, antihypertensives 71.8%, diuretics 48.5%, anti-hyperlipidemics45.5%, anti-diabetics 16.7%.<br><br>≥3 flares group: NSAIDS 67.1%, Corticosteroids 47.7%, colchicine 64.2%, antihypertensives 76.3%, diuretics 55.1%, anti-hyperlipidemics 46.5%, anti-diabetics 19.3%<br><br>no gout flares group: NSAIDS 54.3%, Corticosteroids 16.2%, colchicine 33%, antihypertensives 74.8%, diuretics 47.6%, anti-hyperlipidemics 49.8%, anti-diabetics 19.9% |
| Indirectness of population | No indirectness |
| Interventions | (n=4377) Intervention 1: Diuretics use. Duration 12 months. Concurrent medication/care N/A<br><br>Indirectness: No indirectness<br><br>(n=4451) Intervention 2: No diuretics. Duration 12 months. Concurrent medication/care N/A |
| Funding | This study was supported by a research grant provided by Savient Pharmaceuticals, Inc. All authors do not have any other financial interests or potential conflict of interest with regards to the work. |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use | |

| | |
|---|---|
| Protocol outcome 1: frequency of flares<br>- Actual outcome: 1-2 flares at 12 months post index; Group 1: 4798/8828, Group 2: 2780/8828; Adjusted OR 1.19 (1.05 to 1.35); Comments: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30);<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 2: frequency of flares<br>- Actual outcome: ≥3 flares at 12 months post index; Group 1: 1250/8828, Group 2: 2780/8828; Adjusted OR 1.233 (1.01 to 1.50); Comments: multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m2:15-19, 20-24, 25-29, ≥30);<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Health-related quality of life at short (up to two weeks); Health-related quality of life |

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| | |
|---|---|
| **Study** | Rothenbacher 2011[28] |
| Study type | Cohort study |
| Number of studies (number of participants) | 1 (n=23857) |
| Countries and setting | Conducted in UK; Setting: primary care |
| Line of therapy | Not applicable |
| Duration of study | January 1, 2000–December 31, 2008: 9 years |
| Method of assessment of guideline condition | Unclear, not stated |

| | |
|---|---|
| Stratum | Not applicable |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Cohort population with a first-ever diagnosis of gout recorded in the database using READ codes from January 2000 to December 2007 and who were between 20 and 89 years of age. |
| Exclusion criteria | Subjects with any prescription of anti-gout treatment or any code suggesting gout before the start date were subsequently excluded from the cohort and considered as prevalent patients. All patients with cancer before the start date were also excluded. |
| Recruitment/selection of patients | Consecutive |
| Age, gender and ethnicity | Age – mean (SD): 61.9 (14.5). Gender (M:F): 17358:6499. Ethnicity: not reported |
| Further population details | Previous treatment: no previous treatment |
| Indirectness of population | No indirectness |
| Interventions | (n=880) Intervention 1: Renal impairment – history of chronic kidney failure. Duration 8 years. Concurrent medication/care. Indirectness: No indirectness<br><br>(n=22977) Intervention 2: Renal impairment – no history of chronic kidney failure. Duration 8 years. Concurrent medication/care: overall Allopurinol 3815 (16%), Colchicine 3245 (13.6%). Indirectness: No indirectness |
| Funding | The study was sponsored by Novartis Pharma AG |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use | |

| | |
|---|---|
| Protocol outcome 1: frequency of flares<br>- Actual outcome: 1 or more flares over 3.8 years of observation period; Group 1: 8806/23857, Group 2: 15051/23857; HR (95% CI)1.33 (1.20, 1.48). Comments:<br><br>Multivariable analysis, confounders studied: sex; age (20-49, 50-59, 60-69, 70-79, 80-89 years);number of GP visits (0-4, 5-9, 10-19, >20 visits); smoking (non-smoker, smoker, former); alcohol consumption (none, 1-9, 10-24, 25-42, >42 U/week); BMI (categories in kg/m 2:15-19, 20-24, 25-29, ≥30);<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Health-related quality of life at short (up to two weeks); Health-related quality of life |

