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## Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

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3 **Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic**  
4 **review of clinical practice guidelines and consensus statements**  
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8 **Running title:** AGREE II assessment for hyperuricemia and gout guidelines  
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39 **AUTHOR'S CONTRIBUTION**

40 HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion  
41 criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the  
42 appraisal strategy of each included guideline and consensus. QL, XL and SL drafted  
43 the protocol. All authors discussed actively in the protocol of the study.  
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## ABSTRACT

**Introduction:** Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining the diagnosis and treatment for hyperuricemia and gout, and summarize recommendations.

**Methods:** We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

**Ethics and dissemination:** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Discussion:** This proposed review might improve the clinical application of guidelines and consensus, and assist future development of high quality guidance documents.

**Protocol registration number:** PROSPERO CRD42016046104.

## KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

## INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged older than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population being 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in more than 75% gout patients [12]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, by the pathophysiology and manifestation of the condition, are published by academies of rheumatology, endocrinology, and cardiology. The two most influential series of guidelines worldwide are the American College of Rheumatology (ACR) guidelines [13,14], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [15,16], updated in 2011. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [17]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [18], Italy [19], Japan [20], Malaysia [21], the UK [22,23], and so forth.

Obvious inconsistencies in the diagnosis and management of hyperuricemia and gout exhibit in different international and national guidance documents. One most noted inconsistency is the timing to initiate urate lowering therapy (ULT) in patients with

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3 acute gout attack. The ACR guideline [13] suggests that pharmacologic ULT could be  
4 started during an acute gout attack as long as anti-inflammatory management is  
5 effective. However, the guidelines released by the Japanese Society of Gout and  
6 Nucleic Acid Metabolism [20] and by the Rheumatologic Associates of Long Island  
7 [24] emphasize that pharmacologic ULT should never be initiated during acute attacks  
8 because the change of serum urate level during an attack could exacerbate the  
9 condition. In the meantime, the 3e Initiative guideline [17] put it that when to started  
10 ULT after an acute attack is unclear.  
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18 Inconsistencies also lie in several other aspects. The cut-off uric acid level for  
19 hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [13,18,20,24]. The target  
20 serum urate level is generally set as below 6mg/dL [13,17,24], which is the saturation  
21 point for monosodium urate. However, as for managing asymptomatic hyperuricemic  
22 patients without comorbidities, the EULAR [16] and the 3e Initiative [17] guidelines  
23 do not recommend pharmacologic ULT regardless of the urate level, while a guideline  
24 from the aforementioned Japanese Society suggests application of ULT with a target  
25 uric acid of below 8mg/dL [20]. The consensus from the Chinese Society of  
26 Endocrinology suggests that the adoption of pharmacologic ULT in asymptomatic  
27 patients should be dependent on cardiovascular risks and serum uric acid level [18].  
28 As for ULT options, the ACR guideline [13] recommends both allopurinol and  
29 febuxostat as first line option, without prioritization, while the EULAR guideline [16]  
30 and the 3e Initiative guideline [17] suggest febuxostat as an alternative only for  
31 patients intolerant or not responding to allopurinol. In the meantime, the Chinese  
32 consensus [18] suggests that drugs promoting the excretion of uric acid, such as  
33 benzbromarone, are most widely used, because the majority of hyperuricemic cases  
34 are caused by uric acid underexcretion instead of overproduction.  
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48 These inconsistencies among guidance documents may result from ethnical and social  
49 differences, however, can also be consequences of nonstandard development  
50 processes. Low quality guidelines affect the outcomes of patients and the compliance  
51 of practitioners to guidance documents. Hence we conduct this study to explore the  
52 quality and concordance of guidelines and consensus statements on the diagnosis and  
53 management of hyperuricemia and gout.  
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## OBJECTIVE

The aim of this protocol study is to explore the quality and consistency of published guidance documents for the diagnosis and treatment of hyperuricemia and gout using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.

## METHODS

This protocol is developed based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses for Protocols (PRISMA-P) [25,26] and is registered with PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is provided as table 1.

### **Inclusion/exclusion criteria for study selection**

We will include international or national/regional clinical practice guideline and consensus statements on the diagnosis and treatment of hyperuricemia and gout published from 2000 to present. We define clinical practice guidelines and consensus statements as documents providing recommendations for patient care, which are derived from a systematic review of existing evidence or from a collective opinion of an expert panel [27]. A document will be included if it: (1) is presented as a clinical practice guideline or a consensus statement; (2) specifically provides recommendations for diagnosis and/or management for hyperuricemia or gout; (3) is produced by related professional associations, institutes, societies, or communities for national or international use; (4) published in English or Chinese.

The exclusion criteria are as follows: (1) original investigation, study protocols, comments on existing guidelines or consensus, and conference abstracts or posters; (2) draft documents that are under development or not finalized; (3) previous documents replaced by updated versions from the same organization.

### **Search strategies**

We will search PubMed, EMBASE, and guideline databases to present for guidelines pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline databases to be searched include the National Guideline Clearinghouse [28], the Guidelines International Network [29], the National Institute for Health and Care Excellence (NICE) website [30], the National Health Service (NHS) Evidence

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3 website [31], the Scottish Intercollegiate Guidelines Network (SIGN) website [32],  
4 the Guidelines and Audit Implementation Network (GAIN) [33], the Chinese  
5 Biomedical Literature Database (CBM) [34], and the Wanfang database [35]. Search  
6 strategy will be tailored in different databases using the combination of the following  
7 keywords: “hyperuricemia”, “gout”, “uric acid”, “urate”, “guideline”, “consensus”,  
8 “statement”, “recommendation”, and “policy”. Sample search strategy for EMBASE  
9 using the OVID interface is provided as Table 2. These strategies may be revised to  
10 improve sensitivity and specificity. Search results will be managed with the EndNote  
11 X6 reference manager (Thomson Reuters Co., New York, New York, USA).  
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20 We will also conduct search on Google [36] and on Google scholar [37] for  
21 potentially eligible guidelines and consensus statements that are not indexed in the  
22 aforementioned databases. We will search the internet via Google chrome browser  
23 using the strategy “Region AND (hyperuricemia OR gout) AND (guideline OR  
24 consensus OR recommendation OR statement)” and screen the first 100 records for  
25 each region. Name of regions to be searched are: America, Australia, Canada, China,  
26 European, Hong Kong, India, Japan, Singapore, South Africa, and the United  
27 Kingdom. We will search via the Google scholar engine using the strategy  
28 “(hyperuricemia OR gout) AND (guideline or consensus or recommendation or  
29 statement)” and screen the first 200 records.  
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### 38 **Study selection and data extraction**

39 Two reviewers will independently screen the titles and abstracts of all searched  
40 documents and determine the ones for full-text review. Documents excluded after full-  
41 text review will be reported with reasons for exclusion. Disagreements will be  
42 resolved through discussion with a consultant endocrinologist.  
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48 We will extract the following data from each included document: document  
49 characteristics (e.g., first author, year of publication, title, issuing organization,  
50 country, funding body), recommendations for diagnosis and investigation of  
51 hyperuricemia and gout, and recommendations for management (e.g., treatment and  
52 prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).  
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### 58 **Appraisal of guidance documents**



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3 All included documents will be assessed by four reviewers (Q.L., X.L., J.S.W.K. and  
4 S.L.) independently using the Appraisal of Guidelines for Research and Evaluation  
5 (AGREE) II instrument [38]. AGREE II is an international, validated, and rigorously  
6 developed tool to evaluate the quality of clinical practice guidelines [39,40] and it also  
7 applies to consensus statements [41,42]. This tool is composed by 23 items and  
8 evaluates six domains of guideline development and report: scope and purpose,  
9 stakeholder involvement, rigor of development, clarity of presentation, applicability,  
10 and editorial independence. Reviewers score each item on a seven-point Likert scale,  
11 with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each  
12 domain of each document is calculated as follows: (obtained score-minimal possible  
13 score)/(maximal possible score-minimal possible score). The minimum possible score  
14 is calculated as: (number of questions) x (number of reviewers) x 1. The maximum  
15 possible score is calculated as: (number of questions) x (number of reviewers) x 7 [38].  
16 This score calculation will be conducted using the My AGREE PLUS platform.  
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28 All reviewers will complete the online training tutorial [43] before the  
29 commencement of appraisal to ensure standardization. A meeting will be held among  
30 reviewers after the appraisal and every item with scores differed more than one point  
31 will be discussed. Reviewers can revise their scores or keep the original evaluation  
32 after discussion and records will be made for the scores revised with reasons for  
33 revision. When the scoring process is completed, the inter-rater reliability on the  
34 AGREE II will be examined using the intra-class correlation coefficient (ICC) via  
35 IBM SPSS (IBM Co., Armonk, New York, USA). An ICC  $\geq 0.7$  is considered  
36 acceptable [44].  
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### 45 **Recommendation synthesis**

