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

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

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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ABSTRACT

Objectives

Despite the publication of hundreds of trials on gout and hyperuricemia, management of these conditions remains suboptimal. We aimed to assess the quality and consistency of guidance documents for gout and hyperuricemia.

Design

Systematic review.

Interventions

We searched PubMed and EMBASE (in October 2016), ten guideline databases, and Google and Google scholar (in July 2017) for the latest version of international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese. The quality of guidance documents was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. Recommendations were tabulated and visualized in a coloured grid.

Results

Twenty-four guidance documents (16 clinical practice guidelines and 8 consensus statements) published between 2003 and 2017 were included. Included documents performed well in the domains of scope and purpose (median 85.4%, range 66.7%-100.0%) and clarity of presentation (median 81.3%, range 48.6%-98.6%), but unsatisfied in applicability (median 9.9%, range 0.0%-66.7%) and editorial independence (median 28.1%, range 0.0%-83.3%). The 2017 British Society of Rheumatology guideline received the highest scores. Recommendations were concordant on the target serum uric acid level for long-term control, on some indications for urate-lowering therapy, and on the first-line drugs for urate-lowering therapy and for acute attack. Substantially inconsistent recommendations were provided for many items, especially for the timing of initiation of urate-lowering therapy and for treatment for asymptomatic hyperuricemia.

Conclusions

Methodological quality needs improvement in guidance documents on gout and hyperuricemia. Evidence for certain clinical questions is lacking, despite numerous trials in this field. Promoting standard guidance development methods and synthesizing high-quality clinical evidence are potential approaches to help reduce inconsistency in recommendations.

Study registration

PROSPERO (CRD42016046104).

Keywords

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The first systematic review to assess the quality of clinical practice guidelines and consensus statements on the diagnosis and treatment for hyperuricemia and gout.
2. The first systematic review to summarise recommendations for best practice in hyperuricemia and gout.
3. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument was used for evaluation, which was an international, validated, and rigorously developed tool.
4. Only guidance documents in English and Chinese were included.

BACKGROUND

Gout is an inflammatory arthritis occurring in response to monosodium urate crystals formation, a common and necessary pathogenic factor of which is hyperuricemia. The prevalence of gout and hyperuricemia [1-4], as well as their disease burden [5, 6], are rising globally. More than six hundred clinical studies [7], including observational studies, randomised clinical trials, and mendelian randomization studies, have been published to date. However, the quality of care for gout and hyperuricemia remains suboptimal. The goal of treatment is to reduce the body's total uric acid pool [8, 9] and consequently to minimize the risk of acute flares, arthropathy, nephrolithiasis, and other complications [7, 10, 11]. A study in the United States found that only 22% patients with gout received therapy adhering to all quality indicators [12] and a nationwide population study in the United Kingdom reported that only 48% of prevalent patients received proper consultation and only 27% of incident patients were provided with urate-lowering therapy (ULT) within one year of diagnosis [6].

High-quality guidance documents are important for improving the quality of diagnosis and management of gout and hyperuricemia at individual, community, and national levels [13]. Current guidance documents for hyperuricemia and gout have been developed by rheumatology, endocrinology, and cardiology groups, at regional, national or international levels. Among these documents, the American College of Rheumatology (ACR) guidelines [14, 15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16-18], updated in 2016, have the most substantial global influence. The most recent documents (released in 2017) are two national guidelines, from the American College of Physicians (ACP) [19, 20] and from the British Society of Rheumatology (BSR) [21], and one consensus statement, from the Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases [22].

However, current guidance documents on gout and hyperuricemia provide inconsistent recommendations, even those released by highly respected professional organizations, such as the ACP and the ACR [23]. Some distinct differences lie in key aspects for patient care, such as the pharmacological treatment for asymptomatic hyperuricemic patients, the timing of initiation of ULT in patients with gout flare [24], and indications for ULT [25]. These discrepancies may result from ethnic and social differences, but can be consequences of inconsistent guideline development [23]. Low-quality guidance documents put individual patients and communities at risk, and impede clinicians' application of the guidance in daily practice [26]. Hence, we conducted this study to systematically evaluate the quality of guidance documents on gout and hyperuricemia and to compare all key recommendations from different documents.

METHODS

Detailed methods of the study have been published previously [27] and this study was registered with PROSPERO (registration number: CRD42016046104).

Literature search and selection criteria

We systematically searched PubMed and EMBASE from inception to 27 October 2016 using a comprehensive search strategy (Supplementary Table 1 and Supplementary Table 2) to identify guidance documents pertaining to the diagnosis and treatment of hyperuricemia and gout. We searched guideline databases from inception to 24 July 2017 using search strategies tailored to different databases (Supplementary Table 3). We also searched Google and Google scholar in July 2017 for potentially eligible guidelines and consensus statements that were not indexed in the aforementioned databases.

We included the latest versions of all international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese. Two reviewers (Q.L., X.L.) independently screened all searched papers. Reasons for exclusion were provided for documents excluded during the full-text review (Supplementary Table 4). Disagreements were resolved through discussion with a third reviewer (S.L.).

Data extraction

We extracted the following data from each included document: document characteristics (e.g., year of publication, funding body, evidence base), recommendations for diagnosis and monitoring of hyperuricemia and gout, and recommendations for management. Data were extracted by one investigator (Q.L.) and were checked by a second investigator (X.L.).

Appraisal of guidance documents

All included documents were assessed by four reviewers (Q.L., X.L., J.W., and H.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [28]. AGREE II is an internationally developed and validated tool to evaluate the quality of clinical practice guidelines [29-31] and consensus statements [32, 33].

All reviewers completed the online training tutorial [34] before the commencement of appraisal to ensure standardization. We adapted detailed instructions for scoring from the AGREE II User's Manual [28] and provided objective scoring criteria for each item (Supplementary File 1). We selected four guidance documents for pilot scoring, during which our objective scoring criteria were discussed and clarified. A meeting was held among reviewers after the appraisal and every item with scores differed more than one point was discussed. Reviewers were given the opportunity to revise their scores or to

keep the original scores after the meeting. We recorded all original scores, revised scores, and reasons for modifying scores. We calculated the inter-rater reliability on the AGREE II using the intra-class correlation coefficient (ICC) via IBM SPSS (IBM Co., Armonk, New York, USA) when the entire scoring process was completed. An ICC >= 0.7 was considered acceptable [35].

Recommendation synthesis

We manually extracted descriptive data from all included guidance documents and tabulated them into the following tables to summarize recommendations: the diagnosis of gout and hyperuricemia, the treatment of hyperuricemia, the treatment of acute gout, and the treatment of tophi. Data were extracted by one investigator (Q.L.) and were checked by a second investigator (X.L.). We plot the summarized recommendations in a five-colour grid to illustrate inconsistencies. The most frequently stated content was used as the reference content. Cells of guidance documents providing consistent recommendations were coloured in green, while cells of those providing partially consistent recommendations, which was defined as recommendations including but not the same as reference contents, were coloured in blue, and of inconsistent recommendations in red. Where recommendations were not given and were not applicable, the cell was coloured in yellow and in grey, respectively.

RESULTS

Search results

Overall, we identified 5811 items across the academic databases, guideline databases, Google, and Google Scholar. After applying the inclusion and exclusion criteria, 24 guidance documents from 26 papers [14-22, 36-52] were included in the final appraisal and recommendation synthesis (Figure 1). Studies excluded after full-text review and reasons for exclusion were provided as Supplementary Table 4.

Characteristics of the included guidelines and consensus statements

Table 1 summarized the characteristics of the included guidance documents, among which 16 were clinical practice guidelines [14-21, 38, 41, 44-46, 48-52] and eight were consensus statements [22, 36, 37, 39, 40, 42, 43, 47]. 16 national or regional organizations and three international groups, namely the 3e (Evidence, Expertise, Exchange) Initiative, the EULAR, and the development group for the Treat-to-target (T2T) recommendations, published these documents between 2003 to 2017. 16 documents [14-18, 21, 22, 36-38, 40, 42, 43, 45, 46, 49, 50] were issued by rheumatology organizations and seven [16-18, 36, 39, 42, 43] were developed by multinational development groups. 17 documents [14-18, 21, 22, 36, 38-41, 43-46, 49, 51] provided information on guideline development group, among which 11 [14-17, 19-21, 36, 41-43, 45, 46] explicitly stated the involvement of a methodologist. 12 documents [14-18, 21, 22, 38-41, 43-46, 49, 51] provided information on the target audience, among which only three [16, 38, 44] included the patients. 18 documents [14-21, 36, 39-43, 45, 46, 48-52] reported conducting a systematic literature review in the development, among which 17 documents [14-21, 36, 39-41, 43, 45, 46, 48-52] reported the level of evidence in support of recommendations and 16 [16-21, 36, 39-41, 43, 45, 46, 48-52] graded the strength of recommendations. Ten documents [16, 19-21, 39, 42, 46, 48, 49, 51, 52] clearly stated being externally reviewed. Five [19-21, 46, 49, 50] provided a clear time of update plan. 12 documents [14, 15, 17-21, 36, 39, 42, 46, 49, 51, 52] provided information on the funding body, among which six [17, 36, 39, 46, 49, 51] were fully or partially funded by the pharmaceutical industry. The other half did not clearly declare the funding body, which made the impact of industry on the recommendations ambiguous.

Appraisal of guidelines and consensus statements

Figure 2 showed the standardized domain score for each guidance document for the six quality domains assessed with the AGREE II tool. Domain scores

were provided in value as Supplementary Table 5. Mean score across reviewers for individual items were provided as Supplementary Table 6. Item scores and reasons for scoring for each item were provided as Supplementary Table 7). The overall quality of guidelines, as assessed by AGREE II, varied both between guidance documents across domains and within guidance documents between domains. The document with the highest domain scores was published by the BSR in 2017 [21], with five domains scoring above the upper quartile, followed by the documents published by the ACP in 2017 [19, 20], and by the ACR and the EULAR jointly in 2015 [42], both with four domains scoring above the upper quartile. Guidelines did not always score higher than consensus statements. The standardized domain scores for each domain of all guidance documents were visualized by the year of publication in Supplementary Figure 1. No tendency of improvement in the quality score was observed.

The AGREE II instrument evaluated guidelines and consensus statements in six domains, from the development, dissemination, to implementation. The scope and purpose (domain 1) clarifies the clinical questions. Proper involvement of stakeholders (domain 2) balances individuals' biases. Rigour of development (domain 3) is the domain most concerned by clinicians and ensures the validity of development methodology [53]. Clearly presented recommendations (domain 4) conveyed precise and accessible information from the development group to clinicians. Good performances in the applicability (domain 5) and the editorial independence (domain 6) guarantee the usefulness and the independence of documents.

Guidance documents received the highest scores for the scope and purpose (domain 1, median 85.42%, range 66.67% to 100.00%) and the clarity of presentation (domain 4, median 79.17%, range 48.61% to 98.61%), and the lowest scores for the applicability (domain 5, median 10.94%, range 0.00% to

66.67%) and the editorial independence (domain 6, median 28.13%, range 0.00% to 83.33%). The worst scored item was the monitoring or auditing criteria (mean score 1.2, range 1.0-4.0), followed by the implementation advice or tools (mean 1.7, range 1.0-4.8), the external review (mean 2.1, range 1.0-6.0), and the updating procedure (mean 2.1, range 1.0-6.5).

The ICC was 0.896. Group discussion modified 365/2208 (16.53%) of individual scores. The original and modified item scores and reasons for modification were provided as Supplementary Table 8.

Synthesis of recommendations

The included guidance documents addressed four major themes: diagnosis of gout and hyperuricemia, treatment for hyperuricemia, treatment for acute gout attack, and treatment for tophi. Figure 3 showed the key recommendations and their inconsistencies.

Approaches to diagnostic strategies for gout and hyperuricemia

Thirteen guidance documents [17-20, 22, 36, 38, 40-43, 46, 49, 51] covered the diagnosis of gout and 11 [17, 22, 37, 38, 45-51] covered diagnosis of hyperuricemia. Supplementary Table 9 showed the key recommendations. Three aspects were evaluated commonly in gout diagnosis, which is the clinical manifestation, considered by all documents, the laboratory result, considered by all but one document [49], and the imaging result, considered by all but four documents [17, 19, 20, 49, 51]. Identification of monosodium urate crystals in synovial fluid or tophi was required for definite diagnosis by all documents.

Guidance documents differed when recommending the cut-off serum uric acid (SUA) level to diagnose hyperuricemia. For any patient with elevates SUA, four documents [38, 47, 48, 51] recommended 7.0 mg/dL (or 420 μmol/L) as

the cut-off, while two [17, 45] preferred 6.8 mg/dL. Five documents [22, 37, 46, 49, 50] provided gender-specific cut-offs, recommending 6.0 mg/dL (or 360 μmol/L) in female and 7.0 mg/dL (or 420 μmol/L) in male. Asymptomatic hyperuricemia was defined in seven [36, 38, 46-50] documents, among which six [36, 38, 46-48, 50] clarified the exclusion of patients with gout and two [36, 48] clarified the exclusion of patients with tophi when making the diagnosis. Patients with renal diseases were not allowed to be diagnosed with asymptomatic hyperuricemia in the Japanese [48] and the Philippine [50] guidelines, but patients with pre-existing renal or cardiovascular diseases were allowed in the 3e initiative document [36].

Approaches to treatment for hyperuricemia

Twenty-two guidance documents [14-17, 19-22, 36-41, 43-52] covered the treatment for hyperuricemia and Supplementary Table 10 summarized the key recommendations. All but three documents [19, 20, 44, 52] explicitly recommended the target levels for long-term SUA control, most of which preferred 6.0 mg/dL (or 360 μmol/L), except the South African guideline [51] that preferred 5.0mg/dL (300 μmol/L). Only two documents [16, 22] recommended a lower limit of 3.0 mg/dL (or 180 μmol/L) for long-term SUA management and only the 2016 EULAR guideline [16] provided evidence that low SUA might increase the risk of neurodegenerative diseases, although the level of evidence and the grade of recommendation were low.

All but six guidance documents [36, 39, 40, 43, 44, 52] provided indications for long-term ULT. Recurrent attacks [14-17, 19-22, 41, 45, 48-51], tophi [14-17, 19-22, 38, 41, 45, 48-51], urate nephrolithiasis [14-17, 19-22, 37, 38, 49, 50], arthropathy [16, 17, 21, 22, 38, 41, 45, 49], and comorbidities [14-16, 19-22, 37, 47, 49, 50] were the most commonly recommended indications. The definition of recurrent attacks varied from at least once per year [17] to at least three times per year [49], while the majority of documents [14-16, 19-21, 41]

recommended twice per year as the cut-off.

Regarding the timing to initiate ULT, agreement was not made whether to start pharmacological ULT after an acute attack [17, 21, 22, 36-38, 40, 48, 49, 51, 52] or during an attack [14, 15, 37], and when recommending to start ULT after an attack, the preferred time to wait since the resolution of attack varied from two weeks [37, 48] to six weeks [52]. All guidance documents based this recommendation on expert opinions due to insufficient evidence. Considerations supporting not starting ULT during an attack included that ULT was better discussed when the patient was not painful [21], and that ULT initiation could prolong or worsen the acute attack [51]. Two documents [16, 39] explicitly presented the currently conflicting views and insufficient evidence and stated consequently no recommendation for this issue.

When pharmacological ULT options were provided with prioritization, allopurinol was recommended by all guidance documents [14-17, 21, 36, 40, 43, 45, 46, 48-50] to be the first-line drug, while febuxostat was recommended by three documents [14, 15, 17, 46] to be the first-line and by six documents [16, 21, 36, 40, 43, 45] to be the second-line. However, recommendations on the dosage of allopurinol varied largely. The maximum dose per day recommended for allopurinol varied from 300 mg [51], 600 mg [22, 37, 47], 800 mg [14, 15, 17, 38, 45], to 900 mg [21, 43, 46], and the daily starting dose recommended in patients with normal renal function varied between 50 mg [19, 20, 22, 47, 48, 51] and 200 mg [21]. As for patients with impaired renal function, the cut-off to initiate dose adjustment was provided diversely as creatinine clearance (CCr) 20-140 mL/min [37, 45, 46, 49, 51], or estimated glomerular filtration rate (eGFR) 130 ml/min/1.73m^2 [21]. One document preferred to depend allopurinol dose solely on eGFR by limiting the maximum dose to 1.5 mg/eGFR in patients with renal impairment [22]. HLA-B*5801 gene screening prior to allopurinol use was recommended by five guidance documents [14, 15,

21, 22, 37, 38].

For patients with asymptomatic hyperuricemia, 14 guidance documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52] commented on the option of pharmacological ULT, among which, five [17, 21, 38, 51, 52] explicitly recommended no treatment and three [47-49] recommended pharmacological treatments in patients with comorbidities [47, 48] or with very high SUA levels [40, 47-49]. The cut-off SUA level to indicate ULT in patients with asymptomatic hyperuricemia varied from 8.0 mg/dL [47, 48] to 13.0 mg/dL [49]. The Portuguese document [40] was incoherent itself by generally stating that pharmacological treatment was not recommended while also considered it in patients with SUA higher than 9 mg/dL. No evidence was provided by these documents to support pharmacological treatment for asymptomatic hyperuricemia directly, and such recommendations were made in concern of the onset of gout [40] and the risk of cardiovascular disorders [47, 48].

Approaches to treatment for the acute gout attack

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for acute gout attack and Supplementary Table 11 summarized their key recommendations. Non-steroidal anti-inflammatory drugs (NSAIDs) was recommended by all but three documents [19, 20, 39, 44] as the first line pharmacological treatment, while colchicine by 11 documents [14-17, 21, 22, 36, 37, 40, 43, 45, 48]. Colchicine was recommended to be given in a fixed dose by three documents [38, 40, 48] and in a loading dose followed by different doses by six documents [14-17, 19, 20, 22, 38, 51, 52]. Seven documents [21, 36, 41, 43, 45, 49, 50] only provided the total daily dose for colchicine regardless of the regimen, the doses recommended by which varied from 1 mg [21, 49, 50] to 2.4 mg [49], except that one document [43] recommended 1.8 g in 24 hours without any further explanation. Systemic steroids were recommended by all but three documents [37, 39, 44], among

which six [14-17, 19, 20, 36, 43] recommended them as the first-line option and ten [21, 22, 38, 41, 45, 46, 48, 50-52] recommended them when NSAIDs and colchicine were contraindicated or intolerant. Intra-articular steroids injection was recommended by 14 documents [14-17, 21, 22, 36, 38, 40, 43, 45, 46, 49, 51, 52], among which five [14-16, 21, 36, 43] clearly recommended it as the first-line option.

Approaches to treatment for tophi

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for tophi and Supplementary Table 12 showed their key recommendations. Surgery was recommended by nine documents [22, 36, 38, 40, 43, 48, 49, 51], among which five [22, 36, 38, 43, 49] explicitly presented the indications, most commonly nerve compression [22, 36, 38, 43] and infection [36, 38, 43]. The risk for surgery was discussed by one document [51] and it only mentioned wound healing. Long-term ULT was recommended by all but two documents [44, 52], but the pharmacological treatment was only explicitly recommended by eight of them [15-17, 21, 37, 43, 46, 51].

DISCUSSION

Principal findings and interpretations

This systematic review, including 16 guidelines and eight consensus statements, generally found low in quality and inconsistent recommendations from guidance documents covering the diagnosis and management of gout and hyperuricemia. Despite the increase in the number of guidance documents released between 2003 and 2017, the quality of documents in all domains did not seem to improve with time. To date, this is the first systematic appraisal for the quality of hyperuricemia and gout guidance documents.

Comparison with existing research

Guidance documents assessed in our study performed acceptable in the

scope and purpose and the clarity of presentation, but unsatisfied in the applicability. These results were consistent with one previous review [54], which assessed the quality of guidance documents released by the 3e initiative [36], the ACR [14, 15], and the EULAR [18, 55], respectively. Our study systematically included all guidelines and consensus statements in this field and further suggested that this trend of differed quality by domains and differed recommendations was shared by all guidance documents for gout and hyperuricemia.

Previous reviews of guidance documents in endocrinology and rheumatology diseases, such as diabetes [56, 57], thyroid disorders [31, 58], rheumatoid arthritis [32, 59, 60], and systemic lupus erythematosus [61], as well as reviews for guidance in other specialities [33, 62-64], gave similarly high scores in the scope and purpose and the clarity and presentation, and similarly low scores in the applicability and the editorial independence. Despite generally low and varied scores in the applicability, guidance documents on gout and hyperuricemia performed poorer in this domain comparing to the majority of other documents [31-33, 56-58, 60-64], suggesting that the negligence of the usefulness of guidance being more challenging in gout and hyperuricemia. The time and cost of the economic evaluations and pilot studies require a stable and long-term task force of guideline development, putting applicability scoring in idealism. Although the practical difficulties, the guidance documents were suggested to at least inform audience the need to consider these issues [62]. Low scores in the editorial independence often resulted from lacking detailed information on the influence of funding body and conflict of interests. We found that 50% of documents declaring funding sources were supported by the pharmaceutical industry, calling for awareness of the potential influence of pharmaceutical industry on clinical guidance and for the need of promoting transparency in the financial declaration.

Clinical implications and future research

Guidance documents were concordant and recommended to target for SUA < 6.0 mg/dL (or 360umol/L) for long-term control, to consider recurrent attacks as one of the indications for ULT, although the definitions for recurrent attacks differed, to consider allopurinol as the first-line ULT and NSAIDs as the first-line drug in acute attack, and to consider long-term ULT in patient with tophi. Despite these similarities, recommendations differed in the majority of items and these discrepancies might come from several sources, including ethnic difference, quality of documents, and lacking of evidence.

Ethnical and social differences are important sources for recommendation diversity and such diversity is encouraged to improve the precision of guidance. Ethnicity difference explained the tendency of positive recommendations on HLA-B*5801 gene screening before prescribing allopurinol by Asian guidance documents [22, 37, 38]. The risk of hypersensitivity reactions associated with allopurinol is significantly increased in individuals carrying the variant allele HLA-B*5801, the frequency of which in Han Chinese, Korean, and Tai people are higher than that in the Caucasian population [14, 15, 21]. Providing ethnicity-specific recommendations or explicitly specifying the ethnicity of target audience help clarify the source of inconsistency and improve the precision of recommendations.

However, the low quality of guidance documents also leads to discrepant recommendations and consequently chaos in application. Such discrepancies were concerned by clinicians when applying these recommendations in clinical practice and were observed to affect recommendations in the guidance documents for hyperuricemia and gout. Comparing to documents with high quality (scoring above the upper quartile in at least three out of the six AGREE II domains) [16, 19-21, 36, 42, 46], those with low quality (scoring below the lower quartile in at least three out of the six AGREE II domains) [22, 37, 38, 44,

47, 52] provided ambiguous prioritization of ULT drugs for hyperuricemia and of steroid options for acute attack. Among all domains assessed by the AGREE II instrument, those pertaining to stakeholder involvement, rigor of development, applicability and editorial independence could be primarily improved by standardizing the developing processes, which consequently improved the reliability of recommendations. Guidance documents from China are facing even greater challenges to adopt standard developing processes [13].

Guidance documents were considered as the starting point to identify evidence gaps and to prioritize research questions [65]. Evidence gap was an issue commonly discussed in the recommendations of treatment for asymptomatic hyperuricemia, by five [14, 15, 36, 37, 39, 43] out of 14 documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52], and of timing to initiate ULT, by two [16, 39] out of 14 documents [14-17, 21, 22, 36-40, 48, 49, 51, 52]. Although the rest of documents provided explicit recommendations, they based their recommendations either on indirect evidence or expert opinions. Evidence synthesis for the effects of pharmacological ULT in patients with asymptomatic hyperuricemia and for the optimal timing to initiate ULT in patients with the acute attack is warranted to improve the strength and consistency of these recommendations.

Strengths and limitations

Strengths of our review included a systematic approach to identify guidance documents pertaining to the diagnosis and management of hyperuricemia and gout. Both guidelines and consensus statements were evaluated and compared. We used the AGREE II instrument, an international, validated and rigorously developed tool, to assess the quality of document development and we tailored the AGREE II instrument to point-by-point scoring criteria (Supplementary File 1) to improve the objectivity and reproducibility of our

study. We summarized all key recommendations and compared and visualized the inconsistencies among them, providing concise but informative overview for clinicians and researchers.

Our study also has limitations. Firstly, we only included documents published in English or Chinese, which could lead to a risk of neglecting essential documents from regions not using English or Chinese as the first language. We attempted to mitigate this risk by tailoring our search strategy to identify the English versions of guidance documents published from these regions. Secondly, unconscious bias from a subjective rating of documents was inevitable. We avoided inviting co-authors of guidance documents as a reviewer to prevent subconscious competing interest and conducted two rounds of group discussions to minimize subjective bias. Thirdly, the AGREE II instrument itself has weaknesses [31, 56, 64, 66], although it was the most commonly used tool to assess the quality of guidance documents. The AGREE system assigned equal weight to all six domains, regardless of their relative importance [67]. Although the higher quality of development methodology and more transparency of reporting is associated with recommendations that are more reliable, proper methodology and transparency do not guarantee better patient outcomes. Hence, the quality scores assessed by the AGREE II should be interpreted with caution when used to indicate which guidelines to follow in clinical practice. Moreover, the subjective interpretation of scoring criteria impeded the replicability of AGREE II studies and direct comparison of quality scores in guidance documents provided by different reviews.

CONCLUSIONS

The methodological quality needs to be improved in the current guidelines on the diagnosis and management of hyperuricemia and gout, as assessed by the AGREE II. Inconsistent recommendations are common, even in some key aspects. Promoting standard methods for guidance documents development

and synthesizing high-quality clinical evidence to fill in evidence gaps are warranted to improve the quality of guidance documents.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

HT and SL conceived this study. QL, JSWK, and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC, LL, and XS designed the appraisal strategy of each included guideline and consensus. QL and XL searched literature search and extracted data. QL, XL, JW, HL, and SL assessed the quality of each document. QL analysed and visualized the outcomes. SC, AS, YC, AZ, XS, and HH provided critical review. QL, XL, and SL drafted the manuscript. All authors discussed actively in the protocol of the study.

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TABLES AND FIGURES

Table 1. Characteristics of included guidelines and consensus statements

3e: Evidence, Expertise, Exchange; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; CS: consensus statement; CVD: cardiovascular diseases; ER: external review; EULAR: European League Against Rheumatism; LOE: level of evidence; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; Multi: multidisciplinary development group; NG: not given; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; Phy: physicians; Pt: patients; Rheu: rheumatologists; SLR: systematic literature review; SOR: strength of recommendation.

Document	Issuing organization	Year of publication	Country	Funding body	Target population	Target audience	Guideline development	Guideline review	Guideline update	Evidence base	LOE	SOR
Guidelines												
SAMA_2003 [51]	South African Medical Association	2003	South Africa	Pharmaceutical company	Gout	Phy	Multi	ER	Intermittent	NG	-	-
EULAR_2006 [18]	EULAR	2006	Europe	EULAR	Gout	NG	Rheu	NG	NG	SLR	+	+
MOH_MSR_AMM_2008 [49]	MOH, MSR, AMM	2008	Malaysia	Pharmaceutical company	Adults (>16y) with gout	Phy	Multi	ER	2012 or sooner	SLR	+	+
PRA_2008 [50]	Philippine Rheumatology Association	2008	Philippine	NG	Gout	Phy	NG	NG	Three or more years	SLR	+	+
UTAustin_2009 [52]	University of Texas at Austin	2009	US	University of Texas at Austin	Adults with gout	Phy	NG	ER	NG	SLR	+	+
EULAR_2011 [17]	EULAR	2011	Multination	Pharmaceutical company, ASCR	Gout	Phy	Multi	NG	NG	SLR	+	+

JSGNAM_2011 [48]	Japanese Society of Gout and Nucleic Acid Metabolism	2011	Japan	NG	Hyperuricemia or gout	NG	NG	ER	NG	SLR	+	+
ACR_2012 [14, 15]	ACR	2012	US	ACR, NIAMS, NIH	Gout	Phy	Multi	NG	Intermittent	SLR	+	-
SER_2013 [46]	Spanish Society of Rheumatology	2013	Spain	Pharmaceutical company	Gout	Phy	Multi	ER	Four years	SLR	+	+
SIR_2013 [45]	Italian Society of Rheumatology	2013	Italy	NG	Gout	Phy	Multi	NG	NG	SLR	+	+
FMOH_2014 [44]	Federal Ministry of Health (Nigeria)	2014	Nigeria	NG	Gout	Phy, Pts in Nigeria	Multi	NG	NG	NG	-	-
CRA_2016 [41]	Chinese Rheumatology Association	2016	China	NG	Gout in China	Phy	Multi	NG	NG	SLR	+	+
EULAR_2016 [16]	EULAR	2016	Europe	NG	Gout	Phy, Pts	Multi	ER	Intermittent	SLR	+	+
TRA_2016 [38]	Taiwan Rheumatology Association	2016	Taiwan, China	NG	Hyperuricemia or gout	Phy, Pts	Multi	NG	NG	NG	-	-
ACP_2017 [19, 20]	ACP	2017	US	ACP	Acute and recurrent gout	Phy	NG	ER	Five years	SLR	+	+
BSR_2017 [21]	The British Society for Rheumatology	2017	UK	No specific funding.	Gout in the UK	Phy	Multi	ER	Planned in 2020	SLR	+	+
Consensus statements												
CCCP_2012 [47]	Chinese College of Cardiovascular Physicians	2012	China	NG	Asymptomatic hyperuricemia with CVD	NG	NG	NG	NG	CS	-	-
3e_2013 [36]	3e Initiative	2013	Multination	Pharmaceutical company	Gout	NG	Rheu	NG	NG	SLR	+	+
CSE_2013 [37]	Chinese Society of Endocrinology	2013	China	NG	Hyperuricemia or gout	NG	NG	NG	NG	CS	-	-
3e_PT_2014 [40]	Portuguese 3e Initiative	2014	Portugal	NG	Gout in Portuguese	NG	Rheu	NG	NG	SLR	+	+
3e_AU_NZ_2015 [43]	Australian and New Zealand 3e Initiative	2015	Multination	NG	Gout	NG	Rheu	NG	NG	SLR	+	+

ACR_EULAR_2015 [42]	ACR/EULAR	2015	Multination	ACR, EULAR	Gout	NG	NG	ER	Intermittent	SLR	-	-
T2T_2016 [39]	NG	2016	Multination	Pharmaceutical company	Gout	NG	Rheu	ER	NG	SLR	+	+
CRA_multi_2017 [22]	Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases	2017	China	NG	Hyperuricemia	Phy	Multi	NG	NG	CS	-	-

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.

Figure 2. Standardized domain scores for each guidance document

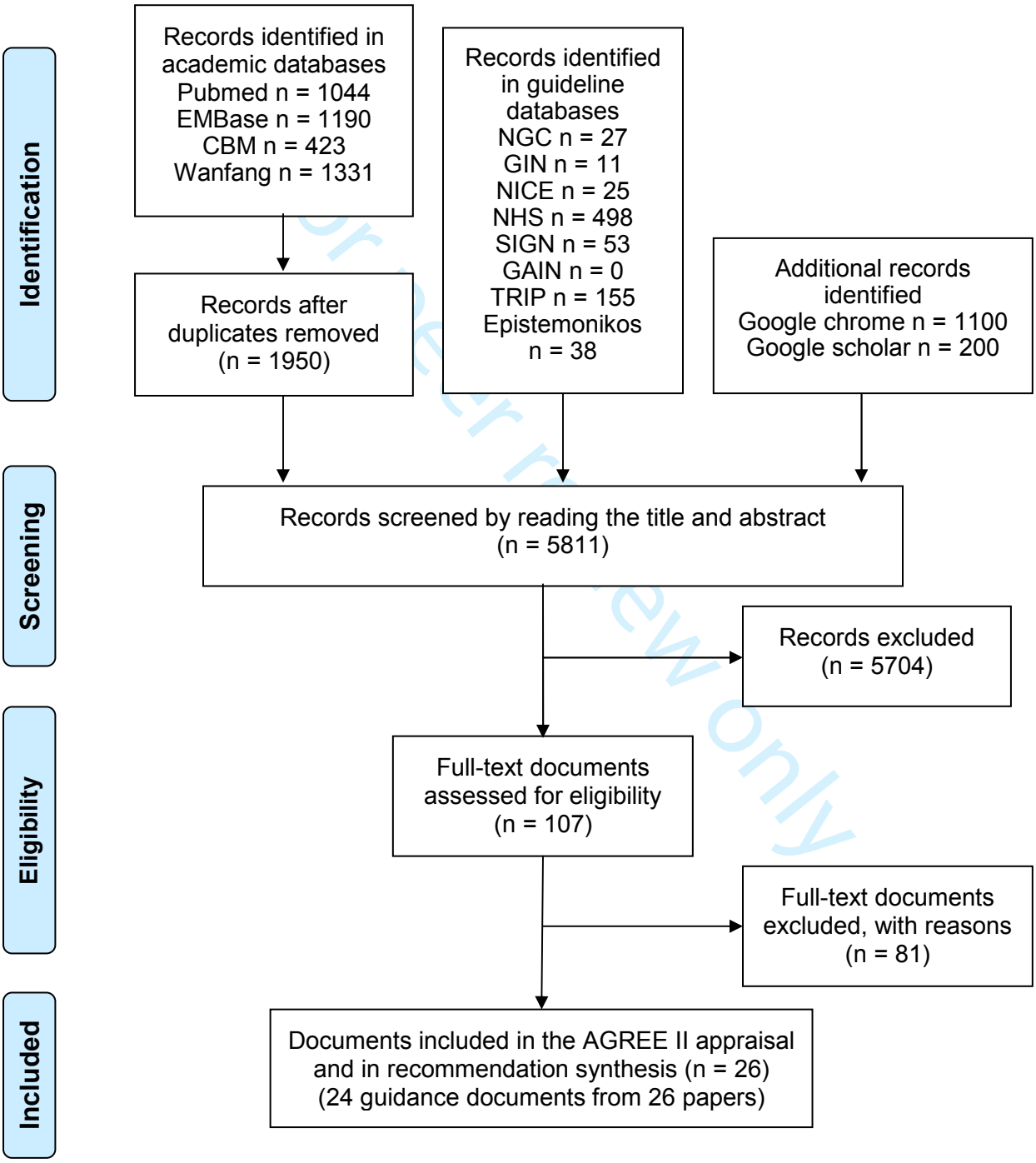
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia

3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

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.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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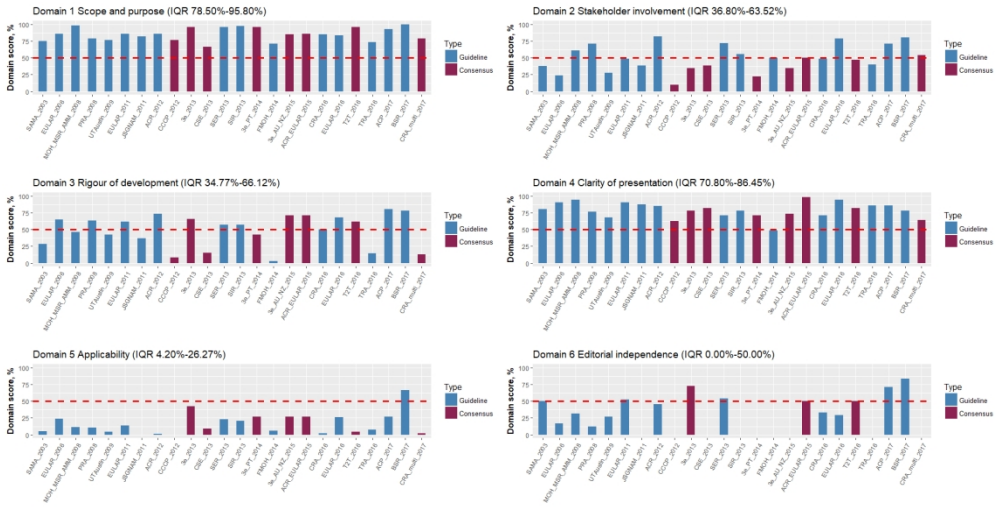


Figure 2. Standardized domain scores for each guidance document
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

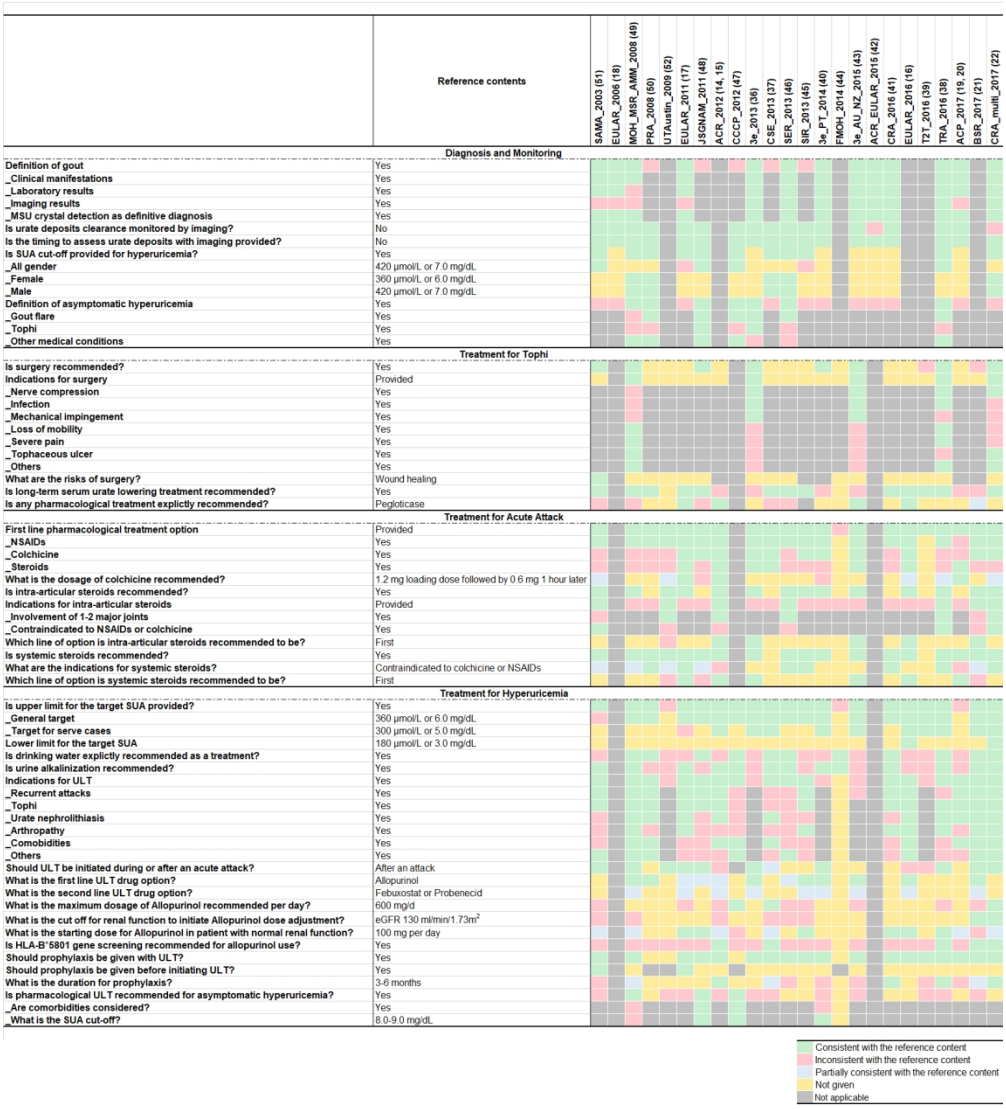


Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Supplementary Materials

Contents

Supplementary Table 1. Search strategy in Pubmed

1	urate* OR uric acid OR gout OR hyperuricemia OR hyperuricaemia
2	guideline OR guideline* OR consensus OR policy OR polic* OR statement* OR recommendation*
3	1 AND 2

Supplementary Table 2. Search strategy in EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	gout.m_titl.
6	uric acid.m_titl.
7	urate$.m_titl.
8	hyperuric?emia.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.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

Supplementary Table 3. Searches in guideline databases

Databases	Date of search	Search strategy	Results found	Full text screened	Included documents	URL
National Guideline Clearinghouse	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	27	6	4	www.guideline.gov
Guidelines International Network	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, Search mode: Guidelines	11	5	5	www.g-i-n.net
National Institute for Health and Care Excellence	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	25	2	0	www.nice.org.uk
National Health Service	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter type: guidance and policy	498	5	3	www.evidence.nhs.uk
Scottish Intercollegiate Guidelines Network	2017/07/24	NA	53	0	0	www.sign.ac.uk/our-guidelines.html
Guidelines and Audit Implementation Network	2017/07/24	“hyperuricaemia” OR “hyperuricemia” OR “gout”	0	0	0	rqia.org.uk/search-result
Turning Research Into Practice Database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: all secondary evidence	155	9	3	www.tripdatabase.com
Epistemonikos database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: Broad syntheses OR Structured summaries	38	2	1	www.epistemonikos.org
Chinese Biomedical Literature Database	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	423	7	5	202.115.54.56/index.jsp
Wanfang Data	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	1331	19	4	www.wanfangdata.com.cn/

Abbreviations: NA: Not applicable.