1

2

| **Study** | **Scire 2013[29]** |
|---|---|
| Study type | Retrospective cohort study |
| Number of studies (number of participants) | 1 (n=446) |
| Countries and setting | Conducted in Italy; Setting: rheumatology clinics |
| Line of therapy | Not applicable |
| Duration of study | June 2011 and January 2012: 6 months |
| Method of assessment of guideline condition | Unclear, gout diagnosis confirmed by rheumatologists |
| Stratum | Not applicable |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Clinical diagnosis of gout |

| | |
|---|---|
| Exclusion criteria | Patients without gout |
| Recruitment/selection of patients | Consecutive |
| Age, gender and ethnicity | Age – mean (SD): 63.9 (11.6). Gender (M:F): 403:446. Ethnicity: not reported |
| Further population details | Previous treatment: overall at baseline: corticosteroids 125 (28%), NSAIDs or colchicine 189 (42.4%), Allopurinol 303 (67.9%), Febuxostat 60 (13.4%) |
| Indirectness of population | No indirectness |
| Interventions | (n=87) Intervention 1: Presence of tophi. Duration 6 months. Concurrent medication/care unclear not stated<br>Indirectness: No indirectness<br><br>(n=359) Comparison 1: No presence of tophi. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness<br><br>(n=unclear) Intervention2: Presence of any joint damage – swollen joints. Duration 6 months. Concurrent medication/care: unclear not stated Indirectness: No indirectness<br><br>n=unclear) Comparison 2: Presence of any joint damage – no swollen joints. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness<br><br>(n=unclear) Intervention 3: Presence of any joint damage – tender joints. Duration 6 months. Concurrent medication/care: unclear not stated Indirectness: No indirectness<br><br>n=unclear) Comparison 3: Presence of any joint damage – no tender joints. Duration 6 months. Concurrent medication/care: unclear not stated. Indirectness: No indirectness |
| Funding | Not stated |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Diuretics use versus no diuretics use<br><br>Protocol outcome 1: 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:<br><br>- Actual outcome: SF36 physical component; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted MD -3.20 (-5.41, -0.99); number of swollen joints: adjusted MD -0.54 (-0.79, -0.29); number of tender joints: adjusted MD -0.39 (-0.55 to 0.23) Comments: N/A<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 2: 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<br><br>- Actual outcome: SF36 mental component; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted MD 1.26 (-0.88, 3.40); number of swollen joints: -0.2 (-0.45 to 0.04); number of tender joints: adjusted MD -0.24 (-0.39 to 0.09). Comments: N/A<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 3: 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<br><br>- Actual outcome: HAQ-DI; Group 1: unclear/446, Group 2: unclear/446; presence of tophi: adjusted OR 1.92 (1.07 to 3.45); number of swollen joints: adjusted OR 1.23 (1.13 to 1.34); number of tender joints: adjusted OR 1.10 (1.06 to 1.14). Comments: N/A<br><br>Risk of bias: All domain - Low, Selection - Low, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Frequency of flares |

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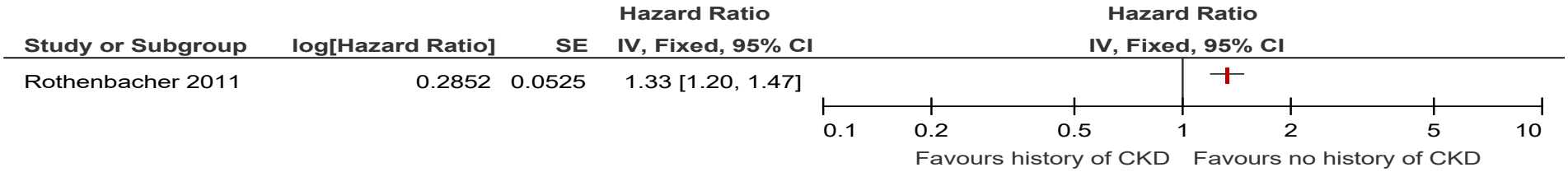
# Appendix E – Forest plots

## E.1 Renal impairment - history of chronic renal failure

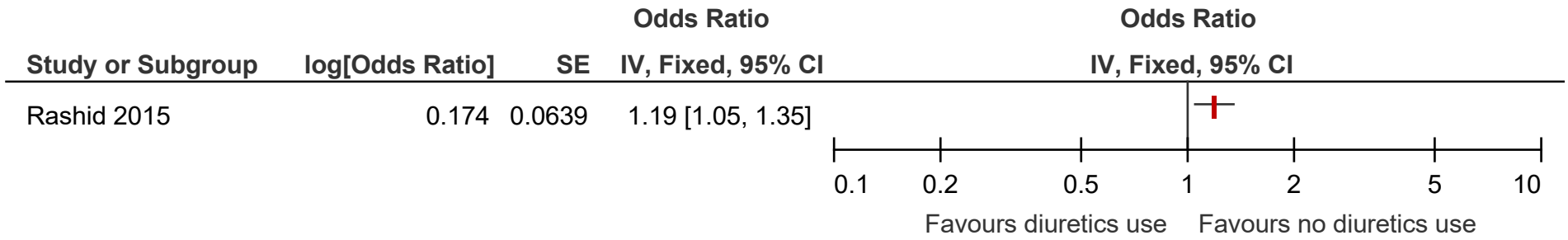
**Figure 2: Frequency of flares (1 or more flares)[a]**