46 We will manually extract descriptive data from included documents and tabulate them  
47 to summarize recommendations of guidance documents and to exhibit consistencies.  
48 Domains of recommendation to summarize will be dependent on the information  
49 provided by available guidance documents. A flow diagram (Figure 1) will be  
50 provided to illustrate the entire study process.  
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### 56 **ETHICS AND DISSEMINATION**

57 The results of the systematic review will be disseminated through relevant scientific  
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3 meetings and peer-reviewed journals.  
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## 6 **DISCUSSION**

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8 Clinical practice guidelines and consensus statements are of important value for  
9 clinical practice. However, guidance documents issued by different organizations for  
10 hyperuricemia and gout are highly inconsistent, which impairs the application of and  
11 compliance to these documents. Hence we conduct this systematic review to identify  
12 the quality and concordance of guidelines and consensus, and provide a  
13 summarization of guideline recommendations.  
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19 To date, no systematic appraisal for hyperuricemia and gout guidelines has been  
20 reported. Our proposed review integrates comprehensive search strategies, applies the  
21 well-established and validated AGREE II tool, and adopts a rigorous appraisal process  
22 to minimize subjective bias. This review might assist clinicians to better understand  
23 and apply recommendations of guidelines and consensus to daily practice, guideline  
24 developer to development higher quality guidance documents, and researchers to  
25 identify knowledge gaps.  
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33 Possible limitations of this research are language restrictions and unconscious bias  
34 from subjective rating of documents. To minimize potential limitations and bias, we  
35 will follow the recommendations by the PRISMA and AGREE.  
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40 In general, it is necessary to systematically review and appraise clinical practice  
41 guidelines and consensus statements pertaining to the diagnosis and management of  
42 hyperuricemia and gout. This protocol provides a clear and structured process for  
43 guidance documents identification, quality evaluation, and recommendation  
44 summarization. The proposed review may help hyperuricemia and gout care delivery.  
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## 49 **FUNDING**

50  
51 This research received no specific grant from any funding agency in the public,  
52 commercial or not-for-profit sectors.  
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## 55 **CONFLICTS OF INTEREST**

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57 The authors declare no conflict of interest.  
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**Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])**

Section and topic	Item No	Checklist item	Page No
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7-8

sources	contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 9
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	n/a
	15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	n/a
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

**Table 2 Sample search strategy for EMBASE using the OVID interface**

1	exphyperuricemia/
2	exp gout/
3	exp uric acid/
4	expurate/
5	hyperuric?emia/
6	gout.m_titl.
7	uricacid.m_titl.
8	urate\$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline\$.m_titl.
12	consensus.m_titl.
13	position statement\$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation\$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16



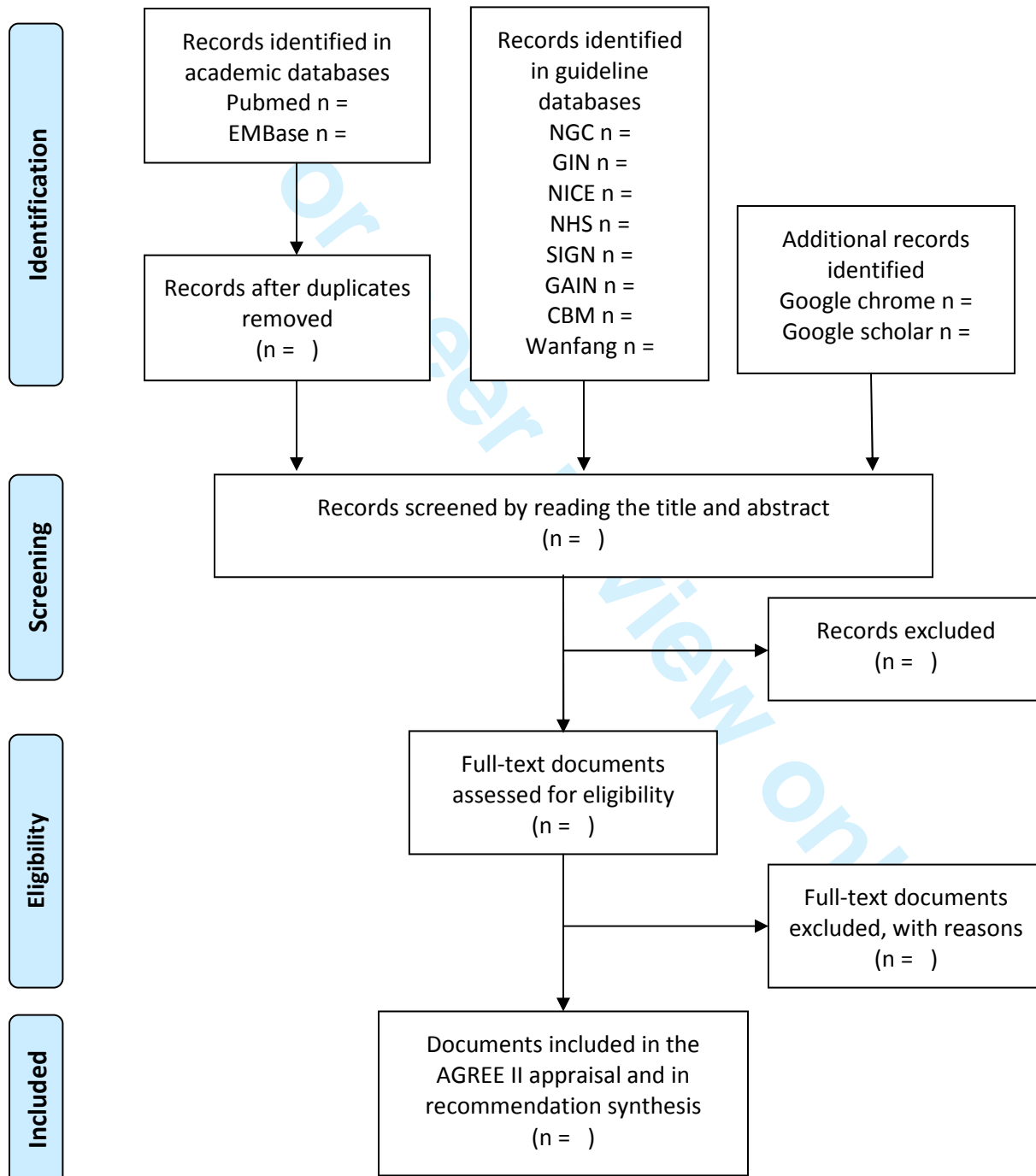
**Figure 1 Flow diagram for literature search**

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network;  
NICE, National Institute for Health and Care Excellence; NHS, National Health  
Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and  
Audit Implementation Network; CBM, Chinese Biomedical Literature Database.

For peer review only

**Figure 1 Flow diagram for literature search**

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; CBM, Chinese Biomedical Literature Database.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])**

Section and topic	Item No	Checklist item	Page No
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7-8

sources	contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 9
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
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Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	n/a
	15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	n/a
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

# BMJ Open

## Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice
Keywords:	Clinical practice guideline, Hyperuricemia, Gout, Systematic review

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3 **Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic**  
4 **review of clinical practice guidelines and consensus statements**  
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8 **Running title:** AGREE II assessment for hyperuricemia and gout guidelines  
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39 **AUTHOR'S CONTRIBUTION**

40 HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion  
41 criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the  
42 appraisal strategy of each included guideline and consensus. QL, XL and SL drafted  
43 the protocol. All authors discussed actively in the protocol of the study.  
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## ABSTRACT

**Introduction:** Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and summarize recommendations.

**Methods:** We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

**Ethics and dissemination:** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number:** PROSPERO CRD42016046104.

## KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.



## INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged older than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population being 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, by the pathophysiology and manifestation of the condition, are published by academies of rheumatology, endocrinology, and cardiology. The two most influential series of guidelines worldwide are the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, physician and patient adherence to guideline recommendations was poor [27,28], one possible reason for which was the inconsistent recommendations between different guidelines.

