

Evidence-based Practice Center Systematic Review Protocol

Project Title: Management of Gout

I. Background and Objectives for the Systematic Review

Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis) that may progress to a chronic intermittent condition, further to the development of tophi (solid deposits of monosodium urate [MSU] crystals in joints, cartilage, and bones), a condition called chronic tophaceous gout.

Based on data from the 2007-2008 National Health and Nutrition Examination Survey (NHANES), the prevalence of gout among adults in the United States was estimated to be 3.9 percent (8.3 million individuals), ranging from 2.0 percent in women to 5.9 percent in men.¹ Comparing the most recent figures for the prevalence of gout to those of previous cycles of NHANES shows that the prevalence of gout appears to be increasing. The rise in the prevalence of gout has paralleled the increase in prevalence of conditions associated with hyperuricemia, including obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, type 2 diabetes and metabolic syndrome, chronic kidney disease, and renal insufficiency. Certain medications also may increase the risk for developing gout (e.g., thiazide diuretics).

A 2013 study of ambulatory care costs associated with gout estimated the costs to be \$933 million (in 2008 figures) or nearly \$1 billion. Of this figure, 32 percent of the costs were attributed to office visits for acute flares, and 61 percent were attributed to expenditures for prescription medications to treat the condition.²

Etiology of Gout. The precipitating factor in a first acute episode of gout is usually hyperuricemia (defined as a serum uric acid (sUA) concentration greater than 6.8 mg per deciliter [dl] in men and greater than 6.0 in women). Hyperuricemia can be the result of either inadequate renal excretion of UA or, less commonly, UA overproduction (UA is a breakdown product of dietary or endogenous purines, which are among the building blocks of nucleic acids) and is associated with the formation and deposition of the UA crystals, usually in a single joint but sometimes may also involve multiple joints. However, for reasons that remain unclear, only a small proportion of individuals with hyperuricemia go on to develop gout; in the rest, hyperuricemia remains asymptomatic.³ The prevalence of hyperuricemia ranges from 21.2 percent in men to 21.6 percent in women, four- to ten-fold higher than the prevalence of gout.

The causes of gout are unclear but appear to be multifactorial: a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout flares.⁴ Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout flares.

Diagnosis of Gout. There are a number of methods proposed to establish the diagnosis of gout. The evidence about method for the diagnosis of gout is the subject of a separate systematic review.⁵

Clinical Presentation and Management. Gout encompasses both acute and chronic phases.

Acute Gouty Arthritis. The acute phase is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but also potentially involving other joints.

A number of pharmacologic agents have been advocated for use in the management of acute gout. Commonly advocated agents to treat acute gout include non-steroidal anti-inflammatories (NSAIDs), colchicine (the microtubule disrupting agent), and/or corticosteroids (intra-articular or systemic) to manage pain and inflammation.

Urate lowering therapy (ULT) has also been advocated in the management of acute gout for patients who are already under treatment with NSAIDs, colchicine, or steroids.

Chronic Gout. Although initial episodes may be brief and rare, acute episodes if untreated, under-treated or improperly treated, may increase in frequency and duration and lead to the development of chronic gout. Chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may deposit in joints, cartilage, bone, and auricular and cutaneous tissues.³ The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years. Untreated or undertreated gout can also be associated with uric acid nephrolithiasis, chronic interstitial **nephropathy caused by MSU deposition in the renal medulla, and in rare instances,** kidney failure. In addition, gout has also been associated with an increased risk for myocardial infarction, heart failure, and stroke.⁶

Advocated non-pharmacologic methods for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, smoking cessation, hydration, and dietary changes. The evidence for the efficacy of specific dietary changes in managing gout (preventing flares) is a topic of this review.

Pharmacologic management of chronic gout has been proposed to consist of ULT agents to decrease sUA levels. These agents include xanthine oxidase inhibitors (XOIs- allopurinol and febuxostat) to reduce sUA production; uricosurics probenecid, which prevents renal reabsorption of uric acid (and increases urine UA excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in combination. Pegloticase will not be included in this review because it would not be prescribed in a primary care setting (see below). Several interleukin-1 β -inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis and in Phase II and III trials for treatment of gout including anakinra, canakinumab, and rilonacept,⁷⁻⁹ will also not be included in this systematic review, because they are not prescribed in the primary care setting.