[a] Hazard ratio was adjusted for sex, age (at start date of follow-up), GP visits (1 year before first-ever diagnosis of gout), smoking, alcohol, BMI, IHD, hypertension, hyperlipidaemia, renal failure and diabetes (anytime before first-ever diagnosis of gout).

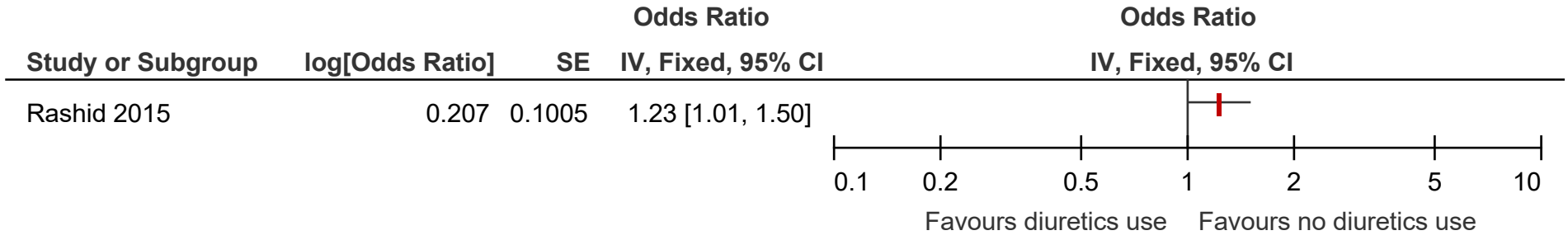
# E.21 Diuretics use

**Figure 3: Frequency of flares (1-2 flares)[a]**



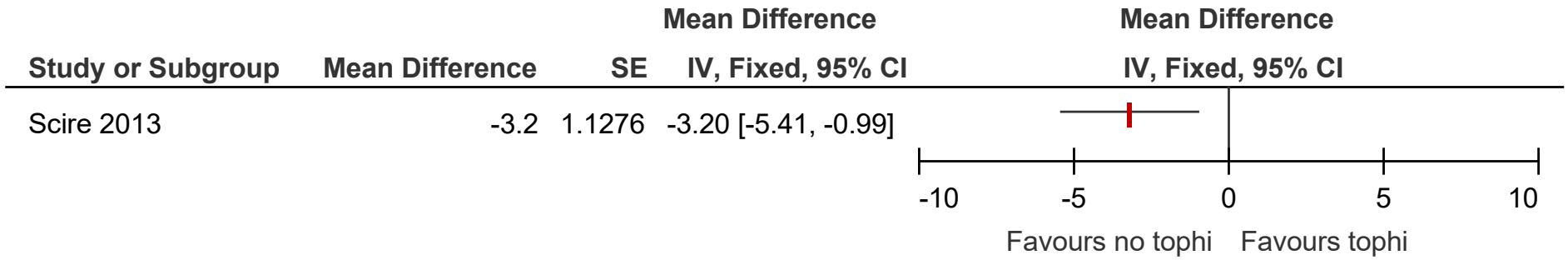

[a] Confounders adjusted for: sex, age, race, sUA levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber