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3 Although current guidelines share general principles, obvious inconsistencies in the  
4 practical recommendations on diagnosis and management of hyperuricemia and gout  
5 have been noted in different international and national guidance documents [29]. One  
6 most discussed inconsistency is the timing to initiate urate lowering therapy (ULT) in  
7 patients with acute gout attack. The guidelines released by the British Society for  
8 Rheumatology and British Health Professionals in Rheumatology [26], by the  
9 Japanese Society of Gout and Nucleic Acid Metabolism [22] and by the  
10 Rheumatologic Associates of Long Island [30] all emphasized that pharmacologic  
11 ULT should never be initiated during acute attacks because the change of serum urate  
12 level during an attack could exacerbate the condition. However, the ACR guideline  
13 [14] suggests that pharmacologic ULT could be started during an acute gout attack as  
14 long as anti-inflammatory management is effective. In the meantime, the 3e Initiative  
15 guideline [19] put it that when to started ULT after an acute attack is unclear and the  
16 latest EULAR guideline stated no specific guidance on the initiation of ULT whether  
17 during a flare or two weeks after its termination [18].  
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30 Inconsistencies also lie in several other aspects. The cut-off uric acid level for  
31 hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although  
32 the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below,  
33 which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact  
34 target recommended by different guidelines varies. Furthermore, the 2016 updated  
35 EULAR guideline introduces additional attention on its lower limit by putting that  
36 serum urate lower than 3mg/dl is not recommended in the long term [18]. As for  
37 managing asymptomatic hyperuricemic patients without comorbidities, the 2006  
38 EULAR [17] and the 3e Initiative [19] guidelines do not recommend pharmacologic  
39 ULT regardless of the urate level, while a guideline from the aforementioned Japanese  
40 Society suggests application of ULT with a target uric acid of below 8mg/dL [22]. To  
41 be noted, the 2016 updated EULAR guideline highlights the concept of early  
42 initiation of ULT, although task force admits lack of adequate clinical evidence [18].  
43 The consensus from the Chinese Society of Endocrinology suggests that the adoption  
44 of pharmacologic ULT in asymptomatic patients should be dependent on  
45 cardiovascular risks and serum uric acid level [20]. As for ULT options, the ACR  
46 guideline [14] recommends both allopurinol and febuxostat as first line option,  
47 without prioritization, while the EULAR guideline [18] and the 3e Initiative guideline  
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3 [19] suggest febuxostat as an alternative only for patients intolerant or not responding  
4 to allopurinol. In the meantime, the Chinese consensus [20] suggests that drugs  
5 promoting the excretion of uric acid, such as benzbromarone, are most widely used,  
6 because the majority of hyperuricemic cases are caused by uric acid underexcretion  
7 instead of overproduction.  
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13 These inconsistencies among guidance documents may result from ethnical and social  
14 differences, however, can also be consequences of nonstandard development  
15 processes. Low quality guidelines affect the outcomes of patients and the compliance  
16 of practitioners to guidance documents. Hence, we conduct this study to explore the  
17 quality and concordance of guidelines and consensus statements on the diagnosis and  
18 management of hyperuricemia and gout.  
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## 24 **OBJECTIVE**

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26 The aim of this protocol study is to explore the quality and consistency of published  
27 guidance documents for the diagnosis and treatment of hyperuricemia and gout using  
28 the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.  
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## 33 **METHODS**

34 This protocol is developed based on the Preferred Reporting Items for Systematic  
35 Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with  
36 PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is  
37 provided as a supplementary document.  
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### 43 **Inclusion/exclusion criteria for study selection**

44 We will include international or national/regional clinical practice guidelines and  
45 consensus statements on the diagnosis and/or treatment of both hyperuricemia and  
46 gout. We define clinical practice guidelines and consensus statements as documents  
47 providing recommendations for patient care, which are derived from a systematic  
48 review of existing evidence or from a collective opinion of an expert panel [33]. A  
49 document will be included if it: (1) is presented as a clinical practice guideline or a  
50 consensus statement; (2) specifically provides recommendations for diagnosis and/or  
51 management for hyperuricemia or gout; (3) is produced by related professional  
52 associations, institutes, societies, or communities for national or international use; (4)  
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3 published in English or Chinese.  
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6 The exclusion criteria are as follows: (1) original investigation, study protocols,  
7 comments on existing guidelines or consensus, and conference abstracts or posters; (2)  
8 draft documents that are under development or not finalized; (3) previous documents  
9 replaced by updated versions from the same organization.  
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### 13 14 15 **Search strategies**

16 We will search PubMed, EMBASE, and guideline databases to present for guidelines  
17 pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline  
18 databases to be searched include the National Guideline Clearinghouse [34], the  
19 Guidelines International Network [35], the National Institute for Health and Care  
20 Excellence (NICE) website [36], the National Health Service (NHS) Evidence  
21 website [37], the Scottish Intercollegiate Guidelines Network (SIGN) website [38],  
22 the Guidelines and Audit Implementation Network (GAIN) [39], the Turning  
23 Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the Chinese  
24 Biomedical Literature Database (CBM) [42], and the Wanfang database [43]. Search  
25 strategy will be tailored in different databases using the combination of the following  
26 keywords: “hyperuricemia”, “gout”, “uric acid”, “urate”, “guideline”, “consensus”,  
27 “statement”, “recommendation”, and “policy”. Sample search strategy for EMBASE  
28 using the OVID interface is provided as Table 1. These strategies may be revised to  
29 improve sensitivity and specificity. Search results will be managed with the EndNote  
30 X6 reference manager (Thomson Reuters Co., New York, New York, USA).  
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43 We will also conduct search on Google [44] and on Google scholar [45] for  
44 potentially eligible guidelines and consensus statements that are not indexed in the  
45 aforementioned databases. We will search the internet via Google chrome browser  
46 using the strategy “Region AND (hyperuricemia OR gout) AND (guideline OR  
47 consensus OR recommendation OR statement)” and screen the first 100 records for  
48 each region. Name of regions to be searched are: America, Australia, Canada, China,  
49 Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom.  
50 We will search via the Google scholar engine using the strategy “(hyperuricemia OR  
51 gout) AND (guideline or consensus or recommendation or statement)” and screen the  
52 first 200 records.  
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### Study selection and data extraction

Two reviewers will independently screen the titles and abstracts of all searched documents and determine the ones for full-text review. Documents excluded after full-text review will be reported with reasons for exclusion. Disagreements will be resolved through discussion with a consultant endocrinologist.

We will extract the following data from each included document: document characteristics (e.g., first author, year of publication, title, issuing organization, country, funding body), recommendations for diagnosis and investigation of hyperuricemia and gout, and recommendations for management (e.g., treatment and prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).

### Appraisal of guidance documents

All included documents will be assessed by four reviewers (Q.L., X.L., J.S.W.K. and S.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines [47,48] and it also applies to consensus statements [49,50]. This tool is composed by 23 items and evaluates six domains of guideline development and report: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Reviewers score each item on a seven-point Likert scale, with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of each document is calculated as follows:  $(\text{obtained score} - \text{minimal possible score}) / (\text{maximal possible score} - \text{minimal possible score})$ . The minimum possible score is calculated as:  $(\text{number of questions}) \times (\text{number of reviewers}) \times 1$ . The maximum possible score is calculated as:  $(\text{number of questions}) \times (\text{number of reviewers}) \times 7$  [46]. This score calculation will be conducted using the My AGREE PLUS platform.

All reviewers will complete the online training tutorial [51] before the commencement of appraisal to ensure standardization. A meeting will be held among reviewers after the appraisal and every item with scores differed more than one point will be discussed. Reviewers can revise their scores or keep the original evaluation after discussion and records will be made for the scores revised with reasons for

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3 revision. When the scoring process is completed, the inter-rater reliability on the  
4 AGREE II will be examined using the intra-class correlation coefficient (ICC) via  
5 IBM SPSS (IBM Co., Armonk, New York, USA). An ICC  $\geq 0.7$  is considered  
6 acceptable [52].  
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### 10 11 **Recommendation synthesis**

12 We will manually extract descriptive data from included documents and tabulate them  
13 to summarize recommendations of guidance documents and to exhibit consistencies.  
14 Domains of recommendation to summarize will be dependent on the information  
15 provided by available guidance documents and will be pertaining to the diagnosis and  
16 treatment strategies of hyperuricemia and gout, such as the target uric acid level, the  
17 timing to initiate ULT in patients with acute gout attack, the prioritization of ULT  
18 options, the allopurinol dosing, the prophylaxis management against acute gout attack,  
19 the treatment for asymptomatic hyperuricemic patients without comorbidities, the  
20 timing to assess urate deposits with imaging techniques, the monitor of urate deposits  
21 clearance, and so forth. A flow diagram (Figure 1) will be provided to illustrate the  
22 entire study process.  
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### 32 33 **ETHICS AND DISSEMINATION**

34 The results of the systematic review will be disseminated through relevant scientific  
35 meetings and peer-reviewed journals.  
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### 39 40 **DISCUSSION**