Table 1 lists the drugs used to treat gout and notes the ones covered in this systematic review.

Table 1. Pharmacologic agents used in the treatment of gout

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatories*		
	NSAIDS (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids	Numerous
	Colchicine/Colcrys	URL Pharma
	IL-1B Receptor Antagonists:**	
	Anakinra/kineret	Sobi
	Canakinumab/Ilaris	Novartis
	Rilonacept/Arcalyst	Regeneron
Uricosurics		
	Probenecid/Benemid	Multiple
Xanthine Oxidase Inhibitors		
	Allopurinol/Zyloprim	Prometheus Labs
	Febuxostat/Uloric	Teijin Pharma Ltd., Takeda
Uricase		
	Pegloticase/Krystexxa**	Savient Pharmaceuticals
Combination agents		
	Colchicine-probenecid/Proben-C	Merck
Table notes: *NSAIDS and corticosteroids will be considered only for their use in treating inflammation associated with gout; **these agents will not be considered in this review, because they are not prescribed in the primary care setting.		

Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; and calcium channel blockers (in patients being treated with these agents for other indications). These will not be included in this review.

Issues of Concern for Management of Gout in Primary Care Settings

The treatment of gout has spawned a proliferation of evidence-based guidelines,¹⁰⁻¹⁶ including a recently completed set of guidelines by the American College of Rheumatology (ACR) that considered both the treatment of acute gout and of hyperuricemia associated with chronic gout.^{13, 14}

However, the majority of individuals with gout are initially seen, diagnosed, and treated in primary care or emergent care settings and may continue to receive their care in these settings. Therefore primary care physicians (PCPs) and emergency physicians are well-positioned to diagnose early-stage gout and implement management strategies. It is well established that specialists systematically rate the benefits and harms of treatment more favorably than do generalists,¹⁷ and there have been some notable situations when guidelines on the same clinical topic developed by specialists or by generalists have had somewhat different recommendations.¹⁸ Therefore, a new guideline, developed by primary care practitioners and focused on primary care practice, is warranted. This review is intended to provide the evidence for such a guideline.

II. The Key Questions

The draft key questions underwent some revisions and were posted for public comment from 1/22/14 through 2/13/14. None of the key questions were initially revised in response to public comments; however, additional categories were added to the PICOTs (below) to ensure inclusion of particular subgroups and potential interventions. Revisions in response to discussion by the Technical Expert Panel (TEP) (including suggestions that some of the revisions in public comments be incorporated) are highlighted in bold.

Key Question 1: Acute Gout Treatment

- a. In patients with *acute* gout, what are the benefits and harms of different pharmacological therapies
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
- c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement **and time since start of flare**) and laboratory values (serum and/or urine UA levels)?

Key Question 2: Dietary and Lifestyle Management of Gout

- a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
- b. **Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?**

Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

- a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
- b. Does effectiveness and comparative effectiveness **of urate lowering therapy** differ according to **disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia**, or baseline demographic and co-morbid characteristics?
- c. **What is the effect of dietary modification in combination with pharmacologic therapy?**

Key Question 4: Treatment Monitoring of Patients with Gout

- a. In adults with gout, does monitoring serum uric acid levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes? b. Is achieving lower subsequent serum uric acid levels (less than 5 vs. 5–7 mg/dL) associated with decreased risk for recurrent

acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

- a. urate lowering therapy?
- b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