Supplementary Table 4. Excluded studies and reasons for exclusion

First author	Year	Reason for exclusion
Wuthrich [68]	2016	Review
Ceriotti [69]	2016	Primary study
Liote [70]	2016	Editorial
de Lautour [71]	2016	Primary study
de Lautour [72]	2014	Conference abstract
Dalbeth [73]	2015	Review
Terslev [74]	2015	Primary study
Turk [75]	2016	Not providing specific recommendations for hyperuricemia or gout
Stewart Coats [76]	2016	Editorial
Sullivan [77]	2015	Review
Gutierrez [78]	2015	Primary study
Grainger [79]	2015	Primary study
Robinson [80]	2015	Review
Chaudhary [81]	2013	Review
Bakris [82]	2014	Multimedia section
Terkeltaub [83]	2013	Review
Lyseng-Williamson [84]	2013	Review
Deodhar [85]	2013	Review
Simao [86]	2012	Review
Stamp [87]	2011	Review
Jansen [88]	2010	Not produced by related professional associations, institutes, societies, or communities
Grainger [89]	2009	Review
Grainger [90]	2008	Review
Dalbeth [91]	2007	Review
Jordan [92]	2007	Replaced by updated versions from the same organization
Becker [93]	2007	Not providing specific recommendations for hyperuricemia or gout

Zhang [55]	2006	Replaced by updated versions from the same organization
Caramia [94]	2004	Review
Terkeltaub [95]	2003	Case report
Cleland [96]	1995	Review
Hande [97]	1984	Case series
Committee on the Review of Medicines [98]	1978	Not providing specific recommendations for hyperuricemia or gout
Mourgues [99]	2016	Conference abstract
Bakris [100]	1970	Not providing specific recommendations for hyperuricemia or gout
Pai [101]	2015	Review
Vargas-Santos [102]	2016	Review
Filiopoulos [103]	2016	Comment letter
Chinchilla [104]	2016	Review
Rimler [105]	2016	Review
Saito [106]	2016	Not providing specific recommendations for hyperuricemia or gout
Mody [107]	2015	Review
Richette [108]	2014	Conference abstract
Richette [109]	2014	Conference abstract
Gutierrez [110]	2014	Conference abstract
Furst [111]	2013	Not providing specific recommendations for hyperuricemia or gout
Hershfield [112]	2013	Not providing specific recommendations for hyperuricemia or gout
Andres [113]	2012	Conference abstract
Stevenson [114]	2011	Technology appraisal
Diaz-Borjon [115]	2009	Review
Furst [116]	2010	Not providing specific recommendations for hyperuricemia or gout
Taylor [117]	2009	Primary study
Taylor [118]	2008	Primary study
Bussieres [119]	2008	Not providing specific recommendations for hyperuricemia or gout
Brooks [120]	2007	Review

Bestermann [121]	2005	Not providing specific recommendations for hyperuricemia or gout
Schumacher Jr [122]	2004	Review
Bartlett [123]	2002	Not providing specific recommendations for hyperuricemia or gout
Furst [124]	2013	Not providing specific recommendations for hyperuricemia or gout
Newberry [125]	2017	Review
Shekelle [126]	2017	Review
Sandberg [127]	2015	Not providing specific recommendations for hyperuricemia or gout
Kallinich [128]	2007	Not providing specific recommendations for hyperuricemia or gout
Preminger [129]	2007	Not providing specific recommendations for hyperuricemia or gout
TA164 [130]	2008	Technology appraisal
Phoon [131]	2012	Not providing specific recommendations for hyperuricemia or gout
Li [132]	2011	Review
Zhang [133]	2013	Review
Deng [134]	2016	Primary study
Chinese Rheumatology Association [135]	2004	Replaced by updated versions from the same organization
Chinese College of Cardiovascular Physicians [136]	2010	Replaced by updated versions from the same organization
Chinese Rheumatology Association [137]	2011	Replaced by updated versions from the same organization
National Department of Health, Pretoria, South Africa [138]	2006	Not providing specific recommendations for hyperuricemia or gout
European Medicines Agency [139]	2012	Not providing specific recommendations for hyperuricemia or gout
Agency for Healthcare Research and Quality [140]	2017	Review
Agency for Healthcare Research and Quality [141]	2017	Review
National Institute for Health and Care Excellence [142]	2013	Technology appraisal
Agency for Healthcare Research and Quality [143]	2016	Review
National Health System, United Kingdom [144]	2013	Not providing specific recommendations for hyperuricemia or gout
Canadian Expert Drug Advisory Committee [145]	2011	Not providing specific recommendations for hyperuricemia or gout
CME Academic Detailing Service [146]	2013	Presented as a 'handout', not a clinical practice guideline.
Henderson [147]	2015	Not released by a professional association

Supplementary Table 5. Domain score for each included guidance document

Document	Domain 1, %	Domain 2, %	Domain 3, %	Domain 4, %	Domain 5, %	Domain 6, %
3e_2013 [36]	95.8	34.7	65.6	77.8	42.7	72.9
3e_AU_NZ_2015 [43]	84.7	34.7	71.4	73.6	27.1	0.0
3e_PT_2014 [40]	95.8	22.2	42.7	70.8	27.1	0.0
ACP_2017 [19, 20]	93.1	70.8	80.2	86.1	27.1	70.8
ACR_2012 [14, 15]	86.1	81.9	73.4	84.7	1.0	45.8
ACR_EULAR_2015 [42]	86.1	50.0	71.4	98.6	27.1	50.0
BSR_2017 [21]	100.0	80.6	78.1	77.8	66.7	83.3
CCCP_2012 [47]	76.4	9.7	8.3	62.5	0.0	0.0
CRA_2016 [41]	84.7	48.6	50.5	70.8	2.1	33.3
CRA_multi_2017 [22]	79.2	54.2	13.0	63.9	2.1	0.0
CSE_2013 [37]	66.7	38.9	15.6	81.9	9.4	0.0
EULAR_2006 [18]	86.1	23.6	65.1	90.3	24.0	16.7
EULAR_2011 [17]	86.1	48.6	61.5	90.3	13.5	52.1
EULAR_2016 [16]	83.3	79.2	67.7	94.4	26.0	29.2
FMOH_2014 [44]	70.8	50.0	3.1	48.6	6.3	0.0
JSGNAM_2011 [48]	81.9	38.9	37.0	87.5	0.0	0.0
MOH_MSR_AMM_2008 [49]	98.6	61.1	46.4	94.4	11.5	31.3
PRA_2008 [50]	79.2	70.8	63.5	76.4	10.4	12.5
SAMA_2003 [51]	75.0	37.5	28.1	80.6	5.2	50.0
SER_2013 [46]	95.8	72.2	56.8	70.8	22.9	54.2
SIR_2013 [45]	97.2	55.6	56.8	77.8	20.8	0.0
T2T_2016 [39]	95.8	47.2	61.5	81.9	4.2	50.0
TRA_2016 [38]	73.6	40.3	14.1	86.1	7.3	0.0
UTAustin_2009 [52]	76.4	27.8	42.2	68.1	4.2	27.1
Median	85.4	48.6	56.8	79.2	10.9	28.1
Minimum	66.7	9.7	3.1	48.6	0.0	0.0
Maximum	100.0	81.9	80.2	98.6	66.7	83.3

Supplementary Table 6. Mean scores across reviewers for the individual AGREE II domain items

Document	Domain 1			Domain 2			Domain 3								Domain 4			Domain 5				Domain 6	
Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3e_2013 [36]	6.8	6.5	7.0	7.0	1.3	1.0	6.3	3.8	6.3	5.8	5.8	6.8	4.0	1.0	6.0	7.0	4.0	6.8	1.0	5.3	1.3	7.0	3.8
3e_AU_NZ_2015 [43]	6.0	5.5	6.8	5.8	1.0	2.5	6.5	6.8	7.0	6.5	6.5	6.8	1.3	1.0	5.8	6.0	4.5	5.8	1.0	2.8	1.0	1.0	1.0
3e_PT_2014 [40]	6.5	7.0	6.8	4.8	1.3	1.0	2.8	2.3	5.5	3.5	5.5	6.8	1.3	1.0	5.5	6.3	4.0	4.5	1.3	2.8	2.0	1.0	1.0
ACP_2017 [19, 20]	6.0	6.8	7.0	6.3	5.3	4.3	6.8	6.8	6.5	5.0	6.5	5.3	4.8	5.0	5.3	6.8	6.5	2.5	1.8	5.3	1.0	4.0	6.5
ACR_2012 [14, 15]	6.5	5.5	6.5	7.0	5.3	5.5	7.0	7.0	6.8	6.0	5.8	6.0	1.5	3.3	5.8	7.0	5.5	1.0	1.0	1.0	1.3	3.3	4.3
ACR_EULAR_2015 [42]	6.5	5.0	7.0	5.3	4.8	2.0	7.0	6.8	5.3	6.0	7.0	5.5	1.8	3.0	6.8	7.0	7.0	3.8	4.0	1.8	1.0	3.8	4.3
BSR_2017 [21]	7.0	7.0	7.0	5.5	5.3	6.8	7.0	6.0	6.5	6.8	6.3	6.0	5.0	2.0	6.8	6.8	3.5	4.8	4.8	6.5	4.0	7.0	5.0
CCCP_2012 [47]	6.8	3.0	7.0	2.0	1.0	1.8	1.0	1.0	1.0	1.0	3.8	2.0	1.3	1.0	4.5	5.8	4.0	1.0	1.0	1.0	1.0	1.0	1.0
CRA_2016 [41]	6.3	5.0	7.0	5.5	1.0	5.3	5.0	3.3	6.3	3.5	6.0	5.5	1.8	1.0	5.3	6.5	4.0	1.3	1.0	1.3	1.0	1.0	5.0
CRA_multi_2017 [22]	7.0	3.5	6.8	4.8	1.3	6.8	1.0	1.0	1.0	1.3	5.0	2.8	1.3	1.0	5.0	6.5	3.0	1.0	1.3	1.0	1.3	1.0	1.0
CSE_2013 [37]	7.0	1.8	6.3	3.0	1.0	6.0	1.0	1.0	2.0	1.0	5.0	3.5	1.0	1.0	5.5	5.5	6.8	3.0	1.0	1.0	1.3	1.0	1.0
EULAR_2006 [18]	6.0	5.5	7.0	5.0	1.0	1.3	7.0	7.0	5.8	4.3	6.0	5.8	1.3	2.3	6.0	6.8	6.5	1.0	2.5	5.3	1.0	3.0	1.0
EULAR_2011 [17]	6.5	5.0	7.0	5.0	1.0	5.8	4.0	4.5	6.8	6.0	7.0	7.0	1.3	1.0	5.8	6.8	6.8	1.3	1.3	3.8	1.0	3.8	4.5
EULAR_2016 [16]	6.3	4.8	7.0	5.8	5.0	6.5	5.0	2.0	6.3	6.8	6.0	6.5	6.0	2.0	6.5	6.8	6.8	3.0	1.3	5.0	1.0	1.5	4.0
FMOH_2014 [44]	6.5	2.8	6.5	5.3	1.0	5.8	1.0	1.0	1.0	1.0	2.0	1.5	1.0	1.0	3.0	4.5	4.3	1.0	1.3	2.3	1.0	1.0	1.0
JSGNAM_2011 [48]	5.3	5.5	7.0	1.8	4.3	4.0	1.3	1.0	6.8	3.3	6.3	3.8	2.5	1.0	6.8	6.3	5.8	1.0	1.0	1.0	1.0	1.0	1.0
MOH_MSR_AMM_2008 [49]	6.8	7.0	7.0	5.5	1.5	7.0	4.3	1.0	5.8	1.5	5.8	4.8	2.5	4.8	6.5	6.8	6.8	1.8	3.0	1.0	1.0	4.0	1.8
PRA_2008 [50]	6.5	5.5	5.3	3.8	5.0	7.0	5.0	4.3	7.0	4.8	6.5	4.8	1.3	5.0	5.3	6.5	5.0	1.8	1.3	2.5	1.0	1.0	2.5
SAMA_2003 [51]	6.5	3.0	7.0	4.0	1.3	4.5	1.0	1.0	1.0	4.0	6.5	2.8	2.5	2.8	5.0	6.5	6.0	1.0	2.0	1.3	1.0	7.0	1.0
SER_2013 [46]	7.0	6.3	7.0	6.8	5.0	4.3	3.3	1.0	7.0	4.0	6.8	4.8	2.0	6.5	5.8	6.8	4.3	3.5	2.3	2.8	1.0	6.5	2.0
SIR_2013 [45]	6.8	6.8	7.0	6.3	1.0	5.8	4.0	6.8	6.3	4.3	6.3	5.5	1.3	1.0	6.3	6.8	4.0	2.5	1.0	4.5	1.0	1.0	1.0
T2T_2016 [39]	6.3	7.0	7.0	5.3	5.0	1.3	7.0	6.5	6.5	6.5	3.3	4.0	1.8	2.0	5.0	6.3	6.5	2.0	1.0	1.0	1.0	3.5	4.5
TRA_2016 [38]	5.8	3.5	7.0	5.0	1.5	3.8	1.0	1.3	1.0	1.3	5.5	2.5	1.3	1.0	5.5	6.5	6.5	1.0	1.5	2.3	1.0	1.0	1.0
UTAustin_2009 [52]	7.0	2.8	7.0	3.0	1.0	4.0	4.3	2.0	7.0	2.5	4.3	5.3	2.0	1.0	4.8	5.3	5.3	1.3	1.5	1.3	1.0	4.0	1.3

Supplementary Table 7. Scores and reasons for scoring for the individual AGREE II domain items by each reviewer

	Reviewer_1, scores	Reviewer_1, comments	Reviewer_2, scores	Reviewer_2, comments	Reviewer_3, scores	Reviewer_3, comments	Reviewer_4, scores	Reviewer_4, comments
3e_2013 [36]								
Item 1	7	Abstract and Introduction.	6	Easy to find. "we aimed to develop evidence-based multinational recommendations for the diagnosis and management of gout." -1: the "introduction" part introduced the harm of gout and the difficulty of its management, but expected benefit or outcome of this guideline is not clearly stated.	7	All included	7	Well described
Item 2	7	Table 1.	7	Table 1, well written & easy to find.	5	Contained "ab"	7	Well described
Item 3	7	Abstract and Introduction.	7	Patient with "gout", easy to find.	7	All included	7	Well described
Item 4	7	Methods section and Contributors.	7	Complete & easy to find. "Method" part & "Contributor" part. An experienced librarian (LF) is in the development group.	7	All included	7	Well described
Item 5	1	Not sought.	1	-6: Patients with gout are not involved in the development progress.	2	Participation in the guideline development group,	1	Not found
Item 6	1	Not provided.	1	-6: No description about target users.	1	Not mentioned	1	Not found
Item 7	6	Methods section. B) was not provided.	6	"Method" part & figure S1 S2; well written; easy to find. -1: the searched time periods are not provided.	7	All included	6	No time periods
Item 8	4	Methods section. Only the language criterion of included articles was provided.	2	There is a description of inclusion & exclusion criteria: "published in English or in a language in which at least one member of the bibliographic group was fluent (Dutch, French, German, Spanish)." -5: target population characteristics, study design or outcomes are not included in the criteria.	5	Not mentioned the study design	4	The details are unclear
Item 9	4	Results section. The most informative recommendation was Recommendation 6, in which b) and c) were not provided.	7	"The level of evidence for each recommendation was appraised and graded in accordance with the Oxford Centre for Evidence-based Medicine Levels of Evidence".	7	All included	7	Well described

		Besides, only some of the evidences met these criteria.		Pooled data were "sufficiently homogeneous".				
Item 10	5	Methods section. Although a modified Delphi process was adopted, c) was not provided.	5	Clearly stated in "Methods" part. -2: No outcomes of the process.	6	All included	7	Well described
Item 11	7	Results section.	6	Most informative: recommendation 5. -1: Not all recommendations reflect the consideration of benefits and harms, example: recommendation 9.	5	Subtract 1’	5	Some recommends give the harms but no supporting data
Item 12	7	Results section.	7	Table 2. Each recommendation include a paragraph that describes the key evidences.	6	All included	7	Well described
Item 13	2	Provenance and peer review section. It was only stated that (the guideline was) externally peer reviewed.	4	The guideline is published through a peer-reviewed journal; it was Received on 21 January 2013，Revised on 15 May 2013，Accepted on 29 June 2013. -1：The purpose and intent of external review is not provided. -1: the outcome/information gathered from the external review is not described. -1: the external reviewers are not described.	5	Externally peer reviewed.	5	External peer review
Item 14	1	Not provided.	1	-6: no update information or services provided	1	Not mentioned the study design	1	Not found
Item 15	6	Results section. Some recommendations did not provide b).	6	The most informative: recommendation 5. -1: Not all recommendations are specific enough. Example: recommendation 9, information about surgery doesn't include all the required aspects.	5	Subtract 1	7	A figure
Item 16	7	Results section.	7	The different options for management of the condition or health issue are clearly presented.	7	All included	7	Well described
Item 17	4	Recommendations were summarized as table 2, but were not grouped in a certain section.	4	Table 2. -3: recommendations are not grouped in the guideline.	4	Not grouped	4	The key part is unclear
Item 18	7	Table 3 and Discussion section.	7	Barriers: recommendation 1. Facilitators: Table 3 & "Discussion" part ("the high level of agreement with the final recommendations and the multinational participation increases their utility and will hopefully facilitate their dissemination and implementation worldwide. Most participating rheumatologists either follow the recommendations or are willing to change their practice according to them, suggesting a solid potential impact	7	All included	6	In recommendation 1,table 1 and discussion

				of this set of recommendations.")				
Item 19	1	Not provided.	1	-6: No such information.	1	Not mentioned the study design	1	Not found
Item 20	5	Available evidence for cost-efficacy was discussed.	6	Example: recommendation 1 & 5. Evidences about cost are included and influenced the recommendation. -1: Information/description of the cost information that emerged from the inquiry is not described.	5	Identification of the types of cost information that were considered	5	The discussion part mentions cost
Item 21	1	Not provided.	1	-6: No such information.	2	Mentioned a	1	Not found
Item 22	7	Funding section.	7	"Funding" part, clear & easy to find.	7	All included	7	Well described
Item 23	4	Competing interests section. B) and d) were not provided.	4	"Competing interests" part, easy to find. -2: no information about how they influenced the guideline. -1: methods by which they were sought are not provided.	3	Mentioned ac	4	No statement
3e_AU_NZ_2015 [43]								
Item 1	5	Abstract and Introduction. b) was provided as epidemiology. But not easy to find.	7	To develop evidence-based recommendations for the diagnosis and management of gout in Australia and New Zealand as part of the multi-national 3e Initiative in abstract & "the aim of improving patient care" in "discussion" part.	5	All included	7	Well described
Item 2	5	Page 342. It was stated that a set of clinical questions were investigated but the question list was not provided.	5	10 international & 1 national question. -2: the details of questions are not provided.	7	Contained "ab"	5	It has questions but not all the five aspects
Item 3	7	Abstract	7	Gout	7	All included	6	Not easy to be found
Item 4	7	Pages 341, 348.	7	Clear & easy to find. An epidemiologist (rb) involved.	4	Not mentioned expertise	5	The expertise is not stated
Item 5	1	Not provided.	1	-6: patients with gout are not involved.	1	Not mentioned	1	Not found
Item 6	2	Inferred from Abstract and Introduction section. But the item was not clearly stated throughout the paper.	1	-6: not mentioned.	4	No Clear description of intended guideline audience	3	Analyze from the abstract
Item 7	7	References 7-16.	5	Same as 3e. -1: no time period. -1: no description of the literature search of the one national question.	7	All included	7	"A comprehensive search strategy was developed with the aid of an experienced librarian, for MEDLINE, EMBASE, CENTRAL as well as hand searches of the reference list of the selected articles and of abstracts presented at the 2010

								and 2011 ACR and EULAR scientific meetings"
Item 8	7	References 7-16.	7	It is described in References 7-16.	7	All included	6	In the methods and appendix
Item 9	7	Page 342. Oxford Centre for Evidence-based Medicine Level of Evidence.	7	It is described in References 7-16.	7	All included	7	Well described
Item 10	7	Methods section. Outcomes as table 1 - agreement mean.	6	Not all outcomes are missing, some are described.	7	All included	6	Can be found in the methods
Item 11	7	Recommendations section.	6	Most informative (recommendation 4) -1: not all recommendations reflect the consideration of benefits and harms (recommendation 6)	7	All included	6	Well described
Item 12	7	Methods and Results section. Evidence summary was provided.	7	Table 1 & methods. Each recommendation has a paragraph describing relative evidences.	7	All included	6	Well described
Item 13	2	Published in a peer reviewed journal.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	'-6; not mentioned.	1	Not mentioned	1	Not found
Item 15	5	Recommendations section. B) was not provided.	6	The intent or purpose of each recommendation is not provided.	6	All included	6	Well described but no purpose
Item 16	6	Recommendations section. B) was not provided in recommendation 4.	7	All points are included.	5	Only some options are provided with the most appropriate population or clinical situation.	6	Well described, ex:recommend 6
Item 17	4	Not grouped in a certain section.	4	Table 1 -3: recommendations are not grouped.	6	Contained ab	4	Table 1
Item 18	6	Discussion section, the second paragraph.	6	"A high level of agreement was seen among the experts for the final recommendations, providing further support for their validity and hopefully facilitating their dissemination and implementation." -1: no influence of the development.	6	All included	5	Be discussed in the discussion part
Item 19	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 20	2	Page 345. Only the cost-efficacy issue was mentioned.	4	E.g. Recommendation 4. -2: no methods described. -1: no description of the cost information that emerged from the inquiry.	2	Mentioned a	3	In some recommends, the cost is considered but without methods
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found

Item 22	1	Not provided.	1	-6: no information about funding.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: no information about competing interests.	1	Not mentioned	1	Not found
3e_PT_2014 [40]								
Item 1	6	Title and abstract. B) was only provided as epidemiological information.	6	"To develop Portuguese evidence-based recommendations for the Diagnosis and Management of Gout" & "purpose of improving patient care" -1: Not very easy to find.	7	All included	7	Can be found in the objective part
Item 2	7	Table 1.	7	Table 1.	7	All included	7	There is a single table describing the questions
Item 3	7	Title and abstract	7	Gout in Portugal	6	. Subtract 1 for population	7	Analysed from the text
Item 4	5	Methods section. The role of each member was not fully provided.	5	The development group members are not completely listed.	5	Mentioned part of the member	4	No epidemiologist; no expertise
Item 5	1	Not provided.	1	-6: Patients with gout are not involved in the development progress.	2	Literature review of values	1	Not found
Item 6	1	Not provided.	1	-6: No description about target users.	1	Not mentioned	1	Not found
Item 7	3	Methods section. B), c) and d) not provided.	3	Databases are named. -1: No time period. -1: No search terms. -2: No full search strategy.	2	Mentioned a	3	Without b) c) and d)
Item 8	1	No specific criterion provided.	1	-6: No description about selection criteria.	1	Not mentioned	6	Methods and appendix
Item 9	7	Table 2. The Oxford Level of Evidence system.	7	Oxford levels of evidence	6	Table 2	2	The description is unclear
Item 10	3	Methods section. Although Delphi approach was adopted, b) and c) were not provided	3	"discuss and vote" -2: No outcomes. -2: No influence.	5	Missed outcome of vote	3	Without b) and c)
Item 11	6	Results section. Harms were not fully discussed (e.g., for allopurinol).	6	Most informative example: recommendation 5. -1: Not all recommendations reflect the consideration of benefits and harms. (e.g. Recommendation 1)	4	Mentioned ab	6	Every recommendation has
Item 12	7	Methods and Results section. Evidences were summarized in table 1.	7	Methods. Each recommendation has an evidence description. Table 2 & 3.	6	All included	7	Each recommendation is linked to a key evidence
Item 13	2	Published in peer reviewed journal.	1	-6: No description about external review.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: No statement about updating.	1	Not mentioned	1	Not found
Item 15	5	Results section. B) not provided.	6	Some purposes of recommendations are not clearly stated.	5	Subtract 1	6	Well described

Item 16	6	Results section. The appropriate population was not provided clearly in recommendations 4-6.	7	All points are included.	6	All included	6	Well described
Item 17	4	Recommendations were summarized as table 2, but were not grouped in a certain section.	4	Table 2. -3: recommendations are not grouped in the guideline.	4	Missed b	4	No summary
Item 18	4	Table IV. Willingness of applying the guideline in daily practice was voted on and discussed.	6	"The impact of the recommendations was apparent through willingness to change the clinical practice" -1: No influence	4	Drug unavailable, and method	4	In the recommendation 1 last paragraph
Item 19	1	Not provided.	1	-6: No such information.	2	Mentioned a	1	Not found
Item 20	5	Clinical question 5 and Recommendation 1. c) and d) not provided.	3	Question 5. -4: But the question about cost is not answered.	2	Mentioned "What is the efficacy, cost efficacy and safety for urate-lowering therapy"	1	Not found
Item 21	1	Not provided.	1	-6: No such information.	5	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: There's no such description about competing interests.	1	Not mentioned	1	Not found
ACP_2017 [19, 20]								
Item 1	6	Section - Guideline focus and target population. B) was only provided as epidemiological information.	6	To provide guidance on diagnosing acute gout in patients with gout symptoms, including joint inflammation & "to provide guidance on the management of acute and recurrent gout in adults". -1: the epidemiology is provided, but there's no specific statement of expected benefit or outcome.	6	Not mentioned b, but mentioned the epi	6	The outcome and benefit don't be mentioned
Item 2	7	Appendix	7	Appendix Key questions.	7	All included	6	Analysed from the paragraph, but it not easy to find
Item 3	7	Abstracts.	7	Adults with joint inflammation suspected to be gout & "adults with acute or recurrent gout"	7	No subtract	7	Well described
Item 4	6	The first page and online (http://annals.org/aim/article/2578528/management-acute-recurrent-gout-clinical-practice-guideline-from-american-college). The disciplines of each author were not provided.	6	Easy to find. Statistical expertise: a. Qaseem. -1: the discipline of each member is not provided.	6	Online	7	At the end of the text
Item 5	5	Reference (PMID: 20679562). C) was not provided.	5	The method is described in reference [10]. -2: The outcomes are not shown.	6	Contained abcd in methods	5	In the appendix

Item 6	4	Appendix - Target audience. B) was not provided.	4	"All clinicians". -3: no description of how the guideline may be used by its target audience.	3	Missed b	6	Can be found in the Target population part but without b)
Item 7	7	Reference (https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/gout_research.pdf), Methods section.	7	The details are in reference [8].	6	Mentioned in Search Strategy	7	In the method part and in the appendix
Item 8	7	Reference (https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/gout_research.pdf), Methods section.	7	Appendix & methods.	6	All included in APPENDIX: DETAILEDMETHODS	7	In the method part and in the appendix
Item 9	7	Section - Methods. The GRADE approach was adopted.	7	Methods and Appendix Quality assessment.	6	Contained a b1 3 4 5	6	The table, but the details are not clear
Item 10	5	Reference (PMID: 20679562). B) was not provided.	5	The detailed methods are in reference [10]. -2: the outcomes are not provided.	6	Grading the Evidence and Developing Recommendations and vote	4	In the method part and in the appendix
Item 11	7	Pages 59-65 (Guideline: Management of Acute and Recurrent Gout).	7	Benefits and Harms and their supporting data are listed in specific sections.	6	Subtract 1	6	Well described
Item 12	5	Pages 59-65 (Guideline: Management of Acute and Recurrent Gout) and Reference (PMID: 20679562). C) was not provided.	5	-2: how the guideline development group linked and used the evidence to inform recommendations is not described.	5	Subtract 1	6	Can be found in the methods
Item 13	5	Sections - Methods and Peer review and Reference (PMID: 20679562). A and d) were not provided.	5	Appendix peer review. -1: outcomes are not described. -1: no purpose provided.	4	Peer Review abe	5	Peer review
Item 14	5	Appendix - Note and Reference (PMID: 20679562). B) was not provided.	4	The content of updating is in reference [10]. -2: the time interval is not stated. -1: no statement about updating in the guideline itself, so the information is very hard to find.	5	Missed c	6	In the note
Item 15	5	Pages 59-65 (Guideline: Management of Acute and Recurrent Gout). B) was not provided.	6	-1: not all recommendations provide purpose (e.g. Recommendation 4)	5	Subtract 1	5	No b)
Item 16	7	Pages 59-65 (Guideline: Management of Acute and Recurrent Gout).	7	The different options for management of the condition or health issue are clearly presented.	6	All included	7	Well described
Item 17	7	Pages 59-65 (Guideline: Management of Acute and Recurrent Gout).	7	E.g. Figures. Specific recommendations are grouped (e.g. Diagnosis & management)	6	All included	6	A figure

Item 18	2	Page 55 (Guideline: Diagnosis of Acute Gout). The difficulty to perform synovial fluid analysis in primary care was stated.	4	Summary of diagnosis，bout synovial fluid analysis. -2: Method by which the information was sought is not described. -1: They are not about the barriers or facilitators of the whole guideline.	2	Mentioned a	2	Not found
Item 19	2	A summary for patients was provided online (http://annals.org/aim/article/2584392/diagnosis-management-gout-clinical-practice-guidelines-from-american-college-physicians).	3	The summary figures. -1: the summary figures include a clinical consideration part, but there's no specific implementation section in the guideline. -3: No other information about implementation advice or tools for this guideline.	1	Not mentioned	1	Not found
Item 20	4	Page 59 (Guideline: Management of Acute and Recurrent Gout). A) and d) were not provided.	7	Management Table 1. & recommendation1 & recommendation 4. & High-value Care.	5	Tables contained;high value part	5	It mentions cost in the part of management
Item 21	1	Not provided.	1	-6: No description of monitoring or auditing.	1	Not mentioned	1	Not found
Item 22	4	Appendix - Financial support. B) was not provided.	4	Financial Support. -3: No statement that the funding body did not influence the content of the guideline.	4	No statement that the funding body did not influence the content of the guideline	4	No statement
Item 23	7	Appendix - Disclosures of the guideline document and the Conflict of Interests section of Reference (PMID: 20679562).	7	Disclosures. Clear and detailed.	6	All included	6	Well described
ACR_2012 [14, 15]								
Item 1	6	Guideline part 1. Page 1443. This content was not easy to find.	6	All included, but difficult to find.	7	All included	7	Well described
Item 2	5	Guideline part 1. Page 1434. Multiple clinical questions were presented but not listed in the guideline.	7	Scenarios are clearly described.	5	Contained "ab"	5	There were multiple questions of interest and alternative options presented for each case scenario.
Item 3	7	Titles.	7	Gout	7	All included	5	The description is unclear
Item 4	7	Guideline part 1. Pages 1431, 1434, 1444.	7	Clearly stated. An experienced librarian is included.	7	All included	7	Well described
Item 5	5	Guideline part 1. Page 1434. A patient representative participated in the task force. C) was not provided.	7	2 patient representatives are included in the task force.	5	Not mentioned "participation in the literature review of values and preferences"	4	It involves but is unclear
Item 6	7	Guideline part 1. Page 1433.	4	Intended audience are discribed.P1433.	7	All included	4	Analysed from the article

				-3: no description of how to use.				
Item 7	7	Guideline part 1. Page 1434 and Appendix A.	7	Figure 4 & appendix a.	7	All included	7	Well described
Item 8	7	Guideline part 1. Page 1434 and Appendix A.	7	P1434 & appendix a.	7	All included	7	Well described
Item 9	6	Guideline part 1. Page 1434. Evidence levels were graded only based on b1) and b5).	7	Materials and methods	7	All included	7	Well described
Item 10	6	Guideline part 1. Page 1435. Some outcomes were not provided.	6	Clearly described. -1: one example of outcome is provided, but other outcomes are not provided.	6	All included	6	Well described
Item 11	6	Results section. Some recommendations (e.g., diet on page 1438) did not consider harms.	6	Most recommendations reflect the consideration of benefits and harms. -1: not all recommendations, e.g. Diet.	5	Subtract 1	6	Not every recommendation has
Item 12	5	Results section. C) was not provided.	5	Evidence summaries or tables are not provided.	7	All included	7	Well described
Item 13	2	This guideline was published in a peer-reviewed journal.	2	Revised before publication -5: no other details.	1	Not mentioned	1	Not found
Item 14	3	Guideline part 1. Pages 1431. It was only stated that the guideline organization will periodically revise the guideline.	3	Is "subject to periodic revision". -4: no other detail	3	To be updated but without details	4	The information is unclear
Item 15	5	Results section. B) was not provided.	6	-1: some purposes are not provided.	5	Subtract 1	7	Well described
Item 16	7	Results section.	7	All points are included.	7	All included	7	Well described
Item 17	4	An algorithm was provided on page 1437, but the recommendations were not grouped in a certain section.	7	There are summary tables and they are grouped.	7	All included	4	No summary
Item 18	1	Not provided.	1	Not provided.	1	Not mentioned	1	It mentions but don't discuss cause of the methodology
Item 19	1	Not provided.	1	Not provided.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	Costs are not considered when forming the recommendations.	1	Not mentioned	1	Not mentioned
Item 21	1	Not provided.	1	Not provided.	2	Mentioned a	1	Not found
Item 22	3	Guideline part 1. Page 1432. B) was not provided.	4	-3: no statement that the funding body did not influence the content of the guideline	3	Mentioned "The name of the funding body or source of funding"	3	No b)
Item 23	4	Guideline part 1. Page 1434. Conflict of interest was mentioned but no detail was	4	-1: no method. -2: no influence	4	No detail	5	The TFP had a majority of members

		given.						without a perceived potential conflict of interest
ACR_EULAR_2015 [42]								
Item 1	6	Abstract and Introduction section. b) was provided as epidemiological information. Information was not easy to find.	6	"The current effort was undertaken to develop new classification criteria for gout" & "to address these issues" & "this classification criteria set will enable a standardised approach to identifying a relatively homogeneous group of individuals who have the clinical entity of gout for enrolment into studies" -1: not easy to find.	7	All included	7	In the objective part and introduction
Item 2	5	Abstract. D) and e) were not provided.	5	"Factors to discriminate gout from other rheumatic diseases" -2: there is an topic, but it's not clearly stated.	5	Contained "ab"	5	Analyse from the summary and recommends
Item 3	7	Abstract.	7	Gout.	7	All included	7	Analyse from the text
Item 4	6	Pages 1789, 1791, 1797. Disciplines were not provided.	5	Easy to find. An epidemiologist involved. -1: no discipline of each member. -1: the relationship of authors and the expert panel is unknown.	5	Mentioned ab	5	No expertise or a description of the member's role
Item 5	6	Page 1790. A patient participated in phase 1.	6	Patients with gout were involved in phase 1. Reference 20 -1: not easy to find.	6	Included in "method"	1	Not found
Item 6	2	Inferred from abstract. But the item was not clearly stated throughout the paper.	1	-6: not mentioned.	2	Description of how the guideline may be used by its target audience	3	Without clear description
Item 7	7	Reference (PMID: 24915980)	7	Reference 23.	7	All included	7	Well described
Item 8	7	Reference (PMID: 24915980)	7	Reference 23.	7	All included	6	The description of criteria is not that clear
Item 9	7	Reference 20. QUADAS tool was used.	6	QUADAS -1: QUADAS has been revised into QUADAS-2, but they still used the old version.	7	All included	1	Not found
Item 10	7	Methods section.	6	Clearly described in "methods" part. -1: Some outcomes are provided (Table 1). But some are not (the vote of the willingness).	6	All included	5	Not clear
Item 11	7	Not applicable.	7	As a diagnostic guideline, it did consider the specificity and sensitivity.	7	All included	7	This item is not apply to this guideline
Item 12	5	Results section. C) was not provided.	5	Evidences are described in reference 23, thought how a specific evidence is linked to a recommendation is not described in detail.	5	Supporting data	7	Recommendation has certain link

Item 13	2	Page 1797. Detailed external peer review information was not given.	2	"Externally peer reviewed". -5: no any other information about the external peer review.	2	Some recommendations meet criterion	1	Not found
Item 14	3	Page 1789. B) and c) were not provided.	3	"All ACR/EULAR approved criteria sets are expected to undergo intermittent updates." -2: no time interval. -2: no methodology.	3	Externally peer reviewed.	3	Although it has description of update, it is not clear
Item 15	7	Results section.	7	Very specific and unambiguous.	7	All included	6	Well described
Item 16	7	Not applicable.	7	Details of each domain are clearly described.	7	All included	7	Well described
Item 17	7	Table 2 and abstract.	7	Table 2. There's no need to group.	7	All included	7	Well described
Item 18	3	Page 1796. Clinicians' access to imaging was discussed. A) and b) were not provided.	5	"We also realised that some investigators may not have access to imaging and therefore aimed to develop criteria that would still perform well in the absence of imaging data. In the discrete-choice experiments, the lack of imaging data was weighted the same as for studies performed with negative results, supporting the validity of using the scoring system in the absence of imaging data." -2: no methods.	3	Mentioned the facilitator in page 1791	4	In the article" We also realised that some investigators may not have access to imaging and therefore aimed to develop criteria that would still perform well in the absence of imaging data."
Item 19	3	Pilot test was conducted (table 3) and a web-based calculator was provided (page 1794).	7	"Results of testing of the new gout classification criteria and comparison with existing published criteria" part. "A web-based calculator can be accessed at http://goutclassificationcalculator.auckland.ac.nz, as well as through the ACR and EULAR websites".	3	Gout classification calculator web page.	3	Page 1794 has a tool
Item 20	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	4	General population survey to determine the public health burden of gout for resource planning
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	4	Page 1797. B) was not provided.	4	"Funding" part. -3: no statement of influence.	3	Not mentioned that the funding body did not influence the content of the guideline	4	No statement
Item 23	4	Page 1797. B) and d) were not provided.	4	"Competing interest" part. -1: not method. -2: no description of influence.	4	Missed d	5	No statement
BSR_2017 [21]								