41 Clinical practice guidelines and consensus statements are of important value for  
42 clinical practice. However, guidance documents issued by different organizations for  
43 hyperuricemia and gout are highly inconsistent, which impairs the application of and  
44 compliance to these documents. Hence, we conduct this systematic review to identify  
45 the quality and concordance of guidelines and consensus, and provide a  
46 summarization of guideline recommendations.  
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53 To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines  
54 has been reported in the English or Chinese literature. Although a quality appraisal  
55 [53] of four recent guidelines in gout was published in 2014, it did not systematically  
56 review all published guidance documents. Additionally, only two appraisers were  
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3 involved, while the AGREE II developer recommended four [52], and one of them  
4 was a co-author of one of the rated guidelines. Our proposed review integrates  
5 comprehensive search strategies, applies the well-established and validated AGREE II  
6 tool, and adopts a rigorous appraisal process to minimize subjective bias. This review  
7 might assist clinicians to better understand and apply recommendations of guidelines  
8 and consensus to daily practice, guideline developer to development higher quality  
9 guidance documents, and researchers to identify knowledge gaps.  
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16 Possible limitations of this research are language restrictions and unconscious bias  
17 from subjective rating of documents. To minimize potential limitations and bias, we  
18 will follow the recommendations by the PRISMA and AGREE.  
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23 In general, it is necessary to systematically review and appraise clinical practice  
24 guidelines and consensus statements pertaining to the diagnosis and management of  
25 hyperuricemia and gout. This protocol provides a clear and structured process for  
26 guidance documents identification, quality evaluation, and recommendation  
27 summarization. The proposed review may help hyperuricemia and gout care delivery.  
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35 developing the search strategy.  
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42 commercial or not-for-profit sectors.  
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### 46 47 **CONFLICTS OF INTEREST**

48 The authors declare no conflict of interest.  
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**Table 1 Sample search strategy for EMBASE using the OVID interface**

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate\$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline\$.m_titl.
12	consensus.m_titl.
13	position statement\$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation\$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

**Figure 1 Flow diagram for literature search**

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network;  
NICE, National Institute for Health and Care Excellence; NHS, National Health  
Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and  
Audit Implementation Network; TRIP, Turning Research Into Practice Database;  
CBM, Chinese Biomedical Literature Database.

For peer review only

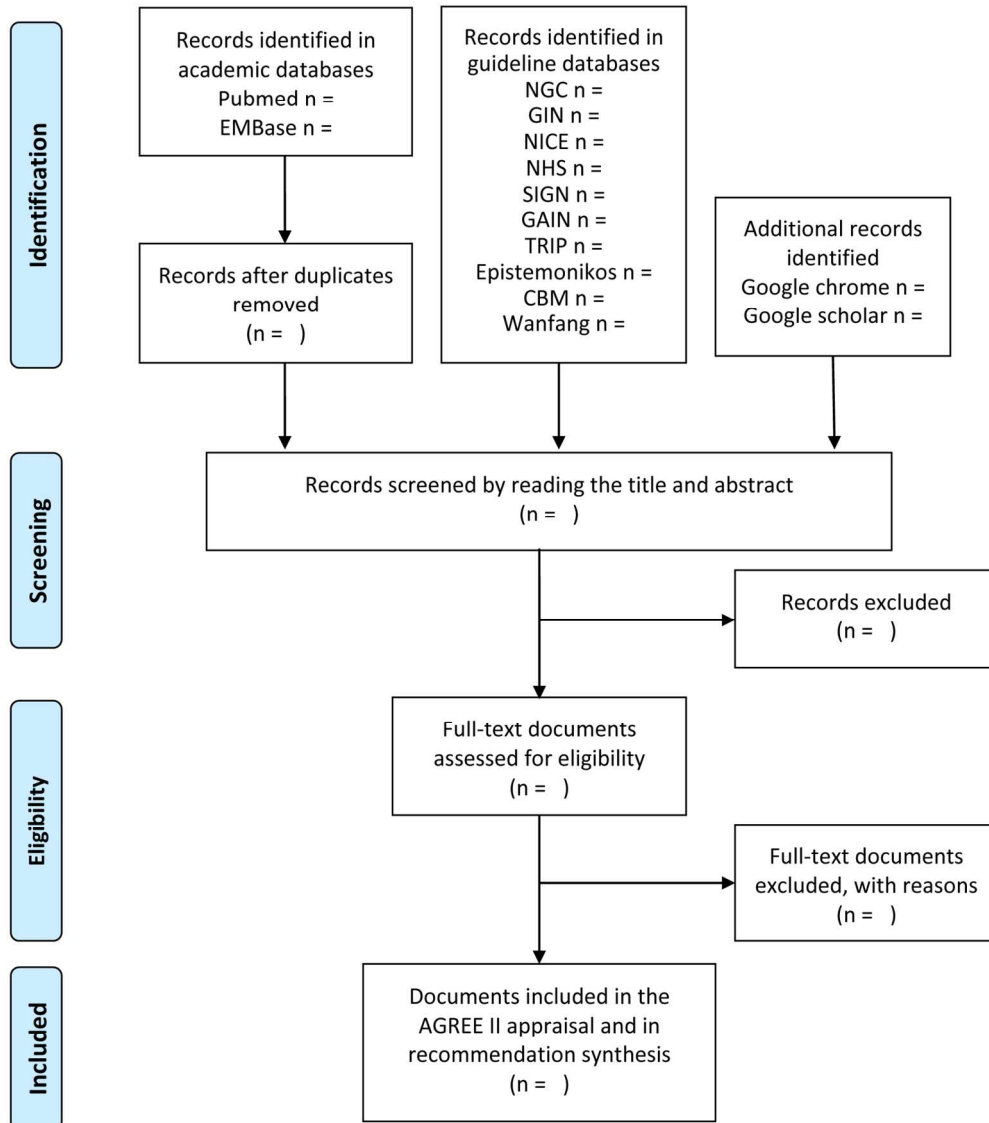


Figure 1 Flow diagram for literature search. !! † NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)

**Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])**

Section and topic	Item No	Checklist item	Page No
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources	contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	n/a
	15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	n/a
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

# BMJ Open

## Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice
Keywords:	Clinical practice guideline, Hyperuricemia, Gout, Systematic review

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3 **Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic**  
4 **review of clinical practice guidelines and consensus statements**  
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8 **Running title:** AGREE II assessment for hyperuricemia and gout guidelines  
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40 **AUTHOR'S CONTRIBUTION**

41 HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion  
42 criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the  
43 appraisal strategy of each included guideline and consensus. QL, XL and SL drafted  
44 the protocol. All authors discussed actively in the protocol of the study.  
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## ABSTRACT

**Introduction:** Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and to summarize recommendations.

**Methods:** We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

**Ethics and dissemination:** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number:** PROSPERO CRD42016046104.

## KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

## INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged older than 20 years old in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population were 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practices. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, are published by academies of rheumatology, endocrinology, and cardiology. The two series of guidelines with the strongest global influence are the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, the adherence of physicians and patients to guideline recommendations was poor [27,28]. One possible reason was the inconsistency of recommendations between different guidelines [29],

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3 despite their shared general principles. One mostly discussed inconsistency is the  
4 timing to initiate urate lowering therapy (ULT) in patients with acute gout attack. The  
5 guidelines released by the British Society for Rheumatology and British Health  
6 Professionals in Rheumatology [26], by the Japanese Society of Gout and Nucleic  
7 Acid Metabolism [22] and by the Rheumatologic Associates of Long Island [30] all  
8 emphasized that pharmacologic ULT should never be initiated during acute attacks  
9 because the change of serum urate level during an attack could exacerbate the  
10 condition. However, the ACR guideline [14] suggested that pharmacologic ULT could  
11 be started during an acute gout attack as long as anti-inflammatory management was  
12 effective. In the meantime, the 3e Initiative guideline [19] did not recommend a clear  
13 time to start ULT for an acute attack, and the latest EULAR guideline stated no  
14 specific guidance on the initiation of ULT whether during a flare or two weeks after  
15 its termination [18].  
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26 Inconsistencies also lie in several other aspects. The cut-off uric acid level for  
27 hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although  
28 the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below,  
29 which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact  
30 targets recommended by different guidelines are diverse. Furthermore, the 2016  
31 updated EULAR guideline paid additional attention to its lower limit, stating that  
32 serum urate below 3mg/dl was not recommended for long-term management [18]. As  
33 for managing asymptomatic hyperuricemic patients without comorbidities, the 2006  
34 EULAR [17] and the 3e Initiative [19] guidelines did not recommend pharmacologic  
35 ULT regardless of the urate level, while a guideline from the aforementioned Japanese  
36 Society suggested application of ULT with a target uric acid of below 8mg/dL [22]. To  
37 be noted, the 2016 updated EULAR guideline highlighted the concept of early  
38 initiation of ULT, although the Task Force admitted the lack of adequate clinical  
39 evidence [18]. The consensus from the Chinese Society of Endocrinology suggested  
40 that the adoption of pharmacologic ULT in asymptomatic patients should be  
41 dependent on cardiovascular risks and serum uric acid level [20]. As for ULT options,  
42 the ACR guideline [14] recommended both allopurinol and febuxostat as first line  
43 options, without prioritization, while the EULAR guideline [18] and the 3e Initiative  
44 guideline [19] suggested febuxostat as an alternative only for patients intolerant of or  
45 not responding to allopurinol. In the meantime, the Chinese consensus [20] suggested  
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3 that drugs promoting the excretion of uric acid, such as benzbromarone, were most  
4 widely used, because the majority of hyperuricemic cases were caused by uric acid  
5 underexcretion instead of overproduction.  
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10 These inconsistencies among guidance documents may result from ethnical and social  
11 differences, however, can also be consequences of nonstandard developing processes.  
12 Low-quality guidelines affect the outcomes of patients and the compliance of  
13 practitioners to guidance documents. Hence, we will conduct this study to evaluate the  
14 guidance documents on gout and hyperuricemia.  
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### 18 19 20 **OBJECTIVE**