PICOTs

- Population(s)
 - Adults (≥ 18 years of age)
 - Subgroups
 - Male and female patients (KQ1-5)
 - Patients presenting with an acute episode (KQ1, 2, 5) and those with a history of gout (KQ1-5)
 - Patients with higher vs. lower serum UA (e.g., <5 vs. ≥ 5)
 - Patients who are HLA-B5801-positive (KQ1)
 - Older (≥ 65) vs. younger patients (KQ1-5)
 - Tophaceous and non-tophaceous gout patients (KQ1-5)
 - Patients with comorbidities, including hypertension, Type 2 diabetes, chronic kidney disease (renal insufficiency: CKD 1-4) (KQ1-5)
- Interventions
 - Dietary interventions (KQ2, 4)
 - Low purine diet
 - Fructose restriction, other carbohydrate restriction
 - Ethanol restriction
 - Sour cherry juice (proposed to be a XO1)
 - Dairy products and vegetables
 - Mediterranean diet
 - DASH diet
 - Other Lifestyle Measures (KQ2, 4)
 - Smoking cessation
 - Exercise
 - Hydration
 - Dietary supplements and other alternative treatments (KQ2, 4)
 - Vitamin C
 - Traditional Chinese Medicine (acupuncture or Chinese herbal

remedies: Ermiao wan, Meadow saffron, Dandelion, Burdock root; Huzhang gout granule; Jinhuang ointment; Yinlian gout granule, Si Miao San, Gout chi)

- Pharmacologic agents
 - Acute gout treatment (KQ1, 4, 5b)
 - Anti-inflammatories (NSAIDs, corticosteroids [intra-articular and/or oral])
 - Microtubule inhibitors (colchicine)
 - Combination therapy (colchicine and NSAIDs/ oral corticosteroids; intra-articular corticosteroids/anti-inflammatories)
 - Urate Lowering Therapies (KQ3, 5a)
 - Xanthine oxidase inhibitors (XOIs: allopurinol, febuxostat) (KQ3, 5)
 - Uricosuric agents (probenecid) (KQ3, 5a)
 - Combination medications
 - Probenecid/colchicine (KQ3)
 - XOIs/anti-inflammatories (KQ3)
 - Co-interventions (KQ3-5)
 - Included pharmacologic agents plus included diet and life style measures (KQ2, 3,4)
 - Included pharmacologic agents and included Traditional Chinese Medicine
- Comparators
 - Placebo or usual care (KQ 1, 3-5)
 - Active comparators (that are included interventions) (KQ1, 3-5)
 - Usual diet or level of activity or other dietary changes or dietary supplements that are included interventions (KQ2)
 - Early initiation of treatment (KQ 1, 2, 3)
- Outcomes:
 - For acute gout treatment (KQ1)
 - Efficacy
 - Short-term health outcomes (days following acute flare)
 - Pain
 - Joint swelling, tenderness
 - Longer-term health outcomes:
 - sUA
 - Pain
 - Joint swelling, tenderness
 - Activities of daily living (ADLs)
 - Patient global assessment
 - Recurrence

- Safety
 - Gastrointestinal and renal side effects (NSAIDS, colchicine)
 - Steroid induced osteoporosis, diabetes
 - For diet and other lifestyle therapy (KQ2)
 - Efficacy
 - Intermediate outcomes: serum and/or urine uric acid
 - Health outcomes: recurrence
 - Harms
 - For chronic gout treatment (uric acid lowering therapy), monitoring, and discontinuation (KQ3-5)
 - Efficacy:
 - intermediate outcomes: sUA
 - Final Health outcomes: pain, joint swelling, tenderness associated with the development of tophi, ADLs, patient global assessment, risk for comorbidities/mortality, recurrence of gout flares (attacks)
 - Safety
 - Inflammatory effects, including skin rash
 - Hematologic effects
 - Cardiovascular effects
 - Liver dysfunction
 - Renal dysfunction
 - For anti-inflammatory prophylaxis with ULT therapy (same outcomes as for acute gout therapy)
- Timing
 - Acute treatment (KQ1): 24-72 hours follow-up
 - Chronic treatment (KQ2-4): any follow-up time
 - Delayed vs. immediate treatment (KQ1)
- Setting (all KQ)
 - Priority will be given to patients given being seen in primary care settings, which also includes urgent care clinics and emergency departments. If evidence from primary care settings is sparse, then we will include patients in outpatient specialist settings

III. Analytic Frameworks

We provide two analytic frameworks: one for acute gout and one for chronic gout.