Item 1	7	Sections 1) Scope and purpose and 2) Objective.	7	Well written & easy to find. Clearly stated in "Need to revise" & "Objective" parts.	7	All included	7	Well described
Item 2	7	Table 1. Principal clinical questions were listed.	7	Table 1. Well written & easy to find.	7	All included	7	Well described
Item 3	7	Section Objective - Gout in the UK.	7	"gout in the UK" in "Objective" part. Easy to find.	7	All included	7	Well described
Item 4	6	Section Objective - Stakeholder involvement. The role of each member was not provided.	6	Clear and easy to find. An epidemiologist (W.Z.) was involved in the development group. -1: No description of each member's role.	4	Mentioned "The guideline development group" and the name, discipline/content expertise	6	No roles
Item 5	5	Section Objective - Stakeholder involvement. Two lay patients involved in the guideline development group.	5	Two patients (H.F. & A.P.) participated in the development group. Recommendations were based on "patients experience" (in Rationales of many recommendations). -2: the outcomes/information gathered from patients were not provided.	5	Participation in the guideline development group,	6	2 patients took part in
Item 6	7	Section Objective - Target audience.	7	"Target audience" part in "Objective". Well written & easy to find.	6	All included	7	Well described
Item 7	7	Section Rigour of development - Systematic literature search. Search strategies were provided as Supplementary table 1.	7	"Systematic literature search" of "Rigour of development" part & Table S1. Well written & easy to find.	7	All included	7	Well described
Item 8	6	Section Rigour of development - Inclusion criteria & Exclusion criteria. A) was not provided.	6	"Inclusion criteria" & "Exclusion criteria" of "Rigour of development" part. Easy to find. -1: target population characteristics were not included in the criteria.	7	All included	5	No a2)
Item 9	6	Section Rigour of development - Level of evidence. Only study design was considered.	6	"Level of evidence" part clearly stated the method used to evaluate evidence strengths and limitations. -1: the method considered two aspects, study design & methodology limitations.	7	All included	7	Well described
Item 10	7	Section Rigour of development - Delphi exercise to generate consensus recommendations.	6	Easy to find in "Delphi exercise to generate consensus recommendations" part. -1: No detail of outcomes of the development process (vote for the first draft, final vote for each recommendation)	7	All included	7	Well described
Item 11	6	Section Recommendations.	7	Most informative example: recommendation iii.	5	Subtract 1	7	Well described

Item 12	6	Evidence summary table was not provided.	5	-2: no evidence summary or evidence table provided.	6	All included	7	Well described
Item 13	5	Section Objective - Stakeholder involvement. A) and d) were not provided.	5	1）The draft guideline was presented and discussed in open session by a multidisciplinary audience at the annual scientific meetings of the BSR in 2014 and 2016. 2）This guideline has been reviewed and endorsed by the Royal College of General Practitioners. -1：No objective or intent of external review. -1: no outcomes/information gathered from the external review.	5	Externally peer reviewed.	5	There's an external review but no details
Item 14	2	Online information: https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines/ArtMID/1256/ArticleID/18. This content was very difficult to be found.	2	Time: 2020 (https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines/artmid/1256/articleid/18). -5: No information about updating in the guideline itself, very difficult to find on the website.	1	Not mentioned	3	Not easy to be found and unclear
Item 15	7	Section Recommendations.	7	Recommendations are specific and unambiguous. Example: recommendation iii. The uncertainty is explicitly stated. Purposes of recommended actions are clear. The relevant population is clear. The qualifying statements are clear.	6	Subtract 1	7	Well described
Item 16	7	Section Recommendations.	7	Description of options & description of population or clinical situation most appropriate to each option are clear. Example: recommendation iv.	6	All included	7	Well described
Item 17	4	Figure 1. B) was not provided.	3	Fig 1. -3: recommendations are not grouped in the guideline.	3	Not grouped	4	No b)
Item 18	5	Section Applicability and utility - Statement of potential organizational barriers to introduction. B) was not provided.	5	"Statement of potential organizational barriers to introduction" part & recommendation vi. Easy to find. -2: Methods by which the information was sought are not provided.	4	Identification of the types of facilitators and barriers that were considered; Information/description of the types of facilitators and barriers that emerged from the inquiry	5	In "Statement of potential organizational barriers to introduction" part
Item 19	4	An algorithm (figure 1) and an executive summary was available (https://academic.oup.com/rheumatology/article/56/7/1056/3855178/The-British-Society-for-Rheumatology-Guideline-for?searchresult=1). C) was not provided	5	1)"Applicability and utility" section is about implementation. 2)There is a summary of the guideline on the website, but not mentioned in the guideline itself and not easy to find. (https://academic.oup.com/rheumatology/article/56/7/1056/3855178/The-British-Society-for-Rheumatology-Guideline-for?Searchresult=1）. 3)solutions to barriers: "Potential cost implications for	5	No summary	5	"An audit tool is available on the website of the British Society for Rheumatology."

				implementation of the guideline" talks about the solution to unlicensed drugs. -2: No direction on how to access the summary.				
Item 20	7	Section Applicability and utility - Potential cost implications for implementation of the guideline.	7	"Potential cost implications for implementation of the guideline" part.	6	All included	6	It mentions cost
Item 21	2	An audit tool was available (https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines/ArtMID/1262/ArticleID/166/Guideline-on-the-management-of-gout).	5	Audit tool: https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines/artmid/1262/articleid/166/Guideline-on-the-management-of-gout. -1: No link to the audit tool in the guideline. -1: no advice on the frequency of measurement.	2	Identification of criteria to assess guideline implementation or adherence to recommendations	2	Audit tool available
Item 22	7	Section Objective - Stakeholder involvement & Funding.	7	"Stakeholder involvement" part & "funding" part at the end. Clear and easy to find.	7	All included	7	Well described
Item 23	5	Section Objective - Stakeholder involvement & Disclosure statement. D) was not provided.	5	"stakeholder involvement" part & "Disclosure statement" part. Clear and easy to find. -2: No clear description of how the competing interests influenced the guideline.	5	Influence not provided	5	No influence
CCCP_2012 [47]								
Item 1	6	Page 49, Title and Section 1 - Epidemiology. B) was only provided as epidemiological information.	7	Well written & easy to find.	7	All included	7	Well described
Item 2	3	Clinical questions can be inferred from the guideline but not clearly stated.	3	The topic can only be inferred from the content.	3	Clinical questions was not clearly stated.	3	Analysed from the article but the questions don't be explicitly mentioned
Item 3	7	Title.	7	Asymptomatic HA with CAD	7	All included	7	Well described
Item 4	2	Page 49. Only the name of the guideline development group was provided.	2	The names of development groups are provided. -5: no any other information about group membership.	2	Not mentioned the members' detail	2	Only development group and names are given
Item 5	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 6	2	Introduction. The target user was not clearly stated throughout the paper.	1	-6: not mentioned.	1	Not mentioned	3	Without clear description
Item 7	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 8	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 9	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 10	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found

Item 11	3	Pages 52-54. Supporting data for benefits and harms were not provided.	4	Most informative: page 53 benzbromarone. -1: no supporting data for benefits. -1: no supporting data for harms. -1: not all recommendations reflect the consideration of benefits and harms.(page 52 life style change)	4	Subtract 1	4	Some recommends involve
Item 12	1	Not provided.	3	-2: no description of how they linked and used the evidence. -1: only some recommendations are linked to a key evidence description. -1: page 52: 6. This part can only be considered as an incomplete evidence summary.	2	Mentioned a	2	Some recommends are linked evidence
Item 13	2	The guideline was published in a peer reviewed journal.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 15	3	Pages 52-54. A) and b) were not provided.	4	-2: uncertainty is not stated. -1: not all recommendations provide intent or purpose.	6	Subtract 1	5	Only some recommendations report
Item 16	6	Pages 52-54. Some options did not define proper population.	5	-1: only some options are provided with the most appropriate population or clinical situation (e.g. Alkalization fo urine is not.) -1: some options are not provided with description (page 52 “ proper amount of wine”)	6	Subtract 1	6	Describe clearly
Item 17	4	Pages 53-54. Recommendations were not grouped in a certain section.	4	Figure 1. -3: recommendations are not grouped.	4	Recommendations were not grouped together in one section	4	Specific recommendations don't be grouped together in one section
Item 18	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
CRA_2016 [41]								
Item 1	5	Paragraph 3. B) was only provided as epidemiological information. Contents of this item were not easy to find.	7	Easy to find,	7	All included	6	In the 2nd and 3rd paragraph, the health intent and epi. Can be found
Item 2	5	Appendix 5. A set of clinical questions were selected but no detail was given.	5	Methods in the Appendix. The details of the questions are not provided. There was some misunderstanding of this item. The scoring criteria were clarified after discussion.	5	Contained "ab"	5	Analysed from the summary and recommends

Item 3	7	Paragraph 3 and Appendix 2.	7	Gout in China (supplementary)	7	All included	7	Analysed from the text
Item 4	6	Appendix. The role of each member was not provided.	6	Clear & easy to find. An methodologist is involved (Yaolong Chen (GRADE Chinese Centre) -1: role of each member is not described.	5	Mentioned name and institution and performance	5	The development group; name, institution, a description of the members' role and it is well-written
Item 5	1	Not provided.	1	'-6: The views and preferences of the target population are not mentioned.	1	Not mentioned	1	Not found
Item 6	4	Appendix 2. B) was not provided.	5	Easy to find. '-2: how the guideline may be used is not complete.	6	Mentioned in abstract	6	Can be found in the appendix
Item 7	5	Appendix 6. D) was not provided.	4	Supplementary. Databases are named. Time periods are described. -1: No search terms. -2: No full search strategy.	5	Mentioned	6	Can be found in the appendix
Item 8	3	Appendix 6.	3	The inclusion criteria only include study design.	3	Mentioned study design	4	In the appendix, but not that clear
Item 9	7	Appendix 7. GRADE method.	6	Supplementary. -1: The description is ambiguous. The evaluation methods described in the supplementary don't fit the levels of evidence that used in the recommendations	6	Amstar	6	In the appendix the LOE is given, and in the recommends, the evidence level is clear.
Item 10	3	Appendix 8. Although the Delphi method was used, the outcome and the influence on guideline development was not given.	4	Supplementary. -1: only name of the process, no description. -2: outcomes are not provided.	1	Not mentioned	6	In the appendix
Item 11	7	Recommendations.	6	Most informative example: recommendation 6&7. -1: recommendation 9 (benefits and harms with supporting data are provided, but the recommendation doesn't reflect the consideration of them)	5	Subtract 1	6	Well described
Item 12	5	Recommendations and Appendix 8. C) was not provided.	5	-2: No evidence summary or table.	6	All included	6	Well described
Item 13	2	Published in a peer reviewed journal.	3	Methods in the Appendix. External experts are involved the question choosing process, but it is not a review.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	'-6：not mentioned.	1	Not mentioned	1	Not found
Item 15	5	Uncertainty was not stated.	6	Some purposes of recommendations are not clearly stated.	5	Subtract 1	5	Well described
Item 16	7	Recommendations.	7	All points are included.	6	Some options are provided with the most appropriate population or clinical situation.	6	Well described

Item 17	4	Recommendations were presented in bold but were not grouped in a certain section.	4	Recommendations are typed in bold. -3: recommendations are not grouped.	4	MISSED b	4	Important advice has a key tag
Item 18	1	Not provided.	1	-6: No relevant information.	1	Not mentioned	2	In the recommendation 1,the barrier is described
Item 19	1	Not provided.	1	-6: No relevant information.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	-6: No relevant information.	2	Mentioned in CT	1	Not found
Item 21	1	Not provided.	1	-6: No relevant information.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	1	Not found
Item 23	4	Appendix. A) and b) were not provided.	4	Appendix. I didn't find this information.	6	No potential competing interests	6	Well described
CRA_multi_2017 [22]								
Item 1	7	Title and Paragraph 1.	7	"promote multidiscipline cooperation, guide and regular the clinical practice of HUA related diseases" & "aims at promoting multi-disciplinary collaboration and providing guidelines in clinical practice for general practitioners, doctors from different disciplines at different levels." Well written & easy to find.	7	All included	7	Can be found in the title and summary
Item 2	3	Clinical questions considered could be indicated from the guideline but no clear statement was given.	3	-4: No specifically described question is provided in the guideline.	3	Contained "ab"	5	Analysed from the paragraph, but it not easy to find
Item 3	7	Paragraph 1.	7	Hua	7	No subtract	6	The population is not clearly described
Item 4	5	Page 244. The role of each member was not provided and a methodologist was not involved.	5	Easy to find. -1: no description of member's role. -1: No methodologist include.	4	No discipline/content expertise and a description of the member's role in the guideline development group	5	The guideline development is stated in the last paragraph with their names, discipline/content expertise and institution, but doesn't describe the role of each member and no epidemiologist among them.
Item 5	1	Not sought.	1	'-6: The views and preferences of the target population are not mentioned.	2	A has been mentioned	1	Not found
Item 6	7	Paragraph 1.	7	"Promoting multi-disciplinary collaboration and providing guidelines in clinical practice for general practitioners, doctors from different disciplines at different levels."	6	All included	7	Can be found in the title and summary
Item 7	1	Not provided.	1	-6: Searching method is no provided.	1	Not mentioned	1	Not found

Item 8	1	Not provided.	1	-6: Criteria are no provided.	1	Not mentioned	1	Not found
Item 9	1	Not provided.	1	-6: Strengths and Limitations of The Evidence are not described.	1	Not mentioned	1	Not found
Item 10	1	Not provided.	2	The guideline was developed though discussion of experts from multi-discipline. -5: No any other details about the formulation (detailed process, outcomes or influence) is provided.	1	Not mentioned	1	Not found
Item 11	5	Pages 237-242. For the most informative recommendation (the ULT recommendations), c) was not provided. A) was not provided for the allopurinol recommendation.	5	Most informative examples: Page 241 "HUA with cardiovascular diseases". -1: No supporting data of harms. -1: Not all recommendations reflect the consideration of benefits and harms.	5	Subtract 1	5	The benefits and side effects are considered in some tips, but the evidence are limited
Item 12	3	Pages 237-242. A) and c) were not provided.	2	Some recommendations (e.g. Page 241 "HUA with metabolic syndrome") are linked to evidence description. -2: How they linked and used the evidence to inform recommendations are not described. -2: No link between recommendations and evidence summary. -1: Not all recommendations include an evidence description (e.g. Page 237 "smoking") .	5	Only some recommendations meet criteria, and no table	1	Not found
Item 13	2	The guideline was published in a peer-reviewed journal, but no information on external review provided.	1	-6: No description about external review.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: No statement about updating.	1	Not mentioned	1	Not found
Item 15	5	Pages 237-242. B) was not provided in the non-pharmacological treatment recommendation.	5	Most informative example: Page 237 "management of patients with gout". -1: Some recommendations are without an intent or purpose (e.g. Page 237 Non-drug therapy). -1: Some uncertainty exists, but not reflected in recommendations, and is not explicitly stated.	5	Subtract 1	5	Can be found in some recommendation but without purpose
Item 16	7	Pages 237-242.	7	The different options for management of the condition or health issue are clearly presented.	5	Subtract 1	7	Well described
Item 17	2	Pages 237-242. No summarized paragraph, table, or algorithm was provided.	3	'-1: Table 1&2 are only summary of a very little part not the summary of the guideline. -3: recommendations can not be easily distinguished form other content, and they are not grouped.	3	Description of recommendations were not in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms	4	No summary

Item 18	1	Not provided.	1	-6: No description of facilitators or barriers to application.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	1	-6: No information about implementation.	1	Not mentioned	2	Gives some tools in the appendix
Item 20	1	Not provided.	1	-6: cost is not mentioned.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: No description of monitoring or auditing.	2	Identification of criteria to assess guideline implementation or adherence to recommendations	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: There's no such description about competing interests.	1	Not mentioned	1	Not found
CSE_2013 [37]								
Item 1	7	Title and Introduction.	7	The Objectives is clearly stated as "to provide guidance for effectively controlling HUA clinically", and the epidemiology and harm are provided as background information.	7	All included	7	Well described
Item 2	1	Not provided.	3	-6: No specifically described question is provided in the guideline.	1	Not mentioned	2	Analysed from the article
Item 3	6	The target population indicated from the title (patients with hyperuricemia or gout) and from the guideline (patient with hyperuricemia) was conflicted.	6	-1: From the title the target population should be patients with "HUA & gout", but from the objective it should be patients with "HUA" only. Besides, the detailed recommendations are mainly for HUA. So the target population is not clearly described.	7	All included	6	Analysed from the article
Item 4	3	Page 918. Only the names of the group member were provided.	4	The development group is clearly stated below the title, and all members' names are provided at the end. -3: The discipline/content expertise, the institution and the role of each member are all missing, and there's no statement that a methodologist is included.	2	Mentioned "The guideline development group"	3	Only group and name
Item 5	1	Not sought.	1	-6: The views and preferences of the target population are not mentioned.	1	Not mentioned	1	Not found
Item 6	6	The target user could be indicated from the guideline but was not clearly stated.	6	The target audience can be inferred as clinical practitioners from the word "clinically", and the guideline may be used by "providing guidance". -1: The target audience is not clearly described.	7	All included	5	Analysed from the article
Item 7	1	Not provided.	1	-6: Searching method is no provided.	1	Not mentioned	1	Not found
Item 8	1	Not provided.	1	-6: Criteria are not provided.	1	Not mentioned	1	Not found
Item 9	2	Pages 915-918. Only a) and c) in some evidences were provided.	3	The most informative evidence: Table 1. The table and its explanation below provide study designs, relevance of outcomes	2	Mentioned"b123",subtract 1	1	Not found

				and consistency of results. -3: The method to evaluate the strengths and limitations of evidence is not provided. -1: The information is only reported for some of the evidences.				
Item 10	1	Not provided.	1	-6: The methods are not described.	1	Not mentioned	1	Not found
Item 11	5	Pages 915-918. Some recommendations did not provide the harms.	5	Most informative recommendation: Page 915, Five (One) 2. Alkalization of Urine. Benefits & supporting data are reported; Risks are reported; the balance is reported; and the recommendation reflects the consideration of both. -1: No supporting data for the risks. -1: Only some of the recommendations report all the information.	5	Subtract 1	5	Some recommendations give the harms
Item 12	5	Page 915. An evidence summary table was provided. A) was not provided.	3	Some recommendations are linked to a key evidence description, for example: Table 1, Page 915 Five (One) 1. General treatment。 -2： how the guideline development group linked and used the evidence to inform recommendations is not reported. -1: Not all recommendations are linked to a supporting evidence. -1: There is an evidence table, but it's not a summary for all recommendations. It's only for one recommendation.	3	Key evidence description	3	Some recommendations are linked to a key evidence description
Item 13	1	Not provided.	1	-6: No statement of external review is provided.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: Updating procedure is not provided.	1	Not mentioned	1	Not found
Item 15	5	Pages 915-918.	6	Most recommendations are specific and unambiguous. The uncertainty is explicitly stated (Page 918 Five (Five) 5. Traditional Chinese medicine. Purposes of recommended actions are clear (Page 918 Five (Five) 2. (1) benzbromarone). The relevant population is clear (Page 918 Five (Five) 2. (1) benzbromarone: indication ）. The qualifying statements are clear (Page 918 Five (Five) 2. (1) benzbromarone contraindication & caution). -1: The relevant population is not clearly stated in some recommendations (Page 918 Five (Five) 2. (2)).	6	Subtract 1	5	Most recommendations are well described
Item 16	6	Pages 915-918. The appropriate population was not provided in some management options (e.g., probenecid).	6	Management options with appropriate populations are clearly described. -1: Some options are without a description of appropriate	6	All included	4	No b)

				population or situation (Page 918 Five (Five) 2. (2) no contraindication provided.				
Item 17	7	The recommendations were summarized in the abstract and presented by two flow charts (page 916).	7	The key points are at the beginning. Two flow charts are provided. Relevant recommendations are grouped together.	6	All included	7	Well described
Item 18	3	The availability of uricase (page 918) was discussed but no detail was given.	3	A barrier was identified (Page 918 Five (Five) 2.(3) "not in the market in China"). -4: Other information about this barrier is provided.	3	Uricase availability	3	The availability of uricase is given
Item 19	1	Not provided.	1	-6: No such advice or tool is provided.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	-6: Resource implications are not considered.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: Such criteria are not provided.	2	A was mentioned	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: There's no such description about competing interests.	1	Not mentioned	1	Not found
EULAR_2006 [18]								
Item 1	5	Abstract and the first paragraph. B) was only provided as epidemiological information. This item was not easy to find.	6	Easy to find. -1: expected benefit can be inferred, but is not clearly stated.	7	All included	6	Can be found in the 1st paragraph,1‘ for the performance
Item 2	5	Page 1301. 10 key propositions were collected, but no detail was given.	5	The 10 initial propositions -2: they are not listed.	7	All included	5	Analysed from the recommends
Item 3	7	Abstract and the first paragraph.	7	Gout	7	All included	7	Well described
Item 4	5	Page 1310. The name of group and detailed information of the members were provided. But the role of each member was not provided and a methodologist was not involved.	5	Clear and easy to find. -1: no methodologist involved. -1: role of each member is not stated.	5	Missed description of the member’s role in the guideline development group	5	Can be found in the methods and the appendix, but is unclear
Item 5	1	Not sought.	1	-6: "patient opinion was omitted".	1	Not mentioned	1	Not found
Item 6	1	Not provided.	1	This is not described.	1	Not mentioned	2	The description is unclear
Item 7	7	Page 1302 and Appendix.	7	Appendix, but I can't find.	7	All included	7	In the methods and appendix
Item 8	7	Page 1302.	7	Page 1302 inclusion/exclusion criteria	7	All included	7	Can be found in the methods and the appendix
Item 9	5	Pages 1302-1303. Evidence levels were measured but only based on the design of study.	6	-1: only study design and methodology limitations are considered.	6	Subtract 1	6	Grade of evidence
Item 10	3	Methods section. Although Delphi	5	-2: some outcomes are not provided.	5	C was not mentioned	4	Is mentioned in the methods, but

		technique was adopted for proposition synthesis, when coming to the formulation of recommendations, the process was not clearly described.						without clear description
Item 11	6	Results section. Some of the recommendations did not consider the harms (e.g., Recommendation 4).	6	Most informative: recommendation 1. -1: not all recommendations reflect the consideration of benefits and harms. (e.g. Recommendation 4)	7	All included	5	Some recommendations have all above
Item 12	5	Methods and Results section. C) was not provided.	6	Table 4 & 5. -1: recommendation 4 is not linked to evidence.	6	Subtract 1	6	A figure
Item 13	2	Published in a peer reviewed journal.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	6	Updated information and services can be found at a web
Item 15	5	Results section. B) was not provided clearly.	6	-1: not all recommendations provide intent or purpose.	7	All included	6	Well described
Item 16	7	Not applicable.	7	All points are included.	7	All included	6	Well described
Item 17	7	Results sec. Recommendations were grouped in Table 3.	6	Table 3. Recommendations are in bold. "propositions are grouped by topic (clinical, urate crystals, biochemical, radiographic, and risk factors/comorbidities) with no weighting according to order." -1: the groups are not easy to identify.	7	All included	6	It has a figure
Item 18	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 19	2	Page 1309. The specificity and sensitivity of the diagnostic methods were tested.	4	Figure 4. & the explanation below. -2: no implementation section for the guideline. -1: no other tools.	1	All included	3	Some recommends
Item 20	5	Methods (page 1303) was given but the outcomes were not clearly provided.	6	Recommendation 3 & 8. Cost-effectiveness ratios are considered, but lack of sufficient evidence. -1: no description of informing the development.	5	Mentioned Incremental cost-effectiveness ratio	5	Some recommends cover it
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	4	Acknowledgement section.	4	"thank the European League Against Rheumatism for financial support" -3: no statement of influence	1	Not mentioned	3	One sentence: “thank the European League Against Rheumatism for financial support"
Item 23	1	Not provided.	1	-6: no information about competing interests.	1	Not mentioned	1	Not found

EULAR_2011 [17]								
Item 1	6	Abstract. B) was provided as epidemiological information.	6	Easy to find. -1: expected benefit can be inferred, but is not clearly stated.	7	All included	7	Well described
Item 2	5	Page 4. Clinical topics were proposed, but no detail was provided.	5	"Important patient-centred diagnostic and management outcomes were created for each recommendation". -2: these topics are not provided with details.	5	Included ab	5	Analysed from the recommends
Item 3	7	Abstract.	7	Gout	7	All included	7	Well described
Item 4	4	Page 3-4. Only the names, disciplines, and institutes of authors were provided. No methodologist was involved.	5	Easy to find. A methodologist (bonny p. Mcclain) involved. -1: role of each member is not provided. -1: the development group is not stated.	6	No methodologist	5	No epidemiologist
Item 5	1	Not sought.	1	-6: no information about patient views.	1	Not mentioned	1	Not found
Item 6	7	Abstract and the first paragraph.	3	"Paying special attention to the needs of primary care physicians". -2: no clear statement of target users. -2: no description of how to use, it can only be inferred. Primary care physicians can be inferred as part of the target users.	7	All included	6	Well described
Item 7	4	Page 5. The names of databases searched and the time period were provided.	4	"Literature Inclusion/Exclusion Criteria" part. -1: search terms are not provided. -2: full search strategy is not provided.	4	Missed cd, target research was conducted through Pubmed, from Feb 2005 through Feb. 2011	4	C) and d) are not found
Item 8	1	Not provided.	7	"Literature Inclusion/Exclusion Criteria" part.	4	Description of the inclusion criteria, study design	6	Well described
Item 9	7	Page 4. GRADE approach.	7	Grade	7	All included	6	Literature Inclusion/Exclusion Criteria is unclear
Item 10	7	The process was provided both in description (page 5) and as a diagram (figure 1). The outcomes of strength of recommendations were provided in tables 1&2.	4	"Methods" part. -1: the development process is described, but some of it is not provided with details. (e.g. How they created the "important patient-centred diagnostic and management outcomes") -2: outcomes are not provided.	7	All included	6	In figure 1
Item 11	7	Results section.	7	The level of recommendation reflects the consideration of benefits and harms.(end of page 5). Most informative: management recommendation 4.	7	All included	7	It mentions all of the aspects
Item 12	7	Methods and Results section. Evidence was	7	How they linked is described.	7	All included	7	Each recommendation has certain

		summarized into tables.		Each recommendation is linked to a key evidence paragraph. Evidence summaries: table 3&7.				link
Item 13	2	Published in a peer reviewed journal.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	It's already updated from 2006
Item 15	5	Results section. B) was not provided.	6	-1: not all recommendations provide intent or purpose.	6	Subtract 1	6	Well described
Item 16	7	Results section.	7	All points are included.	7	All included	6	Well described
Item 17	7	Recommendations were typed in bold (Results section) and summarized (Discussion section).	7	Recommendations are in bold. Table 1&2. Recommendations are grouped as "diagnosis" & "management".	7	All included	6	Can be found in table 2
Item 18	2	Page 27. The limited FDA approval for NSAIDs was discussed.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	2	Only table 6 mentions some
Item 20	2	Pages 24&26. The cost-effectiveness of drugs were considered.	5	Recommendations 9 & 11. -1: no description of the cost information that emerged. -1: no description of how it was used to inform the development of guideline.	4	Mentioned drug acquisition costs	4	In figure 1,the last step considers resource use ,but not clearly
Item 21	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 22	4	Acknowledgement section. B) was not provided.	4	Acknowledge part. -3: no statement of influence.	4	Funding for the preparation of the article was received from URL Pharma, and from the American Society of Clinical Rheumatologists.	3	Give the funding body but no statements
Item 23	4	Page 31. The conflict of interest statement was provided, but a) and d) were not given.	4	Conflict of interest part. -2: no statement of influence. -1: no methods.	6	Page 31,missed b	4	The description of competing interests is not specific
EULAR_2016 [16]								
Item 1	7	Abstract	7	"These recommendations aim to inform physicians and patients about the non-pharmacological and pharmacological treatments for gout and to provide the best strategies to achieve the predefined urate target to cure the disease." Well written, eays to find.	5	Not mentioned outcome	6	The epidemiology is provided, and other information can be found in the last paragraph of the introduction
Item 2	7	Results section.	1	-6: No specifically described question is provided in the guideline.	5	No questions	6	Analysed from the recommends
Item 3	7	Abstract.	7	Gout	7	All included	7	Well described

Item 4	6	Methods section and Author affiliations section. The role of each member was not provided.	6	Clear & easy to find. 3 experts in epidemiology/methodology are included. Role: Methods & Contributors. -1: role of each member is not clearly stated.	5	Subtract 2' for no role	6	The methods and appendix provide the authors' information
Item 5	5	Two patients were in the task force. C) was not provided.	5	-2: the outcome is not provided.	5	2 patients	5	It has a) b) and d)
Item 6	7	Abstract.	7	"These recommendations aim to inform physicians and patients about the non-pharmacological and pharmacological treatments for gout and to provide the best strategies to achieve the predefined urate target to cure the disease." Well written, easy to find.	5	Mentioned ab	7	In the conclusion
Item 7	5	Methods section. D) was not provided.	5	-2: The full search strategy is not provided.	5	No strategy	5	No full strategy
Item 8	2	Methods section. Only general criteria on study design was provided.	2	-5: the supplementary material mentioned the inclusion criteria, but the criteria are not specifically described.	1	Not mentioned	3	It is unclear
Item 9	7	Methods section. The Oxford Centre for Evidence Based Medicine standard and the GRADE method.	7	Oxford levels of evidence. Details in supplementary material	6	GRADE method	5	The quality of evidence and grades of recommendation were determined according to the standards of the Oxford Centre for Evidence-Based Medicine
Item 10	7	Method section. Delphi approach was adopted.	7	Very clear in Methods. Outcomes in supplementary material.	6	All included	7	The description is clear
Item 11	7	Results section.	6	Most informative example: recommendation 3 & 8. -1: Not all recommendations reflect the consideration of benefits and harms (e.g. Recommendation 5)	5	Subtract 1	6	Well described
Item 12	7	Methods and Results section.	7	Methods & Table 2. Each recommendation has an evidence description.	6	All included	6	Well described
Item 13	6	Page 28, second paragraph to the right. The influence of external review on guideline development was not clearly stated. The outcome of external review was provided in supplementary data.	6	Methods & Acknowledgement. Outcomes in supplementary material. -1: the influence is not described.	6	The external evaluation is provided as	6	Well described
Item 14	1	Not provided.	3	"These novel EULAR recommendations will undoubtedly require updating over the next few years". -2: No specific time interval. -2: No description of updating procedure.	2	Online supplementary material, and the research agenda appears	2	It is updated from the guideline of 2006
Item 15	7	Results section.	7	All points are included.	5	Subtract 1	7	Well described

Item 16	7	Results section.	7	All points are included.	6	All included	7	Well described
Item 17	7	Recommendations were summarized in table 1 and were grouped in the abstract.	7	Figure 1&2. Recommendation are grouped (overarching & others)	6	All included	7	Well described
Item 18	2	Page 36 - "The task force was aware that not all ULTs mentioned in this paper, especially the uricosurics, are readily available in all European countries".	4	Barrier: "not all ULTs mentioned in this paper, especially the uricosurics, are readily available in all European countries". -2: No methods. -1: No influence.	4	Mentioned in Overarching principles	2	Only a little
Item 19	2	Algorithm as figure 1.	1	-6: No such information.	1	Not mentioned	1	Not found
Item 20	5	Page 35, 37, 38. b) not provided.	6	Recommendation 8. -1: no description of the cost information.	4	Mentioned ad	5	In the discussion part, the cost is discussed
Item 21	1	Not provided.	1	-6: No such information.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	3	The statement doesn't be found
Item 23	4	Page 38. b) and d) not provided.	4	-1: the methods are not described. -2: no description of influence.	4	Mentioned abc	4	No b) or d)
FMOH_2014 [44]								
Item 1	7	Title and Foreword.	7	"Foreword" & "1.6 purpose of the guideline"	6	Contained ab and performance	6	In the foreword and the purpose of the guideline
Item 2	3	The clinical topic could be inferred from throughout the guideline, but was not clearly stated.	3	The core topic can be inferred. -4: no statement that certain health questions or topics are covered.	2	Contained "bd"	3	No questions but analysed from the text
Item 3	7	Foreword.	7	NCD	5	Subtract 2 points for the population is not clearly described	7	Analysed from the text
Item 4	6	Acknowledgement section. No methodologist.	5	"Acknowledgement" -1: role of each member is not provided. -1：no methodologist involved in the development group.	5	Mentioned a, name ,expertise, institution and performance	5	Group, name ,institution and role are provided
Item 5	1	Not provided.	1	-6: no information about target population preferences.	1	Not mentioned	1	Not found
Item 6	4	Foreword. B) was not provided.	7	"Foreword" & "1.5 purpose of the guideline"	6	No Clear description of intended guideline audience	6	The purpose of the guideline
Item 7	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 8	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 9	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 10	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found

Item 11	2	Pages 54-55. Harms were not discussed and no reference was provided.	2	-5: only benefits are considered, but without evidence.	1	Not mentioned	3	Some recommends consider the harm
Item 12	1	Not provided.	1	-6: not mentioned in the guideline.	2	Clear description of intended guideline audience	2	Each recommendation is linked to a key evidence
Item 13	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 15	3	Section 5.6.1. A) and b) were not provided.	4	-2: uncertainty is not stated. -1: the relevant population is not clearly stated. (e.g. The recommendation is for prevention and management of gout, all? For patient with gout? For those who want to prevent gout?)	2	Identification of the intent or purpose of the recommended action	3	The uncertain is not described
Item 16	1	Not provided	4	-1: not all options are described. -2: not all recommendations provide the most appropriate population or situation. (e.g. 5.6.1 recommendation f)	7	All included	6	Well described
Item 17	4	Section 5.6.1. Table 16. A) was not provided.	4	E.g. Table 6. -3: recommendations are not well grouped.	6	All included	3	Table, but it is not clear enough
Item 18	1	Not provided.	1	-6: no information about facilitators or barriers to application in the "gout" part.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	2	Table 16. -5: no other information about implementation in the "gout" part.	1	Not mentioned	1	Not found
Item 20	2	Section 1.1. Background. Cost information was discussed.	3	Price is considered in policy part.	1	Not mentioned	3	Some consider the price
Item 21	1	Not provided.	1	-6: no mentioned in the guideline.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
JSGNAM_2011 [48]								
Item 1	5	Page 1018. B) was only provided as epidemiological information. This item was not easy to find.	6	Easy to find. -1 : the expected benefit can be understand but not clearly stated.	5	Statements were not clear	5	Not easy to be found
Item 2	5	Page 1019. It was stated that 41 clinical questions were collected for the development of the guideline, but the detailed questions were not provided.	5	There were 41 clinical questions. -2: the questions are not provided with details.	7	All included	5	Not easy to be found

Item 3	7	Abstract.	7	Gout and HUA	7	All included	7	Well described
Item 4	2	Only the name of group (the Japanese Society of Gout and Nucleic Acid Metabolism) was provided.	2	The name of development group is stated. -5: no other information.	1	Not mentioned	2	Only the development group
Item 5	4	Page 1020, Methods section. A patient participated in reviewing the guideline. C) and d) were not provided.	4	The draft was reviewed by a patient. -2: no outcomes. -1: no description of the information was used to inform the recommendations.	4	The guideline revising committee collected clinical questions for the management of gout and hyperuricemia, and based on 41 clinical questions, a systematic literature search was conducted. From the results of this search, 492 articles were selected and reviewed by committee members, and recommendations for the management of gout and hyperuricemia were proposed as statements with evidence levels	5	A draft version of this guideline was reviewed by internal and external reviewers as well as a patient.
Item 6	4	Abstract. A) was not clearly stated.	4	How to use is involved. “guideline is appropriately used for the standard management and care of patients with hyperuricemia and gout in daily practice".	4	Used for the standard management and care of patients with hyperuricemia and gout in daily practice.	4	Analysis from the paragraph 1
Item 7	1	Not provided.	1	-6: all the required information is not provided.	1	Not mentioned	2	Unclear
Item 8	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 9	6	Page 1020, Methods section. Evidence levels were measured but only based on the design of study and on the consistency of original studies included in meta analysis.	7	Methods - evidence level part.	7	Not mentioned	7	It has level of evidence
Item 10	3	Page 1019. A Delphi exercise was conducted to determine the consensus level, but b) and c) were not provided.	4	Methods part. -1: lack of some details of the development process (e.g. How the questions were collected.)	1	Not mentioned	5	Delphi