21 The aim of this protocol study is to explore the quality and consistency of published  
22 guidance documents for the diagnosis and treatment of hyperuricemia and gout using  
23 the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.  
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### 27 28 **METHODS**

29 This protocol is developed based on the Preferred Reporting Items for Systematic  
30 Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with  
31 PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is  
32 provided as a supplementary document.  
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### 38 **Inclusion/exclusion criteria for study selection**

39 We will include international and national/regional clinical practice guidelines and  
40 consensus statements for the diagnosis and/or treatment of both hyperuricemia and  
41 gout. We define clinical practice guidelines and consensus statements as documents  
42 providing recommendations for patient care, which are derived from a systematic  
43 review of existing evidence or from collective opinions of an expert panel [33]. A  
44 document will be included if it: (1) is presented as a clinical practice guideline or a  
45 consensus statement; (2) specifically provides recommendations for diagnosis and/or  
46 management for hyperuricemia or gout; (3) is produced by related professional  
47 associations, institutes, societies, or communities for national or international use; (4)  
48 is published in English or Chinese.  
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58 The exclusion criteria are as follows: (1) original investigation, study protocols,  
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3 comments on existing guidelines or consensus, and conference abstracts or posters; (2)  
4 draft documents that are under development or not finalized; (3) previous documents  
5 replaced by updated versions from the same organization.  
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### 8 9 10 **Search strategies**

11 We will search PubMed, EMBASE, and guideline databases to present for guidelines  
12 pertaining to the diagnosis and treatment of hyperuricemia and gout. Guideline  
13 databases to be searched include the National Guideline Clearinghouse [34], the  
14 Guidelines International Network [35], the National Institute for Health and Care  
15 Excellence (NICE) website [36], the National Health Service (NHS) Evidence  
16 website [37], the Scottish Intercollegiate Guidelines Network (SIGN) website [38],  
17 the Guidelines and Audit Implementation Network (GAIN) [39], the Turning  
18 Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the Chinese  
19 Biomedical Literature Database (CBM) [42], and the Wanfang database [43]. Search  
20 strategy was developed in consultation with a librarian and would be tailored in  
21 different databases using the combination of the following keywords:  
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23 “hyperuricemia”, “gout”, “uric acid”, “urate”, “guideline”, “consensus”, “statement”,  
24 “recommendation”, and “policy”. Sample search strategy for EMBASE using the  
25 OVID interface is provided as Table 1. These strategies may be revised to improve  
26 sensitivity and specificity. Search results will be managed with the EndNote X6  
27 reference manager (Thomson Reuters Co., New York, New York, USA).  
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31 We will also conduct search on Google [44] and Google scholar [45] for potentially  
32 eligible guidelines and consensus statements that are not indexed in the  
33 aforementioned databases. We will search the internet via Google chrome browser  
34 using the strategy “Region AND (hyperuricemia OR gout) AND (guideline OR  
35 consensus OR recommendation OR statement)” and screen the first 100 records for  
36 each region. Name of regions to be searched are: America, Australia, Canada, China,  
37 Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom.  
38 We will search via the Google scholar engine using the strategy “(hyperuricemia OR  
39 gout) AND (guideline or consensus or recommendation or statement)” and screen the  
40 first 200 records.  
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### 56 57 58 **Study selection and data extraction**

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3 Two reviewers will independently screen the titles and abstracts of all searched  
4 documents and determine the ones for full-text review. Documents excluded after full-  
5 text review will be reported with reasons for exclusion. Disagreements will be  
6 resolved through discussion with a consultant endocrinologist.  
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11 We will extract the following data from each included document: document  
12 characteristics (e.g., first author, year of publication, title, issuing organization,  
13 country, funding body), recommendations for diagnosis and investigation of  
14 hyperuricemia and gout, and recommendations for management (e.g., treatment and  
15 prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).  
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### 20 21 **Appraisal of guidance documents**

22 All included documents will be assessed by four reviewers (Q.L., X.L., J.SW.K. and  
23 S.L.) independently using the Appraisal of Guidelines for Research and Evaluation  
24 (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously  
25 developed tool to evaluate the quality of clinical practice guidelines [47,48] and it also  
26 applies to consensus statements [49,50]. This tool is composed by 23 items and  
27 evaluates six domains of guideline development and report: scope and purpose,  
28 stakeholder involvement, rigor of development, clarity of presentation, applicability,  
29 and editorial independence. Reviewers score each item on a seven-point Likert scale,  
30 with 1 point for Strongly Disagree and 7 points for Strongly Agree. The score for each  
31 domain of each document is calculated as follows: (obtained score-minimal possible  
32 score)/(maximal possible score-minimal possible score). The minimum possible score  
33 is calculated as: (number of questions) x (number of reviewers) x 1. The maximum  
34 possible score is calculated as: (number of questions) x (number of reviewers) x 7 [46].  
35 This score calculation will be conducted using the My AGREE PLUS platform.  
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48 All reviewers will complete the online training tutorial [51] before the  
49 commencement of appraisal to ensure standardization. A meeting will be held among  
50 reviewers after the appraisal and every item with scores differed more than one point  
51 will be discussed. Reviewers can revise their scores or keep the original evaluation  
52 after discussion, and records will be made for the scores revised with reasons for  
53 revision. When the scoring process is completed, the inter-rater reliability on the  
54 AGREE II will be examined using the intra-class correlation coefficient (ICC) via  
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3 IBM SPSS (IBM Co., Armonk, New York, USA). An ICC  $\geq 0.7$  is considered  
4 acceptable [52].  
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### 8 **Recommendation synthesis**

9 We will manually extract descriptive data from included documents and tabulate them  
10 to summarize recommendations of guidance documents and to exhibit consistencies.  
11 Domains of recommendation to summarize will be dependent on the information  
12 provided by available guidance documents and will be pertaining to the diagnosis and  
13 treatment strategies of hyperuricemia and gout, such as the target uric acid level, the  
14 timing to initiate ULT in patients with acute gout attack, the prioritization of ULT  
15 options, the allopurinol dosing, the prophylaxis management against acute gout attack,  
16 the treatment for asymptomatic hyperuricemic patients without comorbidities, the  
17 timing to assess urate deposits with imaging techniques, the monitor of urate deposits  
18 clearance, and so forth. A flow diagram (Figure 1) will be provided to illustrate the  
19 entire study process.  
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### 29 **ETHICS AND DISSEMINATION**

30 The results of the systematic review will be disseminated through relevant scientific  
31 meetings and peer-reviewed journals.  
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### 36 **DISCUSSION**

37 Clinical practice guidelines and consensus statements are of important value for  
38 clinical practice. However, guidance documents issued by different organizations for  
39 hyperuricemia and gout are highly inconsistent, which impairs the application of and  
40 compliance to these documents. Hence, we will conduct this systematic review to  
41 identify the quality and concordance of guidelines and consensus, and provide a  
42 summarization of guideline recommendations.  
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49 To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines  
50 has been reported in the English or Chinese literature. Although a quality appraisal  
51 [53] of four recent guidelines for gout was published in 2014, it did not systematically  
52 review all published guidance documents. Additionally, only two appraisers were  
53 involved, while one of them was a co-author of one of the rated guidelines, and while  
54 the AGREE II developer recommended four appraisers [52]. Our proposed review  
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3 integrates comprehensive search strategies, applies the well-established and validated  
4 AGREE II tool, and adopts a rigorous appraisal process to minimize subjective bias.  
5 This review will assist clinicians to better understand and apply recommendations of  
6 guidelines and consensus to daily practice, guideline developer to develop guidance  
7 documents of higher quality, and researchers to identify knowledge gaps.  
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12 Possible limitations of this research are language restrictions and unconscious bias  
13 from subjective rating of documents. To minimize publication bias, we will search  
14 grey literature on the internet via Google.  
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19 In general, it is necessary to systematically review and appraise clinical practice  
20 guidelines and consensus statements for diagnosis and management of hyperuricemia  
21 and gout. This protocol provides a clear and structured process for guidance  
22 documents identification, quality evaluation, and recommendation summarization.  
23 The proposed review will help hyperuricemia and gout care delivery.  
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## 28 29 30 **ACKNOWLEDGEMENTS**

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39 commercial or not-for-profit sectors.  
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## 43 44 **CONFLICTS OF INTEREST**

45 The authors declare no conflict of interest.  
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**Table 1 Sample search strategy for EMBASE using the OVID interface**

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate\$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline\$.m_titl.
12	consensus.m_titl.
13	position statement\$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation\$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

**Figure 1 Flow diagram for literature search**

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network;  
NICE, National Institute for Health and Care Excellence; NHS, National Health  
Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and  
Audit Implementation Network; TRIP, Turning Research Into Practice Database;  
CBM, Chinese Biomedical Literature Database.