**Figure 4: Frequency of flares (≥3 flares)**



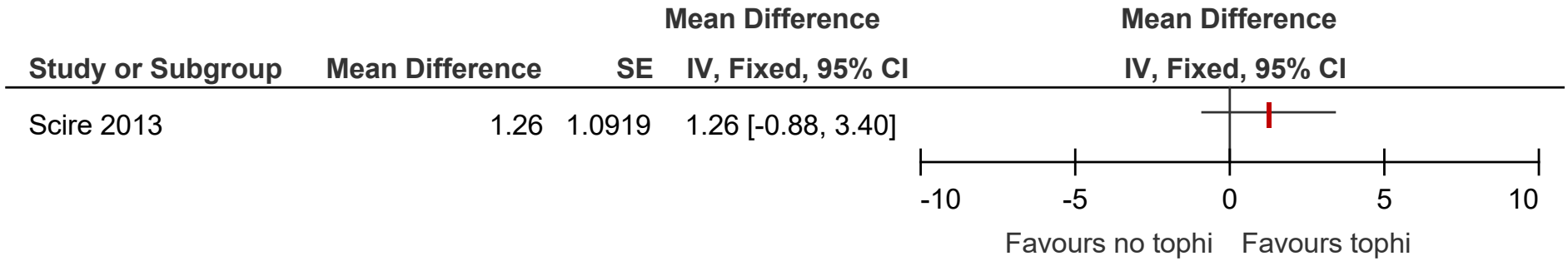

[a] Confounders adjusted for: sex, age, race, sUA levels, comorbidities, anti-inflammatory medications, diuretic use, and rheumatologist as a prescriber

**Figure 5: SF 36 physical component**



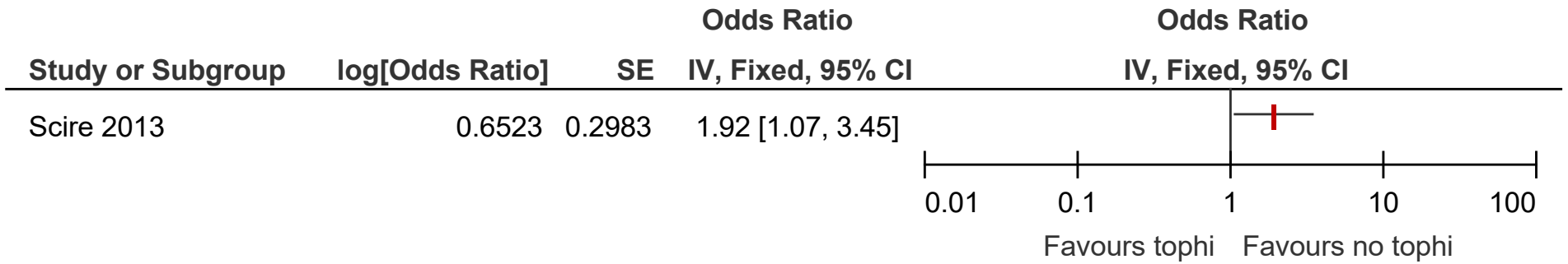

[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

**Figure 6: SF 36 mental component**




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

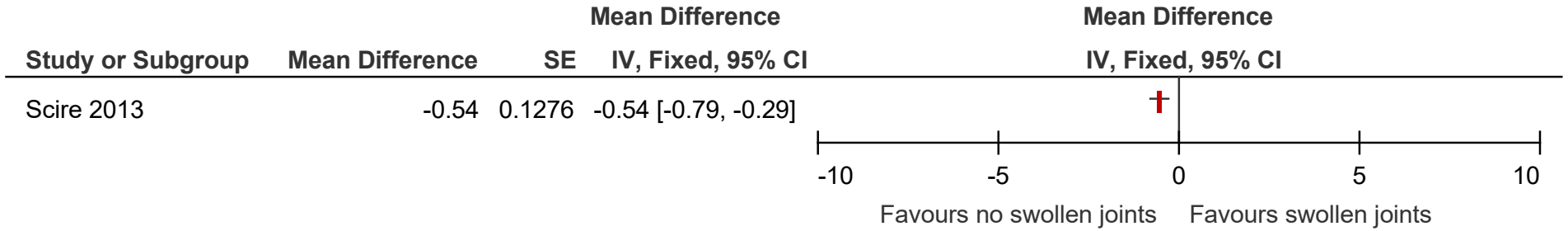
**Figure 7: HAQ-DI**




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

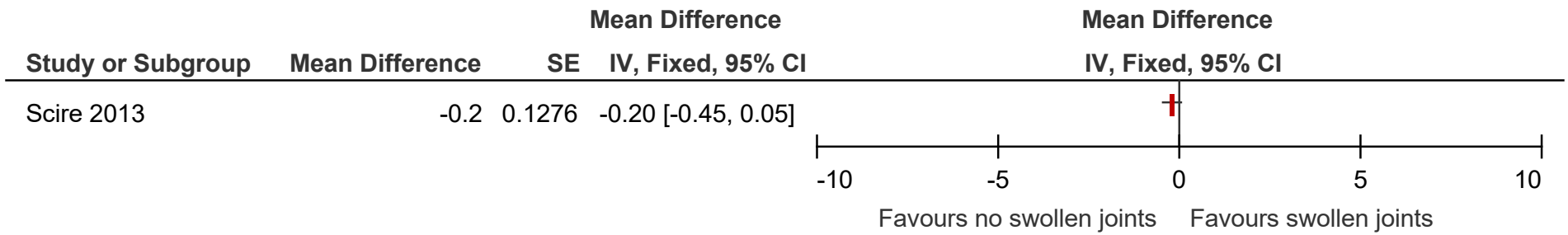
## E.3 Presence of any joint damage – number of swollen joints