				-2: no outcomes.				
Item 11	6	As for the Therapy of Hyperuricemia, all four aspects were provided. But the harms of treatment were not stated in some other recommendations.	6	Most informative: "Therapy of Hyperuricemia - Therapeutic Goal". Not all recommendations showed the supporting data and report of harms and benefits.(e.g. Therapy of Gouty Arthritis/Gouty Tophus)	7	All included	6	Well described
Item 12	3	B) was provided for all recommendations, but a) and c) were not.	4	Methods. -1: each recommendation has a level of evidence, but is not linked to a key evidence paragraph. -2: no evidence summary.	4	Missed a	4	Some recommends are linked with the evidence
Item 13	2	Page 1020. External review was conducted, but no detail was given.	3	"A draft version of this guideline was reviewed by trustee members of the Japanese Society of Gout and Nucleic Acid Metabolism, and subsequently, public comments were requested by external reviewers" -1: no purpose. -1: no outcomes. -2: no description of how the information is used.	2	A draft version of this guideline was reviewed by internal and external reviewers as well as a patient.	3	The description is unclear
Item 14	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 15	7	Results section.	7	All points are included.	7	All included	6	Well described
Item 16	7	Results section.	6	-1:only some options are provided with the most appropriate population or clinical situation (e.g. Lifestyle intervention is not).	6	Subtract 1	6	Well described
Item 17	4	Recommendations were provided in a box but not grouped together.	7	Figure 2. Recommendations are in boxes. Recommendations are grouped.	7	All included	5	B) is not mentioned
Item 18	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
MOH_MSR_AMM_2008 [49]								
Item 1	6	Page IV. A) and c) were provided. B) was only provided as epidemiological	7	Page 3, rational 1st paragraph. Page 4, objectives.	7	All included	7	Can be found in the page 4,objective

		information (page 1).						
Item 2	7	Page IV.	7	Page 4, clinical questions.	7	All included	7	In the clinical questions part
Item 3	7	Page IV.	7	Page 4, target population	7	All included	7	In the target population part
Item 4	5	The name of the group (page III) and detailed information of members (page V-VI) were provided. But the role of each member was not provided and a methodologist was not involved.	5	Clear and easy to find. -1: no methodologist involved. -1: role of each member is not provided.	7	All included	5	No role
Item 5	1	Not sought.	3	The draft was on the website for comments and feedbacks from the public. -1:this is not a clear statement that the target population is exactly involved. -2: no outcomes. -1: no influence.	1	Not mentioned	1	Not found
Item 6	7	Page II.	7	All information is described.	7	All included	7	Target group is well described
Item 7	4	Page III. Only the names of databases searched and the search terms were provided.	4	Databases and search terms are provided. -1: no time periods. -2: no full search strategy.	4	Named electronic database and search terms	5	3rd paragraph of the rationale, but without the time period
Item 8	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 9	5	Page 25. Evidence levels were measured only basing on the design of study.	6	Page 25 level of evidence scale. -1: only study design and methodology limitations are considered.	6	Subtract 1	6	The level of evidence only be graded by the type of article
Item 10	1	Not provided.	2	-5: the description of the process is not very detailed. The outcomes are not provided. The influence is not detailed.	1	Not mentioned	2	In the rationale part
Item 11	6	Pages 9-17. Side effects of some treatments (e.g., NSAIDS, COX-2 inhibitors) were not provided.	6	Most informative: page 14 allopurinol. -1: not all recommendations reflect the consideration of benefits and harms.	6	Subtract 1	5	Found in the recommends
Item 12	5	A) was presented as the grades of recommendations. C) was not provided.	4	Rationale. -1: not every recommendation is linked to a key evidence description/paragraph and/or reference list. -2: no evidence summary.	5	Not described how the guideline development group linked and used the evidence to inform recommendations	5	A) was presented as the grades of recommendations
Item 13	2	External reviewers were provided (page VI) but no other detail was given.	3	Methods and description of reviewers are provided. -4: no other information.	2	Mentioned the name of external review	3	No details
Item 14	4	The guideline was expected to be reviewed in 2012 (page II) but no methodology was provided. And at the time of scoring, no statement confirming the review/update	5	"This guideline will be reviewed in 2012 or sooner if new evidence becomes available" -2: no methodology	5	Mentioned in statement of intent	5	In the 3rd paragraph

		was found online.						
Item 15	7	Page 9-17	6	-1: not all recommendations provide intent or purpose.(e.g. 5.3)	7	All included	6	Well described
Item 16	7	Page 9-17	7	All points are included.	7	All included	6	Well described
Item 17	7	An algorithm (page IX) was provided and recommendations were summarized in a group (page VII-VIII).	7	Page 9 algorithms. Recommendations are summarized and grouped in the summary (page 7-8).	7	All included	6	Well described
Item 18	2	Page 7, section 4.2. The availability of diagnostic service was discussed.	3	Barrier: page 7, 4.2. But it is only a simple description, no any other information is provided.	1	Not mentioned	1	Not found
Item 19	3	Pages VIII - XI. A summary and algorithm were provided.	5	The summary, algorithm. -2: no implementation section	1	Not mentioned	3	Appendix 1
Item 20	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	4	Page 22. The name of the funding body was provided but b) was not given.	4	Source of funding part at the end. -3: no statement of influence.	4	The name of the funding body or source of funding	4	Unrestricted educational grant
Item 23	1	Not provided.	2	Only the method is provided. -5: no other information.	2	Members have completed disclosure statement	2	Disclosure statement
PRA_2008 [50]								
Item 1	5	Introduction section. B) was only provided as epidemiological information. This item was not easy to find.	7	Abstract, objective. Well written, easy to find.	7	All included	7	In the abstract
Item 2	3	This item can be inferred from the last paragraph of the Introduction section but was not clearly given.	7	The issues are detailed.	7	All included	5	Analysed from the recommends
Item 3	5	Inconsistent expressions. The Title and Recommendations were targeting patients with gout, while the Objectives in Abstract narrowed to patients with gouty arthritis.	4	Patients with gouty arthritis. Or with gout? Phase 1 is not about gout. -3: not consistent through the whole guideline.	7	All included	5	Title and recommendations have conflicting descriptions
Item 4	4	Page 1. The name of group and detailed information of the technical review committee were provided. But the role of each member was not provided and a methodologist was not clearly indicated.	3	Easy to find. -2: discipline and institution of panel members are not provided. -1: role of each member is not described. -1: no methodologist involved.	4	No discipline/content expertise, no description of the member's role in the guideline development group	4	No the description of the member's role or epidemiologist
Item 5	5	Page 1. A patient was included in the panel.	5	A patient was in the panel. -2: outcomes are not provided.	5	Mentioned in method	5	Well described
Item 6	7	Introduction section.	7	Introduction	7	All included	7	Well described

Item 7	5	Methodology section. The time periods, names of databases, and the search terms were provided.	5	Methodology -2: no full search strategy.	5	Full search strategy was not clear	5	In the method part
Item 8	1	Not provided.	6	Methodology -1: outcomes are not included in the criteria.	5	No outcomes	5	It mentions but unclear
Item 9	7	Methodology section. GRADE system.	7	Grade	7	All included	7	Well described
Item 10	4	Methodology section. A voting procedure was conducted and the GRADE system was used to evaluate the strength of recommendations. But the details of the voting was not provided (subtract 1') and how the voting and evaluation process influenced the guideline development were not provided (subtract 2').	4	Methods part. -1: lack of some details of the development process (e.g. How the issues were created.) -2: no outcomes.	6	Panel members cast their votes to finalize the recommendations.	5	In the method part
Item 11	7	Results section.	6	Most informative: phase 2 & recommendation 8. -1: not all recommendations reflect the consideration of benefits and harms.	7	All included	6	Phase 3 and 4
Item 12	5	Methodology section. C) was not provided.	4	Methodology. -1: evidence descriptions are linked to phases but not to each recommendation. -2: no evidence summary.	5	Each recommendation was not linked to a key evidence description/paragraph and/or reference list	5	No summary
Item 13	1	Not provided.	2	"The Steering Committee would like to thank Dr. H Ralph Schumacher Jr for providing helpful comments on the contents". -5: no other information.	1	Not mentioned	1	Not found
Item 14	5	The last sentence of the guideline.	5	"Updates in management issues will be integrated as deemed necessary in the next 3 or more years" -2: no methodology	5	Updates in management issues will be integrated as deemed necessary in the next 3 or more years.	5	Updates in management issues will be integrated as deemed necessary in the next 3 or more years
Item 15	5	Results section. B) was not provided.	5	-2: some uncertainty is not stated.	6	Subtract 1	5	No purpose
Item 16	7	Results section.	6	-1:some options are not provided with the most appropriate population or clinical situation.	7	All included	6	Well described
Item 17	4	Recommendations were summarised as Table 1. A) was not provided.	7	Recommendations are summarized and grouped in table 1.	5	A was not concluded	4	In table 1
Item 18	2	Page 9, the first sentence. The availability of allopurinol was discussed.	3	"Allopurinol is the only drug available in this class in the Philippines."	1	Not mentioned	1	Not found

				-4: no other information.				
Item 19	1	Not provided.	2	Table 1.	1	Not mentioned	1	Not found
Item 20	2	The cost of treatment was taken into consideration (Phase 2, paragraph 2; also reference 38).	3	Cost-effectiveness is considered in phase 3&4. "the Philippine guidelines recommend that the choice of drug for acute gouty arthritis be individualized taking into consideration drug efficacy, safety, and cost". -4: no other information	2	Consider about the cost	3	Phase 2 ,paragraph 2
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 23	2	Disclosures statements. This item can be inferred, but no detail was provided.	4	Disclosures. -1: no methods. -2: no statement of influence	2	Only mentioned the Disclosures	2	Only one sentence: JLY serves as consultant to Novartis and trial investigator for Pfizer. EOS and JJL serve as trial investigators for Pfizer. Other members of TRC have nothing to disclose.
SAMA_2003 [51]								
Item 1	6	Section 1. Objective and scope. B) was only provided as epidemiological information (Epidemiology section).	7	"These guidelines have been developed to: provide an understanding of gout ; promote the cost-effective management of gout by doctors and other health care providers."	7	All included	6	Without the target
Item 2	3	Section 11. Management.	3	The questions can be inferred.	3	Not provided in questions	3	Is not easy to be found and don't cover all aspects
Item 3	7	Section 1. Objective and scope.	7	Gout	7	All included	7	Well described
Item 4	5	Annexure B. The disciplines were not provided. Methodologists were not clearly stated to be involved.	4	Easy to find. -1: only organization of each member is provided. -1: no role of each member. -1: no methodologist involved	2	Only mentioned the name	5	No expertise, not easy to be found
Item 5	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	2	Only mentions that consumer groups took part in.
Item 6	4	Section 1. Objective and scope. B) was not clearly provided.	5	"Doctors and other health care providers" "for reference and education only" -2: not clearly stated, difficult to find.	5	Mentioned b	4	No clear description of intended audience
Item 7	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 8	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 9	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found

Item 10	5	Annexure A: Methodology.	5	Annexure A: Methodology。 -2: no outcomes.	1	Not mentioned	5	In the method part
Item 11	7	Section 11. Management.	7	Most informative: Allopurinol.	7	All included	5	16.4:no supporting data ,risks
Item 12	3	Only b) was provided.	2	-2: no description of how they used the evidence. -1: not every recommendation is linked to a key evidence description/paragraph and/or reference list. -2: no evidence summary.	3	Informed recommendations	3	Some recommendations give the evidence
Item 13	2	Annexure A. A meeting revising the draft guideline was held.	4	"The endorsement document was circulated to all participants and many other interested persons" "Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received". -1: no purpose. -1: no outcomes. -1: this is not a clear statement of external review.	1	Not mentioned	3	It mentions Observer delegates
Item 14	3	Section 12. Disclaimer. It was inferred that the guideline might be updated.	2	"SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated." -5: this is not a clear statement of updating.	1	Not mentioned	5	SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated
Item 15	3	A) and b) were not provided.	5	-2: No purpose. Uncertainty is not clearly stated.	6	Subtract 1	6	Such as 16.3.3dmards
Item 16	6	Section 11. Management. B) was provided for ULT use but was not provided in some recommendations (e.g., treatment of the acute attack).	7	All points are included.	7	All included	6	Well described
Item 17	7	A 'Summarised Guideline' section was provided.	4	Figure1 & 2. Kind of "grouped together" in the summarized guideline. -3: recommendations and explanations are not clearly distinguished. And in full guideline they are not grouped.	7	All included	6	Well described
Item 18	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	5	Figure1 & 2. The summarized guideline. -2: no implementation section in the guideline.	1	Not mentioned	1	Not found
Item 20	2	Section 11.2.3. The price of ACTH was considered.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	7	Annexure A: Methodology.	7	Annexure a: methodology	7	All included	7	Well described

Item 23	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
SER_2013 [46]								
Item 1	7	Page 21.	7	Page 15, methodology, 1st paragraph. Page 21 objective.	7	All included	7	Well described
Item 2	6	Table 1. A question list was provided but it did not cover all the guideline aspects.	6	Questions are listed but -1: the questions didn't cover the content of the guideline.	7	All included	6	The questions don't cover all aspects
Item 3	7	Title.	7	Gout	7	All included	7	Well described
Item 4	7	Pages 10-14, 16. A methodologist reviewed the document (page 21).	6	Clear & easy to find. Project Manager is an epidemiologist. Reviewers are trained and experienced in systematic reviews.	7	All included	7	Well recommendation
Item 5	5	Page 16. A patient was involved in the development panel.	5	A patient is involved in the panel. -2: the outcomes are not provided.	5	Missed d	5	There was also consensus on the participation of at least one nurse and one patient.
Item 6	4	Chapter III. B) was not clearly given.	3	The 2 aspects can be inferred from page 21 III. -4: None of them is clearly described.	5	How the guideline may be used by its target audience was not mentioned	5	Analysed from the article
Item 7	3	Page 17. The names of databases searched were provided.	3	Only names of databases are provided. -4: no other information.	3	Provided a	4	C) and d) :not found
Item 8	1	Not provided.	1	-6: not provided.	1	Not mentioned	1	Not found
Item 9	7	Levels of Oxford Centre of Evidence Based Medicine.	7	Oxford	7	All included	7	A title
Item 10	3	Chapter II. B) and c) were not provided.	5	-2: outcomes are not provided.	3	Used the Delphi method	5	No description of the detail
Item 11	7	Chapters X-XI.	6	-1: not all recommendations reflect the consideration of benefits and harms.	7	All included	7	Well described
Item 12	5	Chapters II, X, XI. C) was not provided.	4	-1: Most recommendations are linked to evidence descriptions, but a few are not. -2: no evidence summary or evidence table.	6	Subtract 1	4	No c)
Item 13	2	Information of external reviewers were given (page 21)	2	Page 21 "The CPG was assessed by two external reviewers, a rheumatologist expert in this clinical area (FPR) and a methodologist who was expert at conducting clinical practice guidelines (MJGY)".	2	The CPG was assessed by two external reviewers	2	Only one sentence: The CPG was assessed by two external reviewers, a rheumatologist expert in this clinical area (FPR) and a methodologist who was expert at conducting clinical practice guidelines (MJGY).
Item 14	5	The CPG will be updated approximated	7	Page 21 "diffusion" part.	7	All included	7	Update every 4 years

		every 4 years (page 21).						
Item 15	5	Chapters X-XI. B) was not provided.	6	-1: not all recommendations provide intent or purpose.	7	All included	5	No purpose
Item 16	6	Chapters X-XI. B) was not provided for some recommendations.	7	All points are included.	7	All included	7	Well described
Item 17	4	Chapters VI-XII. Recommendations were not grouped.	4	Recommendations are in bold. There are some summary tables. -3: recommendations are not grouped.	missed b	All included	5	No summary
Item 18	2	The conflict between approved medication dosage and prescribed dosage in practice was mentioned (page 110, second paragraph).	4	Page 15, methodology, 2nd paragraph. -2: methods are not provided. -1: description is not provided.	4	Mentioned barrier in METHODOLOGY	4	Some paragraphs mention the barriers but not clearly
Item 19	2	A "Quick Guide" was available but only in paper format (page 15).	5	I.C how to use (page 15) II.E Diffusion (page 21) Table 11, 13,17. -2: no direction on how to access the "Quick Guide".	1	Not mentioned	1	Not found
Item 20	2	Cost information was presented (page 39 and reference 362).	3	With some recommendations mentioning the cost-effective aspect of a drug/test (page 39), they said that they don't consider costs in the recommendations(Page 17 II.C "it was explicitly requested that they be written based on the risk/benefit balance for the patient, regardless of the associated costs").	4	Cost information is mentioned	2	Only one sentence: it was explicitly requested that they be written based on the risk/benefit balance for the patient, regardless of the associated costs.
Item 21	1	Not provided.	1	-6: not mentioned in the guideline.	1	Not mentioned	1	Not found
Item 22	7	Page 14	5	Funding, page 14. -2: not all names of funding companies are provided.	7	All included	7	Well described
Item 23	2	Although it was stated that all members of the development group have made explicit statements of potential conflicts of interest (page 10), no further detail was given.	2	"All participants have made an explicit statement of their potential conflicts of interest". -5: apart from the method, no other detail is provided.	2	Described the competing interests	2	Not clear
SIR_2013 [45]								
Item 1	7	Abstract.	7	Summary. Well written & easy to find.	7	All included	6	Can be found in the objectives and introduction
Item 2	7	Page 5. Four questions were provided.	7	4 queries are listed.	7	All included	6	In total 4 questions
Item 3	7	Abstract and Introduction section.	7	Gout	7	All included	7	Well described
Item 4	6	Page 4. The role of each member was not	6	Easy to find.	6	Mentioned ab	7	Can be found in the summary

		provided.		Evidence-based medicine experts are involved. -1: role of each member is not provided.				
Item 5	1	Not provided.	1	-6: patients with gout are not involved in the development process.	1	Mot mentioned	1	Not found
Item 6	7	Abstract (the last sentence) and Introduction section (the last paragraph).	4	End of "introduction" part. -3: no description of how the guideline may be used.	6	All included	6	It is not easy to be found :"This document is intended for rheumatologists, general practitioners, internists, geriatricians, nephrologists, cardiologists and all healthcare professionals involved in the management of patients with gout"
Item 7	4	Materials and Methods section. C) and d) were not provided.	4	"Methods" part. -1: no search terms. -2: no fully search strategy.	4	The literature search was conducted in November 2011 in the following databases: MEDLINE, Embase, and Cochrane Central.	4	C) and d) are not found
Item 8	7	Page 6.	7	"Methods" part. Clear & easy to find.	7	All included	6	Can be found in the methods
Item 9	5	Page 6 and Table I. The level of evidence was only evaluated based on the study design.	7	Same as EULAR, Oxford.	7	All included	6	A single figure and methods
Item 10	3	Materials and Methods section. B) and c) were not provided.	5	-2: the outcomes are not provided.	6	Subtract 1	3	Not found all of them
Item 11	7	Results section.	6	Most informative: recommendation 4. -1: not all recommendations reflect the consideration of benefits and harms.(e.g. Recommendation 6)	7	All included	5	Some recommends have
Item 12	5	Results section. The evidence summary/table was not provided.	5	-2: evidence summaries or evidence tables are not provided.	6	Subtract 1	6	A figure
Item 13	2	Published in a peer reviewed journal.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	It's the update of 2006
Item 15	7	Results section.	6	Most of the recommendations are specific and unambiguous. -1: purpose of recommendations are not all provided.	6	Subtract 1	6	Well described
Item 16	7	Results section.	7	All points are included.	7	All included	6	Well described

Item 17	4	Results section. B) was not provided.	4	Table IV. Recommendations are in bold. -3: recommendations are not grouped. (the 3 levels are listed, but recommendations are not grouped by the levels.)	4	A is not concluded	4	It has a figure but the figure doesn't cover all
Item 18	2	Page 10. The availability of treatments in Italy was discussed.	4	The guideline emphasizes that it was designed to adapt to Italian, considering current therapeutic options available in Italian.-1: no description. Table 2 & the explanation below the table, Page 12.-2: Methods are not provided.	1	Not mentioned	3	Only some aspects included
Item 19	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 20	4	Pages 6, 7, 15. Cost effectiveness was taken into consideration in the voting, but no detailed information was provided.	6	Recommendation 1. "Methods", end of page 6. -1: description of the cost information is not provided.	4	Included cost effectiveness	4	Some described the cost
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
T2T_2016 [39]								
Item 1	6	Introduction section (the last paragraph). Contents of this item were not easy to find.	7	To improve the management of gout in clinical practice & "recommendations aimed at defining a treatment target and initiate a T2T programme for gout". Well written, easy to find.	5	All included	7	In the abstract
Item 2	7	Table 3.	7	Table 1.	7	Contained "ab"	7	Can be found in the abstract and
Item 3	7	Abstract.	7	Gout	7	All included	7	Can be found in the abstract
Item 4	5	Pages 1&5. A) was not provided. No methodologist was involved.	6	Easy to find. -1: no methodologist involved in the development group.	5	Not mentioned a	5	The name of group is unknown
Item 5	5	A patient was included in the international task force, but c) was not provided.	5	-2: the outcome is not provided.	5	Page 2 mentioned	5	A patient with gout
Item 6	1	Not provided.	1	-6: not described.	2	Only mentioned "To improve the management of"	1	Not found
Item 7	7	Methods section and Supplementary 1&2.	7	Table S1 & S2	7	All included	7	In the appendix
Item 8	7	Supplementary 1 - Eligible criteria.	7	Table S1.	6	All included	6	In the method
Item 9	7	Methods section. Evidences were assessed using a system provided by the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/oxford-centre-eviden	7	Oxford level of evidence.	6	Contained a	6	In the method

		ce-based-medicine-levels-evidence-march-2009/).						
Item 10	7	Methods section. And results were provided as table 1.	7	Methods. Table 1.	6	All included	6	The last paragraph of the methods
Item 11	3	Results section. A) and b) were not provided for individual recommendations but the grade of recommendation, level of evidence, and strength of recommendation were provided.	4	Supporting data and report of benefits are in the "result" part. Recommendations reflect the consideration. -2: supporting data and report of harms are not mentioned. -1: It's only a summary of all evidence, not for each recommendation.	2	Supporting data and report of benefits	4	The recommendation is not clear
Item 12	3	Results section. B) and c) were not provided for individual recommendations.	5	Methods part, Result part & Table 2. -2: no key evidence description for each recommendation.	3	C mentioned	5	A single figure gives the link
Item 13	2	Page 6.	2	Only "externally peer reviewed". -5: no other information.	2	Only mentioned c	1	The last paragraph said no external review
Item 14	1	Not provided.	5	Updated information and services can be found at: http://ard.bmj.com/content/early/2016/09/22/annrheumdis-2016-209467 -2: No time interval.	1	Not mentioned	1	Not found
Item 15	4	Results section. B) and d) were not provided for individual recommendations.	6	Some purposes of recommendations are not clearly stated.	5	Subtract 1	5	Can be found in the recommendations, but the recommendations are not clear enough
Item 16	6	Results section. Some recommendations did not clarify the most appropriate population.	7	All points are included.	6	Subtract 1	6	Well described
Item 17	7	Recommendations were summarized in table 2 and grouped in page 3.	7	Table 2. Recommendations are grouped	6	All included	6	Figure
Item 18	3	Page 5, paragraph 5. A) and b) were not provided.	1	-6: No description of facilitators or barriers to application.	3	Mentioned in discussion	1	Not found
Item 19	1	Not provided.	1	-6: No description about implementation.	1	Not mentioned	1	Not found
Item 20	1	Not provided.	1	-6: No description about resource or cost.	1	Not mentioned	1	Not found
Item 21	1	Not provided.	1	-6: Such criteria are not provided.	1	Not mentioned	1	Not found
Item 22	4	Page 5. B) was not provided.	4	Funding. -3: No statement that the funding body did not influence the content of the guideline.	3	No statement that the funding body did not influence the content of the guideline	3	No statements
Item 23	2	Pages 5-6. A), b) and d) were not provided.	4	Competing interest.	6	All included	6	The competing interests state

				-1: methods by which the information were sought are not described. -2: No description of the influence.				
TRA_2016 [38]								
Item 1	5	Title and Chapter 1 - Abstract. B) was not provided and the contents were not easy to find.	6	The introduction part & epidemiology. -1: easy to find, but the objective is not specifically described.	6	Missed b	6	1' for the performance
Item 2	3	A question list was not provided but the clinical topic can be inferred.	3	-4: No specifically described question is provided in the guideline.	3	Contained "ab"	5	Analysed from the article
Item 3	7	Title and Chapter 1 - Abstract.	7	Hua	7	All included	7	Well described
Item 4	5	Page1. The role of each member was not provided and a methodologist was not involved.	5	Easy to find. -1: no description of member's role. -1: No methodologist include.	5	Mentioned ab	5	No discipline expertise, performance
Item 5	1	Not provided.	1	'-6: The views and preferences of the target population are not mentioned.	3	Mentioned a	1	Not found
Item 6	4	Preface. B) was not clearly provided.	7	"to provide important reference for medical workers and patients with gout and HUA"	1	Not mentioned	3	Can be found in the last sentence of the preface
Item 7	1	Not provided.	1	-6: Searching method is no provided.	1	Not mentioned	1	Not found
Item 8	1	Not provided.	1	-6: Criteria are no provided.	2	Outcomes mentioned	1	Not found
Item 9	1	Not provided.	1	-6: Strengths and Limitations of The Evidence are not described.	1	Not mentioned	1	Not found
Item 10	1	Not provided.	2	The guideline was developed though discussion of experts from multi-discipline. -5: No any other details about the formulation (detailed process, outcomes or influence) is provided.	1	Not mentioned	1	Not found
Item 11	6	Pages 15-22. A) and b) were not provided in recommendation 2 - pharmacological treatment for acute gouty arthritis.	6	Most informative examples: Page 15 "management of asymptomatic HUA". -1: Not all recommendations provide supporting data of benefits and harms (e.g. Page 18 "colchicine" & "corticosteroid").	5	Subtract 1	5	Some of the recommendation have the a),b) and c)
Item 12	2	Pages 15-22. B) and c) were not provided in recommendation 3 - treatment for chronic gouty arthritis. A) was not provided in recommendation 2 - pharmacological treatment for acute gouty arthritis.	2	Some recommendations (e.g. Page 24 "direction of daily life and diet") are linked to evidence description. -2: How they linked and used the evidence to inform recommendations are not described. -2: No link between recommendations and evidence summary. -1: Not all recommendations include an evidence description (e.g. Page 22 "Sulfinpyrazone") .	4	Missed a	2	Just a little

Item 13	2	Published in a peer reviewed journal.	1	-6: No description about external review.	1	Not mentioned	1	Not found
Item 14	1	Not provided.	1	-6: No statement about updating.	1	Not mentioned	1	Not found
Item 15	6	Pages 15-22. B) and c) were not provided in recommendation 3 - treatment for chronic gouty arthritis.	6	Not all recommendations provide purpose (e.g. Page 23 prevention of gout).	5	Subtract 1	5	Not all recommendations have every aspect
Item 16	7	Pages 15-22.	7	The different options for management of the condition or health issue are clearly presented.	6	All included	6	Well described
Item 17	7	Pharmacological treatments for acute gouty arthritis were summarized in Table 3. Recommendations were grouped in Chapter 1 - Abstract.	7	Table 2 & 3 & so on. Image 7 & 8 & so on. Specific recommendation are grouped.	6	All included	6	Figure and table
Item 18	1	Not provided.	1	-6: No description of facilitators or barriers to application.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	3	The abstract is a good summary. -1: but the abstract is not designed as an implementation tool. -3: No any other information about implementation.	1	Not mentioned	1	Not found
Item 20	2	Appendix - Part III.	3	Page 27 Supplementary Part III . So cost is considered. -4: Other information about cost is not provided.	2	Mentioned in page27	2	Mentions health insurance rule
Item 21	1	Not provided.	1	-6: No description of monitoring or auditing.	1	Not mentioned	1	Not found
Item 22	1	Not provided.	1	-6: There's no such description about funding body.	1	Not mentioned	1	Not found
Item 23	1	Not provided.	1	-6: There's no such description about competing interests.	1	Not mentioned	1	Not found
UTAustin_2009 [52]								
Item 1	7	Sections - Scope and Benefits/Harms of Implementing the Guideline Recommendations.	7	"To present a national guideline on the management of acute gout in adults" expected benefit: potential benefits.	7	All included	7	Well described
Item 2	3	Clinical topics can be inferred from the Recommendations section.	3	"Interventions and Practices Considered" are not questions.	2	Not provided in questions	3	It doesn't state the questions or cover every aspect
Item 3	7	Section - Scope.	7	"Adults in the general population diagnosed with or with symptoms indicative of gout (acute attack)"	7	All included	7	Well described
Item 4	4	Section - Identifying information and availability. Only the names of authors and institutes were provided.	2	Only the names of development groups are stated.	2	Mentioned the name	4	No expertise, institution, role description
Item 5	1	Not sought.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 6	4	Section - Scope. B) was not clearly stated.	4	“Advanced Practice Nurses, Dietitians, Nurses, Physician Assistants, Physicians, Podiatrists" -3: no description of how to use.	4	Presented a national guideline on the management of acute gout	4	B) is not stated

						in adults and Target Population		
Item 7	4	Section - Methodology. B) and d) were not provided.	4	Names of databases and key words are provided.	4	Searches were conducted via electronic databases including UpToDate, Cochrane Library, Pubmed, CINAHL, and MEDLINE using keywords: "allopurinol", "colchicine", "corticosteroids", "diet", "febuxostat", "gout", "initial", and "treatment."	5	In methods and appendix, but it is not easy to be found
Item 8	1	Not provided.	1	The information is not provided.	1	Not mentioned	5	No study design
Item 9	7	Section - Methodology. A 3-point rating scheme was used.	7	The "rating scheme"	7	All included	7	Well described
Item 10	3	Section - Methodology. Informal consensus was used as the method to formulate recommendations.	2	"Informal Consensus" -5: no detailed information	1	Not mentioned	4	Informal consensus
Item 11	4	Section - Recommendations. Reports of both benefits and harms were provided but no supporting data for harms was given. C) and d) were not provided.	4	'-1 :not all recommendations reflect the consideration of benefits and harms. (e.g. "discontinue drugs associated with gout when possible"). -2: supporting data are not provided.	6	Subtract 1	3	No supporting data
Item 12	5	Methodology and Recommendations section. c) was not provided.	5	Evidence summaries or tables are not provided.	5	No describes how the guideline development group linked and used the evidence to inform recommendations	6	Well described
Item 13	2	Section - Methodology. It was stated that external review was conducted, but no detailed information was given.	2	"External Peer Review" -5: no detailed information.	2	Only mentioned External Peer Review	2	External peer review
Item 14	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 15	3	Section - Recommendations. A) and b) were not provided.	5	No purpose. No uncertainty.	6	Subtract 1	5	Well described
Item 16	4	First, second, and third line	6	-1:some options are not provided with the most appropriate	6	Subtract 1	5	Well described

		pharmacological options were provided but b) was not given.		population or clinical situation. (e.g. Vitamin c)				
Item 17	4	Section - Recommendations. Recommendations were not presented in a grouped format.	7	This is a summary. Recommendations are grouped.	7	All included	3	No box or others
Item 18	1	Not provided.	2	"Benefits/Harms of Implementing the Guideline Recommendations" exists. But it's not all about facilitators and barriers of application of the guideline.	1	Not mentioned	1	Not found
Item 19	1	Not provided.	3	"Benefits/Harms of Implementing the Guideline Recommendations" exists. But it's not all about implementation advice or tools.	1	Not mentioned	1	Not found
Item 20	1	Cost-analysis was not performed.	1	-6:"A formal cost analysis was not performed and published cost analyses were not reviewed"	1	Not mentioned	2	A formal cost analysis was not performed and published cost analyses were not reviewed.
Item 21	1	Not provided.	1	-6: not mentioned.	1	Not mentioned	1	Not found
Item 22	4	Section - Identifying information and availability. The source of funding was provided but b) was not given.	4	Source of funding. -3: not statement of influence.	4	Source(s) of Funding: University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program	4	Only mentions ,but unclear
Item 23	2	None stated.	1	-6: Not stated.	1	Not mentioned	1	Not found

Supplementary Table 8. Original and modified scores for the individual AGREE II domain items and reasons for modification

N: Not scored.

Document	Item no	Reviewer ID	Original score	Modified score	Reason
3e_2013 [36]	2	#1	5	7	Principal clinical questions were listed in table 1. Scoring criteria for this item were clarified.
3e_2013 [36]	3	#1	5	7	Abstract and Introduction.
3e_2013 [36]	4	#1	5	7	Roles in contributors were provided on page 6.
3e_2013 [36]	10	#1	7	5	Although a modified Delphi process was adopted, c) was not provided.
3e_2013 [36]	17	#1	7	4	Recommendations were not grouped in a certain section.
3e_2013 [36]	2	#2	6	7	The scoring criteria were clarified after discussion.
3e_2013 [36]	3	#2	1	7	Patient with "gout", easy to find.
3e_2013 [36]	7	#2	7	6	-1: the searched time periods are not provided.
3e_2013 [36]	8	#2	6	2	There is a description of inclusion & exclusion criteria. -5: target population characteristics, study design or outcomes are not included in the criteria.
3e_2013 [36]	9	#2	6	7	"The level of evidence for each recommendation was appraised and graded in accordance with the Oxford Centre for Evidence-based Medicine Levels of Evidence". Pooled data were "sufficiently homogeneous".
3e_2013 [36]	10	#2	7	5	-2: No outcomes of the process.
3e_2013 [36]	13	#2	2	4	The scoring criteria were clarified after discussion. -1 ： The purpose and intent of external review is not provided. -1: the outcome/information gathered from the external review is not described. -1: the external reviewers are not described.
3e_2013 [36]	15	#2	2	6	The most informative: recommendation 5. -1: Not all recommendations are specific enough. Example: recommendation 9, information about surgery doesn't include all the required aspects.
3e_2013 [36]	16	#2	3	7	The different options for management of the condition or health issue are clearly presented.
3e_2013 [36]	17	#2	7	4	Table 2.

					-3: recommendations are not grouped in the guideline.
3e_2013 [36]	18	#2	2	7	Barriers: recommendation 1. Facilitators: Table 3 & "Discussion" part.
3e_2013 [36]	20	#2	2	6	Example: recommendation 1 & 5. -1: Information/description of the cost information that emerged from the inquiry is not described.
3e_2013 [36]	21	#2	4	1	The scoring criteria were clarified after discussion. I misunderstood this item.
3e_2013 [36]	4	#3	1	7	The guideline development group is stated
3e_2013 [36]	1	#4	3	7	Scoring criteria modified
3e_2013 [36]	3	#4	1	7	Scoring criteria modified
3e_2013 [36]	8	#4	5	4	The description is unclear
3e_2013 [36]	9	#4	5	7	Scoring criteria modified
3e_2013 [36]	12	#4	5	7	Scoring criteria modified
3e_2013 [36]	13	#4	1	5	Peer review
3e_2013 [36]	15	#4	5	7	Scoring criteria modified
3e_2013 [36]	16	#4	4	7	Scoring criteria modified
3e_2013 [36]	18	#4	4	6	Scoring criteria modified
3e_2013 [36]	19	#4	3	1	Scoring criteria modified
3e_2013 [36]	20	#4	2	5	Scoring criteria modified
3e_2013 [36]	21	#4	5	1	Not found
3e_2013 [36]	23	#4	2	4	Scoring criteria modified
3e_AU_NZ_2015 [43]	2	#1	6	5	A set of clinical questions were investigated (page 342) but the question list was not provided.
3e_AU_NZ_2015 [43]	4	#1	6	7	Rachelle BUCHBINDER was the methodologist.
3e_AU_NZ_2015 [43]	18	#1	1	6	Discussion, paragraph 2
3e_AU_NZ_2015 [43]	8	#2	5	7	It is described in References 7-16.
3e_AU_NZ_2015 [43]	9	#2	1	7	It is described in References 7-16.
3e_AU_NZ_2015 [43]	10	#2	5	6	Not all outcomes are missing, some are described.
3e_AU_NZ_2015 [43]	6	#3	7	4	No clear description of intended guideline audience
3e_AU_NZ_2015 [43]	16	#3	2	5	Only some options are provided with the most appropriate population or clinical situation.
3e_AU_NZ_2015 [43]	2	#4	7	5	The scoring criteria was specified/modified/clarified and the score was modified

					accordingly
3e_AU_NZ_2015 [43]	3	#4	5	6	1' for performance
3e_AU_NZ_2015 [43]	4	#4	5	6	There is a methodologist
3e_AU_NZ_2015 [43]	9	#4	5	7	All included
3e_AU_NZ_2015 [43]	15	#4	7	6	No purpose
3e_AU_NZ_2015 [43]	17	#4	6	4	Scoring criteria modified
3e_AU_NZ_2015 [43]	20	#4	5	3	Only one phase mentions the cost without methods
3e_PT_2014 [40]	1	#1	5	6	Scoring criteria clarified. Epidemiological information provided.
3e_PT_2014 [40]	4	#1	5	5	Bibliographic fellows were considered as methodologists but the role of each member was not fully provided.
3e_PT_2014 [40]	6	#1	4	1	Can not be fully inferred from "in daily clinical practice"
3e_PT_2014 [40]	10	#1	7	3	Although Delphi approach was adopted, b) and c) were not provided
3e_PT_2014 [40]	18	#1	2	4	The voting and discussion on willingness of applying the guideline in daily practice (table IV) was considered as a facilitator.
3e_PT_2014 [40]	19	#1	2	1	The voting and discussion on willingness of applying the guideline in daily practice (table IV) was not considered as a pilot test for implementation.
3e_PT_2014 [40]	4	#2	6	5	The development group members are not completely listed.
3e_PT_2014 [40]	15	#2	7	6	Some purposes of recommendations are not clearly stated.
3e_PT_2014 [40]	10	#3	2	5	Missed outcome of vote
3e_PT_2014 [40]	21	#3	1	2	Mentioned "What is the efficacy, cost efficacy and safety for urate-lowering therapy"
3e_PT_2014 [40]	6	#4	3	1	Not found
3e_PT_2014 [40]	7	#4	6	3	Without b) c) and d)
3e_PT_2014 [40]	9	#4	6	2	The description is unclear
3e_PT_2014 [40]	10	#4	6	3	Without b) and c)
3e_PT_2014 [40]	17	#4	7	4	No summary
3e_PT_2014 [40]	22	#4	3	1	Not found
ACP_2017 [19, 20]	1	#1	5	6	B) was provided as epidemiological information. Scoring criteria for this item were clarified.
ACP_2017 [19, 20]	2	#1	5	7	Key questions were provided in the Appendix. Scoring criteria for this item was clarified.
ACP_2017 [19, 20]	13	#1	3	5	Methods section & Peer review section - All comments were read and carefully

					considered by the authors
ACP_2017 [19, 20]	18	#1	1	2	Diagnosis document, page 55. "...it often is difficult to perform in primary care and even rheumatologic settings"
ACP_2017 [19, 20]	5	#2	3	5	The method is described in reference [10]. -2: The outcomes are not shown.
ACP_2017 [19, 20]	7	#2	5	7	The details are in reference [8].
ACP_2017 [19, 20]	10	#2	3	5	The detailed methods are in reference [10]. -2: the outcomes are not provided.
ACP_2017 [19, 20]	13	#2	6	5	Appendix peer review. -1: outcomes are not described. -1: no purpose provided.
ACP_2017 [19, 20]	14	#2	1	4	The content of updating is in reference [10]. -2: the time interval is not stated. -1: no statement about updating in the guideline itself, so the information is very hard to find.
ACP_2017 [19, 20]	15	#2	7	6	-1: not all recommendations provide purpose (e.g. Recommendation 4)
ACP_2017 [19, 20]	18	#2	5	4	Summary of diagnosis，bout synovial fluid analysis. -2: Method by which the information was sought is not described. -1: They are not about the barriers or facilitators of the whole guideline.
ACP_2017 [19, 20]	19	#2	5	3	The summary figures. -1: the summary figures include a clinical consideration part, but there's no specific implementation section in the guideline. -3: No other information about implementation advice or tools for this guideline.
ACP_2017 [19, 20]	22	#3	1	4	No statement that the funding body did not influence the content of the guideline
ACP_2017 [19, 20]	1	#4	7	6	The outcome/benefit is not provided
ACP_2017 [19, 20]	5	#4	1	5	The patients' preference is provided in the appendix
ACP_2017 [19, 20]	6	#4	7	4	B) is not provided
ACP_2017 [19, 20]	9	#4	5	6	It provides the information but 1' for not easy to find
ACP_2017 [19, 20]	11	#4	4	6	In the second part of the guideline
ACP_2017 [19, 20]	13	#4	1	5	The peer review in the appendix
ACP_2017 [19, 20]	15	#4	7	5	B) is not provided
ACP_2017 [19, 20]	16	#4	1	7	In the second part of the guideline

ACP_2017 [19, 20]	20	#4	1	5	The management part covers cost
ACP_2017 [19, 20]	22	#4	7	4	Only a funding body but no statement
ACR_2012 [14, 15]	1	#1	7	6	This content was not easy to find.
ACR_2012 [14, 15]	2	#1	7	5	Clinical questions were presented (Guideline part 1, page 1434) but not listed in the guideline. Scoring criteria for this item were clarified.
ACR_2012 [14, 15]	4	#1	5	7	The role of each member was provided on page 1444.
ACR_2012 [14, 15]	13	#1	1	2	This guideline was published in a peer-reviewed journal. Scoring criteria for this item were clarified.
ACR_2012 [14, 15]	23	#1	1	4	Conflict of interest was mentioned on page 1434 of guideline part 1.
ACR_2012 [14, 15]	1	#2	7	6	All included, but difficult to find.
ACR_2012 [14, 15]	3	#2	5	7	The scoring criteria were clarified after discussion.
ACR_2012 [14, 15]	6	#2	6	4	Intended audience are discribed.P1433. -3: no description of how to use.
ACR_2012 [14, 15]	23	#2	7	4	-1: no method. -2: no influence
ACR_2012 [14, 15]	9	#3	4	7	All included
ACR_2012 [14, 15]	22	#3	2	3	Mentioned "The name of the funding body or source of funding"
ACR_2012 [14, 15]	1	#4	5	7	Scoring criteria modified
ACR_2012 [14, 15]	3	#4	2	5	Scoring criteria modified
ACR_2012 [14, 15]	6	#4	1	5	Scoring criteria modified
ACR_2012 [14, 15]	9	#4	4	7	Scoring criteria modified
ACR_2012 [14, 15]	13	#4	4	1	Scoring criteria modified
ACR_2012 [14, 15]	17	#4	7	4	Scoring criteria modified
ACR_2012 [14, 15]	18	#4	4	1	Scoring criteria modified
ACR_2012 [14, 15]	21	#4	7	1	Scoring criteria modified
ACR_2012 [14, 15]	23	#4	7	5	Scoring criteria modified
ACR_EULAR_2015 [42]	1	#1	5	6	Scoring criteria clarified. Epidemiological information was provided (1').
ACR_EULAR_2015 [42]	5	#1	1	6	A patient participated in phase 1 (page 1790)
ACR_EULAR_2015 [42]	9	#1	1	7	QUADAS tool was used (reference 20)
ACR_EULAR_2015 [42]	14	#1	1	3	Information on guideline update was provided as 'all ACR-EULAR approved criteria sets are expected to undergo intermittent updates' (page 1789).
ACR_EULAR_2015 [42]	19	#1	2	3	A web-based calculator was provided (page 1794)
ACR_EULAR_2015 [42]	11	#2	1	7	As a diagnostic guideline, it did consider the specificity and sensitivity.