For peer review only

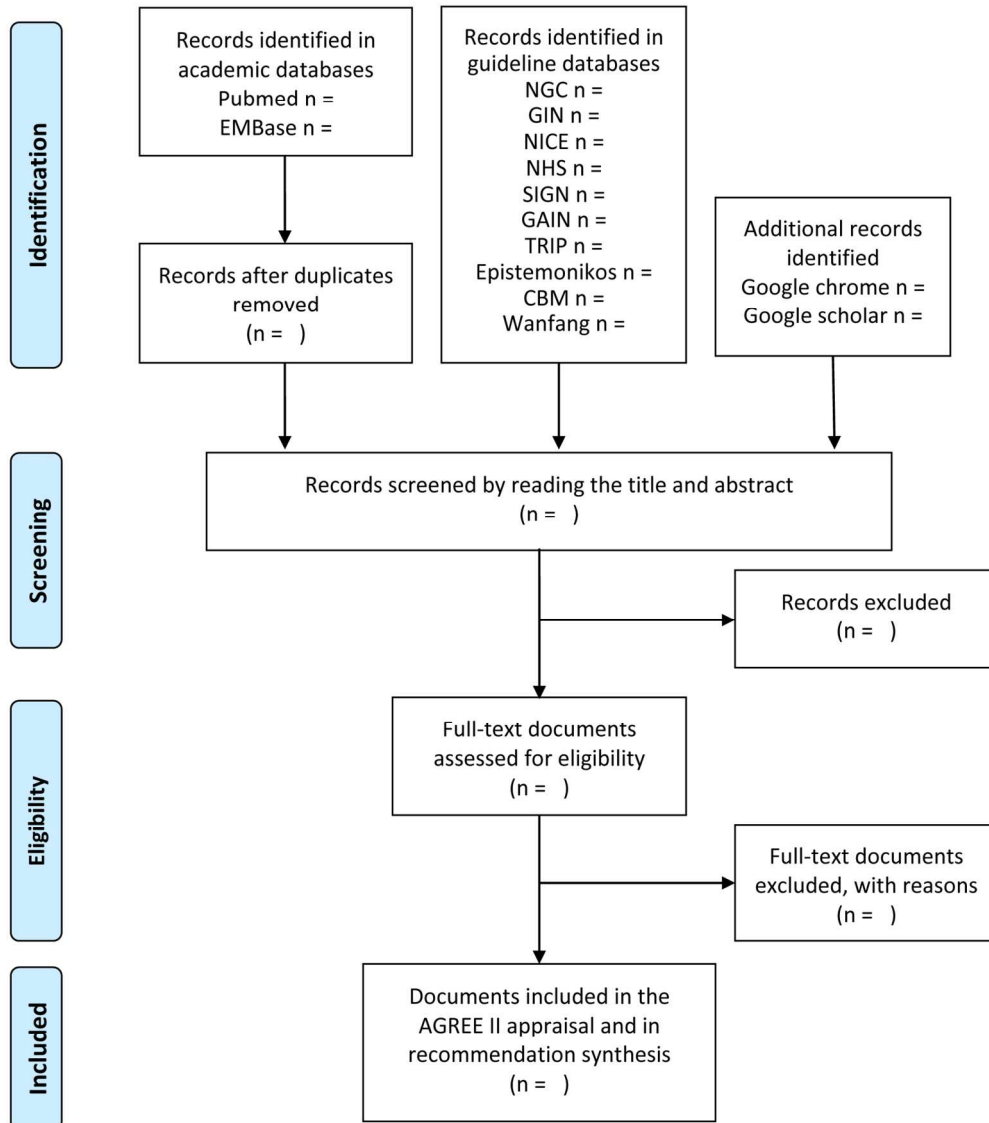


Figure 1 Flow diagram for literature search. !! † NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)



**Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])**

Section and topic	Item No	Checklist item	Page No
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources	contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	n/a
	15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	n/a
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

# BMJ Open

## Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014928.R3
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Date Submitted by the Author:	13-May-2017
Complete List of Authors:	Li, Qianrui; Sichuan University West China Hospital, Department of Endocrinology and Metabolism Li, Xiaodan; Sichuan University West China Hospital, Department of Gastroenterology Kwong, Joey; Taipei Medical University, Cochrane Taiwan; National Center for Child Health and Development, Department of Clinical Epidemiology and Department of Health Policy Chen, Hao; Nanjing University of Chinese Medicine, The second clinical college Sun, Xin; West China Hospital, Sichuan University, Chinese Evidence-based Medicine Center Tian, Hao-Ming; Department of Endocrinology, West China Hospital, Sichuan University Li, Sheyu; Department of Endocrinology and Metabolism, West China Hospital, Sichuan University
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice
Keywords:	Clinical practice guideline, Hyperuricemia, Gout, Systematic review

SCHOLARONE™  
Manuscripts

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3 **Diagnosis and treatment for hyperuricemia and gout: a protocol for a systematic**  
4 **review of clinical practice guidelines and consensus statements**  
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8 **Running title:** AGREE II assessment for hyperuricemia and gout guidelines  
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45 **AUTHOR'S CONTRIBUTION**

46 HT and SL conceived this study. QL, JSWK and SL designed the inclusion/exclusion  
47 criteria and the searching resource and strategy. QL, JSWK, HC and XS designed the  
48 appraisal strategy of each included guideline and consensus. QL, XL and SL drafted  
49 the protocol. All authors discussed actively in the protocol of the study.  
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## ABSTRACT

**Introduction:** Gout and hyperuricemia are major health issues and relevant guidance documents have been released by a variety of national and international organizations. However, these documents contain inconsistent recommendations with unclear quality profiles. We aim to conduct a systematic appraisal of the clinical practice guidelines and consensus statements pertaining to the diagnosis and treatment for hyperuricemia and gout, and to summarize recommendations.

**Methods:** We will search PubMed, EMBASE, and guideline databases to identify published clinical practice guidelines and consensus statements. We will search Google and Google Scholar for additional potentially eligible documents. The quality of included guidelines and consensus statements will be assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and be presented as scores. We will also manually extract recommendations for clinical practice from all included documents.

**Ethics and dissemination:** The results of this systematic review will be disseminated through relevant conferences and peer-reviewed journals.

**Protocol registration number:** PROSPERO CRD42016046104.

## KEYWORDS

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

1. This proposed study is the first systematic review to assess the quality of clinical guidance documents on the diagnosis and treatment for hyperuricemia and gout in English literature.
2. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is used for evaluation, which is an international, validated, and rigorously developed tool.
3. Only guidance documents in English and Chinese are included.

## INTRODUCTION

Gout is a major health problem worldwide, with the prevalence varying from 0.1% to 10% in different regions [1]. The National Health and Nutrition Examination Survey (NHANES) 2007–2008 showed that among adults aged over 20 years in the United States, 3.9% had self-reported gout, while only 2.9% population reported gout in the 1988-1994 survey [2]. As in mainland China, a systematic review of data from 2000-2014 suggested the prevalence of hyperuricemia and gout in the general population were 13.3% and 1.1%, respectively [3]. In general, both developed and developing countries presented with increasing prevalence and incidence of gout in recent decades [1].

Patients with hyperuricemia or gout are at risk of developing a variety of comorbidities, such as hypertension [4,5], chronic kidney disease [6], cardiovascular diseases [7,8], metabolic syndromes [9,10], and psychiatric disorders [11]. A recent survey found that 5-10% of gout patients had at least seven comorbidities and that hypertension was presented in at least 74% gout patients [12,13]. These comorbid conditions add difficulties to gout management and affect patients' quality of life.