Figure 1. Analytic framework for treatment of acute gout

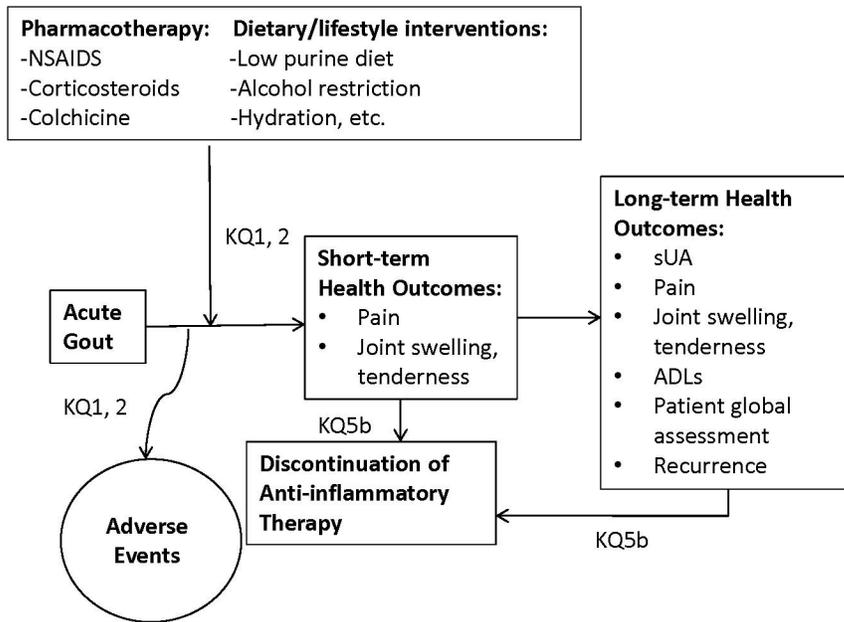
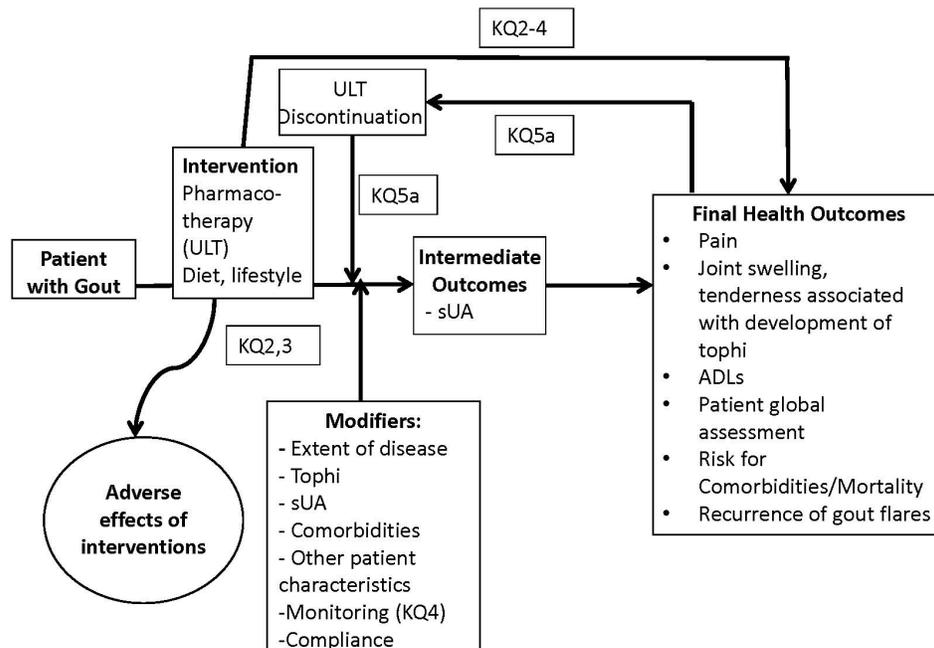