ACR_EULAR_2015 [42]	12	#2	3	5	Evidences are described in reference 23, thought how a specific evidence is linked to a recommendation is not described in detail.
ACR_EULAR_2015 [42]	18	#3	1	3	Mentioned the facilitator in page 1791
ACR_EULAR_2015 [42]	4	#4	4	5	Correction of arithmetical errors
ACR_EULAR_2015 [42]	5	#4	1	6	In phase 1 we can find it
ACR_EULAR_2015 [42]	7	#4	1	7	All included
ACR_EULAR_2015 [42]	9	#4	1	7	QUADAS tool was used (reference 20)
ACR_EULAR_2015 [42]	11	#4	3	7	The scoring criteria was specified/modified/clarified and the score was modified accordingly
ACR_EULAR_2015 [42]	12	#4	7	5	Link Between Recommendations and Evidence
ACR_EULAR_2015 [42]	14	#4	6	3	Only a little, "All ACR-EULAR approved criteria sets are expected to undergo intermittent updates"
ACR_EULAR_2015 [42]	18	#4	1	4	"We also realised that some investigators may not have access to imaging and therefore aimed to develop criteria that would still perform well in the absence of imaging data."
ACR_EULAR_2015 [42]	19	#4	1	3	The tool in page 1794
BSR_2017 [21]	2	#1	4	7	Principal clinical questions were listed in table 1. Scoring criteria for this item were clarified.
BSR_2017 [21]	3	#1	5	7	Target population was defined in Objective, Gout in the UK.
BSR_2017 [21]	5	#1	1	5	Two lay patients involved in the guideline development group (Objective, Stakeholder involvement).
BSR_2017 [21]	12	#1	7	6	Evidence summary table was not provided.
BSR_2017 [21]	14	#1	1	2	Update information was provided online: https://www.rheumatology.org.uk/Knowledge/Excellence/Guidelines/artmid/1256/articleid/18. This content was very difficult to be found.
BSR_2017 [21]	17	#1	7	4	B) was not provided.
BSR_2017 [21]	1	#2	6	7	The scoring criteria were clarified after discussion.
BSR_2017 [21]	3	#2	5	7	Gout in UK. The scoring criteria were clarified after discussion.
BSR_2017 [21]	4	#2	4	6	Clear and easy to find. An epidemiologist (W.Z.) was involved in the development group. -1: No description of each member's role.
BSR_2017 [21]	5	#2	6	5	Miscalculated. -2: the outcomes/information gathered from patients were not provided.
BSR_2017 [21]	14	#2	1	2	Didn't find the updating time, but it is provided.

BSR_2017 [21]	17	#2	7	3	Fig 1. -3: recommendations are not grouped in the guideline.
BSR_2017 [21]	19	#2	2	5	Other information is provided. -2: No direction on how to access the summary.
BSR_2017 [21]	21	#2	7	5	The scoring criteria were clarified after discussion. '-1: No link to the audit tool in the guideline. -1: no advice on the frequency of measurement.
BSR_2017 [21]	18	#3	1	4	Identification of the types of facilitators and barriers that were considered; Information/description of the types of facilitators and barriers that emerged from the inquiry
BSR_2017 [21]	1	#4	5	7	Scoring criteria modified
BSR_2017 [21]	3	#4	5	7	Scoring criteria modified
BSR_2017 [21]	5	#4	4	6	Scoring criteria modified
BSR_2017 [21]	8	#4	4	5	Scoring criteria modified
BSR_2017 [21]	12	#4	2	7	Scoring criteria modified
BSR_2017 [21]	13	#4	1	5	Scoring criteria modified
BSR_2017 [21]	14	#4	4	3	Correction of arithmetical errors
BSR_2017 [21]	19	#4	1	5	"An audit tool is available on the website of the British Society for Rheumatology."
BSR_2017 [21]	20	#4	4	6	Scoring criteria modified
CCCP_2012 [47]	1	#1	5	6	B) was not clearly stated only provided as epidemiology.
CCCP_2012 [47]	2	#1	4	3	Clinical questions can be inferred but not clearly stated. Scoring criteria for this item were clarified.
CCCP_2012 [47]	17	#1	7	4	Recommendations were not grouped together.
CCCP_2012 [47]	12	#2	4	3	Miscalculated.
CCCP_2012 [47]	2	#3	6	3	Clinical questions was not clearly stated.
CCCP_2012 [47]	17	#3	6	4	Recommendations were not grouped together in one section
CCCP_2012 [47]	2	#4	6	3	Scoring criteria modified
CCCP_2012 [47]	11	#4	5	4	Correction of arithmetical errors
CCCP_2012 [47]	17	#4	7	4	No summary
CRA_2016 [41]	1	#1	4	5	B) was provided as epidemiological information. Scoring criteria for this item were clarified.
CRA_2016 [41]	2	#1	6	5	Appendix 5. Clinical questions were selected but no detail was given. Scoring criteria for this item were clarified.

CRA_2016 [41]	6	#1	7	4	B) was not provided.
CRA_2016 [41]	8	#1	1	3	Study design given in Appendix 6.
CRA_2016 [41]	10	#1	7	3	Although Delphi method was used, the outcome and the influence on guideline development was not given.
CRA_2016 [41]	18	#1	4	1	Sensitivity and specificity were not barriers to application.
CRA_2016 [41]	2	#2	3	5	Methods in the Appendix. The details of the questions are not provided. There was some misunderstanding of this item. The scoring criteria were clarified after discussion.
CRA_2016 [41]	8	#2	1	3	The inclusion criteria only include study design.
CRA_2016 [41]	13	#2	5	3	Methods in the Appendix. External experts are involved the question choosing process, but it is not a review.
CRA_2016 [41]	15	#2	7	6	Some purposes of recommendations are not clearly stated.
CRA_2016 [41]	23	#2	1	4	Appendix. I didn't find this information.
CRA_2016 [41]	4	#3	1	5	Mentioned name and institution and performance
CRA_2016 [41]	8	#3	1	3	Mentioned study design
CRA_2016 [41]	16	#3	3	6	Some options are provided with the most appropriate population or clinical situation.
CRA_2016 [41]	17	#4	1	4	Important advice has a key tag
CRA_multi_2017 [22]	1	#1	5	7	B) was stated in the last sentence of paragraph 1.
CRA_multi_2017 [22]	2	#1	5	3	Clinical questions considered could be indicated from the guideline but no clear statement was given.
CRA_multi_2017 [22]	12	#1	5	3	C) evidence table was also not provided.
CRA_multi_2017 [22]	15	#1	4	5	Page 237. The uncertainty between coffee and gout was stated.
CRA_multi_2017 [22]	17	#1	4	2	A) was not provided. The summary box in the document only contained pharmacological treatment, but not all recommendations of the guideline.
CRA_multi_2017 [22]	2	#2	1	3	The questions that this guideline tries to solve are not mentioned, can only be inferred from the context. There was some misunderstanding of this item. The scoring criteria were clarified after discussion.
CRA_multi_2017 [22]	15	#2	7	5	Most informative example: Page 237 "management of patients with gout". -1: Some recommendations are without an intent or purpose (e.g. Page 237 Non-drug therapy). -1: Some uncertainty exists, but not reflected in recommendations, and is not explicitly stated.
CRA_multi_2017 [22]	17	#2	7	3	We discussed the criteria & I had some misunderstanding. -1: Table 1&2 are only summary of a very little part not the summary of the

					guideline. -3: recommendations can not be easily distinguished form other content, and they are not grouped.
CRA_multi_2017 [22]	12	#3	2	5	Only some recommendations meet criteria, and no table
CRA_multi_2017 [22]	11	#4	2	5	Page 241 item (2)
CRA_multi_2017 [22]	15	#4	6	5	Some items don't give the purpose
CRA_multi_2017 [22]	17	#4	7	4	It doesn't have a summary that concludes all recommends
CSE_2013 [37]	3	#1	7	6	The target population indicated from the title (patients with hyperuricemia or gout) and from the guideline (patient with hyperuricemia) was conflicted.
CSE_2013 [37]	6	#1	2	6	This content could be indicated from the guideline but was not clearly stated.
CSE_2013 [37]	12	#1	1	5	An evidence summary table was provided on page 915. A) was not provided.
CSE_2013 [37]	16	#1	7	6	The appropriate population was not provided in some management options for probenecid (page 918).
CSE_2013 [37]	18	#1	1	3	The availability of uricase (page 918) was discussed but no detail was given.
CSE_2013 [37]	2	#2	5	1	The scoring criteria were clarified after discussion. '-6: No specifically described question is provided in the guideline.
CSE_2013 [37]	3	#2	1	6	The scoring criteria were clarified after discussion.
CSE_2013 [37]	6	#2	1	6	The target audience can be inferred as clinical practitioners from the word "in clinical settings", and the guideline may be used by "providing guidance". -1: The target audience is not clearly described.
CSE_2013 [37]	9	#2	1	3	Table 1. -3: The method to evaluate the strengths and limitations of evidence is not provided. -1: The information is only reported for some of the evidences.
CSE_2013 [37]	17	#2	6	7	The key points are at the beginning. Two flow charts are provided. Relevant recommendations are grouped together.
CSE_2013 [37]	18	#2	2	3	Miscalculated.
CSE_2013 [37]	21	#2	6	1	The scoring criteria were clarified after discussion. I misunderstood this item.
CSE_2013 [37]	4	#3	1	2	Mentioned "The guideline development group"
CSE_2013 [37]	15	#3	7	6	Subtract 1
CSE_2013 [37]	19	#3	4	1	Not mentioned
CSE_2013 [37]	1	#4	2	7	Scoring criteria modified
CSE_2013 [37]	2	#4	5	2	Scoring criteria modified

CSE_2013 [37]	3	#4	3	6	Scoring criteria modified
CSE_2013 [37]	4	#4	2	3	Correction of arithmetical errors
CSE_2013 [37]	6	#4	1	5	Scoring criteria modified
CSE_2013 [37]	11	#4	2	5	Scoring criteria modified
CSE_2013 [37]	12	#4	5	3	Scoring criteria modified
CSE_2013 [37]	21	#4	7	1	Scoring criteria modified
EULAR_2006 [18]	11	#1	7	6	Some of the recommendations did not consider the harms (e.g., Recommendation 4).
EULAR_2006 [18]	22	#1	1	4	"Thank the European League Against Rheumatism for financial support" (acknowledgement)
EULAR_2006 [18]	6	#2	7	1	This is not described.
EULAR_2006 [18]	4	#3	3	5	Missed description of the member's role in the guideline development group
EULAR_2006 [18]	20	#3	1	5	Mentioned Incremental cost-effectiveness ratio
EULAR_2006 [18]	1	#4	7	6	1' for performance
EULAR_2006 [18]	4	#4	7	5	Can be found in the methods and the appendix, but is unclear
EULAR_2006 [18]	6	#4	3	2	Only can be analysed from the article
EULAR_2006 [18]	10	#4	7	4	No details
EULAR_2006 [18]	18	#4	5	1	This score is exchanged to item 20
EULAR_2006 [18]	20	#4	1	5	The score is exchanged to item 18
EULAR_2011 [17]	6	#2	2	3	How to use can also be inferred.
EULAR_2011 [17]	7	#3	2	4	Missed cd, target research was conducted through Pubmed, from Feb 2005 through Feb 2011
EULAR_2011 [17]	8	#4	7	4	No c) or d)
EULAR_2011 [17]	11	#4	5	7	Well described
EULAR_2011 [17]	19	#4	5	2	Only table6
EULAR_2011 [17]	23	#4	7	4	"Besides ensuring their availability during the development of the project and its CV, all the panellists were asked to submit a declaration of conflicts of interest."
EULAR_2016 [16]	5	#1	6	5	Outcome weighs 2'
EULAR_2016 [16]	8	#1	6	2	Only general criteria on study design was provided. Inclusion criteria were not provided.
EULAR_2016 [16]	13	#1	2	6	Page 28, second paragraph to the right. The influence of external review on guideline development was not clearly stated. The outcome of external review was provided in supplementary data.

EULAR_2016 [16]	4	#2	7	6	-1: role of each member is not clearly stated.
EULAR_2016 [16]	5	#2	6	5	Miscalculated the score. -2: the outcome is not provided.
EULAR_2016 [16]	6	#3	7	5	No strategy
EULAR_2016 [16]	5	#4	4	5	Correction of arithmetical errors
EULAR_2016 [16]	7	#4	7	5	The full strategy is not provided
EULAR_2016 [16]	8	#4	7	3	It gives some criteria but is unclear
EULAR_2016 [16]	13	#4	3	6	It described the external review clearly
EULAR_2016 [16]	14	#4	4	2	It is updated, but no a) b) or c)
EULAR_2016 [16]	18	#4	1	2	It only gives two information about barrier
FMOH_2014 [44]	2	#1	6	3	The clinical topic could be inferred but not clearly stated.
FMOH_2014 [44]	11	#1	1	2	Benefits were considered but not harms.
FMOH_2014 [44]	15	#1	5	3	Mis-calculation of the score. Uncertainty and purpose were not provided.
FMOH_2014 [44]	17	#1	7	4	A) was not provided. The summarized box only contained a sample menu not the recommendations.
FMOH_2014 [44]	20	#2	1	3	Price is considered in policy part.
FMOH_2014 [44]	4	#3	2	5	Mentioned a, name ,expertise, institution and performance
FMOH_2014 [44]	22	#3	4	1	Not mentioned
FMOH_2014 [44]	2	#4	5	3	Scoring criteria modified
FMOH_2014 [44]	4	#4	3	5	Can be found in Acknowledgements
FMOH_2014 [44]	11	#4	4	3	Benefits were considered but not harms
FMOH_2014 [44]	15	#4	6	3	The uncertainty is not provided
FMOH_2014 [44]	18	#4	4	1	Not found
FMOH_2014 [44]	20	#4	1	3	It mentions price
JSGNAM_2011 [48]	9	#1	5	6	The consistency of original studies included in meta analysis was also considered.
JSGNAM_2011 [48]	6	#2	1	4	How to use is involved. “guideline is appropriately used for the standard management and care of patients with hyperuricemia and gout in daily practice".
JSGNAM_2011 [48]	5	#3	1	4	The guideline revising committee collected clinical questions for the management of gout and hyperuricemia, and based on 41 clinical questions.
JSGNAM_2011 [48]	13	#3	1	2	A draft version of this guideline was reviewed by internal and external reviewers as well as a patient.
JSGNAM_2011 [48]	16	#3	7	6	Subtract 1

JSGNAM_2011 [48]	7	#4	3	2	Unclear, only mentions searching but no details
JSGNAM_2011 [48]	12	#4	6	4	Some recommends are linked with the evidence
JSGNAM_2011 [48]	13	#4	6	3	The description is unclear
JSGNAM_2011 [48]	17	#4	6	5	No b)
JSGNAM_2011 [48]	19	#4	3	1	Not found
MOH_MSR_AMM_2008 [49]	12	#1	3	5	A) was presented as the grades of recommendations
MOH_MSR_AMM_2008 [49]	18	#1	1	2	The availability of diagnostic service was discussed (page 7, subheading 4.2)
MOH_MSR_AMM_2008 [49]	19	#1	1	3	A summary and algorithm were provided (page VIII - XI).
MOH_MSR_AMM_2008 [49]	5	#2	4	3	The draft was on the website for comments and feedbacks from the public. -1:this is not a clear statement that the target population is exactly involved. -2: no outcomes. -1: no influence.
MOH_MSR_AMM_2008 [49]	6	#2	4	7	All information is described.
MOH_MSR_AMM_2008 [49]	10	#2	3	2	Miscalculated.
MOH_MSR_AMM_2008 [49]	18	#2	4	3	Barrier: page 7, 4.2. But it is only a simple description, no any other information is provided.
MOH_MSR_AMM_2008 [49]	7	#3	2	4	Named electronic database and search terms
MOH_MSR_AMM_2008 [49]	22	#3	1	4	The name of the funding body or source of funding
MOH_MSR_AMM_2008 [49]	4	#4	7	5	No roles
MOH_MSR_AMM_2008 [49]	9	#4	7	6	The level of evidence only be graded by the type of article
MOH_MSR_AMM_2008 [49]	12	#4	6	5	Correction of arithmetical errors
MOH_MSR_AMM_2008 [49]	13	#4	7	3	No details
MOH_MSR_AMM_2008 [49]	14	#4	1	5	In the 3rd paragraph
MOH_MSR_AMM_2008 [49]	18	#4	1	2	The last sentence in the first paragraph of 4.2

MOH_MSR_AMM_2008 [49]	22	#4	7	4	Unrestricted educational grant
MOH_MSR_AMM_2008 [49]	23	#4	7	2	Disclosure statement
PRA_2008 [50]	3	#1	7	5	Title and recommendations were targeting patients with gout, while Objectives in the Abstract narrowed to patients with gouty arthritis.
PRA_2008 [50]	18	#1	1	2	Availability of allopurinol was discussed (page 9, first sentence)
PRA_2008 [50]	7	#3	7	5	Full search strategy was not clear
PRA_2008 [50]	3	#4	7	5	Title and recommendations have conflicting descriptions
PRA_2008 [50]	5	#4	1	5	Panel
PRA_2008 [50]	6	#4	1	7	Well described
PRA_2008 [50]	7	#4	7	5	In the rational
PRA_2008 [50]	8	#4	7	5	It has but no details
PRA_2008 [50]	9	#4	4	7	Well described
PRA_2008 [50]	10	#4	6	5	In the method part
PRA_2008 [50]	12	#4	6	5	No summary
PRA_2008 [50]	14	#4	3	5	Updates in management issues will be integrated as deemed necessary in the next 3 or more years
PRA_2008 [50]	15	#4	7	5	No purpose
PRA_2008 [50]	17	#4	1	4	Table 1
PRA_2008 [50]	18	#4	1	2	"is the only drug available in this class in the Philippines"
PRA_2008 [50]	23	#4	1	2	"JLY serves as consultant to Novartis and trial investigator for Pfizer. EOS and JJL serve as trial investigators for Pfizer. Other members of TRC have nothing to disclose."
SAMA_2003 [51]	10	#1	1	5	Annexure a: methodology
SAMA_2003 [51]	22	#1	4	7	Annexure a: methodology
SAMA_2003 [51]	2	#2	1	3	The questions can be inferred.
SAMA_2003 [51]	15	#2	6	5	No purpose. No uncertainty.
SAMA_2003 [51]	2	#3	6	3	Not provided in questions
SAMA_2003 [51]	2	#4	5	3	Scoring criteria modified
SAMA_2003 [51]	5	#4	5	2	The description is unclear
SER_2013 [46]	2	#1	3	6	Table 1. A question list was provided but it did not cover all the guideline aspects.

SER_2013 [46]	6	#1	7	4	Although a) was provided under Chapter III, b) was not clearly given.
SER_2013 [46]	7	#1	1	3	The names of databases were provided (page 17).
SER_2013 [46]	2	#2	7	6	Questions are listed but the questions didn't cover the content of the guideline.
SER_2013 [46]	13	#2	1	2	Page 21 "The CPG was assessed by two external reviewers, a rheumatologist expert in this clinical area (FPR) and a methodologist who was expert at conducting clinical practice guidelines (MJGY)".
SER_2013 [46]	20	#2	4	3	With some recommendations mentioning the cost-effective aspect of a drug/test (page 39), they said that they don't consider costs in the recommendations (Page 17 II.C "it was explicitly requested that they be written based on the risk/benefit balance for the patient, regardless of the associated costs").
SER_2013 [46]	6	#3	7	5	How the guideline may be used by its target audience was not mentioned
SER_2013 [46]	10	#3	1	3	Used the Delphi method
SER_2013 [46]	13	#3	1	2	The CPG was assessed by two external reviewers
SER_2013 [46]	2	#4	7	6	The questions don't include every aspect
SER_2013 [46]	7	#4	7	4	Only the names of databases are provided (page 17
SER_2013 [46]	8	#4	5	1	Not found
SER_2013 [46]	12	#4	7	4	No c)
SER_2013 [46]	13	#4	5	2	Only one word
SER_2013 [46]	15	#4	7	5	No purpose
SER_2013 [46]	17	#4	7	4	No summary
SER_2013 [46]	18	#4	7	4	It mentions barriers but no more descriptions
SER_2013 [46]	23	#4	7	2	It mentions competing interests but no more descriptions
SIR_2013 [45]	18	#1	1	2	Availability of treatments in Italy were stated (page 10).
SIR_2013 [45]	20	#1	2	4	Cost effectiveness was also taken into consideration in the voting (page 6)
SIR_2013 [45]	18	#2	5	4	The guideline emphasizes that it was designed to adapt to Italian, considering current therapeutic options available in Italian.-1: no description. Table 2 & the explanation below the table, Page 12.-2: Methods are not provided.
SIR_2013 [45]	7	#3	1	4	The literature search was conducted in November 2011 in the following databases: MEDLINE, Embase, and Cochrane Central.
SIR_2013 [45]	6	#4	1	6	1' for performance, "This document is intended for rheumatologists, general practitioners, internists, geriatricians, nephrologists, cardiologists and all healthcare professionals involved in the management of patients with gout."
SIR_2013 [45]	7	#4	7	4	No c) or d)
SIR_2013 [45]	8	#4	5	6	Correction of arithmetical errors

SIR_2013 [45]	17	#4	7	4	Scoring criteria modified
SIR_2013 [45]	18	#4	1	3	Availability of treatments in Italy were stated (page 10).
T2T_2016 [39]	5	#2	6	5	Miscalculated the score. -2: the outcome is not provided.
T2T_2016 [39]	15	#2	7	6	Some purposes of recommendations are not clearly stated.
T2T_2016 [39]	6	#3	1	2	Only mentioned "To improve the management of"
T2T_2016 [39]	4	#4	6	5	The name of group is unknown
T2T_2016 [39]	5	#4	1	5	A patient with gout gives the preference
T2T_2016 [39]	6	#4	4	1	Not found
T2T_2016 [39]	7	#4	6	7	The appendix gives all
T2T_2016 [39]	22	#4	6	3	No statement
TRA_2016 [38]	1	#1	4	5	Scoring criteria for this item were clarified. B) was not provided but epidemiology information was given.
TRA_2016 [38]	2	#1	5	3	The clinical topic can only be inferred but a question list was not provided. Scoring criteria for this item were clarified.
TRA_2016 [38]	20	#1	1	2	Appendix, part III
TRA_2016 [38]	2	#2	1	3	The questions that this guideline tries to solve are not mentioned, can only be inferred from the context. There was some misunderstanding of this item. The scoring criteria were clarified after discussion.
TRA_2016 [38]	15	#2	7	6	Not all recommendations provide purpose (e.g. Page 23 prevention of gout).
TRA_2016 [38]	19	#2	4	3	The abstract is a good summary. -1: but the abstract is not designed as an implementation tool. -3: No any other information about implementation.
TRA_2016 [38]	11	#3	7	5	Subtract 1
TRA_2016 [38]	20	#3	1	2	Mentioned in page27
TRA_2016 [38]	1	#4	7	6	1' for the performance
TRA_2016 [38]	4	#4	4	5	Correction of arithmetical errors
TRA_2016 [38]	12	#4	1	2	It provides little link between the recommends and evidence.
TRA_2016 [38]	19	#4	4	1	Not found
TRA_2016 [38]	20	#4	1	2	Mentions health insurance rule
UTAustin_2009 [52]	1	#1	5	7	Potential benefit
UTAustin_2009 [52]	9	#1	4	7	A 3-point rating scheme was described in the Section - Methodology.
UTAustin_2009 [52]	2	#2	4	3	"Interventions and Practices Considered" are not questions.

UTAustin_2009 [52]	7	#2	3	4	Names of databases and key words are provided.
UTAustin_2009 [52]	8	#2	n	1	The information is not provided.
UTAustin_2009 [52]	11	#2	6	4	'-1：not all recommendations reflect the consideration of benefits and harms. (e.g. "discontinue drugs associated with gout when possible"). -2: supporting data are not provided.
UTAustin_2009 [52]	12	#2	2	5	Evidence summaries or tables are not provided.
UTAustin_2009 [52]	15	#2	6	5	No purpose. No uncertainty.
UTAustin_2009 [52]	18	#2	4	2	"Benefits/Harms of Implementing the Guideline Recommendations" exists. But it's not all about facilitators and barriers of application of the guideline.
UTAustin_2009 [52]	19	#2	6	3	"Benefits/Harms of Implementing the Guideline Recommendations" exists. But it's not all about implementation advice or tools.
UTAustin_2009 [52]	12	#3	2	5	No describes how the guideline development group linked and used the evidence to inform recommendations
UTAustin_2009 [52]	16	#3	7	6	Subtract 1
UTAustin_2009 [52]	2	#4	5	3	Scoring criteria modified
UTAustin_2009 [52]	7	#4	7	5	No details
UTAustin_2009 [52]	8	#4	5	1	Not found
UTAustin_2009 [52]	13	#4	7	2	Only one word, no details
UTAustin_2009 [52]	15	#4	7	5	Not that clear
UTAustin_2009 [52]	16	#4	7	5	Not that clear
UTAustin_2009 [52]	19	#4	n	1	Not found

Supplementary Table 9. Summary of recommendations for the diagnosis of gout and hyperuricemia by included guidance document

IE: insufficient evidence; MSU: monosodium urate; NA: not applicable; NG: not given; SUA: serum uric acid.

	SAMA_2003 [51]	EULAR_2006 [18]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	EULAR_2011 [17]	JSGNAM_2011 [48]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	3e_AU_NZ_2015 [43]	ACR_EULAR_2015 [42]	CRA_2016 [41]	TRA_2016 [38]	ACP_2017 [19, 20]	CRA_multi_2017 [22]
Diagnosis of gout	+	+	+	NG	+	NG	NG	+	NG	+	NG	+	+	+	+	+	+	+
_Clinical manifestations	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Laboratory results	+	+	-	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Imaging results	-	+*	-	NA	-	NA	NA	+	NA	+	NA	+	+	+	+	+	IE	+
_MSU crystal as definitive diagnosis	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
Monitor urate deposits clearance by imaging	-	-	-	-	-	-	-	-	-	IE	-	-	-	+	-	-	-	+
Is the timing to assess urate deposits with imaging techniques provided?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUA for hyperuricemia, µmol/L [mg/dL]	+	NG	+	+	+	+	+	NG	+	+	+	NG	NG	NG	NG	+	NG	+
_All gender	420	NG	NG	NG	[6.8]	[7.0]	420 [7.0]	NG	NG	NG	404 [6.8]	NG	NG	NG	NG	[7.0]	NG	NG
_Female	NG	NG	360 [6.0]	357 [6.0]	NG	NG	NG	NG	360	[6.0]	NG	NG	NG	NG	NG	NG	NG	360
_Male	NG	NG	420 [7.0]	416 [7.0]	NG	NG	NG	NG	420	[7.0]	NG	NG	NG	NG	NG	NG	NG	420
Diagnosis of asymptomatic hyperuricemia	NG	NG	+	+	NG	+	+	+.	NG	+	NG	NG	NG	NG	NG	+	NG	NG
_Gout flare	NA	NA	-	+	NA	+	+	+	NA	+	NA	NA	NA	NA	NA	+	NA	NA
_Tophi	NA	NA	-	-	NA	+	-	+	NA	-	NA	NA	NA	NA	NA	-	NA	NA
_Additional medical conditions†	NA	NA	+	+	NA	+	+	-	NA	-	NA	NA	NA	NA	NA	+	NA	NA

*Imaging results are considered for chronic gout, but not for early/acute gout.

†Additional medical conditions considered in the definition of asymptomatic hyperuricemia included complications of gout [47], renal disorder [48], signs or symptoms of

urate deposition [49], and uric acid nephrolithiasis [50]. One document provided a general statement of any clinical presentations [38]. One document explicitly stated that the inclusion of patients with pre-existing renal or cardiovascular disease was allowed [36].

Supplementary Table 10. Summary of recommendations for the treatment of hyperuricemia by included guidance documents

A: allopurinol; Aft: (to initiate ULT) after an acute attack; B: benzbromarone; CCr: creatinine clearance rate; Cr: serum creatinine; CKD: chronic kidney disease; D: (to initiate ULT) during an acute attack; eGFR: estimated glomerular filtration rate; F: febuxostat; IE: insufficient evidence; m: month(s); NA: not applicable; NG: not given; P: probenecid; RF: renal function; SUA: serum uric acid; U: uricosurics without specification; ULT: urate lowering therapy; w: week(s); y: year.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Upper limit for target SUA, µmol/L [mg/dL]																						
_General target*	300	360 [6.0]	[6.0]	NG	[6.0]	[6.0]	[6.0]	357 [6.0]	360 [6.0]	360	[6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]	360 [6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]
_Target for serve cases†	NG	NG	NG	NG	[4.0]	NG	[5.0]	NG	300	300	NG	NG	300 [5.0]	NG	300	NG	300 [5.0]	300 [5.0]	300 [5.0]	NG	300	300 [5.0]
Lower limit for target SUA, µmol/L [mg/dL]	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	[3.0]	NG	NG	NG	NG	180
Drinking water	-	+	+	-	-	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+
Urine alkalinisation	+	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	+	+
Indications for ULT	+	+	+	-	+	+	+	+	-	+	+	+	-	NG	-	+	+	-	+	+	+	+
_Recurrent attacks	+, >2	+, >3/y	+	NA	+, >1/y	+	+, ≥2/y	-	NA	-	-	+	NA	NG	-	+, >2/y	+, ≥2/y	NA	-	+, ≥2/y	+, ≥2/y	+
_Tophi	+	+	+	NA	+	+	+	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	+	+	+
_Urate nephrolithiasis	-	+	+	NA	+	-	+	-	NA	+	-	-	NA	NG	NA	-	+	NA	+	+	+	+
_Arthropathy	-	+	-	NA	+	-	-	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	-	+	+
_Comorbidities‡	-	+	+	NA	-	-	+	+	NA	+	-	-	NA	NG	NA	-	+	NA	-	+	+	+
_Others§	+	+	+	NA	-	-	-	+	NA	-	+	-	NA	NG	NA	-	+	NA	-	-	+	+
Initiate ULT during or after an acute attack (Aft[time after attack])	Aft	Aft	NG	Aft (4-6 w)	Aft	Aft (2w)	D	NA	Aft	D/ Aft (2w)	NG	NG	Aft	NG	NG	NG	IE	IE	Aft	NG	Aft	Aft
First line ULT drug(s)	NG	A	A	NG	A, F	A, B	A, F	NG	A	NG	A, F,	A	A	NG	A	NG	A	NG	NG	NG	A	NG

											B										
Second line ULT drug(s)	NG	P	NG	NG	P	NG	P	NG	U, F	NG	NG	F, P, B	F, B, P, U	NG	P, B, F	NG	F, U	NG	NG	NG	F	NG
Allopurinol use																						
_Maximum dose (mg/d)	300	NG	NG	NG	800	NG	800	600	NG	600	800-900	800	NG	NG	900	NG	NG	NG	800	NG	900	600
_RF to initiate dose adjustment (eGFR in ml/min/1.73m^2, CCr in mL/min)	CCr 60	CCr 80	NG	NG	NG	NG	CKD4	NG	NG	CCr 60	CCr 140	CCr 20	NG	NG	NG	NG	NG	NG	NG	NG	eGFR 130	1.5mg/eGFR‖
_Starting dose in normal RF (mg/d)	50-100	100-150	NG	NG	100	50	≤100	50	NG	100-150	NG	100	NG	NG	NG	100	100	NG	100	50-100	200	50-100
_HLA-B*5801 gene screening	-	-	-	-	-	-	+	-	-	+	-	-	-	NG	-	-	-	-	+	-	+	+
Prophylaxis before ULT	+	NG	NG	NG	+	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Prophylaxis with ULT	+	+	NG	NG	+	+	+	NG	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Duration for prophylaxis	1-3 m¶	1-6 m**	NG	NG	NG	NG	3-6 m††	NG	Un-clear	6m	>6m	NG	>6m	NG	Vari-ed‡‡	3-6 m	NG	>6m	3-6 m	>8w	<6m	3-6m
Pharmacological ULT for asymptomatic hyperuricemia?	-	+	NG	-	-	+	IE	+	IE	IE	NG	NG	-§§	NG	IE	NG	NG	IE	-	NG	-	NG
_Comorbidities	NA	-	NA	NA	NA	+	NA	+	NA	NA	NA	NA	-	NG	NA	NA	NA	NA	NA	NA	NA	NA
_SUA cut-offs, μmol/L [mg/dL]	NA	[10-13]‖‖	NA	NA	NA	[8.0-9.0] ¶¶	NA	[8.0-9.0] ***	NA	NA	NA	NA	[9.0]	NG	NA	NA	NA	NA	NA	NA	NA	NA

* The general target was the target serum uric acid level for long term control recommended for all patients on pharmacological urate lowering therapy.

† The intensive target the intensive target was the target serum uric acid level for long term control recommended for patients with tophi [16, 17, 22, 36, 38, 40, 43], with recurrent attacks [16, 21, 22], or with chronic gouty arthritis [16, 22], or to prevent crystal formation [21], or to improve gout signs and symptoms [14, 15]. One document provided stricter target for any patient with gout [37], and one for patients with severe gout without clear definition [39].

‡ Comorbidities considered as the indication for ULT include renal impairment [14-16, 19-22, 37, 49, 50], cardiovascular risk or cardiovascular diseases [16, 22, 47], glucose intolerance or DM, lipid disorder, and obesity [22].

§ Others indications considered for pharmacological ULT include joint damage [21], diuretic therapy use [21], young age [16, 21, 22] with some documents defined as less than 40 years old [16, 22], high SUA level defined as >8mg/dL (480 umol/L) [16] or >13mg/dl [50], impending cytotoxic chemotherapy or radiotherapy for lymphoma or leukaemia [49], persistently raised uric acid levels and willingness to continue lifelong therapy [51]. Some documents evaluated SUA levels in patients after lifestyle modification and indicated pharmacological ULT in individuals with SUA above 6 mg/dL [46], or with SUA above 8mg/dl with CV risk or CVD and above 9mg/dl without CV risk or CVD [47].

|| The starting dose of allopurinol in patients with renal impairment should not exceed 1.5mg/eGFR.

¶ Prophylaxis should be continued until the serum urate is normal and the patient has not had any attacks for 1-3 months.

** Prophylaxis should be continued until 6 months free of acute attacks or until 1 month with target serum urate level achieved.

†† Prophylaxis should be continued for 1) 6 months' duration, 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination, or 3) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination.

‡‡ The during for prophylaxis varied and depends on the presence of tophi and comorbidities and on serum urate response. But prophylaxis should be continued until the target SUA is reached or until the tophi has resolved.

§§ The recommendations provided were conflict within the same document.

|||| Pharmacological urate lowering therapy is recommended in male patients with serum uric acid >13 mg/dL and in female patients with serum uric acid >10 mg/dL.

¶¶ Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with complications or >9 mg/dL in all patients.

*** Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with cardiovascular disease or cardiovascular risk factors or >9 mg/dL if without cardiovascular disease or cardiovascular risk factors.

Supplementary Table 11. Summary of recommendations for the treatment of acute gout by included guidance documents

NG: not given; NSAIDs: non-steroidal anti-inflammatory drugs.