Evidence-based, accurate, and timely guidance documents are important for clinical practice. They enhance the delivery of high quality care and consequently improve overall patient outcomes. Guidelines for hyperuricemia and gout, are published by academies of rheumatology, endocrinology, and cardiology. Of these, the American College of Rheumatology (ACR) guidelines [14,15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16,17,18], updated in 2016 have the strongest global influence. Additionally, a multinational collaboration involving practicing rheumatologists throughout the world, the 3e (Evidence, Expertise, Exchange) Initiative, released its guidance document in 2014 [19]. Moreover, a variety of countries developed national guidance for clinical practice, such as China [20], Italy [21], Japan [22], Malaysia [23], the UK [24-26], and so forth.

However, despite the availability of various guidance documents, the adherence of physicians and patients to guideline recommendations was poor [27,28]. One possible reason was the inconsistency of recommendations between different guidelines [29], despite their shared general principles. The most discussed inconsistency is the timing

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3 to initiate urate lowering therapy (ULT) in patients with acute gout attack. The  
4 guidelines released by the British Society for Rheumatology and British Health  
5 Professionals in Rheumatology [26], by the Japanese Society of Gout and Nucleic  
6 Acid Metabolism [22] and by the Rheumatologic Associates of Long Island [30] all  
7 emphasized that pharmacologic ULT should never be initiated during acute attacks  
8 because the change of serum urate level during an attack could exacerbate the  
9 condition. However, the ACR guideline [14] suggested that pharmacologic ULT could  
10 be started during an acute gout attack as long as anti-inflammatory management was  
11 effective. In the meantime, the 3e Initiative guideline [19] did not recommend a clear  
12 time to start ULT for an acute attack, and the latest EULAR guideline stated no  
13 specific guidance on the initiation of ULT whether during a flare or two weeks after  
14 its termination [18].  
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24 Inconsistencies also lie in several other aspects. The cut-off uric acid level for  
25 hyperuricemia diagnosis varies from 6.1mg/dL to 7.0mg/dL [14,20,22,30]. Although  
26 the target serum urate level is generally set as 6mg/dL [14,18,19,26,30] or below,  
27 which is lower than the saturation point for monosodium urate (6.8mg/dL), the exact  
28 targets recommended by different guidelines are diverse. Furthermore, the 2016  
29 updated EULAR guideline paid additional attention to its lower limit, stating that  
30 serum urate below 3mg/dl was not recommended for long-term management [18]. As  
31 for managing asymptomatic hyperuricemic patients without comorbidities, the 2006  
32 EULAR [17] and the 3e Initiative [19] guidelines did not recommend pharmacologic  
33 ULT regardless of the urate level, while a guideline from the Japanese Society  
34 suggested application of ULT with a target uric acid of below 8mg/dL [22]. The 2016  
35 update of the EULAR guideline highlighted the concept of early initiation of ULT,  
36 although the Task Force admitted the lack of adequate clinical evidence [18]. The  
37 consensus from the Chinese Society of Endocrinology suggested that the adoption of  
38 pharmacologic ULT in asymptomatic patients should be dependent on cardiovascular  
39 risks and serum uric acid level [20]. As for ULT options, the ACR guideline [14]  
40 recommended both allopurinol and febuxostat as first line options, without  
41 prioritization, while the EULAR guideline [18] and the 3e Initiative guideline [19]  
42 suggested febuxostat as an alternative only for patients intolerant of or not responding  
43 to allopurinol. In the meantime, the Chinese consensus [20] suggested that drugs  
44 promoting the excretion of uric acid, such as benzbromarone, were most widely used,  
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3 because the majority of hyperuricemic cases were caused by uric acid underexcretion  
4 instead of overproduction.  
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8 These inconsistencies among guidance documents may result from ethnical and social  
9 differences, however, can also be consequences of nonstandard developing processes.  
10 Low-quality guidelines affect the outcomes of patients and the compliance of  
11 practitioners to guidance documents. Hence, we will conduct this study to evaluate the  
12 guidance documents on gout and hyperuricemia.  
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### 16 17 18 **OBJECTIVE**

19 The aim of this protocol study is to explore the quality and consistency of published  
20 guidance documents for the diagnosis and treatment of hyperuricemia and gout using  
21 the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool.  
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### 25 26 **METHODS**

27 This protocol is developed based on the Preferred Reporting Items for Systematic  
28 Reviews and Meta Analyses for Protocols (PRISMA-P) [31,32] and is registered with  
29 PROSPERO (registration number: CRD42016046104). A PRISMA-P checklist is  
30 provided as a supplementary document.  
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### 36 **Inclusion/exclusion criteria for study selection**

37 We will include international and national/regional clinical practice guidelines and  
38 consensus statements for the diagnosis and/or treatment of both hyperuricemia and  
39 gout. We define clinical practice guidelines and consensus statements as documents  
40 providing recommendations for patient care, which are derived from a systematic  
41 review of existing evidence or from collective opinions of an expert panel [33]. A  
42 document will be included if it: (1) is presented as a clinical practice guideline or a  
43 consensus statement; (2) specifically provides recommendations for diagnosis and/or  
44 management for hyperuricemia or gout; (3) is produced by related professional  
45 associations, institutes, societies, or communities for national or international use; (4)  
46 is published in English or Chinese.  
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56 The exclusion criteria are as follows: (1) original investigation, study protocols,  
57 comments on existing guidelines or consensus, and conference abstracts or posters; (2)  
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3 draft documents that are under development or not finalized; (3) previous documents  
4 replaced by updated versions from the same organization.  
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### 8 **Search strategies**

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10 We will search PubMed, EMBASE, and guideline databases from the inception of the  
11 database for guidelines pertaining to the diagnosis and treatment of hyperuricemia and  
12 gout. Guideline databases to be searched include the National Guideline  
13 Clearinghouse [34], the Guidelines International Network [35], the National Institute  
14 for Health and Care Excellence (NICE) website [36], the National Health Service  
15 (NHS) Evidence website [37], the Scottish Intercollegiate Guidelines Network (SIGN)  
16 website [38], the Guidelines and Audit Implementation Network (GAIN) [39], the  
17 Turning Research Into Practice Database (TRIP) [40], the Epistemonikos [41], the  
18 Chinese Biomedical Literature Database (CBM) [42], and the Wanfang database [43].  
19 The search strategy was developed in consultation with a librarian and will be tailored  
20 in different databases. Combinations will be searched of the following keywords:  
21 “hyperuricemia”, “gout”, “uric acid”, “urate”, “guideline”, “consensus”, “statement”,  
22 “recommendation”, and “policy”. The draft search strategy for EMBASE using the  
23 OVID interface is provided as Table 1. These strategies may be revised to improve  
24 sensitivity and specificity. Search results will be managed with the EndNote X6  
25 reference manager (Thomson Reuters Co., New York, New York, USA).  
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38 We will also conduct searches on Google [44] and Google scholar [45] for potentially  
39 eligible guidelines and consensus statements that are not indexed in the  
40 aforementioned databases. We will search the internet via Google chrome browser  
41 using the strategy “Region AND (hyperuricemia OR gout) AND (guideline OR  
42 consensus OR recommendation OR statement)” and screen the first 100 records for  
43 each region. Name of regions to be searched are: America, Australia, Canada, China,  
44 Europe, Hong Kong, India, Japan, Singapore, South Africa, and the United Kingdom.  
45 We will search via the Google scholar engine using the strategy “(hyperuricemia OR  
46 gout) AND (guideline or consensus or recommendation or statement)” and screen the  
47 first 200 records.  
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### 56 **Study selection and data extraction**

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58 Two reviewers will independently screen the titles and abstracts of all searched  
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3 documents and determine the papers for full-text review. Documents excluded during  
4 full-text review will be reported with reasons for exclusion. Disagreements will be  
5 resolved through discussion with a consultant endocrinologist.  
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10 We will extract the following data from each included document: document  
11 characteristics (e.g., first author, year of publication, title, issuing organization,  
12 country, funding body), recommendations for diagnosis and investigation of  
13 hyperuricemia and gout, and recommendations for management (e.g., treatment and  
14 prophylaxis for acute gout, ULT options, target serum uric acid levels, comorbidities).  
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### 18 19 20 **Appraisal of guidance documents**