**Figure 8: SF 36 physical component**



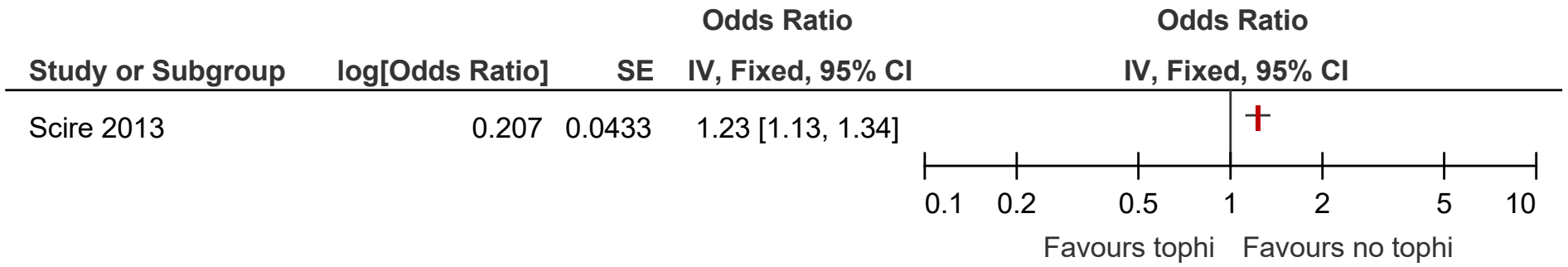

[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

**Figure 9: SF 36 mental component**




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

**Figure 10: HAQ-DI**

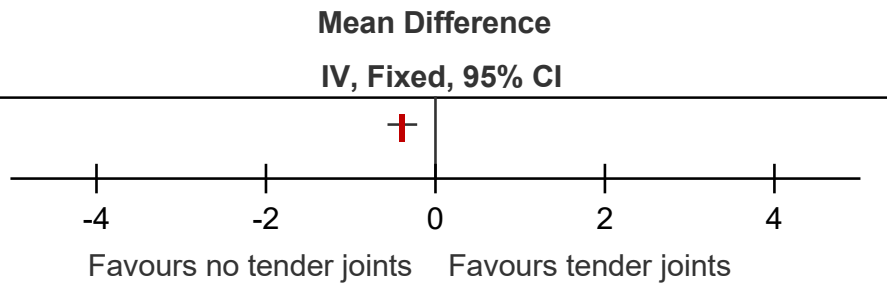



[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

# E.4 Presence of any joint damage – number of tender joints

**Figure 11: SF 36 physical component**

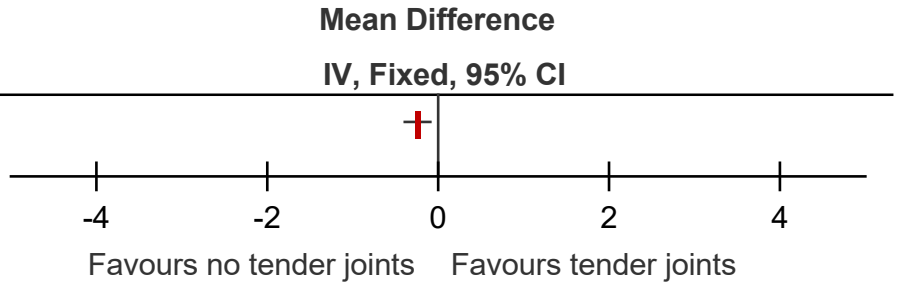
| Study or Subgroup | Mean Difference | SE | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|
| Scire 2013 | -0.39 | 0.0816 | -0.39 [-0.55, -0.23] |