	What is the first line pharmacological treatment option?	Is colchicine recommended to be given as a fixed dose or as a loading dose + followed doses?	Is intra-articular steroids recommended?	What are the indications for intra-articular steroids?	Which line is intra-articular steroids recommended to be?	Is systemic steroids recommended?	What are the indications for systemic steroids?	Which line of option is systemic steroids recommended to be?
SAMA_2003 [51]	NSAIDs	1 mg loading + 0.5 mg 2-hourly	Yes	Contraindicated to NSAIDs and joint accessible	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	NG
MOH_MSR_AMM_2008 [49]	NSAIDs	NG (0.5mg - 0.6mg bd-qds)	Yes	NG	NG	Yes	Elderly people, renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease, and hypersensitivity to NSAIDs	NG
PRA_2008 [50]	NSAIDs	NG (0.5 mg bid-qid)	NG	NG	NG	Yes	Contraindicated to NSAIDs	NG
UTAustin_2009 [52]	NSAIDs	1-1.2 mg loading + 0.5-0.6 mg every 2-3 hours	Yes	Only 1-2 joints is involved	Third	Yes	Contraindicated or not responding to NSAIDs and colchicine and polyarthritis	Third
EULAR_2011 [17]	Colchicine, NSAIDs, glucocorticoids	1.2 mg loading + 0.6 mg 1 hour later	Yes	NG	NG	Yes	Contraindications to NSAIDs and colchicine	First
JSGNAM_2011 [48]	Colchicine, NSAIDs	Fixed (0.5 mg)	NG	NG	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	Second
ACR_2012 [14, 15]	NSAIDs, corticosteroids, colchicine	1.2 mg loading + 0.6 mg 1 hour later	Yes	Involvement of 1 or 2 large joints	First	Yes	Oral steroids for involvement of 1 or 2 joints or when intra-articular joint injection is impractical. Intravenous steroids for the nothing by mouth patients.	First
3e_2013 [36]	NSAIDs, colchicine, glucocorticoids	NG (<2 mg daily)	Yes	NG	First	Yes	NG	First
CSE_2013 [37]	NSAIDs,	NG	NG	NG	NG	NG	NG	NG

	colchicine, corticosteroids							
SER_2013 [46]	NSAIDs	NG	Yes	Monoarthritis	NG	Yes	Contraindicated to NSAIDs	NG
SIR_2013 [45]	NSAIDs, colchicine	NG (<2 mg daily)	Yes	NG	NG	Yes	Intolerance or contraindications to NSAIDs and colchicine	NG
3e_PT_2014 [40]	Colchicine, NSAIDs	Fixed low dose	Yes	NG	NG	Yes	NG	NG
FMOH_2014 [44]	NG	NG	NG	NG	NG	NG	NG	NG
3e_AU_NZ_2015 [43]	NSAIDs, colchicine, glucocorticoids	NG (1.8 g in 24 h)	Yes	NG	First	Yes	NG	First
CRA_2016 [41]	NSAIDs	NG (1.5-1.8 mg/d)	NG	NG	NG	Yes	Contraindications to NSAIDs and colchicine	NG
EULAR_2016 [16]	Colchicine, NSAIDs, corticosteroid	1 mg loading + 0.5 mg 1 hour later	Yes	NG	First	Yes	NG	First
T2T_2016 [39]	Anti-inflammatory medications	NG	NG	NG	NG	NG	NG	NG
TRA_2016 [38]	NSAIDs	Fixed (0.5 mg bid) or 1 mg loading + 0.5 mg tid	Yes	Involvement of 1-2 major joints, contraindications to both colchicine and NSAIDs	NG	Yes	Contraindications to NSAIDs and colchicine	NG
ACP_2017 [19, 20]	Corticosteroids	1.2 mg loading + 0.6 mg 1 hour later	NG	NG	NG	Yes	If not contraindicated.	First
BSR_2017 [21]	NSAIDs, colchicine	NG (500 mg bd-qds)	Yes	Patients with acute illness and comorbidity	First	Yes	Intolerance to NSAIDs and colchicine and intra-articular injection is not feasible.	Second
CRA_multi_2017 [22]	NSAIDs, colchicine	1 mg loading + 0.5 mg at 1h, 12h	Yes	Involvement of 1-2 major joints and not responding to systemic treatment	NG	Yes	Contraindicated to or not responding to NSAIDs and colchicine	NG

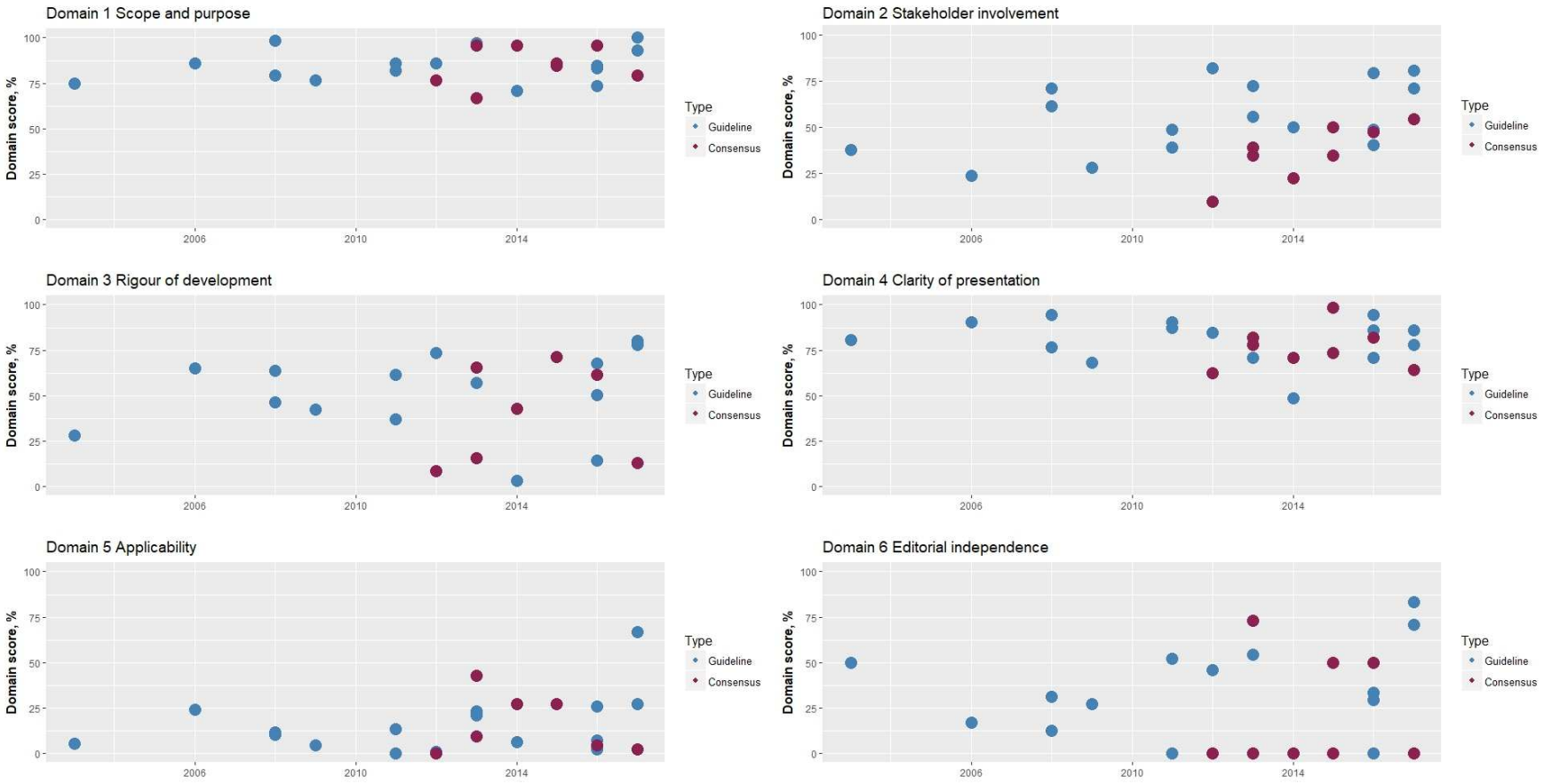
Supplementary Table 12. Summary of recommendations for the treatment of tophi by included guidance documents

A: allopurinol; B: benzbromarone; F: febuxostat; NA: not applicable; NG: not given; P: pegloticase; R: rasburicase; ULT: urate lowering therapy; WH: wound healing.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Is surgery recommended?	+	+	NG	NG	NG	+	NG	+	NG	NG	NG	+	NG	+	NG	NG	IE	+	NG	-	+
Indications for surgery	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	+	NG	NG	+
_Nerve compression	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	+
_Infection	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	-
_Mechanical impingement	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	-	NA	NA	-
_Loss of mobility	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Severe pain	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Tophaceous ulcer	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	-	NA	NA	+
_Others*	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	+
Risks of surgery	WH	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Is long-term ULT recommended?	+	+	+	NG	+	+	+	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Is any ULT drug recommended?	A	-	-	-	P	-	P	-	B	F	NA	-	-	P	-	P	-	-	-	P, R	-

* Other indications for surgery include large tophi [22], persistent tophi [22], joint deformation [38], major joint destruction [49], pressure symptoms [49], and cosmetic [49].

Supplementary Figure 1. Standardized domain scores by the year of publication



Supplementary File 1. Instructions for Guideline Appraisal Using the AGREE II Instrument

TRAINING MATERIALS

- Online tutorial: http://www.agreetrust.org/resource-centre/agree-ii-training-tools/
- User's Manual: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

PROLOGUE

- The Appraisal of Guidelines for REsearch & Evaluation (AGREE) Instrument is an international, validated and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements.
- The AGREE II instrument was published in 2010 and consists of 23 key items organized within 6 domains followed by 2 global rating items ("Overall Assessment"). Each domain captures a unique dimension of guideline quality.
  - Scope and purpose
  - Stakeholder involvement
  - Rigour of development
  - Clarity of presentation
  - Applicability
  - Editorial independence.
- Reviewers score each item on a 7-point Likert Scale.
  - 1 - Strongly disagree
  - 7 - Strongly agree
  - For the majority of items, we use an 'add-up' strategy to score, that is, corresponding scores will be added to 1' if information on predefined aspects is provided. For only one item, we subtract scores from 7'.
- Domain scores will be calculated as: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)

DETAILED INSTRUCTIONS FOR SCORING

(adapted from AGREE II User's Manual [28])

Domain 1 Scope and Purpose

Item 1 Objectives: The overall objective(s) of the guideline is (are) specifically described.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Health intent, i.e., prevention, screening, diagnosis, treatment, etc. (2');

b) Expected benefit or outcome (2');

- *Clarification*: If gout epidemiology is provided as background information (i.e., the importance or significance of the diagnosis and management of gout/hyperuricemia is stated), 1' will be given. If clear statements, such as "to prevent (long term) complications of patients with diabetes mellitus" "to lower the risk of subsequent vascular events in patients with previous myocardial infarction", are provided, 2' will be given.

c) Target, e.g., patient population, society (1').

Performance: Is the item well written and is the content easy to find? (1')

Related *Report Criteria* from *User's Manual*: • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) • expected benefit or outcome • target(s) (e.g., patient population, society)

Item 2 Questions: The health question(s) covered by the guideline is (are) specifically described.

Instructions:

Information on five aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Target population (2');

b) Intervention or exposure (if appropriate, 1');

c) Comparisons (if appropriate, 1');

d) Outcome (1');

e) Health care setting or context (1').

Performance: Is the item well written and is the content easy to find? (1')

Note:

1) If c) is not appropriate, no score will be subtracted.
2) It is not necessary to have this information provided in questions. Reviewers can try to paraphrase 2-3 key recommendations into questions to see the information above is provided and score based on paraphrased questions.

Related *Report Criteria* from *User's Manual*: • target population • intervention(s) or exposure(s) • comparisons (if appropriate) • outcome(s) • health care setting or context

Item 3 Population: The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Instructions:

A default full score (7') should be considered. Subtract 1-2 points where the population is not clearly described or where the descriptions in the guideline is contradictory (e.g., a guideline stating "to treat asymptomatic hyperuricaemia" in the introduction, while stating "to treat hyperuricaemia and gout" in the title and providing no specific definition of patients' condition in recommendations).

Related *Report Criteria* from *User's Manual*: • target population, gender and age • clinical condition (if relevant) • severity/stage of disease (if relevant) • comorbidities (if relevant) • excluded populations (if relevant)

Domain 2 Stakeholder Involvement

Item 4 Group Membership: The guideline development group includes individuals from all relevant professional groups.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) The guideline development group is stated (1');

b) For each member of the guideline development group, the following information is included (1' each): name (1'), discipline/content expertise (e.g., neurosurgeon, methodologist, 1'), institution (e.g., St. Peter's hospital, 1'), a description of the member's role in the guideline development group (1')

- *Clarification*: Please subtract 1' if no methodologist (i.e., epidemiologist) is inferred from the discipline/content expertise.

Performance: Is the item well written and is the content easy to find? (1')

Note: Where the relation between the guideline development group and the authors is unclear, the authors of the guidance document will be considered as equivalent to the guideline development group.

Related *Report Criteria* from *User's Manual*: • For each member of the guideline development group, the following information is included: name, discipline/content expertise (e.g., neurosurgeon, methodologist), institution (e.g., St. Peter's hospital), geographical location (e.g., Seattle, WA), a description of the member's role in the guideline development group

Item 5 Target Population Preferences and Views: The views and preferences of the target population (patients, public, etc.) have been sought.

Instructions:

Information the following four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences, 2');

b) Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups, 1');

c) Outcomes/information gathered on patient/public information (2');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

- *Clarification*: If a patient representative is included in the guideline development panel, scores on aspects a), b), and d) will be given as default.

Related *Report Criteria* from *User's Manual*: • statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) • methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) • outcomes/information gathered on patient/public information • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 6 Target Users: The target users of the guideline are clearly defined.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators, 3');

b) Description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care, 3')

Related *Report Criteria* from *User's Manual*: • clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) • description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)

Domain 3 Rigour of Development

Item 7 Search Methods: Systematic methods were used to search for evidence.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL, 2');
b) Time periods searched (e.g., January 1, 2004 to March 31, 2008, 1');
c) Search terms used (e.g., text words, indexing terms, subheadings, 1');
d) Full search strategy included (e.g., possibly located in appendix, 2')

Related *Report Criteria* from *User's Manual*: • named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) • time periods searched (e.g., January 1, 2004 to March 31, 2008) • search terms used (e.g., text words, indexing terms, subheadings) • full search strategy included (e.g., possibly located in appendix)

Item 8 Evidence Selection Criteria: The criteria for selecting the evidence are clearly described.
Instructions:
Information on both inclusion and exclusion criteria should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the inclusion criteria:
a1) target population (patient, public, etc.) characteristics (2'),
a2) study design (2),
a4) outcomes (1'),
b) Description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement, 1').
Note: if a3), a5), a6), b) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • description of the inclusion criteria, including: target population (patient, public, etc.) characteristics, study design, comparisons (if relevant), outcomes, language (if relevant), context (if relevant) • description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement)

Item 9 Strengths and Limitations of The Evidence: The strengths and limitations of the body of evidence are clearly described.
Instructions:
For each evidence, information on two aspects should be provided. If only some of the evidences report the following information, please first calculate the score based on the most informative evidence (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').
For each evidence, both a general statement of the method and detailed descriptions should be provided:
a) A statement of the method used to evaluate the strengths and limitations of the evidence should be provided (3').
b) The stated method should evaluate at least three of the following aspects (add 1' for each aspect, maximum 3'):
b1) Study design(s);
b2) Study methodology limitations (e.g., sampling, blinding, allocation concealment, analytical methods);
b3) Appropriateness/relevance of primary and secondary outcomes considered;
b4) Consistency of results across studies;
b5) Direction of results across studies;
b6) Magnitude of benefit versus magnitude of harm;

b7) Applicability to practice context

Related *Report Criteria* from *User's Manual*: • descriptions of how the body of evidence was evaluated for bias and how it was interpreted by members of the guideline development group • aspects upon which to frame descriptions include: study design(s) included in body of evidence, study methodology limitations (sampling, blinding, allocation concealment, analytical methods), appropriateness/relevance of primary and secondary outcomes considered, consistency of results across studies, direction of results across studies, magnitude of benefit versus magnitude of harm, applicability to practice context

Item 10 Formulation of Recommendations: The methods for formulating the recommendations are clearly described.

Instructions:

Information on three aspects should be provide (add 2' for each aspect, 6' in total):

a) Description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered, 2');

b) Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures, 2');

c) Description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote, 2')

Related *Report Criteria* from *User's Manual*: • description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) • outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) • description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)

Item 11 Consideration of Benefits and Harms: The health benefits, side effects, and risks have been considered in formulating the recommendations.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Supporting data and report of benefits (2'); b) Supporting data and report of harms/side effects/risks (2');

- *Clarification*: Data on a) and b) can be provided as references.

c) Reporting of the balance/trade-off between benefits and harms/side effects/risks (1');

d) Recommendations reflect considerations of both benefits and harms/side effects/risks (1')

Related *Report Criteria* from *User's Manual*: • supporting data and report of benefits • supporting data and report of harms/side effects/risks • reporting of the balance/trade-off between benefits and harms/side effects/risks • recommendations reflect considerations of both benefits and harms/side effects/risks

Item 12 Link Between Recommendations and Evidence: There is an explicit link between the recommendations and the supporting evidence.

Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) The guideline describes how the guideline development group linked and used the evidence to inform recommendations (2');
- *Clarification*: Can be provided as narrative summaries and/or discussions of evidences.
b) Each recommendation is linked to a key evidence description/paragraph and/or reference list (2');
- *Note*: Please subtract 1' if only some recommendations meet criterium b).
c) Recommendations linked to evidence summaries, evidence tables in the results section of the guideline (2')

Related *Report Criteria* from *User's Manual*: • the guideline describes how the guideline development group linked and used the evidence to inform recommendations • each recommendation is linked to a key evidence description/paragraph and/or reference list • recommendations linked to evidence summaries, evidence tables in the results section of the guideline

Item 13 External Review: The guideline has been externally reviewed by experts prior to its publication.
Instructions:
Information on five aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence, 1');
b) Methods taken to undertake the external review (e.g., rating scale, open-ended questions, 1');
c) Description of the external reviewers (e.g., number, type of reviewers, affiliations, 1');
d) Outcomes/information gathered from the external review (e.g., summary of key findings, 1');
e) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations, 2')
- *Clarification*: Publication through a peer-reviewed journal can be considered as externally reviewed. Note: If dates of revision and acceptance is provided on the document, it is also considered externally reviewed.

Related *Report Criteria* from *User's Manual*: • purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) • methods taken to undertake the external review (e.g., rating scale, open-ended questions) • description of the external reviewers (e.g., number, type of reviewers, affiliations) • outcomes/information gathered from the external review (e.g., summary of key findings) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)

Item 14 Updating Procedure: A procedure for updating the guideline is provided.
Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) A statement that the guideline will be updated (2');
b) Explicit time interval or explicit criteria to guide decisions about when an update will occur (2');
c) Methodology for the updating procedure is reported (2')

Related *Report Criteria* from *User's Manual*: • a statement that the guideline will be updated • explicit

time interval or explicit criteria to guide decisions about when an update will occur • methodology for the updating procedure is reported

Domain 4 Clarity of Presentation

Item 15 Specific and Unambiguous Recommendations: The recommendations are specific and unambiguous.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) If a recommendation is uncertain, the uncertainty should be reflected in the recommendation and also be explicitly stated (2')

b) Identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects, 2');

- *Clarification*: If the benefit for uric acid lowering in patients with CVD is not clearly stated, the score for this aspect should not be added.

c) Identification of the relevant population (e.g., patients, public, 1');

d) Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply, 1').

Note: if c) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • statement of the recommended action • identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) • identification of the relevant population (e.g., patients, public) • caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)

Item 16 Management Options: The different options for management of the condition or health issue are clearly presented.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) Description of options (3');

b) Description of population or clinical situation most appropriate to each option (3')

- *Note*: Please subtract 1' if only some options are provided with the most appropriate population or clinical situation.

Related *Report Criteria* from *User's Manual*: • description of options • description of population or clinical situation most appropriate to each option

Item 17 Identifiable Key Recommendations: Key recommendations are easily identifiable.

Instructions:

Reporting style should follow two criteria (add 3' for each aspect, 6' in total):

a) Description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms (3');

b) Specific recommendations are grouped together in one section (3')

- *Clarification*: If recommendations are summarised in the abstract, scores for aspect b) can also be given.

Related *Report Criteria* from *User's Manual*: • description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms • specific recommendations are grouped together in one section

Domain 5 Applicability

Item 18 Facilitators and Barriers to Application: The guideline describes facilitators and barriers to its application.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of facilitators and barriers that were considered (2');

- *Clarification*: Statements of that certain drugs are not available in certain regions can be considered as identification of the facilitators and barriers.

b) Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation, 2');

c) Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography, 1');

d) Description of how the information influenced the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of facilitators and barriers that were considered • methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) • information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) • description of how the information influenced the guideline development process and/or formation of the recommendations

Item 19 Implementation Advice or Tools: The guideline provides advice and/or tools on how the recommendations can be put into practice.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) An implementation section in the guideline (2');

b) Tools and resources to facilitate application (add 1' for each tool/resource, maximum 2'): guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned;

c) Directions on how users can access tools and resources (2')

Related *Report Criteria* from *User's Manual*: • an implementation section in the guideline • tools and resources to facilitate application: guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned • directions on how users can access

tools and resources

Item 20 Resource Implications: The potential resource implications of applying the recommendations have been considered.

- *Clarification*: The aim of this item is to the cost information considered by the guideline.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs, 2');

b) Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc., 2');

c) Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course, 1');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) • methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) • information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 21 Monitoring or Auditing Criteria: The guideline presents monitoring and/or auditing criteria.

- *Clarification*: The aim of this item is to evaluate the adherence to guidelines, but not to provide follow up parameters for diseases. *Monitoring* in this item refers to the action to monitor physicians' adherence to the guideline in daily practice by a group of investigators, but not to monitor the management of the disease in an individual patient. And the *auditing criteria* are the criteria to assess how well the guideline affects the practice in a region, but not how well the patients achieve the treatment target.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of criteria to assess guideline implementation or adherence to recommendations (2');

b) Criteria for assessing impact of implementing the recommendations (2');

c) Advice on the frequency and interval of measurement (1');

d) Descriptions or operational definitions of how the criteria should be measured (1')

Related *Report Criteria* from *User's Manual*: • identification of criteria to assess guideline implementation or adherence to recommendations • criteria for assessing impact of implementing the recommendations • advice on the frequency and interval of measurement • descriptions or operational definitions of how the criteria should be measured

Domain 6 Editorial Independence

Item 22 Funding Body: The views of the funding body have not influenced the content of the guideline.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) The name of the funding body or source of funding (or explicit statement of no funding, 3');
b) A statement that the funding body did not influence the content of the guideline (3')

Related *Report Criteria* from *User's Manual*: • the name of the funding body or source of funding (or explicit statement of no funding) • a statement that the funding body did not influence the content of the guideline

Item 23 Competing Interests: Competing interests of guideline development group members have been recorded and addressed.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the types of competing interests considered (2');
b) Methods by which potential competing interests were sought (1');
c) Description of the competing interests (1');
d) Description of how the competing interests influenced the guideline process and development of recommendations (2')

Related *Report Criteria* from *User's Manual*: • description of the types of competing interests considered • methods by which potential competing interests were sought • description of the competing interests • description of how the competing interests influenced the guideline process and development of recommendations

Overall Guideline Assessment

Question 1 Overall quality: Rate the overall quality of this guideline.

Instructions:

7' in total. Reviewer's impression on the overall quality of the guideline.

Question 2 Strength of recommendation: I would recommend this guideline for use.

Instructions:

Three options to choose from: a) Yes; b) Yes, with modifications; c) No
Reviewer's impression on whether the guideline is easy to be applied to clinical practice.

Related *Report Criteria* from *User's Manual*: The overall assessment requires the AGREE II user to make a judgment as to the quality of the guideline, taking into account the appraisal items considered in the assessment process.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported -on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21-22

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

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

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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ABSTRACT

Objectives

Despite the publication of hundreds of trials on gout and hyperuricemia, management of these conditions remains suboptimal. We aimed to assess the quality and consistency of guidance documents for gout and hyperuricemia.

Design

Systematic review and quality assessment using the Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Data Sources

PubMed and EMBASE (27 October 2016), two Chinese academic databases, eight guideline databases, and Google and Google scholar (July 2017).

Eligibility Criteria

We included the latest version of international and national/regional clinical practice guidelines and consensus statements for diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese.

Data Extraction and Synthesis

Two reviewers independently screened searched items and extracted data. Four reviewers independently scored documents using the AGREE II. Recommendations from all documents were tabulated and visualized in a coloured grid.

Results

Twenty-four guidance documents (16 clinical practice guidelines and 8 consensus statements) published between 2003 and 2017 were included. Included documents performed well in the domains of scope and purpose (median 85.4%, range 66.7%-100.0%) and clarity of presentation (median 81.3%, range 48.6%-98.6%), but unsatisfied in applicability (median 9.9%, range 0.0%-66.7%) and editorial independence (median 28.1%, range 0.0%-83.3%). The 2017 British Society of Rheumatology guideline received the highest scores. Recommendations were concordant on the target serum uric acid level for long-term control, on some indications for urate-lowering

therapy, and on the first-line drugs for urate-lowering therapy and for acute attack. Substantially inconsistent recommendations were provided for many items, especially for the timing of initiation of urate-lowering therapy and for treatment for asymptomatic hyperuricemia.

Conclusions

Methodological quality needs improvement in guidance documents on gout and hyperuricemia. Evidence for certain clinical questions is lacking, despite numerous trials in this field. Promoting standard guidance development methods and synthesizing high-quality clinical evidence are potential approaches to reduce recommendation inconsistencies.

Study registration

PROSPERO (CRD42016046104).

Keywords

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The first systematic review to assess the quality of clinical practice guidelines and consensus statements on the diagnosis and treatment for both hyperuricemia and gout.
2. The first systematic review to summarise recommendations for best practice in hyperuricemia and gout.
3. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is an international, structured, validated, and rigorously developed tool.
4. Each document was evaluated by four reviewers and differences between reviewers were assessed.
5. Only guidance documents in English and Chinese were included.

BACKGROUND

Gout is an inflammatory arthritis occurring in response to monosodium urate crystals formation, a common and necessary pathogenic factor of which is hyperuricemia. The prevalence of gout and hyperuricemia [1-4], as well as their disease burden [5, 6], are rising globally. More than six hundred clinical studies [7], including observational studies, randomised clinical trials, and mendelian randomization studies, have been published to date. However, the quality of care for gout and hyperuricemia remains suboptimal. The goal of treatment is to reduce the body's total uric acid pool [8, 9] and consequently to minimize the risk of acute flares, arthropathy, nephrolithiasis, and other complications [7, 10, 11]. A study in the United States found that only 22% patients with gout received therapy adhering to all quality indicators [12] and a nationwide population study in the United Kingdom reported that only 48% of prevalent patients received proper consultation and only 27% of incident patients were provided with urate-lowering therapy (ULT) within one year of diagnosis [6].

High-quality guidance documents are important for improving the quality of diagnosis and management of gout and hyperuricemia at individual, community, and national levels [13]. Current guidance documents for hyperuricemia and gout have been developed by rheumatology, endocrinology, and cardiology groups, at regional, national or international levels. Among these documents, the American College of Rheumatology (ACR) guidelines [14, 15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16-18], updated in 2016, have the most substantial global influence. The most recent documents (released in 2017) are two national guidelines, from the American College of Physicians (ACP) [19, 20] and from the British Society of Rheumatology (BSR) [21], and one consensus statement, from the Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases [22].

However, current guidance documents on gout and hyperuricemia provide inconsistent recommendations, even those released by highly respected professional organizations, such as the ACP and the ACR [23]. Some distinct differences lie in key aspects for patient care, such as the pharmacological treatment for asymptomatic hyperuricemic patients, the timing of initiation of ULT in patients with gout flare [24], and indications for ULT [25]. These discrepancies may result from ethnic and social differences, but can be consequences of inconsistent guideline development [23]. Low-quality guidance documents put individual patients and communities at risk, and impede clinicians' application of the guidance in daily practice [26]. Hence, we conducted this study to systematically evaluate the quality of guidance documents on gout and hyperuricemia and to compare all key recommendations from different documents.

METHODS

Detailed methods of the study have been published previously [27] and this study was registered with PROSPERO (registration number: CRD42016046104).

Literature search and selection criteria

We systematically searched PubMed and EMBASE from inception to 27 October 2016 using a comprehensive search strategy (Supplementary Table 1 and Supplementary Table 2) to identify guidance documents pertaining to the diagnosis and treatment of hyperuricemia and gout. We searched two academic databases for Chinese publications (the Chinese Biomedical Literature Database and the Wanfang Data) and eight guideline databases from inception to 24 July 2017 using search strategies tailored to different databases (Supplementary Table 3). We also searched Google and Google scholar in July 2017 for potentially eligible guidelines and consensus

statements that were not indexed in the aforementioned databases.

We included the latest versions of all international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese. Two reviewers (Q.L., X.L.) independently screened all searched papers. Reasons for exclusion were provided for documents excluded during the full-text review (Supplementary Table 4). Disagreements were resolved through discussion with a third reviewer (S.L.).

Data extraction

We extracted the following data from each included document: document characteristics (e.g., year of publication, funding body, evidence base), recommendations for diagnosis and monitoring of hyperuricemia and gout, and recommendations for management. Data were extracted by one investigator (Q.L.) and were checked by a second investigator (X.L.).

Appraisal of guidance documents

All included documents were assessed by four reviewers (Q.L., X.L., J.W., and H.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [28]. AGREE II is an internationally developed and validated tool to evaluate the quality of clinical practice guidelines [29-31] and consensus statements [32, 33].

All reviewers completed the online training tutorial [34] before the commencement of appraisal to ensure standardization. We adapted detailed instructions for scoring from the AGREE II User's Manual [28] and provided objective scoring criteria for each item (Supplementary File 1). We selected four guidance documents for pilot scoring, during which our objective scoring criteria were discussed and clarified. A meeting was held among reviewers

after the appraisal and every item with scores differed more than one point was discussed. Reviewers were given the opportunity to revise their scores or to keep the original scores after the meeting. We recorded all original scores, revised scores, and reasons for modifying scores. We calculated the inter-rater reliability on the AGREE II using the intra-class correlation coefficient (ICC) via IBM SPSS (IBM Co., Armonk, New York, USA) when the entire scoring process was completed. An ICC >= 0.7 was considered acceptable [35].

Recommendation synthesis

We manually extracted descriptive data from all included guidance documents and tabulated them into the following tables to summarize recommendations: the diagnosis of gout and hyperuricemia, the treatment of hyperuricemia, the treatment of acute gout, and the treatment of tophi. Data were extracted by one investigator (Q.L.) and were checked by a second investigator (X.L.). We plot the summarized recommendations in a five-colour grid to illustrate inconsistencies. The most frequently stated content was used as the reference content. Cells of guidance documents providing consistent recommendations were coloured in green, while cells of those providing partially consistent recommendations, which was defined as recommendations including but not the same as reference contents, were coloured in blue, and of inconsistent recommendations in red. Where recommendations were not given and were not applicable, the cell was coloured in yellow and in grey, respectively.

Patient involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

RESULTS

Search results

Overall, we identified 5811 items across the academic databases, guideline

databases, Google, and Google Scholar. After applying the inclusion and exclusion criteria, 24 guidance documents from 26 papers [14-22, 36-52] were included in the final appraisal and recommendation synthesis (Figure 1). Studies excluded after full-text review and reasons for exclusion were provided as Supplementary Table 4.

Characteristics of the included guidelines and consensus statements

Table 1 summarized the characteristics of the included guidance documents, among which 16 were clinical practice guidelines [14-21, 38, 41, 44-46, 48-52] and eight were consensus statements [22, 36, 37, 39, 40, 42, 43, 47]. 16 national or regional organizations and three international groups, namely the 3e (Evidence, Expertise, Exchange) Initiative, the EULAR, and the development group for the Treat-to-target (T2T) recommendations, published these documents between 2003 to 2017. 16 documents [14-18, 21, 22, 36-38, 40, 42, 43, 45, 46, 49, 50] were issued by rheumatology organizations and seven [16-18, 36, 39, 42, 43] were developed by multinational development groups. 17 documents [14-18, 21, 22, 36, 38-41, 43-46, 49, 51] provided information on guideline development group, among which 11 [14-17, 19-21, 36, 41-43, 45, 46] explicitly stated the involvement of a methodologist. 12 documents [14-18, 21, 22, 38-41, 43-46, 49, 51] provided information on the target audience, among which only three [16, 38, 44] included the patients. 18 documents [14-21, 36, 39-43, 45, 46, 48-52] reported conducting a systematic literature review in the development, among which 17 documents [14-21, 36, 39-41, 43, 45, 46, 48-52] reported the level of evidence in support of recommendations and 16 [16-21, 36, 39-41, 43, 45, 46, 48-52] graded the strength of recommendations. Ten documents [16, 19-21, 39, 42, 46, 48, 49, 51, 52] clearly stated being externally reviewed. Five [19-21, 46, 49, 50] provided a clear time of update plan. 12 documents [14, 15, 17-21, 36, 39, 42, 46, 49, 51, 52] provided information on the funding body, among which six [17, 36, 39, 46, 49, 51] were fully or partially funded by the pharmaceutical industry.

The other half did not clearly declare the funding body, which made the impact of industry on the recommendations ambiguous.

Appraisal of guidelines and consensus statements

Figure 2 showed the standardized domain score for each guidance document for the six quality domains assessed with the AGREE II tool. Domain scores were provided in value as Supplementary Table 5. Mean score across reviewers for individual items were provided as Supplementary Table 6. Item scores for each individual AGREE II item were provided as Supplementary Table 7). The overall quality of guidelines, as assessed by AGREE II, varied both between guidance documents across domains and within guidance documents between domains. The document with the highest domain scores was published by the BSR in 2017 [21], with five domains scoring above the upper quartile, followed by the documents published by the ACP in 2017 [19, 20], and by the ACR and the EULAR jointly in 2015 [42], both with four domains scoring above the upper quartile. Guidelines did not always score higher than consensus statements. The standardized domain scores for each domain of all guidance documents were visualized by the year of publication in Supplementary Figure 1. No tendency of improvement in the quality score was observed.

The AGREE II instrument evaluated guidelines and consensus statements in six domains, from the development, dissemination, to implementation. The scope and purpose (domain 1) clarifies the clinical questions. Proper involvement of stakeholders (domain 2) balances individuals' biases. Rigour of development (domain 3) is the domain most concerned by clinicians and ensures the validity of development methodology [53]. Clearly presented recommendations (domain 4) conveyed precise and accessible information from the development group to clinicians. Good performances in the applicability (domain 5) and the editorial independence (domain 6) guarantee

the usefulness and the independence of documents.

Guidance documents received the highest scores for the scope and purpose (domain 1, median 85.42%, range 66.67% to 100.00%) and the clarity of presentation (domain 4, median 79.17%, range 48.61% to 98.61%), and the lowest scores for the applicability (domain 5, median 10.94%, range 0.00% to 66.67%) and the editorial independence (domain 6, median 28.13%, range 0.00% to 83.33%). The worst scored item was the monitoring or auditing criteria (mean score 1.2, range 1.0-4.0), followed by the implementation advice or tools (mean 1.7, range 1.0-4.8), the external review (mean 2.1, range 1.0-6.0), and the updating procedure (mean 2.1, range 1.0-6.5).

The ICC was 0.896. Group discussion modified 365/2208 (16.53%) of individual scores.

Synthesis of recommendations

The included guidance documents addressed four major themes: diagnosis of gout and hyperuricemia, treatment for hyperuricemia, treatment for acute gout attack, and treatment for tophi. Figure 3 showed the key recommendations and their inconsistencies.

Approaches to diagnostic strategies for gout and hyperuricemia

Thirteen guidance documents [17-20, 22, 36, 38, 40-43, 46, 49, 51] covered the diagnosis of gout and 11 [17, 22, 37, 38, 45-51] covered diagnosis of hyperuricemia. Supplementary Table 8 showed the key recommendations. Three aspects were evaluated commonly in gout diagnosis, which is the clinical manifestation, considered by all documents, the laboratory result, considered by all but one document [49], and the imaging result, considered by all but four documents [17, 19, 20, 49, 51]. Identification of monosodium urate crystals in synovial fluid or tophi was required for definite diagnosis by all

documents.

Guidance documents differed when recommending the cut-off serum uric acid (SUA) level to diagnose hyperuricemia. For any patient with elevates SUA, four documents [38, 47, 48, 51] recommended 7.0 mg/dL (or 420 μmol/L) as the cut-off, while two [17, 45] preferred 6.8 mg/dL. Five documents [22, 37, 46, 49, 50] provided gender-specific cut-offs, recommending 6.0 mg/dL (or 360 μmol/L) in female and 7.0 mg/dL (or 420 μmol/L) in male. Asymptomatic hyperuricemia was defined in seven [36, 38, 46-50] documents, among which six [36, 38, 46-48, 50] clarified the exclusion of patients with gout and two [36, 48] clarified the exclusion of patients with tophi when making the diagnosis. Patients with renal diseases were not allowed to be diagnosed with asymptomatic hyperuricemia in the Japanese [48] and the Philippine [50] guidelines, but patients with pre-existing renal or cardiovascular diseases were allowed in the 3e initiative document [36].

Approaches to treatment for hyperuricemia

Twenty-two guidance documents [14-17, 19-22, 36-41, 43-52] covered the treatment for hyperuricemia and Supplementary Table 9 summarized the key recommendations. All but three documents [19, 20, 44, 52] explicitly recommended the target levels for long-term SUA control, most of which preferred 6.0 mg/dL (or 360 μmol/L), except the South African guideline [51] that preferred 5.0mg/dL (300 μmol/L). Only two documents [16, 22] recommended a lower limit of 3.0 mg/dL (or 180 μmol/L) for long-term SUA management and only the 2016 EULAR guideline [16] provided evidence that low SUA might increase the risk of neurodegenerative diseases, although the level of evidence and the grade of recommendation were low.

All but six guidance documents [36, 39, 40, 43, 44, 52] provided indications for long-term ULT. Recurrent attacks [14-17, 19-22, 41, 45, 48-51], tophi [14-17,

19-22, 38, 41, 45, 48-51], urate nephrolithiasis [14-17, 19-22, 37, 38, 49, 50], arthropathy [16, 17, 21, 22, 38, 41, 45, 49], and comorbidities [14-16, 19-22, 37, 47, 49, 50] were the most commonly recommended indications. The definition of recurrent attacks varied from at least once per year [17] to at least three times per year [49], while the majority of documents [14-16, 19-21, 41] recommended twice per year as the cut-off.

Regarding the timing to initiate ULT, agreement was not made whether to start pharmacological ULT after an acute attack [17, 21, 22, 36-38, 40, 48, 49, 51, 52] or during an attack [14, 15, 37], and when recommending to start ULT after an attack, the preferred time to wait since the resolution of attack varied from two weeks [37, 48] to six weeks [52]. All guidance documents based this recommendation on expert opinions due to insufficient evidence. Considerations supporting not starting ULT during an attack included that ULT was better discussed when the patient was not painful [21], and that ULT initiation could prolong or worsen the acute attack [51]. Two documents [16, 39] explicitly presented the currently conflicting views and insufficient evidence and stated consequently no recommendation for this issue.

When pharmacological ULT options were provided with prioritization, allopurinol was recommended by all guidance documents [14-17, 21, 36, 40, 43, 45, 46, 48-50] to be the first-line drug, while febuxostat was recommended by three documents [14, 15, 17, 46] to be the first-line and by six documents [16, 21, 36, 40, 43, 45] to be the second-line. However, recommendations on the dosage of allopurinol varied largely. The maximum dose per day recommended for allopurinol varied from 300 mg [51], 600 mg [22, 37, 47], 800 mg [14, 15, 17, 38, 45], to 900 mg [21, 43, 46], and the daily starting dose recommended in patients with normal renal function varied between 50 mg [19, 20, 22, 47, 48, 51] and 200 mg [21]. As for patients with impaired renal function, the cut-off to initiate dose adjustment was provided diversely as

creatinine clearance (CCr) 20-140 mL/min [37, 45, 46, 49, 51], or estimated glomerular filtration rate (eGFR) 130 ml/min/1.73m^2 [21]. One document preferred to depend allopurinol dose solely on eGFR by limiting the maximum dose to 1.5 mg/eGFR in patients with renal impairment [22]. HLA-B*5801 gene screening prior to allopurinol use was recommended by five guidance documents [14, 15, 21, 22, 37, 38].

For patients with asymptomatic hyperuricemia, 14 guidance documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52] commented on the option of pharmacological ULT, among which, five [17, 21, 38, 51, 52] explicitly recommended no treatment and three [47-49] recommended pharmacological treatments in patients with comorbidities [47, 48] or with very high SUA levels [40, 47-49]. The cut-off SUA level to indicate ULT in patients with asymptomatic hyperuricemia varied from 8.0 mg/dL [47, 48] to 13.0 mg/dL [49]. The Portuguese document [40] was incoherent itself by generally stating that pharmacological treatment was not recommended while also considered it in patients with SUA higher than 9 mg/dL. No evidence was provided by these documents to support pharmacological treatment for asymptomatic hyperuricemia directly, and such recommendations were made in concern of the onset of gout [40] and the risk of cardiovascular disorders [47, 48].