21 All included documents will be assessed by four reviewers (Q.L., X.L., J.S.W.K. and  
22 S.L.) independently using the Appraisal of Guidelines for Research and Evaluation  
23 (AGREE) II instrument [46]. AGREE II is an international, validated, and rigorously  
24 developed tool to evaluate the quality of clinical practice guidelines [47,48] and  
25 consensus statements [49,50]. This tool is composed by 23 items and evaluates six  
26 domains of guideline development and report: scope and purpose, stakeholder  
27 involvement, rigor of development, clarity of presentation, applicability, and editorial  
28 independence. Reviewers score each item on a seven-point Likert scale, with 1 point  
29 for Strongly Disagree and 7 points for Strongly Agree. The score for each domain of  
30 each document is calculated as follows: (obtained score-minimal possible  
31 score)/(maximal possible score-minimal possible score). The minimum possible score  
32 is calculated as: (number of questions) x (number of reviewers) x 1. The maximum  
33 possible score is calculated as: (number of questions) x (number of reviewers) x 7 [46].  
34 This score calculation will be conducted using the My AGREE PLUS platform [51].  
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46 All reviewers will complete the online training tutorial [52] before the  
47 commencement of appraisal to ensure standardization. A meeting will be held among  
48 reviewers after the appraisal and every item with scores differed more than one point  
49 will be discussed. Reviewers can revise their scores or keep the original evaluation  
50 after discussion, and records will be made for the scores revised with reasons for  
51 revision. When the scoring process is completed, the inter-rater reliability on the  
52 AGREE II will be examined using the intra-class correlation coefficient (ICC) via  
53 IBM SPSS (IBM Co., Armonk, New York, USA). An ICC  $\geq 0.7$  is considered  
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3 acceptable [53].  
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### 6 **Recommendation synthesis**

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8 We will manually extract descriptive data from included documents and tabulate them  
9 to summarize recommendations of guidance documents and to highlight consistencies.  
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11 The domains of recommendations summarized will depend on the information  
12 available in guidance documents relating to the diagnosis and treatment strategies for  
13 hyperuricemia and gout, such as target uric acid level, timing to initiate ULT in  
14 patients with acute gout attack, prioritization of ULT options, allopurinol dosing,  
15 prophylaxis management against acute gout attack, treatment for asymptomatic  
16 hyperuricemic patients without comorbidities, timing to assess urate deposits with  
17 imaging techniques, and monitoring of urate deposits clearance. A flow diagram  
18 (Figure 1) will be provided to illustrate the review process.  
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### 26 **ETHICS AND DISSEMINATION**

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28 The results of the systematic review will be disseminated through relevant scientific  
29 meetings and peer-reviewed journals.  
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### 32 **DISCUSSION**

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34 Clinical practice guidelines and consensus statements are of important value for  
35 clinical practice. However, guidance documents issued by different organizations for  
36 hyperuricemia and gout are highly inconsistent, which impairs the application of and  
37 compliance to these documents. Hence, we will conduct this systematic review to  
38 identify the quality and consistency of guidelines and consensus, and provide a  
39 summary of guideline recommendations.  
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46 To date, no systematic appraisal for the quality of hyperuricemia and gout guidelines  
47 has been reported in the English or Chinese literature. Although a quality appraisal  
48 [54] of four recent guidelines for gout was published in 2014, it did not systematically  
49 review all published guidance documents. Additionally, only two appraisers were  
50 involved, one of which was a co-author of one of the rated guidelines, while the  
51 AGREE II developer recommends four appraisers [53]. Our proposed review  
52 integrates comprehensive search strategies, applies the well-established and validated  
53 AGREE II tool and adopts a rigorous appraisal process by four independent reviewers  
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3 to minimize subjective bias.  
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6 Possible limitations of this research are language restrictions and unconscious bias  
7 from subjective rating of documents. To minimize publication bias, we will search  
8 grey literature on the internet via Google and selection bias will be reduced by  
9 involving four independent reviewers.  
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14 It is necessary to systematically review and appraise clinical practice guidelines and  
15 consensus statements for diagnosis and management of hyperuricemia and gout. This  
16 protocol provides a clear and structured process for guidance documents identification,  
17 quality evaluation, and recommendation summarization. This review will assist  
18 clinicians to better understand and apply guidelines and consensus recommendations  
19 to improve hyperuricemia and gout care, guideline developers to develop guidance  
20 documents of high quality, and researchers to identify knowledge gaps for future  
21 research.  
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32 developing the search strategy.  
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39 commercial or not-for-profit sectors.  
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## 43 44 **CONFLICTS OF INTEREST**

45 The authors declare no conflict of interest.  
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**Table 1 Sample search strategy for EMBASE using the OVID interface**

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	hyperuric?emia.m_titl.
6	gout.m_titl.
7	uric acid.m_titl.
8	urate\$.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline\$.m_titl.
12	consensus.m_titl.
13	position statement\$.m_titl.
14	exp health care policy/ or exp policy/
15	recommendation\$.m_titl.
16	10 or 11 or 12 or 13 or 14 or 15
17	9 and 16

**Figure 1 Flow diagram for literature search**

NGC, National Guideline Clearinghouse; GIN, Guidelines International Network;  
NICE, National Institute for Health and Care Excellence; NHS, National Health  
Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and  
Audit Implementation Network; TRIP, Turning Research Into Practice Database;  
CBM, Chinese Biomedical Literature Database.

For peer review only

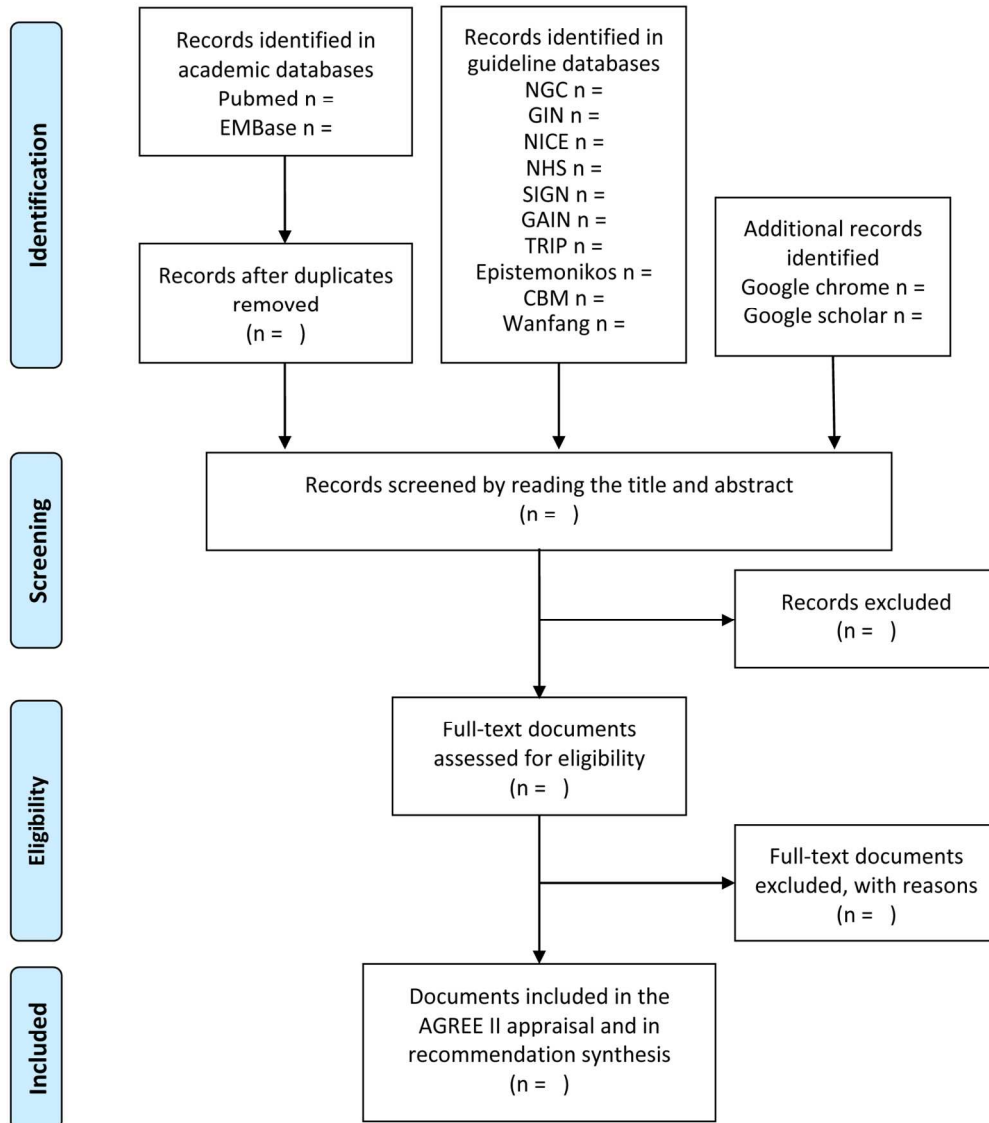


Figure 1 Flow diagram for literature search. !! † NGC, National Guideline Clearinghouse; GIN, Guidelines International Network; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; SIGN, Scottish Intercollegiate Guidelines Network; GAIN, Guidelines and Audit Implementation Network; TRIP, Turning Research Into Practice Database; CBM, Chinese Biomedical Literature Database.

179x204mm (300 x 300 DPI)

**Table 1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (adopted from the PRISMA website [45])**

Section and topic	Item No	Checklist item	Page No
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information	9	Describe all intended information sources (such as electronic databases,	7

sources	contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	n/a
	15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	n/a
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7-9
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9