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

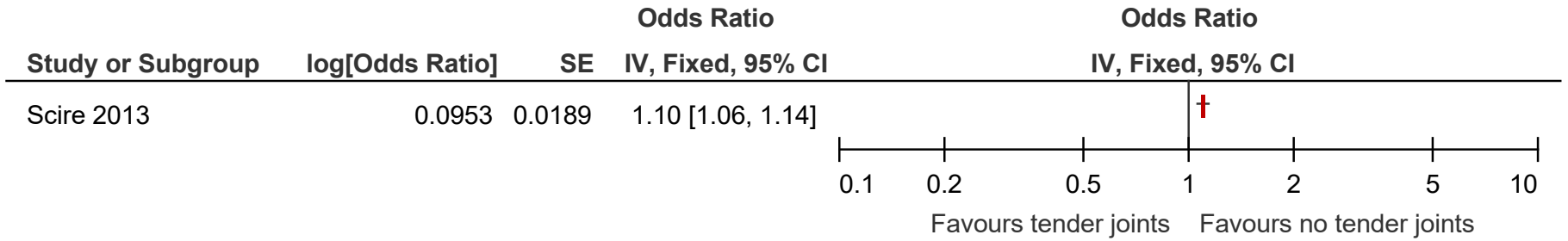
**Figure 12: SF 36 mental component**

| Study or Subgroup | Mean Difference | SE | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|
| Scire 2013 | -0.24 | 0.0765 | -0.24 [-0.39, -0.09] |




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

**Figure 13: HAQ-DI**




[a] Adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

# Appendix F – GRADE tables

**Table 11: Clinical evidence profile: history of renal impairment versus no history of renal impairment**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Renal impairment - history of renal failure | no history of renal failure | Relative (95% CI) | Absolute (95% CI) | | |
| **Frequency of flares (1 or more flares)** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | - | - | **HR 1.33** (1.20 to 1.47) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |

[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.

[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

## Table 12: Clinical evidence profile: diuretics use versus no diuretics use

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | diuretics use | no diuretic use | Relative (95% CI) | Absolute (95% CI) | | |
| **1-2 flares** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | - | - | **OR 1.19** (1.05 to 1.35) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **>=3 flares** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | - | - | **OR 1.23** (1.01 to 1.50) | **1 fewer per 1,000** (from 2 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |

**[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for sex, age, race, sUA levels, comorbidities, anti-inflmmatory medications, diuretic use, and rheumatologist as a prescriber.**

**[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.**

## Table 13: Clinical evidence profile: presence of tophi versus no presence of tophi

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Presence of tophi | no presence of tophi | Relative (95% CI) | Absolute (95% CI) | | |
| **SF36 physical component** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | - | - | - | MD **3.2 lower** (5.41 lower to 0.99 lower) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **SF36 mental component** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Presence of tophi | no presence of tophi | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | observational studies | not serious[1] | not serious | not serious | serious[2] | none | - | - | - | MD **1.26 higher** (0.88 lower to 3.4 higher) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **HAQ-DI** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | - | - | **OR 1.92** (1.07 to 3.45) | **2 fewer per 1,000** (from 3 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |

**[1]. Risk of bias was assessed using QUIPS checklist. The position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line then no serious imprecision was recorded. If the 95% CI crossed the null line then serious imprecision was recorded. Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment.**

[2] Clinical benefit assessed using established MIDs for SF-36 physical/mental- 3.75; GAQ - 6.5; GIS: gout concern overall – 7.2, GIS: unmet gout treatment need – 6.9, GIS: gout well-being during attack – 5.2 and GIS: gout concern during attack – 7.6; SF-6D – 0.041; MOS 20 – 20% change in scores; AIMS – 20% change in scores, HAQ-DI – 0.22; GRADE default MIDs used for all other outcomes.

## Table 14: Clinical evidence profile: swollen joints versus no swollen joints

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Presence of any joint damage - number of swollen joints | no swollen joints | Relative (95% CI) | Absolute (95% CI) | | |
| **SF36 physical component** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | not serious | none | 0 | 0 | - | MD **0.54 lower** (0.79 lower to 0.29 lower) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **SF36 mental component** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | serious[2] | none | 0 | 0 | - | MD **0.2 lower** (0.45 lower to 0.05 higher) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **HAQ-DI** | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | not serious | none | -/0 | -/0 | **OR 1.23** (1.13 to 1.34) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |

1 Method: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

2. Downgraded by 1 increment because the confidence interval crossed the null line

## Table 15: Clinical evidence profile: tender joints versus no tender joints

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Presence of any joint damage - number of tender joints | no tender joints | Relative (95% CI) | Absolute (95% CI) | | |
| **SF36 physical component** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Presence of any joint damage - number of tender joints | no tender joints | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | 0 | 0 | - | MD **0.39 lower** (0.55 lower to 0.23 lower) | ⨁⨁⨁⨁ HIGH | CRITICAL |
| **SF36 mental component** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | 0 | 0 | - | MD **0.24 lower** (0.39 lower to 0.09 lower) | ⨁⨁⨁ HIGH | CRITICAL |
| **HAQ-DI** | | | | | | | | | | | | |
| 1 | observational studies | not serious[1] | not serious | not serious | not serious | none | -/0 | -/0 | **OR 1.10** (1.06 to 1.14) | **1 fewer per 1,000** (from 1 fewer to 1 fewer) | ⨁⨁⨁⨁ HIGH | CRITICAL |

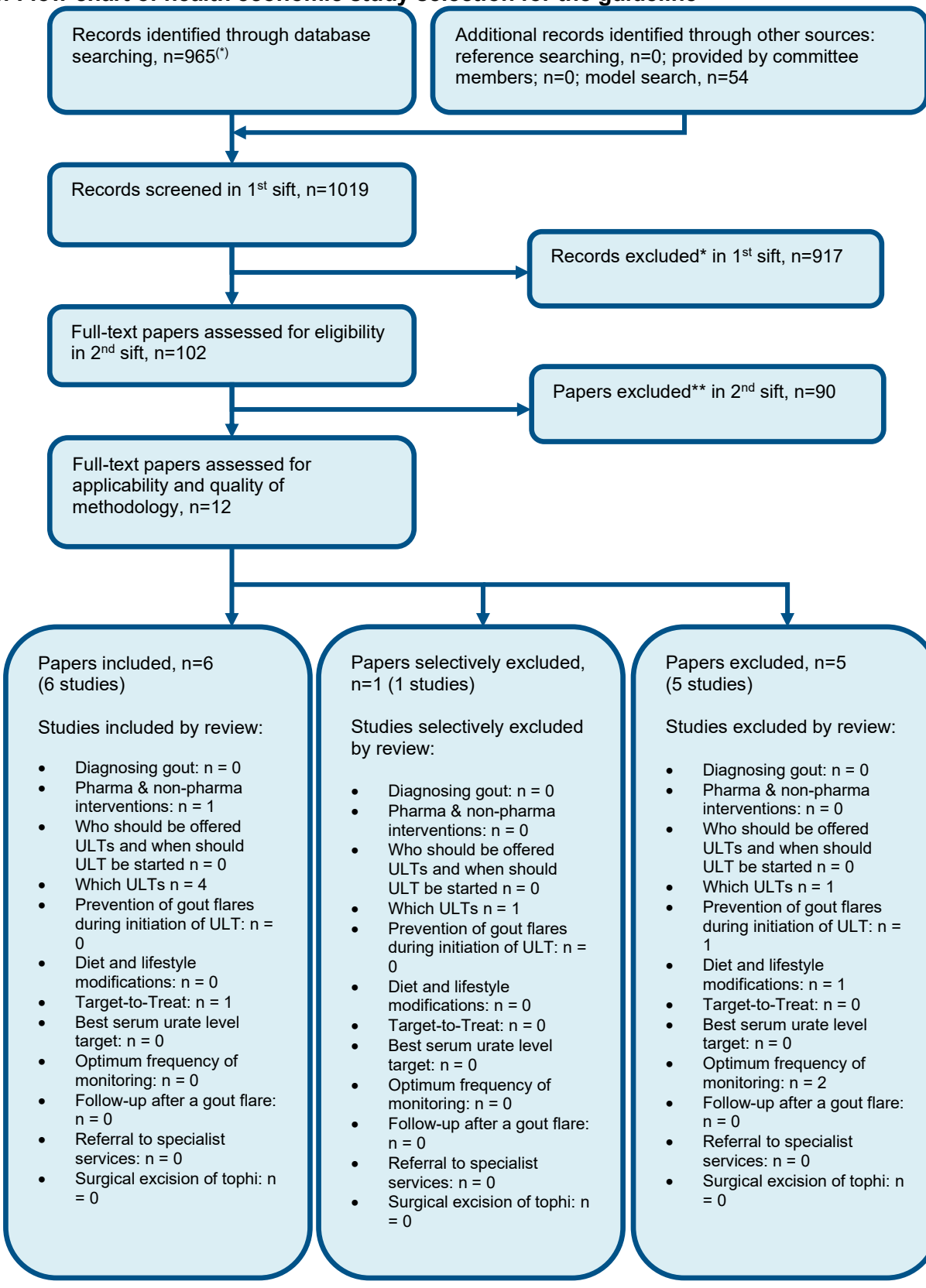
1 1 Methods: multivariable analysis adjusted for age, gender, comorbidities, BMI, high alcohol consumption, education and employment