Approaches to treatment for the acute gout attack

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for acute gout attack and Supplementary Table 10 summarized their key recommendations. Non-steroidal anti-inflammatory drugs (NSAIDs) was recommended by all but three documents [19, 20, 39, 44] as the first line pharmacological treatment, while colchicine by 11 documents [14-17, 21, 22, 36, 37, 40, 43, 45, 48]. Colchicine was recommended to be given in a fixed dose by three documents [38, 40, 48] and in a loading dose followed by different doses by six documents [14-17, 19, 20, 22, 38, 51, 52]. Seven

documents [21, 36, 41, 43, 45, 49, 50] only provided the total daily dose for colchicine regardless of the regimen, the doses recommended by which varied from 1 mg [21, 49, 50] to 2.4 mg [49], except that one document [43] recommended 1.8 g in 24 hours without any further explanation. Systemic steroids were recommended by all but three documents [37, 39, 44], among which six [14-17, 19, 20, 36, 43] recommended them as the first-line option and ten [21, 22, 38, 41, 45, 46, 48, 50-52] recommended them when NSAIDs and colchicine were contraindicated or intolerant. Intra-articular steroids injection was recommended by 14 documents [14-17, 21, 22, 36, 38, 40, 43, 45, 46, 49, 51, 52], among which five [14-16, 21, 36, 43] clearly recommended it as the first-line option.

Approaches to treatment for tophi

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for tophi and Supplementary Table 11 showed their key recommendations. Surgery was recommended by nine documents [22, 36, 38, 40, 43, 48, 49, 51], among which five [22, 36, 38, 43, 49] explicitly presented the indications, most commonly nerve compression [22, 36, 38, 43] and infection [36, 38, 43]. The risk for surgery was discussed by one document [51] and it only mentioned wound healing. Long-term ULT was recommended by all but two documents [44, 52], but the pharmacological treatment was only explicitly recommended by eight of them [15-17, 21, 37, 43, 46, 51].

DISCUSSION

Principal findings and interpretations

This systematic review, including 16 guidelines and eight consensus statements, found generally low methodological quality and inconsistent recommendations from guidance documents covering the diagnosis and management of gout and hyperuricemia. During revision of our work, the English version of two documents, from the Chinese Multidisciplinary Expert

Task Force on Hyperuricemia and Related Diseases [54] and the Taiwan Rheumatologist Association [55], respectively, were released. Despite the increase in the number of guidance documents published between 2003 and 2017, the quality of documents in all domains did not seem to improve with time. To date, this is the first systematic appraisal for the quality of guidelines and consensus statements pertaining to both hyperuricemia.

Comparison with existing research

Guidance documents assessed in our study performed acceptable in the scope and purpose and the clarity of presentation, but unsatisfied in the applicability. These results were consistent with two previous reviews [56, 57], one of which systematically reviewed and assessed the quality of all guidelines for gout and the other assessed three documents released respectively by the 3e initiative [36], the ACR [14, 15], and the EULAR [18, 58]. Our study systematically included both guidelines and consensus statements in the field of both hyperuricemia and gout and further suggested that this trend of differed quality by domains and differed recommendations was shared by all guidance documents for gout and hyperuricemia.

Previous reviews of guidance documents in endocrinology and rheumatology diseases, such as diabetes [59, 60], thyroid disorders [31, 61], rheumatoid arthritis [32, 62, 63], and systemic lupus erythematosus [64], as well as reviews for guidance in other specialities [33, 65-67], gave similarly high scores in the scope and purpose and the clarity and presentation, and similarly low scores in the applicability and the editorial independence. Despite generally low and varied scores in the applicability, guidance documents on gout and hyperuricemia performed poorer in this domain comparing to the majority of other documents [31-33, 59-61, 63-67], suggesting that the negligence of the usefulness of guidance being more challenging in gout and hyperuricemia. Considering the time and cost to perform economic evaluations

and pilot studies, a stable and long-term task force of guideline development is required. Despite the practical difficulties, guidance documents were suggested to at least inform audience the need to consider these issues [65]. Low scores in the editorial independence often resulted from lacking of detailed information on the influence of funding body and conflict of interests. We found that 50% of documents declaring funding sources were supported by the pharmaceutical industry, calling for awareness of the potential influence of pharmaceutical industry on the synthesis of clinical guidance and for the need of promoting transparency in the financial declaration.

Clinical implications and future research

Guidance documents were concordant and recommended to target for SUA < 6.0 mg/dL (or 360umol/L) for long-term control, to consider recurrent attacks as one of the indications for ULT, although the definitions for recurrent attacks differed, to consider allopurinol as the first-line ULT and NSAIDs as the first-line drug in acute attack, and to consider long-term ULT in patient with tophi. Despite these similarities, recommendations differed in the majority of items and these discrepancies might come from several sources, including ethnic difference, quality of documents, and lacking of evidence.

Ethnical and social differences are important sources for recommendation diversity and such diversity is encouraged to improve the precision of guidance. Ethnicity difference explained the tendency of positive recommendations on HLA-B*5801 gene screening before prescribing allopurinol by Asian guidance documents [22, 37, 38]. The risk of hypersensitivity reactions associated with allopurinol is significantly increased in individuals carrying the variant allele HLA-B*5801, the frequency of which in Han Chinese, Korean, and Tai people are higher than that in the Caucasian population [14, 15, 21]. Studies suggested that HLA-B*5801 gene screening prior to allopurinol initiation is cost-effective for Asians but not Caucasians [68,

69]. Providing ethnicity-specific recommendations or explicitly specifying the ethnicity of target audience help clarify the source of inconsistency and improve the precision of recommendations.

However, the low quality of guidance documents also leads to discrepant recommendations and consequently chaos in application. Such discrepancies are concerned by clinicians when applying these recommendations in clinical practice and are observed to affect recommendations in the guidance documents for hyperuricemia and gout. Comparing with documents with high quality (scoring above the upper quartile in at least three out of the six AGREE II domains) [16, 19-21, 36, 42, 46], those with low quality (scoring below the lower quartile in at least three out of the six AGREE II domains) [22, 37, 38, 44, 47, 52] provided ambiguous prioritization of ULT drugs for hyperuricemia and of steroid options for acute attack. Among all domains assessed by the AGREE II instrument, those pertaining to stakeholder involvement, rigor of development, applicability and editorial independence could be primarily improved by standardizing the developing processes, which consequently improved the reliability of recommendations. These results reinforced that it is better for clinicians to refer to high-quality guidance documents instead of the low-quality ones. However, when high-quality documents are unavailable in local language, referring to low-quality local documents might mislead clinical practice in the region. It is thus more challenging for non-English speaking countries, including China[13].

Guidance documents are considered as the starting point to identify evidence gaps and to prioritize research questions [70]. Evidence gap was an issue commonly discussed in the recommendations of treatment for asymptomatic hyperuricemia, by five [14, 15, 36, 37, 39, 43] out of 14 documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52], and of timing to initiate ULT, by two [16, 39] out of 14 documents [14-17, 21, 22, 36-40, 48, 49, 51, 52]. Although the rest of

documents provided explicit recommendations, they based their recommendations either on indirect evidence or expert opinions. Evidence synthesis for the effects of pharmacological ULT in patients with asymptomatic hyperuricemia and for the optimal timing to initiate ULT in patients with the acute attack is warranted to improve the strength and consistency of these recommendations.

Strengths and limitations

Strengths of our review included a systematic approach to identify guidance documents pertaining to the diagnosis and management of hyperuricemia and gout. Both guidelines and consensus statements were evaluated and compared. We used the AGREE II instrument, an international, validated and rigorously developed tool, to assess the quality of document development and we tailored the AGREE II instrument to point-by-point scoring criteria (Supplementary File 1) to improve the objectivity and reproducibility of our study. We summarized all key recommendations and compared and visualized the inconsistencies among them, providing concise but informative overview for clinicians and researchers.

Our study also has limitations. Firstly, we only included documents published in English or Chinese, which could lead to a risk of neglecting essential documents from regions not using English or Chinese as the first language. We attempted to mitigate this risk by tailoring our search strategy to identify the English versions of guidance documents published from these regions. Secondly, unconscious bias from a subjective rating of documents was inevitable. We avoided inviting co-authors of guidance documents as a reviewer to prevent subconscious competing interest and conducted two rounds of group discussions to minimize subjective bias. Thirdly, the AGREE II instrument itself has weaknesses [31, 59, 67, 71], although it was the most commonly used tool to assess the quality of guidance documents. The AGREE

system assigned equal weight to all six domains, regardless of their relative importance [72]. Although the higher quality of development methodology and more transparency of reporting is associated with recommendations that are more reliable, proper methodology and transparency do not guarantee better patient outcomes. Hence, the quality scores assessed by the AGREE II should be interpreted with caution when used to indicate which guidelines to follow in clinical practice. Moreover, the subjective interpretation of scoring criteria impeded the replicability of AGREE II studies and direct comparison of quality scores in guidance documents provided by different reviews.

CONCLUSIONS

The methodological quality needs to be improved in the current guidelines on the diagnosis and management of hyperuricemia and gout, as assessed by the AGREE II. Inconsistent recommendations are common, even in some key aspects. Promoting standard methods for guidance documents development and synthesizing high-quality clinical evidence to fill in evidence gaps are warranted to improve the quality of guidance documents.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

HT and SL conceived this study. QL, JSWK, and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC, LL, and XS designed the appraisal strategy of each included guideline and consensus. QL and XL searched literature search and extracted data. QL, XL, JW, HL, and SL assessed the quality of each document. QL analysed and visualized the outcomes. SC, AS, YC, AZ, XS, and HH provided critical review. QL, XL, and SL drafted the manuscript. All authors discussed actively in the protocol of the study.

DATA AVAILABILITY

All data in this paper were obtained from published studies. No additional data

are available from the authors.

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TABLES AND FIGURES

Table 1. Characteristics of included guidelines and consensus statements

3e: Evidence, Expertise, Exchange; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; CS: consensus statement; CVD: cardiovascular diseases; ER: external review; EULAR: European League Against Rheumatism; LOE: level of evidence; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; Multi: multidisciplinary development group; NG: not given; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; Phy: physicians; Pt: patients; Rheu: rheumatologists; SLR: systematic literature review; SOR: strength of recommendation.

Document	Issuing organization	Year of publication	Country	Funding body	Target population	Target audience	Guideline development	Guideline review	Guideline update	Evidence base	LOE	SOR
Guidelines												
SAMA_2003 [51]	South African Medical Association	2003	South Africa	Pharmaceutical company	Gout	Phy	Multi	ER	Intermittent	NG	-	-
EULAR_2006 [18]	EULAR	2006	Europe	EULAR	Gout	NG	Rheu	NG	NG	SLR	+	+
MOH_MSR_AMM_2008 [49]	MOH, MSR, AMM	2008	Malaysia	Pharmaceutical company	Adults (>16y) with gout	Phy	Multi	ER	2012 or sooner	SLR	+	+
PRA_2008 [50]	Philippine Rheumatology Association	2008	Philippine	NG	Gout	Phy	NG	NG	Three or more years	SLR	+	+
UTAustin_2009 [52]	University of Texas at Austin	2009	US	University of Texas at Austin	Adults with gout	Phy	NG	ER	NG	SLR	+	+
EULAR_2011 [17]	EULAR	2011	Multination	Pharmaceutical company, ASCR	Gout	Phy	Multi	NG	NG	SLR	+	+

JSGNAM_2011 [48]	Japanese Society of Gout and Nucleic Acid Metabolism	2011	Japan	NG	Hyperuricemia or gout	NG	NG	ER	NG	SLR	+	+
ACR_2012 [14, 15]	ACR	2012	US	ACR, NIAMS, NIH	Gout	Phy	Multi	NG	Intermittent	SLR	+	-
SER_2013 [46]	Spanish Society of Rheumatology	2013	Spain	Pharmaceutical company	Gout	Phy	Multi	ER	Four years	SLR	+	+
SIR_2013 [45]	Italian Society of Rheumatology	2013	Italy	NG	Gout	Phy	Multi	NG	NG	SLR	+	+
FMOH_2014 [44]	Federal Ministry of Health (Nigeria)	2014	Nigeria	NG	Gout	Phy, Pts in Nigeria	Multi	NG	NG	NG	-	-
CRA_2016 [41]	Chinese Rheumatology Association	2016	China	NG	Gout in China	Phy	Multi	NG	NG	SLR	+	+
EULAR_2016 [16]	EULAR	2016	Europe	NG	Gout	Phy, Pts	Multi	ER	Intermittent	SLR	+	+
TRA_2016 [38]	Taiwan Rheumatology Association	2016	Taiwan, China	NG	Hyperuricemia or gout	Phy, Pts	Multi	NG	NG	NG	-	-
ACP_2017 [19, 20]	ACP	2017	US	ACP	Acute and recurrent gout	Phy	NG	ER	Five years	SLR	+	+
BSR_2017 [21]	The British Society for Rheumatology	2017	UK	No specific funding.	Gout in the UK	Phy	Multi	ER	Planned in 2020	SLR	+	+
Consensus statements												
CCCP_2012 [47]	Chinese College of Cardiovascular Physicians	2012	China	NG	Asymptomatic hyperuricemia with CVD	NG	NG	NG	NG	CS	-	-
3e_2013 [36]	3e Initiative	2013	Multination	Pharmaceutical company	Gout	NG	Rheu	NG	NG	SLR	+	+
CSE_2013 [37]	Chinese Society of Endocrinology	2013	China	NG	Hyperuricemia or gout	NG	NG	NG	NG	CS	-	-
3e_PT_2014 [40]	Portuguese 3e Initiative	2014	Portugal	NG	Gout in Portuguese	NG	Rheu	NG	NG	SLR	+	+
3e_AU_NZ_2015 [43]	Australian and New Zealand 3e Initiative	2015	Multination	NG	Gout	NG	Rheu	NG	NG	SLR	+	+

ACR_EULAR_2015 [42]	ACR/EULAR	2015	Multination	ACR, EULAR	Gout	NG	NG	ER	Intermittent	SLR	-	-
T2T_2016 [39]	NG	2016	Multination	Pharmaceutical company	Gout	NG	Rheu	ER	NG	SLR	+	+
CRA_multi_2017 [22]	Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases	2017	China	NG	Hyperuricemia	Phy	Multi	NG	NG	CS	-	-

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.

Figure 2. Standardized domain scores for each guidance document

3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia

3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

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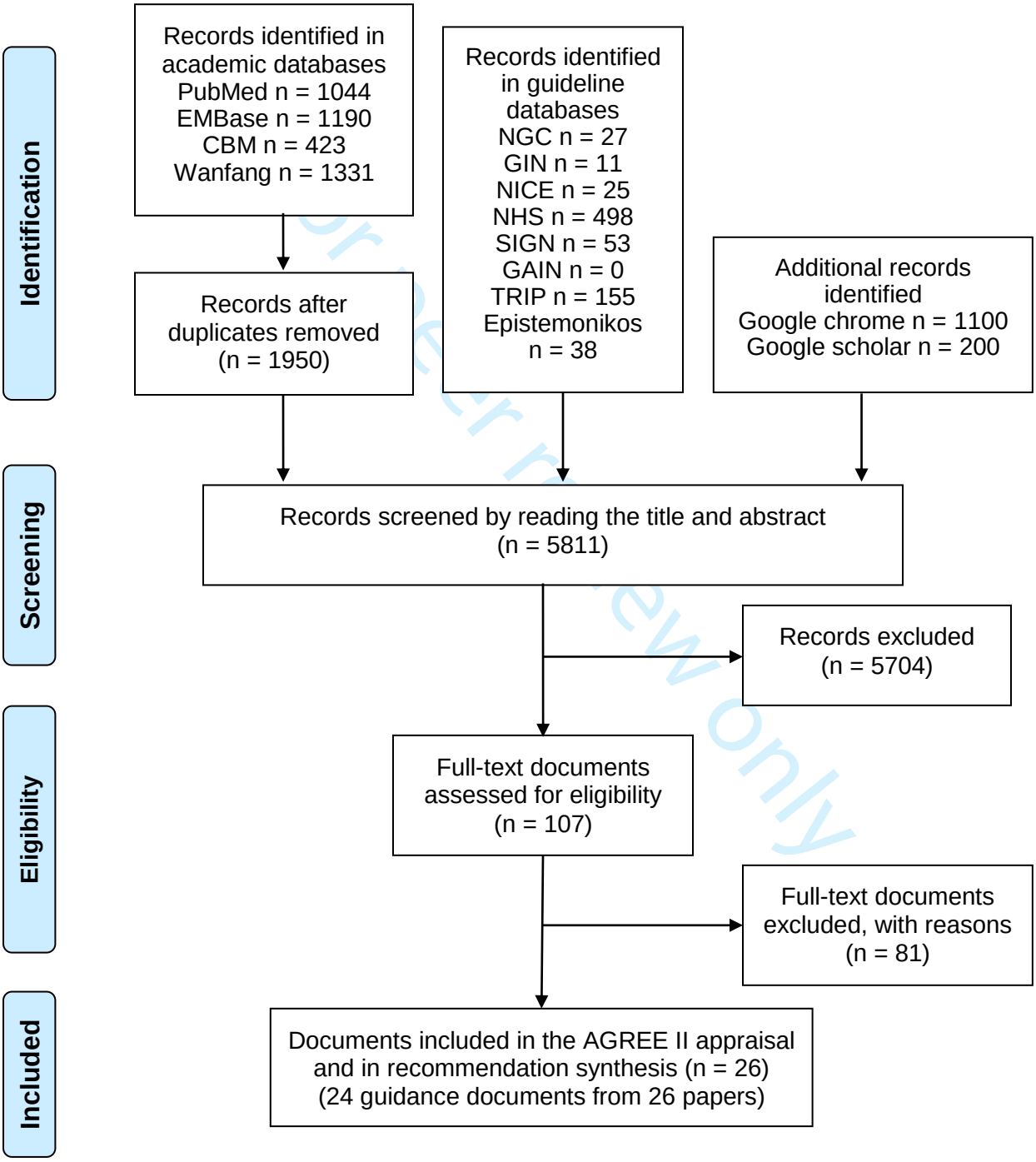


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

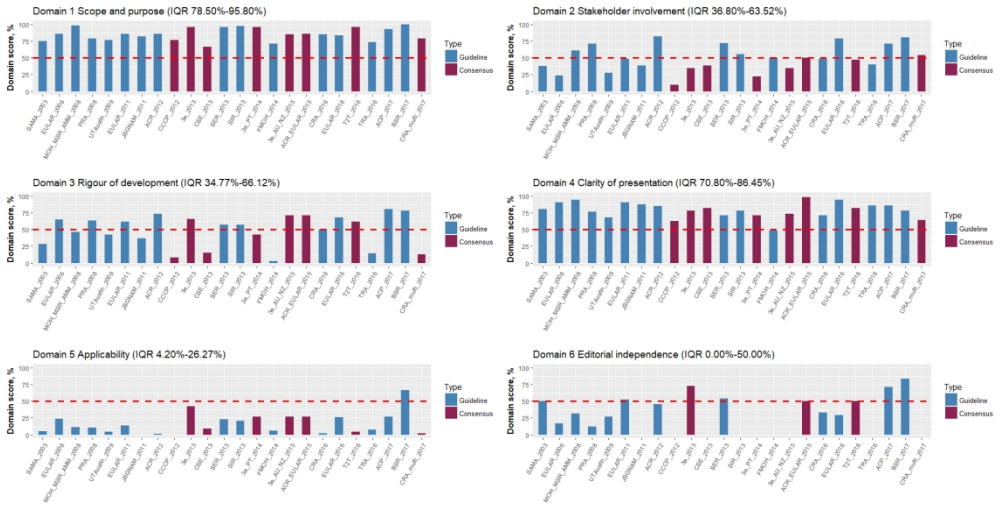


Figure 2. Standardized domain scores for each guidance document3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

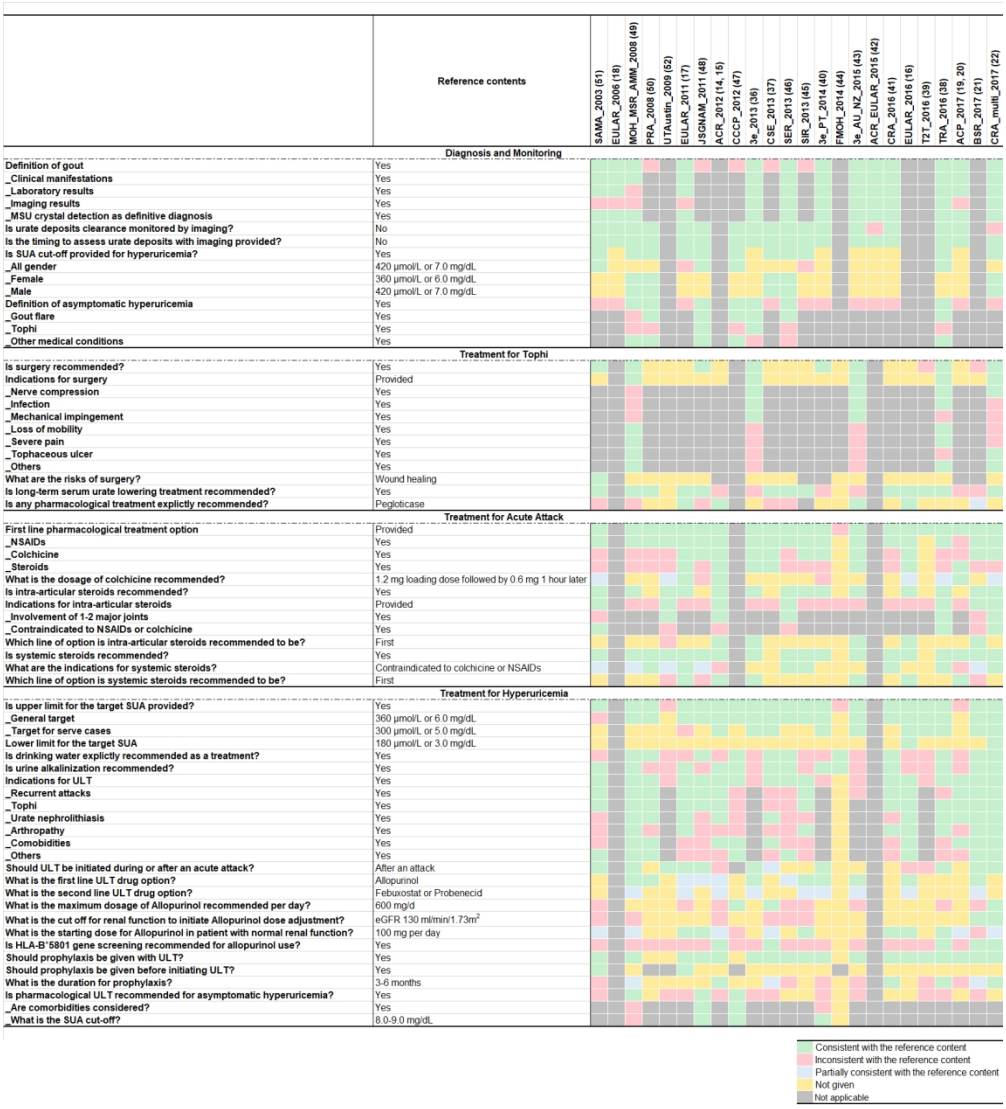


Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Supplementary Materials

Contents

Supplementary Table 1. Search strategy in PubMed

1	urate* OR uric acid OR gout OR hyperuricemia OR hyperuricaemia
2	guideline OR guideline* OR consensus OR policy OR polic* OR statement* OR recommendation*
3	1 AND 2

Supplementary Table 2. Search strategy in EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	gout.m_titl.
6	uric acid.m_titl.
7	urate$.m_titl.
8	hyperuric?emia.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.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

Supplementary Table 3. Searches in guideline databases

Databases	Date of search	Search strategy	Results found	Full text screened	Included documents	URL
National Guideline Clearinghouse	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	27	6	4	www.guideline.gov
Guidelines International Network	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, Search mode: Guidelines	11	5	5	www.g-i-n.net
National Institute for Health and Care Excellence	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	25	2	0	www.nice.org.uk
National Health Service	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter type: guidance and policy	498	5	3	www.evidence.nhs.uk
Scottish Intercollegiate Guidelines Network	2017/07/24	NA	53	0	0	www.sign.ac.uk/our-guidelines.html
Guidelines and Audit Implementation Network	2017/07/24	“hyperuricaemia” OR “hyperuricemia” OR “gout”	0	0	0	rqia.org.uk/search-result
Turning Research Into Practice Database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: all secondary evidence	155	9	3	www.tripdatabase.com
Epistemonikos database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: Broad syntheses OR Structured summaries	38	2	1	www.epistemonikos.org
Chinese Biomedical Literature Database	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	423	7	5	202.115.54.56/index.jsp
Wanfang Data	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	1331	19	4	www.wanfangdata.com.cn/

Abbreviations: NA: Not applicable.

Supplementary Table 4. Excluded studies and reasons for exclusion

First author	Year	Reason for exclusion
Wuthrich [68]	2016	Review
Ceriotti [69]	2016	Primary study
Liote [70]	2016	Editorial
de Lautour [71]	2016	Primary study
de Lautour [72]	2014	Conference abstract
Dalbeth [73]	2015	Review
Terslev [74]	2015	Primary study
Turk [75]	2016	Not providing specific recommendations for hyperuricemia or gout
Stewart Coats [76]	2016	Editorial
Sullivan [77]	2015	Review
Gutierrez [78]	2015	Primary study
Grainger [79]	2015	Primary study
Robinson [80]	2015	Review
Chaudhary [81]	2013	Review
Bakris [82]	2014	Multimedia section
Terkeltaub [83]	2013	Review
Lyseng-Williamson [84]	2013	Review
Deodhar [85]	2013	Review
Simao [86]	2012	Review
Stamp [87]	2011	Review
Jansen [88]	2010	Not produced by related professional associations, institutes, societies, or communities
Grainger [89]	2009	Review
Grainger [90]	2008	Review
Dalbeth [91]	2007	Review
Jordan [92]	2007	Replaced by updated versions from the same organization
Becker [93]	2007	Not providing specific recommendations for hyperuricemia or gout

Zhang [55]	2006	Replaced by updated versions from the same organization
Caramia [94]	2004	Review
Terkeltaub [95]	2003	Case report
Cleland [96]	1995	Review
Hande [97]	1984	Case series
Committee on the Review of Medicines [98]	1978	Not providing specific recommendations for hyperuricemia or gout
Mourgues [99]	2016	Conference abstract
Bakris [100]	1970	Not providing specific recommendations for hyperuricemia or gout
Pai [101]	2015	Review
Vargas-Santos [102]	2016	Review
Filiopoulos [103]	2016	Comment letter
Chinchilla [104]	2016	Review
Rimler [105]	2016	Review
Saito [106]	2016	Not providing specific recommendations for hyperuricemia or gout
Mody [107]	2015	Review
Richette [108]	2014	Conference abstract
Richette [109]	2014	Conference abstract
Gutierrez [110]	2014	Conference abstract
Furst [111]	2013	Not providing specific recommendations for hyperuricemia or gout
Hershfield [112]	2013	Not providing specific recommendations for hyperuricemia or gout
Andres [113]	2012	Conference abstract
Stevenson [114]	2011	Technology appraisal
Diaz-Borjon [115]	2009	Review
Furst [116]	2010	Not providing specific recommendations for hyperuricemia or gout
Taylor [117]	2009	Primary study
Taylor [118]	2008	Primary study
Bussieres [119]	2008	Not providing specific recommendations for hyperuricemia or gout
Brooks [120]	2007	Review

Bestermann [121]	2005	Not providing specific recommendations for hyperuricemia or gout
Schumacher Jr [122]	2004	Review
Bartlett [123]	2002	Not providing specific recommendations for hyperuricemia or gout
Furst [124]	2013	Not providing specific recommendations for hyperuricemia or gout
Newberry [125]	2017	Review
Shekelle [126]	2017	Review
Sandberg [127]	2015	Not providing specific recommendations for hyperuricemia or gout
Kallinich [128]	2007	Not providing specific recommendations for hyperuricemia or gout
Preminger [129]	2007	Not providing specific recommendations for hyperuricemia or gout
TA164 [130]	2008	Technology appraisal
Phoon [131]	2012	Not providing specific recommendations for hyperuricemia or gout
Li [132]	2011	Review
Zhang [133]	2013	Review
Deng [134]	2016	Primary study
Chinese Rheumatology Association [135]	2004	Replaced by updated versions from the same organization
Chinese College of Cardiovascular Physicians [136]	2010	Replaced by updated versions from the same organization
Chinese Rheumatology Association [137]	2011	Replaced by updated versions from the same organization
National Department of Health, Pretoria, South Africa [138]	2006	Not providing specific recommendations for hyperuricemia or gout
European Medicines Agency [139]	2012	Not providing specific recommendations for hyperuricemia or gout
Agency for Healthcare Research and Quality [140]	2017	Review
Agency for Healthcare Research and Quality [141]	2017	Review
National Institute for Health and Care Excellence [142]	2013	Technology appraisal
Agency for Healthcare Research and Quality [143]	2016	Review
National Health System, United Kingdom [144]	2013	Not providing specific recommendations for hyperuricemia or gout
Canadian Expert Drug Advisory Committee [145]	2011	Not providing specific recommendations for hyperuricemia or gout
CME Academic Detailing Service [146]	2013	Presented as a 'handout', not a clinical practice guideline.
Henderson [147]	2015	Not released by a professional association

Supplementary Table 5. Domain score for each included guidance document

Document	Domain 1, %	Domain 2, %	Domain 3, %	Domain 4, %	Domain 5, %	Domain 6, %
3e_2013 [36]	95.8	34.7	65.6	77.8	42.7	72.9
3e_AU_NZ_2015 [43]	84.7	34.7	71.4	73.6	27.1	0.0
3e_PT_2014 [40]	95.8	22.2	42.7	70.8	27.1	0.0
ACP_2017 [19, 20]	93.1	70.8	80.2	86.1	27.1	70.8
ACR_2012 [14, 15]	86.1	81.9	73.4	84.7	1.0	45.8
ACR_EULAR_2015 [42]	86.1	50.0	71.4	98.6	27.1	50.0
BSR_2017 [21]	100.0	80.6	78.1	77.8	66.7	83.3
CCCP_2012 [47]	76.4	9.7	8.3	62.5	0.0	0.0
CRA_2016 [41]	84.7	48.6	50.5	70.8	2.1	33.3
CRA_multi_2017 [22]	79.2	54.2	13.0	63.9	2.1	0.0
CSE_2013 [37]	66.7	38.9	15.6	81.9	9.4	0.0
EULAR_2006 [18]	86.1	23.6	65.1	90.3	24.0	16.7
EULAR_2011 [17]	86.1	48.6	61.5	90.3	13.5	52.1
EULAR_2016 [16]	83.3	79.2	67.7	94.4	26.0	29.2
FMOH_2014 [44]	70.8	50.0	3.1	48.6	6.3	0.0
JSGNAM_2011 [48]	81.9	38.9	37.0	87.5	0.0	0.0
MOH_MSR_AMM_2008 [49]	98.6	61.1	46.4	94.4	11.5	31.3
PRA_2008 [50]	79.2	70.8	63.5	76.4	10.4	12.5
SAMA_2003 [51]	75.0	37.5	28.1	80.6	5.2	50.0
SER_2013 [46]	95.8	72.2	56.8	70.8	22.9	54.2
SIR_2013 [45]	97.2	55.6	56.8	77.8	20.8	0.0
T2T_2016 [39]	95.8	47.2	61.5	81.9	4.2	50.0
TRA_2016 [38]	73.6	40.3	14.1	86.1	7.3	0.0
UTAustin_2009 [52]	76.4	27.8	42.2	68.1	4.2	27.1
Median	85.4	48.6	56.8	79.2	10.9	28.1
Minimum	66.7	9.7	3.1	48.6	0.0	0.0
Maximum	100.0	81.9	80.2	98.6	66.7	83.3

Supplementary Table 6. Mean scores across reviewers for the individual AGREE II domain items

Document	Domain 1			Domain 2			Domain 3								Domain 4			Domain 5				Domain 6	
Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3e_2013 [36]	6.8	6.5	7.0	7.0	1.3	1.0	6.3	3.8	6.3	5.8	5.8	6.8	4.0	1.0	6.0	7.0	4.0	6.8	1.0	5.3	1.3	7.0	3.8
3e_AU_NZ_2015 [43]	6.0	5.5	6.8	5.8	1.0	2.5	6.5	6.8	7.0	6.5	6.5	6.8	1.3	1.0	5.8	6.0	4.5	5.8	1.0	2.8	1.0	1.0	1.0
3e_PT_2014 [40]	6.5	7.0	6.8	4.8	1.3	1.0	2.8	2.3	5.5	3.5	5.5	6.8	1.3	1.0	5.5	6.3	4.0	4.5	1.3	2.8	2.0	1.0	1.0
ACP_2017 [19, 20]	6.0	6.8	7.0	6.3	5.3	4.3	6.8	6.8	6.5	5.0	6.5	5.3	4.8	5.0	5.3	6.8	6.5	2.5	1.8	5.3	1.0	4.0	6.5
ACR_2012 [14, 15]	6.5	5.5	6.5	7.0	5.3	5.5	7.0	7.0	6.8	6.0	5.8	6.0	1.5	3.3	5.8	7.0	5.5	1.0	1.0	1.0	1.3	3.3	4.3
ACR_EULAR_2015 [42]	6.5	5.0	7.0	5.3	4.8	2.0	7.0	6.8	5.3	6.0	7.0	5.5	1.8	3.0	6.8	7.0	7.0	3.8	4.0	1.8	1.0	3.8	4.3
BSR_2017 [21]	7.0	7.0	7.0	5.5	5.3	6.8	7.0	6.0	6.5	6.8	6.3	6.0	5.0	2.0	6.8	6.8	3.5	4.8	4.8	6.5	4.0	7.0	5.0
CCCP_2012 [47]	6.8	3.0	7.0	2.0	1.0	1.8	1.0	1.0	1.0	1.0	3.8	2.0	1.3	1.0	4.5	5.8	4.0	1.0	1.0	1.0	1.0	1.0	1.0
CRA_2016 [41]	6.3	5.0	7.0	5.5	1.0	5.3	5.0	3.3	6.3	3.5	6.0	5.5	1.8	1.0	5.3	6.5	4.0	1.3	1.0	1.3	1.0	1.0	5.0
CRA_multi_2017 [22]	7.0	3.5	6.8	4.8	1.3	6.8	1.0	1.0	1.0	1.3	5.0	2.8	1.3	1.0	5.0	6.5	3.0	1.0	1.3	1.0	1.3	1.0	1.0
CSE_2013 [37]	7.0	1.8	6.3	3.0	1.0	6.0	1.0	1.0	2.0	1.0	5.0	3.5	1.0	1.0	5.5	5.5	6.8	3.0	1.0	1.0	1.3	1.0	1.0
EULAR_2006 [18]	6.0	5.5	7.0	5.0	1.0	1.3	7.0	7.0	5.8	4.3	6.0	5.8	1.3	2.3	6.0	6.8	6.5	1.0	2.5	5.3	1.0	3.0	1.0
EULAR_2011 [17]	6.5	5.0	7.0	5.0	1.0	5.8	4.0	4.5	6.8	6.0	7.0	7.0	1.3	1.0	5.8	6.8	6.8	1.3	1.3	3.8	1.0	3.8	4.5
EULAR_2016 [16]	6.3	4.8	7.0	5.8	5.0	6.5	5.0	2.0	6.3	6.8	6.0	6.5	6.0	2.0	6.5	6.8	6.8	3.0	1.3	5.0	1.0	1.5	4.0
FMOH_2014 [44]	6.5	2.8	6.5	5.3	1.0	5.8	1.0	1.0	1.0	1.0	2.0	1.5	1.0	1.0	3.0	4.5	4.3	1.0	1.3	2.3	1.0	1.0	1.0
JSGNAM_2011 [48]	5.3	5.5	7.0	1.8	4.3	4.0	1.3	1.0	6.8	3.3	6.3	3.8	2.5	1.0	6.8	6.3	5.8	1.0	1.0	1.0	1.0	1.0	1.0
MOH_MSR_AMM_2008 [49]	6.8	7.0	7.0	5.5	1.5	7.0	4.3	1.0	5.8	1.5	5.8	4.8	2.5	4.8	6.5	6.8	6.8	1.8	3.0	1.0	1.0	4.0	1.8
PRA_2008 [50]	6.5	5.5	5.3	3.8	5.0	7.0	5.0	4.3	7.0	4.8	6.5	4.8	1.3	5.0	5.3	6.5	5.0	1.8	1.3	2.5	1.0	1.0	2.5
SAMA_2003 [51]	6.5	3.0	7.0	4.0	1.3	4.5	1.0	1.0	1.0	4.0	6.5	2.8	2.5	2.8	5.0	6.5	6.0	1.0	2.0	1.3	1.0	7.0	1.0
SER_2013 [46]	7.0	6.3	7.0	6.8	5.0	4.3	3.3	1.0	7.0	4.0	6.8	4.8	2.0	6.5	5.8	6.8	4.3	3.5	2.3	2.8	1.0	6.5	2.0
SIR_2013 [45]	6.8	6.8	7.0	6.3	1.0	5.8	4.0	6.8	6.3	4.3	6.3	5.5	1.3	1.0	6.3	6.8	4.0	2.5	1.0	4.5	1.0	1.0	1.0
T2T_2016 [39]	6.3	7.0	7.0	5.3	5.0	1.3	7.0	6.5	6.5	6.5	3.3	4.0	1.8	2.0	5.0	6.3	6.5	2.0	1.0	1.0	1.0	3.5	4.5
TRA_2016 [38]	5.8	3.5	7.0	5.0	1.5	3.8	1.0	1.3	1.0	1.3	5.5	2.5	1.3	1.0	5.5	6.5	6.5	1.0	1.5	2.3	1.0	1.0	1.0
UTAustin_2009 [52]	7.0	2.8	7.0	3.0	1.0	4.0	4.3	2.0	7.0	2.5	4.3	5.3	2.0	1.0	4.8	5.3	5.3	1.3	1.5	1.3	1.0	4.0	1.3

Supplementary Table 7. Scores for each individual AGREE II domain items by each reviewer

	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14	Item15	Item16	Item17	Item18	Item19	Item20	Item21	Item22	Item23
3e_2013 [36]																							
Rev1	7	7	7	7	1	1	6	4	4	5	7	7	2	1	6	7	4	7	1	5	1	7	4
Rev2	6	7	7	7	1	1	6	2	7	5	6	7	4	1	6	7	4	7	1	6	1	7	4
Rev3	7	5	7	7	2	1	7	5	7	6	5	6	5	1	5	7	4	7	1	5	2	7	3
Rev4	7	7	7	7	1	1	6	4	7	7	5	7	5	1	7	7	4	6	1	5	1	7	4
3e_AU_NZ_2015 [43]																							
Rev1	5	5	7	7	1	2	7	7	7	7	7	7	2	1	5	6	4	6	1	2	1	1	1
Rev2	7	5	7	7	1	1	5	7	7	6	6	7	1	1	6	7	4	6	1	4	1	1	1
Rev3	5	7	7	4	1	4	7	7	7	7	7	7	1	1	6	5	6	6	1	2	1	1	1
Rev4	7	5	6	5	1	3	7	6	7	6	6	6	1	1	6	6	4	5	1	3	1	1	1
3e_PT_2014 [40]																							
Rev1	6	7	7	5	1	1	3	1	7	3	6	7	2	1	5	6	4	4	1	5	1	1	1
Rev2	6	7	7	5	1	1	3	1	7	3	6	7	1	1	6	7	4	6	1	3	1	1	1
Rev3	7	7	6	5	2	1	2	1	6	5	4	6	1	1	5	6	4	4	2	2	5	1	1
Rev4	7	7	7	4	1	1	3	6	2	3	6	7	1	1	6	6	4	4	1	1	1	1	1
ACP_2017 [19, 20]																							
Rev1	6	7	7	6	5	4	7	7	7	5	7	5	5	5	5	7	7	2	2	4	1	4	7
Rev2	6	7	7	6	5	4	7	7	7	5	7	5	5	4	6	7	7	4	3	7	1	4	7
Rev3	6	7	7	6	6	3	6	6	6	6	6	5	4	5	5	6	6	2	1	5	1	4	6
Rev4	6	6	7	7	5	6	7	7	6	4	6	6	5	6	5	7	6	2	1	5	1	4	6
ACR_2012 [14, 15]																							
Rev1	6	5	7	7	5	7	7	7	6	6	6	5	2	3	5	7	4	1	1	1	1	3	4
Rev2	6	7	7	7	7	4	7	7	7	6	6	5	2	3	6	7	7	1	1	1	1	4	4
Rev3	7	5	7	7	5	7	7	7	7	6	5	7	1	3	5	7	7	1	1	1	2	3	4
Rev4	7	5	5	7	4	4	7	7	7	6	6	7	1	4	7	7	4	1	1	1	1	3	5
ACR_EULAR_2015 [42]																							
Rev1	6	5	7	6	6	2	7	7	7	7	7	5	2	3	7	7	7	3	3	1	1	4	4