Figure 2. Analytic framework for management of chronic gout



IV. Methods

In general, this systematic review will follow the procedures of the January 2014 edition of the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹⁹

Criteria for Inclusion/Exclusion of Studies in the Review - Included studies will be limited to those that fit the PICOTs described above, namely those that assess the effects of pharmacologic agents (alone or in combination) or diet/lifestyle modifications in

community-dwelling adults 18 years of age and over for the treatment of acute or chronic gout (studies that assess effects of treatment on asymptomatic hyperuricemia only in patients not diagnosed with gout will not be included). Studies will also be included if they assess the effects of comorbidities, other potential modifying factors, and treatment monitoring on treatment outcomes.

Outcomes for acute gout management will include short-term pain, joint swelling and tenderness, and adverse events (AEs); and longer term control of serum UA concentrations, pain, joint swelling and tenderness, ADLs, patient global assessment, and prevention of future flares (recurrence) (Figure 1).

Outcomes for chronic gout management will include sUA, pain and swelling (tenderness) associated with development of tophi, ADLs, patient global assessment, risk for or progression of comorbidities/mortality, recurrence, and AEs.

Studies in any clinical setting will may be accepted as long as they satisfy all other inclusion/exclusion criteria. The results of the report are intended for primary care and acute care settings, and therefore primary and acute settings are preferred. Case reports will be excluded.

Studies will not be limited by language. For studies of efficacy and effectiveness, we will limit the inclusion to randomized controlled trials. Observational studies will be included for the assessment of rare adverse events. If the situation arises where there are no randomized controlled trials for an intervention of interest, we may consider observational studies of efficacy or effectiveness if their study is sufficiently strong to support a causal inference.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions – The search strategy will be designed by our reference librarian in collaboration with our local content expert, who has participated in the two ACR systematic reviews on gout (see Appendix below). We will search PubMed, EMBASE, the Cochrane Collection, and the Web of Science using the search terms “gout”, “gouty”, and terms for tophi. We will also obtain relevant references from at least 22 recent systematic reviews, that cover nearly all of the Key Questions. We will also conduct a search for grey literature, we will search Clinicaltrials.gov for recently completed studies, and we will request that manufacturers of pharmacologic agents approved for use in the US for the treatment of gout (and listed in the PICOTs) be contacted for unpublished data limited to the use of these agents for gout treatment. Searches will proceed from January 2010 to the present (at least one year to the search dates for the recent systematic reviews). The search strategy appears at the end of this protocol. Any relevant studies identified for the searches we are conducting for a simultaneous review on diagnosis of gout will also be included if not identified in the searches for this review. Finally, we will ask the Technical Expert panel (TEP) to assess our included studies and to provide references for any studies they believe should also be included. An update search will be conducted after submission of the draft report.

The DistillerSR software package will be used to manage the search outputs, screening, and data abstraction. Titles and abstracts identified by the searches will be

dually screened by the literature reviewers, and all selections will be accepted without reconciliation for further, full-text review. Full-text articles will be dually reviewed; disagreements regarding inclusion at the full-text stage will be reconciled, with the input of the project lead if necessary. Included studies will go on for dual abstraction of study-level details and outcomes and for assessment of risk of bias. Studies provided in information packets or suggested by peer reviewers will undergo the same process. While the draft report is being peer reviewed, an update search will be conducted, and studies identified in this search will also undergo the same review process.

Data Abstraction and Data Management – Data abstraction will follow the procedures described above. Data collection forms will be designed by the project team in Distiller SR, piloted by the reviewers, further modified, and then the final forms piloted with a random selection of included studies to ensure agreement of interpretation. Studies based on large prospective cohorts will be identified in their Distiller records to allow comparison to ensure data are not duplicated. Study-level data will include PICOTs, inclusion/exclusion criteria, study design, comorbidities, other potential effect modifiers (such as prior history of similar symptoms, results of HLA typing), analytic methods, and characteristics necessary to assess risk of bias, including recruitment, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest. At the end of the project, abstracted data will be uploaded to the Systematic Review Data Repository.