2

3

# 1 Appendix G – Economic evidence study selection

**Figure 14: 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 16: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Abhishek 2016[2] | Incorrect study design - case-control study, cases comprised participants with >2 gout flares, controls <=2 gout flares, binary logistic regression |
| Abhishek 2017[1] | Incorrect study design - cross sectional study, bivariate logistic regression (adjusted for missing data), outcome - self-reported trigger of gout attacks |
| Alvarez-Nemegyei 2005[4] | Incorrect study design - cohort nested case-control study, patients with disability were compared to patients without disability |
| Avarado-de laBarrera 2020[3] | incorrect comparison - study aimed to determine the proportion of patients achieving SU target level of <6 for patients with non-severe gout and <5 mg/dL for patients with severe gout, as well as patients achieving remission after 5 years of follow-up, no multivariate analysis |
| Chandratre 2018[6] | Linear regression, to examine gout-related, comorbid and socio demographic characteristics associated with generic and disease specific HRQOL in gout, no multivariate analysis |
| Changchien 2015[7] | Incorrect comparison - primary endpoint was diagnosis of depressive disorders during follow-up in people with gout versus people without gout |
| Chapron 2019[8] | Incorrect study design/incorrect comparison - descriptive study of non-pharmacological management of gout. Secondary objective was to identify non-pharmacological management compliance among patients |
| Dalbeth 2013[9] | Incorrect comparison/analysis - factors independently associated with presence and number of tophi were analysed |
| Dalbeth 2018[10] | Incorrect comparison/analysis - dual energy CT assessed crystal deposition assessed crystal deposition in patients with gout treated with stable dose of allopurinol and investigated potential clinical determinants for crystal deposition. No multivariate analysis |
| Edwards 2011[11] | Incorrect comparison/analysis, the objective of this study was to assess how gout flares affect these activities in patients with chronic gout refractory to conventional therapy. No multivariate analysis. Nonrelevant outcomes |
| Fu 2017[13] | Incorrect study design - case-control study, survey was administered to gout patients and controls of gender-matched healthy individuals, study aimed to analyse prevalence of depression |

| Study | Exclusion reason |
|---|---|
| Fu 2018[12] | Incorrect study design - case-control study, study analysed risk factors for depression and anxiety in gout patients |
| Khanna 2011[18] | Incorrect comparison/analysis - before and after study, SF36 at baseline and SF36 at follow-up |
| Khanna 2012[17] | Incorrect comparison/analysis - association between QoL measures and frequency of gout flares, no multivariate analysis |
| Khanna 2015[19] | Incorrect comparison/analysis - mean scores of SF-12, for all patients and by gout status, no multivariate analysis |
| Khanna 2016[16] | Incorrect study design - cross-sectional study, no multivariate analysis |
| Mak 2009[20] | No relevant outcomes |
| Mitnala 2016[21] | Incorrect comparison/analysis - case-control study examined the clinical and genetic features of diuretic-associated gout, logistic regression of diuretic status with SLC2A9 , ABCG2 and SLC22A11 risk alleles |
| Pascart 2019[24] | Incorrect analysis/incorrect comparisons - study analysed variables associated with early onset group vs common gout group |
| Prior 2016[25] | Incorrect comparison/analysis/ no relevant outcomes - study aimed to determine the prevalence of depression and anxiety in gout, association between anxiety and depression and gout characteristics |
| Proudman 2019[26] | Incorrect comparison/analysis - prevalence study, no multivariate analysis |
| So 2011[30] | Incorrect analysis - multivariate analysis not adjusted for age and sex |
| Stewart 2018[33] | Incorrect analysis - stepwise linear regression |
| Taylor 2008[34] | Incorrect comparison/analysis - Rasch analysis was used to determine the internal validity of summated scores as a measure of physical disability, no multivariate analysis |
| Youssef 1995[35] | Incorrect population - included 42% patients without gout, no multivariate analysis |
| Zhang 2016[36] | Incorrect analysis - linear regression model for flare frequency and cumulative number of involved joints was used, factors analysed were onset age, duration and sUA, no multivariate analysis |

## Health Economic studies

**None.**