Assessment of Methodological Risk of Bias of Individual Studies - Risk of bias of individual included studies will be assessed using the Cochrane Risk of Bias assessment criteria.²⁰ In particular we will focus on assessment of participant recruitment, blinding, allocation concealment, completeness of outcome data, appropriateness of follow-up, adherence to interventions, and transparency of conflict of interest.

Data Synthesis – If three or more studies are deemed sufficiently homogeneous with respect to intervention, outcome measures, participants, and follow-up times, we will consider pooling their reported effect sizes; the method of pooling, whether random- or fixed-effect, will depend on the types and varieties of outcomes reported. If studies to be pooled are of similar sample size, we will explore using the Hartung, Knapp, Sidik and Jonkman method, as described by Inthout.²¹

If head-to-head trials are insufficient to reach comparative effectiveness conclusions, we may pursue a network meta-analysis if data permits.

For studies not included in pooled analyses, outcomes will be described narratively, stratified by comparisons of interest and study design, and presented in summary tables. If appropriate, sensitivity analysis will be conducted by age group; particular comorbidities, such as patients with hypertension, type 2 DM, or renal insufficiency; sex; and other potential effect modifiers.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes
We will assess the overall strength of evidence for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs, and

differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.¹⁹ This method is based on one developed by the GRADE Working Group and classifies the grade of evidence as High, Moderate, Low or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. Publication bias will be assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test;^{22,23} selective outcome reporting bias will also be assessed as part of the risk of bias assessment for individual studies. Three additional domains (plausible confounding, dose-response, and magnitude of effect) can also be included if appropriate.²⁴

Assessing Applicability – Because the charge for this review is clear on the setting, care providers, and patient population the review is intended to cover, applicability assessment will be based primarily on the similarity of the settings and populations to those for which this report is intended, namely primary and acute care settings that treat individuals, a high proportion of whom have comorbidities or are at risk for comorbidities such as hypertension and renal insufficiency.²⁵ In addition to comorbidities, we will determine whether studies report factors such as sex, duration of the condition, and stage (e.g., history of flares, extent of tophus development, serum uric acid control).

V. References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011 Oct;63(10):3136-41. PMID: 21800283.
2. Li C, Martin B, Cummins D, et al. Ambulatory Resource Utilization and Cost for Gout in United States. *AM J Pharm Benefits.* 2013;5(2):e46-54.
3. Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. *Postgrad Med.* 2012 Nov;124(6):98-109. PMID: 23322143.
4. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol.* 2011 Mar;23(2):192-202. PMID: 21285714.
5. Diagnosis of Gout Protocol. Rockville, MD: Agency for Health Care Research and Quality, Effective Health Care Program,; July 17, 2014.
<http://effectivehealthcare.ahrq.gov/ehc/products/564/1937/gout-protocol-140716.pdf>. Accessed on July 17 2014.
6. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med.* 2012 Jul;125(7):679-87 e1. PMID: 22626509.
7. Anderson A, Singh JA. Pegloticase for chronic gout. *Cochrane Database Syst Rev.* 2010(3):CD008335. PMID: 20238366.
8. Crittenden DB, Pillinger MH. New therapies for gout. *Annu Rev Med.* 2013;64:325-37. PMID: 23327525.
9. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev.* 2012;11:CD008653. PMID: 23152264.
10. Hamburger M, Baraf HS, Adamson TC, 3rd, et al. 2011 Recommendations for the diagnosis and management of gout and hyperuricemia. *Postgrad Med.* 2011 Nov;123(6 Suppl 1):3-36. PMID: 22156509.
11. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2006 Oct;65(10):1301-11. PMID: 16707533.
12. Glazebrook KN, Guimaraes LS, Murthy NS, et al. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: initial evaluation. *Radiology.* 2011 Nov;261(2):516-24. PMID: 21926378.

13. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012 Oct;64(10):1431-46. PMID: 23024028.
14. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012 Oct;64(10):1447-61. PMID: 23024029.
15. The University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program. Management of initial gout in adults. Austin (TX): University of Texas at Austin, School of Nursing; 2009 May.
16. The University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program. Management of chronic gout in adults. Austin (TX): University of Texas at Austin, School of Nursing; 2012 May.
17. Kahan JP, Park RE, Leape LL, et al. Variations by specialty in physician ratings of the appropriateness and necessity of indications for procedures. *Med Care*. 1996 Jun;34(6):512-23. PMID: 8656718.
18. Garber AM, Browner WS. Cholesterol screening guidelines. Consensus, evidence, and common sense. *Circulation*. 1997 Mar 18;95(6):1642-5. PMID: 9118535.
19. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
20. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. PMID: 22008217.
21. Inthout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14(1):25. PMID: 24548571.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994 Dec;50(4):1088-101. PMID: 7786990.
23. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997 Sep 13;315(7109):629-34. PMID: 9310563.
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6. PMID: 18436948.

25. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Agency for Healthcare Research and Quality; December 2010. Methods Guide for Comparative Effectiveness Reviews. AHRQ Publication No. 11-EHC019-EF.

VI. Definition of Terms

ACR: American College of Radiology

EULAR: European League Against Rheumatism

sUA: serum uric acid

ULT: urate lowering therapy

XOI: xanthine oxidase inhibitor

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

(NOTE THE FOLLOWING PROTOCOL ELEMENTS ARE STANDARD SECTIONS TO BE ADDED TO ALL PROTOCOLS)

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Search Strategy

GOUT MANAGEMENT SEARCH METHODOLOGY

DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 1/1/2010-present

SEARCH STRATEGY:

"Gout"[Mesh] OR gout[tiab] OR gouty[tiab] OR toph*

DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 1/1/2010-present

SEARCH STRATEGY:

Gout suppressants[mh]

NOT
"Gout"[Mesh] OR gout[tiab] OR gouty[tiab] OR toph*

DATABASE SEARCHED & TIME PERIOD COVERED:

Embase – 1/1/2010-present

SEARCH STRATEGY:

gout:de,ab,ti OR gouty:de,ab,ti OR toph*:de,ab,ti
AND
[humans]/lim
AND
[embase]/lim

DATABASE SEARCHED & TIME PERIOD COVERED:

Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 1/1/2010-present

SEARCH STRATEGY:

TS=(gout OR gouty OR toph*)
NOT
ts=(Aicardi-Goutieres)

DATABASE SEARCHED & TIME PERIOD COVERED:

Cochrane Databases – 1/1/2010-present

SEARCH STRATEGY:

'gout OR gouty OR toph*' in Title, Abstract, Keywords

FORWARD SEARCHES ON THE FOLLOWING ARTICLE:

EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT)

By:Zhang, W; Doherty, M; Bardin, T;Pascual, E; Barskova, V; Conaghan, P; Gerster, J; Jacobs, J; Leeb, B; Liote, F

Annals Of The Rheumatic Diseases, Volume: 65, Issue: 10, Pages: 1312-1324

Published: OCT 2006

DATABASE SEARCHED & TIME PERIOD COVERED:

Web of Science – 1/1/2010-present

SEARCH STRATEGY:

CITED AUTHOR: (zhang w*) AND CITED WORK: (ann rheum dis) AND CITED YEAR: (2006)

DATABASE SEARCHED & TIME PERIOD COVERED:

SCOPUS – 1/1/2010-present

SEARCH STRATEGY:

AUTHOR-NAME(zhang w*) AND TITLE-ABS-KEY(gout) AND PUBYEAR > 2005
Select citations to this article

MANUAL FILTERING IN ENDNOTE TO REMOVE DUPLICATES, ANIMAL-ONLY STUDIES, “GOUT” AS FRENCH FOR “TASTE,” “TOPHAT” (Re: GENETICS), HISTORICAL ACCOUNTS, AUTHORS NAMED “GOUT” OR “TOPH*