Rev2	6	5	7	5	6	1	7	7	6	6	7	5	2	3	7	7	7	5	7	1	1	4	4
Rev3	7	5	7	5	6	2	7	7	7	6	7	5	2	3	7	7	7	3	3	1	1	3	4
Rev4	7	5	7	5	1	3	7	6	1	5	7	7	1	3	6	7	7	4	3	4	1	4	5
BSR_2017 [21]																							
Rev1	7	7	7	6	5	7	7	6	6	7	6	6	5	2	7	7	4	5	4	7	2	7	5
Rev2	7	7	7	6	5	7	7	6	6	6	7	5	5	2	7	7	3	5	5	7	5	7	5
Rev3	7	7	7	4	5	6	7	7	7	7	5	6	5	1	6	6	3	4	5	6	2	7	5
Rev4	7	7	7	6	6	7	7	5	7	7	7	7	5	3	7	7	4	5	5	6	2	7	5
CCCP_2012 [47]																							
Rev1	6	3	7	2	1	2	1	1	1	1	3	1	2	1	3	6	4	1	1	1	1	1	1
Rev2	7	3	7	2	1	1	1	1	1	1	4	3	1	1	4	5	4	1	1	1	1	1	1
Rev3	7	3	7	2	1	1	1	1	1	1	4	2	1	1	6	6	4	1	1	1	1	1	1
Rev4	7	3	7	2	1	3	1	1	1	1	4	2	1	1	5	6	4	1	1	1	1	1	1
CRA_2016 [41]																							
Rev1	5	5	7	6	1	4	5	3	7	3	7	5	2	1	5	7	4	1	1	1	1	1	4
Rev2	7	5	7	6	1	5	4	3	6	4	6	5	3	1	6	7	4	1	1	1	1	1	4
Rev3	7	5	7	5	1	6	5	3	6	1	5	6	1	1	5	6	4	1	1	2	1	1	6
Rev4	6	5	7	5	1	6	6	4	6	6	6	6	1	1	5	6	4	2	1	1	1	1	6
CRA_multi_2017 [22]																							
Rev1	7	3	7	5	1	7	1	1	1	1	5	3	2	1	5	7	2	1	1	1	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	2	5	2	1	1	5	7	3	1	1	1	1	1	1
Rev3	7	3	7	4	2	6	1	1	1	1	5	5	1	1	5	5	3	1	1	1	2	1	1
Rev4	7	5	6	5	1	7	1	1	1	1	5	1	1	1	5	7	4	1	2	1	1	1	1
CSE_2013 [37]																							
Rev1	7	1	6	3	1	6	1	1	2	1	5	5	1	1	5	6	7	3	1	1	1	1	1
Rev2	7	3	6	4	1	6	1	1	3	1	5	3	1	1	6	6	7	3	1	1	1	1	1
Rev3	7	1	7	2	1	7	1	1	2	1	5	3	1	1	6	6	6	3	1	1	2	1	1
Rev4	7	2	6	3	1	5	1	1	1	1	5	3	1	1	5	4	7	3	1	1	1	1	1
EULAR_2006 [18]																							
Rev1	5	5	7	5	1	1	7	7	5	3	6	5	2	1	5	7	7	1	2	5	1	4	1

Rev2	6	5	7	5	1	1	7	7	6	5	6	6	1	1	6	7	6	1	4	6	1	4	1
Rev3	7	7	7	5	1	1	7	7	6	5	7	6	1	1	7	7	7	1	1	5	1	1	1
Rev4	6	5	7	5	1	2	7	7	6	4	5	6	1	6	6	6	6	1	3	5	1	3	1
EULAR_2011 [17]																							
Rev1	6	5	7	4	1	7	4	1	7	7	7	7	2	1	5	7	7	2	1	2	1	4	4
Rev2	6	5	7	5	1	3	4	7	7	4	7	7	1	1	6	7	7	1	1	5	1	4	4
Rev3	7	5	7	6	1	7	4	4	7	7	7	7	1	1	6	7	7	1	1	4	1	4	6
Rev4	7	5	7	5	1	6	4	6	6	6	7	7	1	1	6	6	6	1	2	4	1	3	4
EULAR_2016 [16]																							
Rev1	7	7	7	6	5	7	5	2	7	7	7	7	6	1	7	7	7	2	2	5	1	1	4
Rev2	7	1	7	6	5	7	5	2	7	7	6	7	6	3	7	7	7	4	1	6	1	1	4
Rev3	5	5	7	5	5	5	5	1	6	6	5	6	6	2	5	6	6	4	1	4	1	1	4
Rev4	6	6	7	6	5	7	5	3	5	7	6	6	6	2	7	7	7	2	1	5	1	3	4
FMOH_2014 [44]																							
Rev1	7	3	7	6	1	4	1	1	1	1	2	1	1	1	3	1	4	1	1	2	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	1	2	1	1	1	4	4	4	1	2	3	1	1	1
Rev3	6	2	5	5	1	6	1	1	1	1	1	2	1	1	2	7	6	1	1	1	1	1	1
Rev4	6	3	7	5	1	6	1	1	1	1	3	2	1	1	3	6	3	1	1	3	1	1	1
JSGNAM_2011 [48]																							
Rev1	5	5	7	2	4	4	1	1	6	3	6	3	2	1	7	7	4	1	1	1	1	1	1
Rev2	6	5	7	2	4	4	1	1	7	4	6	4	3	1	7	6	7	1	1	1	1	1	1
Rev3	5	7	7	1	4	4	1	1	7	1	7	4	2	1	7	6	7	1	1	1	1	1	1
Rev4	5	5	7	2	5	4	2	1	7	5	6	4	3	1	6	6	5	1	1	1	1	1	1
MOH_MSR_AMM_2008 [49]																							
Rev1	6	7	7	5	1	7	4	1	5	1	6	5	2	4	7	7	7	2	3	1	1	4	1
Rev2	7	7	7	5	3	7	4	1	6	2	6	4	3	5	6	7	7	3	5	1	1	4	2
Rev3	7	7	7	7	1	7	4	1	6	1	6	5	2	5	7	7	7	1	1	1	1	4	2
Rev4	7	7	7	5	1	7	5	1	6	2	5	5	3	5	6	6	6	1	3	1	1	4	2
PRA_2008 [50]																							
Rev1	5	3	5	4	5	7	5	1	7	4	7	5	1	5	5	7	4	2	1	2	1	1	2

Rev2	7	7	4	3	5	7	5	6	7	4	6	4	2	5	5	6	7	3	2	3	1	1	4
Rev3	7	7	7	4	5	7	5	5	7	6	7	5	1	5	6	7	5	1	1	2	1	1	2
Rev4	7	5	5	4	5	7	5	5	7	5	6	5	1	5	5	6	4	1	1	3	1	1	2
SAMA_2003 [51]																							
Rev1	6	3	7	5	1	4	1	1	1	5	7	3	2	3	3	6	7	1	1	2	1	7	1
Rev2	7	3	7	4	1	5	1	1	1	5	7	2	4	2	5	7	4	1	5	1	1	7	1
Rev3	7	3	7	2	1	5	1	1	1	1	7	3	1	1	6	7	7	1	1	1	1	7	1
Rev4	6	3	7	5	2	4	1	1	1	5	5	3	3	5	6	6	6	1	1	1	1	7	1
SER_2013 [46]																							
Rev1	7	6	7	7	5	4	3	1	7	3	7	5	2	5	5	6	4	2	2	2	1	7	2
Rev2	7	6	7	6	5	3	3	1	7	5	6	4	2	7	6	7	4	4	5	3	1	5	2
Rev3	7	7	7	7	5	5	3	1	7	3	7	6	2	7	7	7	4	4	1	4	1	7	2
Rev4	7	6	7	7	5	5	4	1	7	5	7	4	2	7	5	7	5	4	1	2	1	7	2
SIR_2013 [45]																							
Rev1	7	7	7	6	1	7	4	7	5	3	7	5	2	1	7	7	4	2	1	4	1	1	1
Rev2	7	7	7	6	1	4	4	7	7	5	6	5	1	1	6	7	4	4	1	6	1	1	1
Rev3	7	7	7	6	1	6	4	7	7	6	7	6	1	1	6	7	4	1	1	4	1	1	1
Rev4	6	6	7	7	1	6	4	6	6	3	5	6	1	1	6	6	4	3	1	4	1	1	1
T2T_2016 [39]																							
Rev1	6	7	7	5	5	1	7	7	7	7	3	3	2	1	4	6	7	3	1	1	1	4	2
Rev2	7	7	7	6	5	1	7	7	7	7	4	5	2	5	6	7	7	1	1	1	1	4	4
Rev3	5	7	7	5	5	2	7	6	6	6	2	3	2	1	5	6	6	3	1	1	1	3	6
Rev4	7	7	7	5	5	1	7	6	6	6	4	5	1	1	5	6	6	1	1	1	1	3	6
TRA_2016 [38]																							
Rev1	5	3	7	5	1	4	1	1	1	1	6	2	2	1	6	7	7	1	1	2	1	1	1
Rev2	6	3	7	5	1	7	1	1	1	2	6	2	1	1	6	7	7	1	3	3	1	1	1
Rev3	6	3	7	5	3	1	1	2	1	1	5	4	1	1	5	6	6	1	1	2	1	1	1
Rev4	6	5	7	5	1	3	1	1	1	1	5	2	1	1	5	6	6	1	1	2	1	1	1
UTAustin_2009 [52]																							
Rev1	7	3	7	4	1	4	4	1	7	3	4	5	2	1	3	4	4	1	1	1	1	4	2

Rev2	7	3	7	2	1	4	4	1	7	2	4	5	2	1	5	6	7	2	3	1	1	4	1
Rev3	7	2	7	2	1	4	4	1	7	1	6	5	2	1	6	6	7	1	1	1	1	4	1
Rev4	7	3	7	4	1	4	5	5	7	4	3	6	2	1	5	5	3	1	1	2	1	4	1

Supplementary Table 8. Summary of recommendations for the diagnosis of gout and hyperuricemia by included guidance document

IE: insufficient evidence; MSU: monosodium urate; NA: not applicable; NG: not given; SUA: serum uric acid.

	SAMA_2003 [51]	EULAR_2006 [18]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	EULAR_2011 [17]	JSGNAM_2011 [48]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	3e_AU_NZ_2015 [43]	ACR_EULAR_2015 [42]	CRA_2016 [41]	TRA_2016 [38]	ACP_2017 [19, 20]	CRA_multi_2017 [22]
Diagnosis of gout	+	+	+	NG	+	NG	NG	+	NG	+	NG	+	+	+	+	+	+	+
_Clinical manifestations	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Laboratory results	+	+	-	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Imaging results	-	+*	-	NA	-	NA	NA	+	NA	+	NA	+	+	+	+	+	IE	+
_MSU crystal as definitive diagnosis	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
Monitor urate deposits clearance by imaging	-	-	-	-	-	-	-	-	-	IE	-	-	-	+	-	-	-	+
Is the timing to assess urate deposits with imaging techniques provided?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUA for hyperuricemia, µmol/L [mg/dL]	+	NG	+	+	+	+	+	NG	+	+	+	NG	NG	NG	NG	+	NG	+
_All gender	420	NG	NG	NG	[6.8]	[7.0]	420 [7.0]	NG	NG	NG	404 [6.8]	NG	NG	NG	NG	[7.0]	NG	NG
_Female	NG	NG	360 [6.0]	357 [6.0]	NG	NG	NG	NG	360	[6.0]	NG	NG	NG	NG	NG	NG	NG	360
_Male	NG	NG	420 [7.0]	416 [7.0]	NG	NG	NG	NG	420	[7.0]	NG	NG	NG	NG	NG	NG	NG	420
Diagnosis of asymptomatic hyperuricemia	NG	NG	+	+	NG	+	+	+.	NG	+	NG	NG	NG	NG	NG	+	NG	NG
_Gout flare	NA	NA	-	+	NA	+	+	+	NA	+	NA	NA	NA	NA	NA	+	NA	NA
_Tophi	NA	NA	-	-	NA	+	-	+	NA	-	NA	NA	NA	NA	NA	-	NA	NA
_Additional medical conditions†	NA	NA	+	+	NA	+	+	-	NA	-	NA	NA	NA	NA	NA	+	NA	NA

*Imaging results are considered for chronic gout, but not for early/acute gout.

†Additional medical conditions considered in the definition of asymptomatic hyperuricemia included complications of gout [47], renal disorder [48], signs or symptoms of

urate deposition [49], and uric acid nephrolithiasis [50]. One document provided a general statement of any clinical presentations [38]. One document explicitly stated that the inclusion of patients with pre-existing renal or cardiovascular disease was allowed [36].

Supplementary Table 9. Summary of recommendations for the treatment of hyperuricemia by included guidance documents

A: allopurinol; Aft: (to initiate ULT) after an acute attack; B: benzbromarone; CCr: creatinine clearance rate; Cr: serum creatinine; CKD: chronic kidney disease; D: (to initiate ULT) during an acute attack; eGFR: estimated glomerular filtration rate; F: febuxostat; IE: insufficient evidence; m: month(s); NA: not applicable; NG: not given; P: probenecid; RF: renal function; SUA: serum uric acid; U: uricosurics without specification; ULT: urate lowering therapy; w: week(s); y: year.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Upper limit for target SUA, μmol/L [mg/dL]																						
_General target*	300	360 [6.0]	[6.0]	NG	[6.0]	[6.0]	[6.0]	357 [6.0]	360 [6.0]	360	[6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]	360 [6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]
_Target for serve cases†	NG	NG	NG	NG	[4.0]	NG	[5.0]	NG	300	300	NG	NG	300 [5.0]	NG	300	NG	300 [5.0]	300 [5.0]	300 [5.0]	NG	300	300 [5.0]
Lower limit for target SUA, μmol/L [mg/dL]	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	[3.0]	NG	NG	NG	NG	180
Drinking water	-	+	+	-	-	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+
Urine alkalinisation	+	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	+	+
Indications for ULT	+	+	+	-	+	+	+	+	-	+	+	+	-	NG	-	+	+	-	+	+	+	+
_Recurrent attacks	+, >2	+, >3/y	+	NA	+, >1/y	+	+, ≥2/y	-	NA	-	-	+	NA	NG	-	+, >2/y	+, ≥2/y	NA	-	+, ≥2/y	+, ≥2/y	+
_Tophi	+	+	+	NA	+	+	+	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	+	+	+
_Urate nephrolithiasis	-	+	+	NA	+	-	+	-	NA	+	-	-	NA	NG	NA	-	+	NA	+	+	+	+
_Arthropathy	-	+	-	NA	+	-	-	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	-	+	+
_Comorbidities‡	-	+	+	NA	-	-	+	+	NA	+	-	-	NA	NG	NA	-	+	NA	-	+	+	+
_Others§	+	+	+	NA	-	-	-	+	NA	-	+	-	NA	NG	NA	-	+	NA	-	-	+	+
Initiate ULT during or after an acute attack (Aft[time after attack])	Aft	Aft	NG	Aft (4-6 w)	Aft	Aft (2w)	D	NA	Aft	D/ Aft (2w)	NG	NG	Aft	NG	NG	NG	IE	IE	Aft	NG	Aft	Aft
First line ULT drug(s)	NG	A	A	NG	A, F	A, B	A, F	NG	A	NG	A, F,	A	A	NG	A	NG	A	NG	NG	NG	A	NG

											B										
Second line ULT drug(s)	NG	P	NG	NG	P	NG	P	NG	U, F	NG	NG	F, P, B	F, B, P, U	NG	P, B, F	NG	F, U	NG	NG	NG	F	NG
Allopurinol use																						
_Maximum dose (mg/d)	300	NG	NG	NG	800	NG	800	600	NG	600	800-900	800	NG	NG	900	NG	NG	NG	800	NG	900	600
_RF to initiate dose adjustment (eGFR in ml/min/1.73m^2, CCr in mL/min)	CCr 60	CCr 80	NG	NG	NG	NG	CK D4	NG	NG	CCr 60	CCr 140	CCr 20	NG	NG	NG	NG	NG	NG	NG	NG	eGFR 130	1.5mg/ eGFR‖
_Starting dose in normal RF (mg/d)	50-100	100-150	NG	NG	100	50	≤100	50	NG	100-150	NG	100	NG	NG	NG	100	100	NG	100	50-100	200	50-100
_HLA-B*5801 gene screening	-	-	-	-	-	-	+	-	-	+	-	-	-	NG	-	-	-	-	+	-	+	+
Prophylaxis before ULT	+	NG	NG	NG	+	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Prophylaxis with ULT	+	+	NG	NG	+	+	+	NG	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Duration for prophylaxis	1-3 m¶	1-6 m**	NG	NG	NG	NG	3-6 m††	NG	Un-clear	6m	>6m	NG	>6m	NG	Vari-ed‡‡	3-6 m	NG	>6m	3-6 m	>8w	<6m	3-6m
Pharmacological ULT for asymptomatic hyperuricemia?	-	+	NG	-	-	+	IE	+	IE	IE	NG	NG	-§§	NG	IE	NG	NG	IE	-	NG	-	NG
_Comorbidities	NA	-	NA	NA	NA	+	NA	+	NA	NA	NA	NA	-	NG	NA	NA	NA	NA	NA	NA	NA	NA
_SUA cut-offs, µmol/L [mg/dL]	NA	[10-13]‖‖	NA	NA	NA	[8.0-9.0] ¶¶	NA	[8.0-9.0] ***	NA	NA	NA	NA	[9.0]	NG	NA	NA	NA	NA	NA	NA	NA	NA

* The general target was the target serum uric acid level for long term control recommended for all patients on pharmacological urate lowering therapy.

† The intensive target the intensive target was the target serum uric acid level for long term control recommended for patients with tophi [16, 17, 22, 36, 38, 40, 43], with recurrent attacks [16, 21, 22], or with chronic gouty arthritis [16, 22], or to prevent crystal formation [21], or to improve gout signs and symptoms [14, 15]. One document provided stricter target for any patient with gout [37], and one for patients with severe gout without clear definition [39].

‡ Comorbidities considered as the indication for ULT include renal impairment [14-16, 19-22, 37, 49, 50], cardiovascular risk or cardiovascular diseases [16, 22, 47], glucose intolerance or DM, lipid disorder, and obesity [22].

§ Others indications considered for pharmacological ULT include joint damage [21], diuretic therapy use [21], young age [16, 21, 22] with some documents defined as less than 40 years old [16, 22], high SUA level defined as >8mg/dL (480 umol/L) [16] or >13mg/dl [50], impending cytotoxic chemotherapy or radiotherapy for lymphoma or

leukaemia [49], persistently raised uric acid levels and willingness to continue lifelong therapy [51]. Some documents evaluated SUA levels in patients after lifestyle modification and indicated pharmacological ULT in individuals with SUA above 6 mg/dL [46], or with SUA above 8mg/dl with CV risk or CVD and above 9mg/dl without CV risk or CVD [47].

|| The starting dose of allopurinol in patients with renal impairment should not exceed 1.5mg/eGFR.

¶ Prophylaxis should be continued until the serum urate is normal and the patient has not had any attacks for 1-3 months.

** Prophylaxis should be continued until 6 months free of acute attacks or until 1 month with target serum urate level achieved.

†† Prophylaxis should be continued for 1) 6 months' duration, 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination, or 3) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination.

‡‡ The during for prophylaxis varied and depends on the presence of tophi and comorbidities and on serum urate response. But prophylaxis should be continued until the target SUA is reached or until the tophi has resolved.

§§ The recommendations provided were conflict within the same document.

|||| Pharmacological urate lowering therapy is recommended in male patients with serum uric acid >13 mg/dL and in female patients with serum uric acid >10 mg/dL.

¶¶ Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with complications or >9 mg/dL in all patients.

*** Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with cardiovascular disease or cardiovascular risk factors or >9 mg/dL if without cardiovascular disease or cardiovascular risk factors.

Supplementary Table 10. Summary of recommendations for the treatment of acute gout by included guidance documents

NG: not given; NSAIDs: non-steroidal anti-inflammatory drugs.

	What is the first line pharmacological treatment option?	Is colchicine recommended to be given as a fixed dose or as a loading dose + followed doses?	Is intra-articular steroids recommended?	What are the indications for intra-articular steroids?	Which line is intra-articular steroids recommended to be?	Is systemic steroids recommended?	What are the indications for systemic steroids?	Which line of option is systemic steroids recommended to be?
SAMA_2003 [51]	NSAIDs	Loading dose + followed doses	Yes	Contraindicated to NSAIDs and joint accessible	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	NG
MOH_MSR_AMM_2008 [49]	NSAIDs	NG	Yes	NG	NG	Yes	Elderly people, renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease, and hypersensitivity to NSAIDs	NG
PRA_2008 [50]	NSAIDs	NG	NG	NG	NG	Yes	Contraindicated to NSAIDs	NG
UTAustin_2009 [52]	NSAIDs	Loading dose + followed doses	Yes	Only 1-2 joints is involved	Third	Yes	Contraindicated or not responding to NSAIDs and colchicine and polyarthritis	Third
EULAR_2011 [17]	Colchicine, NSAIDs, glucocorticoids	Loading dose + followed doses	Yes	NG	NG	Yes	Contraindications to NSAIDs and colchicine	First
JSGNAM_2011 [48]	Colchicine, NSAIDs	Fixed	NG	NG	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	Second
ACR_2012 [14, 15]	NSAIDs, corticosteroids, colchicine	Loading dose + followed doses	Yes	Involvement of 1 or 2 large joints	First	Yes	Oral steroids for involvement of 1 or 2 joints or when intra-articular joint injection is impractical. Intravenous steroids for the nothing by mouth patients.	First
3e_2013 [36]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CSE_2013 [37]	NSAIDs, colchicine,	NG	NG	NG	NG	NG	NG	NG

	corticosteroids							
SER_2013 [46]	NSAIDs	NG	Yes	Monoarthritis	NG	Yes	Contraindicated to NSAIDs	NG
SIR_2013 [45]	NSAIDs, colchicine	NG	Yes	NG	NG	Yes	Intolerance or contraindications to NSAIDs and colchicine	NG
3e_PT_2014 [40]	Colchicine, NSAIDs	Fixed low dose	Yes	NG	NG	Yes	NG	NG
FMOH_2014 [44]	NG	NG	NG	NG	NG	NG	NG	NG
3e_AU_NZ_2015 [43]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CRA_2016 [41]	NSAIDs	NG	NG	NG	NG	Yes	Contraindications to NSAIDs and colchicine	NG
EULAR_2016 [16]	Colchicine, NSAIDs, corticosteroid	Loading dose + followed doses	Yes	NG	First	Yes	NG	First
T2T_2016 [39]	Anti-inflammatory medications	NG	NG	NG	NG	NG	NG	NG
TRA_2016 [38]	NSAIDs	Fixed or Loading dose + followed doses	Yes	Involvement of 1-2 major joints, contraindications to both colchicine and NSAIDs	NG	Yes	Contraindications to NSAIDs and colchicine	NG
ACP_2017 [19, 20]	Corticosteroids	Loading dose + followed doses	NG	NG	NG	Yes	If not contraindicated.	First
BSR_2017 [21]	NSAIDs, colchicine	NG	Yes	Patients with acute illness and comorbidity	First	Yes	Intolerance to NSAIDs and colchicine and intra-articular injection is not feasible.	Second
CRA_multi_2017 [22]	NSAIDs, colchicine	Loading dose + followed doses	Yes	Involvement of 1-2 major joints and not responding to systemic treatment	NG	Yes	Contraindicated to or not responding to NSAIDs and colchicine	NG

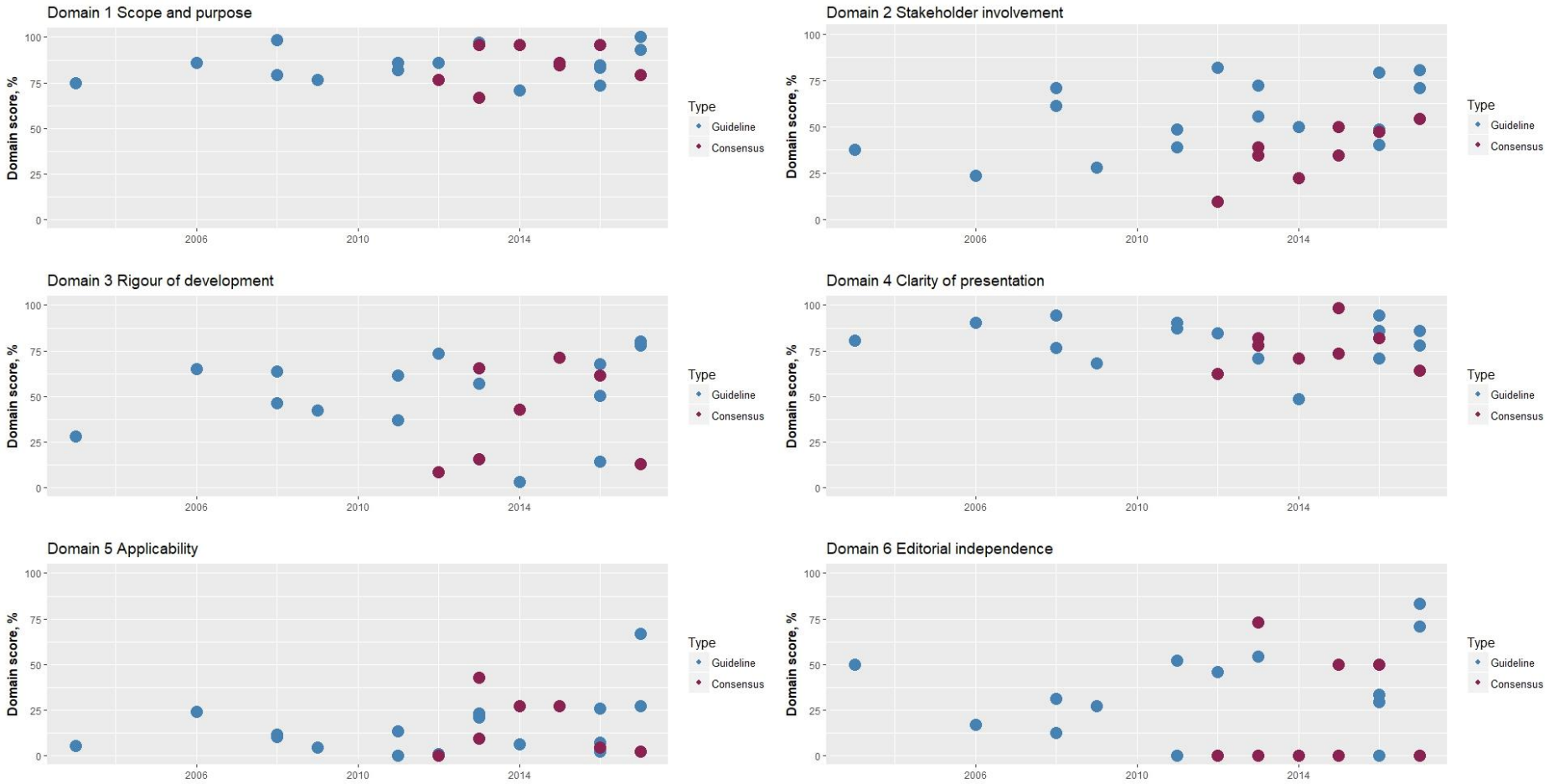
Supplementary Table 11. Summary of recommendations for the treatment of tophi by included guidance documents

A: allopurinol; B: benzbromarone; F: febuxostat; NA: not applicable; NG: not given; P: pegloticase; R: rasburicase; ULT: urate lowering therapy; WH: wound healing.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Is surgery recommended?	+	+	NG	NG	NG	+	NG	+	NG	NG	NG	+	NG	+	NG	NG	IE	+	NG	-	+
Indications for surgery	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	+	NG	NG	+
_Nerve compression	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	+
_Infection	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	-
_Mechanical impingement	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	-	NA	NA	-
_Loss of mobility	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Severe pain	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Tophaceous ulcer	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	-	NA	NA	+
_Others*	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	+
Risks of surgery	WH	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Is long-term ULT recommended?	+	+	+	NG	+	+	+	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Is any ULT drug recommended?	A	-	-	-	P	-	P	-	B	F	NA	-	-	P	-	P	-	-	-	P, R	-

* Other indications for surgery include large tophi [22], persistent tophi [22], joint deformation [38], major joint destruction [49], pressure symptoms [49], and cosmetic [49].

Supplementary Figure 1. Standardized domain scores by the year of publication



Supplementary File 1. Instructions for Guideline Appraisal Using the AGREE II Instrument

TRAINING MATERIALS

- Online tutorial: http://www.agreetrust.org/resource-centre/agree-ii-training-tools/
- User's Manual: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

PROLOGUE

- The Appraisal of Guidelines for REsearch & Evaluation (AGREE) Instrument is an international, validated and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements.
- The AGREE II instrument was published in 2010 and consists of 23 key items organized within 6 domains followed by 2 global rating items ("Overall Assessment"). Each domain captures a unique dimension of guideline quality.
  - Scope and purpose
  - Stakeholder involvement
  - Rigour of development
  - Clarity of presentation
  - Applicability
  - Editorial independence.
- Reviewers score each item on a 7-point Likert Scale.
  - 1 - Strongly disagree
  - 7 - Strongly agree
  - For the majority of items, we use an 'add-up' strategy to score, that is, corresponding scores will be added to 1' if information on predefined aspects is provided. For only one item, we subtract scores from 7'.
- Domain scores will be calculated as: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)

DETAILED INSTRUCTIONS FOR SCORING

(adapted from AGREE II User's Manual [28])

Domain 1 Scope and Purpose

Item 1 Objectives: The overall objective(s) of the guideline is (are) specifically described.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Health intent, i.e., prevention, screening, diagnosis, treatment, etc. (2');

b) Expected benefit or outcome (2');

- *Clarification*: If gout epidemiology is provided as background information (i.e., the importance or significance of the diagnosis and management of gout/hyperuricemia is stated), 1' will be given. If clear statements, such as "to prevent (long term) complications of patients with diabetes mellitus" "to lower the risk of subsequent vascular events in patients with previous myocardial infarction", are provided, 2' will be given.

c) Target, e.g., patient population, society (1').

Performance: Is the item well written and is the content easy to find? (1')

Related *Report Criteria* from *User's Manual*: • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) • expected benefit or outcome • target(s) (e.g., patient population, society)

Item 2 Questions: The health question(s) covered by the guideline is (are) specifically described.

Instructions:

Information on five aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Target population (2');

b) Intervention or exposure (if appropriate, 1');

c) Comparisons (if appropriate, 1');

d) Outcome (1');

e) Health care setting or context (1').

Performance: Is the item well written and is the content easy to find? (1')

Note:

1) If c) is not appropriate, no score will be subtracted.
2) It is not necessary to have this information provided in questions. Reviewers can try to paraphrase 2-3 key recommendations into questions to see the information above is provided and score based on paraphrased questions.

Related *Report Criteria* from *User's Manual*: • target population • intervention(s) or exposure(s) • comparisons (if appropriate) • outcome(s) • health care setting or context

Item 3 Population: The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Instructions:

A default full score (7') should be considered. Subtract 1-2 points where the population is not clearly described or where the descriptions in the guideline is contradictory (e.g., a guideline stating "to treat asymptomatic hyperuricaemia" in the introduction, while stating "to treat hyperuricaemia and gout" in the title and providing no specific definition of patients' condition in recommendations).

Related *Report Criteria* from *User's Manual*: • target population, gender and age • clinical condition (if relevant) • severity/stage of disease (if relevant) • comorbidities (if relevant) • excluded populations (if relevant)

Domain 2 Stakeholder Involvement

Item 4 Group Membership: The guideline development group includes individuals from all relevant professional groups.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) The guideline development group is stated (1');

b) For each member of the guideline development group, the following information is included (1' each): name (1'), discipline/content expertise (e.g., neurosurgeon, methodologist, 1'), institution (e.g., St. Peter's hospital, 1'), a description of the member's role in the guideline development group (1')

- *Clarification*: Please subtract 1' if no methodologist (i.e., epidemiologist) is inferred from the discipline/content expertise.

Performance: Is the item well written and is the content easy to find? (1')

Note: Where the relation between the guideline development group and the authors is unclear, the authors of the guidance document will be considered as equivalent to the guideline development group.

Related *Report Criteria* from *User's Manual*: • For each member of the guideline development group, the following information is included: name, discipline/content expertise (e.g., neurosurgeon, methodologist), institution (e.g., St. Peter's hospital), geographical location (e.g., Seattle, WA), a description of the member's role in the guideline development group

Item 5 Target Population Preferences and Views: The views and preferences of the target population (patients, public, etc.) have been sought.

Instructions:

Information the following four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences, 2');

b) Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups, 1');

c) Outcomes/information gathered on patient/public information (2');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

- *Clarification*: If a patient representative is included in the guideline development panel, scores on aspects a), b), and d) will be given as default.

Related *Report Criteria* from *User's Manual*: • statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) • methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) • outcomes/information gathered on patient/public information • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 6 Target Users: The target users of the guideline are clearly defined.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators, 3');

b) Description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care, 3')

Related *Report Criteria* from *User's Manual*: • clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) • description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)

Domain 3 Rigour of Development

Item 7 Search Methods: Systematic methods were used to search for evidence.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL, 2');
b) Time periods searched (e.g., January 1, 2004 to March 31, 2008, 1');
c) Search terms used (e.g., text words, indexing terms, subheadings, 1');
d) Full search strategy included (e.g., possibly located in appendix, 2')

Related *Report Criteria* from *User's Manual*: • named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) • time periods searched (e.g., January 1, 2004 to March 31, 2008) • search terms used (e.g., text words, indexing terms, subheadings) • full search strategy included (e.g., possibly located in appendix)

Item 8 Evidence Selection Criteria: The criteria for selecting the evidence are clearly described.
Instructions:
Information on both inclusion and exclusion criteria should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the inclusion criteria:
a1) target population (patient, public, etc.) characteristics (2'),
a2) study design (2),
a4) outcomes (1'),
b) Description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement, 1').
Note: if a3), a5), a6), b) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • description of the inclusion criteria, including: target population (patient, public, etc.) characteristics, study design, comparisons (if relevant), outcomes, language (if relevant), context (if relevant) • description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement)

Item 9 Strengths and Limitations of The Evidence: The strengths and limitations of the body of evidence are clearly described.
Instructions:
For each evidence, information on two aspects should be provided. If only some of the evidences report the following information, please first calculate the score based on the most informative evidence (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').
For each evidence, both a general statement of the method and detailed descriptions should be provided:
a) A statement of the method used to evaluate the strengths and limitations of the evidence should be provided (3').
b) The stated method should evaluate at least three of the following aspects (add 1' for each aspect, maximum 3'):
b1) Study design(s);
b2) Study methodology limitations (e.g., sampling, blinding, allocation concealment, analytical methods);
b3) Appropriateness/relevance of primary and secondary outcomes considered;
b4) Consistency of results across studies;
b5) Direction of results across studies;
b6) Magnitude of benefit versus magnitude of harm;

b7) Applicability to practice context

Related *Report Criteria* from *User's Manual*: • descriptions of how the body of evidence was evaluated for bias and how it was interpreted by members of the guideline development group • aspects upon which to frame descriptions include: study design(s) included in body of evidence, study methodology limitations (sampling, blinding, allocation concealment, analytical methods), appropriateness/relevance of primary and secondary outcomes considered, consistency of results across studies, direction of results across studies, magnitude of benefit versus magnitude of harm, applicability to practice context

Item 10 Formulation of Recommendations: The methods for formulating the recommendations are clearly described.

Instructions:

Information on three aspects should be provide (add 2' for each aspect, 6' in total):

a) Description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered, 2');

b) Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures, 2');

c) Description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote, 2')

Related *Report Criteria* from *User's Manual*: • description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) • outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) • description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)

Item 11 Consideration of Benefits and Harms: The health benefits, side effects, and risks have been considered in formulating the recommendations.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Supporting data and report of benefits (2'); b) Supporting data and report of harms/side effects/risks (2');

- *Clarification*: Data on a) and b) can be provided as references.

c) Reporting of the balance/trade-off between benefits and harms/side effects/risks (1');

d) Recommendations reflect considerations of both benefits and harms/side effects/risks (1')

Related *Report Criteria* from *User's Manual*: • supporting data and report of benefits • supporting data and report of harms/side effects/risks • reporting of the balance/trade-off between benefits and harms/side effects/risks • recommendations reflect considerations of both benefits and harms/side effects/risks

Item 12 Link Between Recommendations and Evidence: There is an explicit link between the recommendations and the supporting evidence.

Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) The guideline describes how the guideline development group linked and used the evidence to inform recommendations (2');
- *Clarification*: Can be provided as narrative summaries and/or discussions of evidences.
b) Each recommendation is linked to a key evidence description/paragraph and/or reference list (2');
- *Note*: Please subtract 1' if only some recommendations meet criterium b).
c) Recommendations linked to evidence summaries, evidence tables in the results section of the guideline (2')

Related *Report Criteria* from *User's Manual*: • the guideline describes how the guideline development group linked and used the evidence to inform recommendations • each recommendation is linked to a key evidence description/paragraph and/or reference list • recommendations linked to evidence summaries, evidence tables in the results section of the guideline

Item 13 External Review: The guideline has been externally reviewed by experts prior to its publication.
Instructions:
Information on five aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence, 1');
b) Methods taken to undertake the external review (e.g., rating scale, open-ended questions, 1');
c) Description of the external reviewers (e.g., number, type of reviewers, affiliations, 1');
d) Outcomes/information gathered from the external review (e.g., summary of key findings, 1');
e) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations, 2')
- *Clarification*: Publication through a peer-reviewed journal can be considered as externally reviewed. Note: If dates of revision and acceptance is provided on the document, it is also considered externally reviewed.

Related *Report Criteria* from *User's Manual*: • purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) • methods taken to undertake the external review (e.g., rating scale, open-ended questions) • description of the external reviewers (e.g., number, type of reviewers, affiliations) • outcomes/information gathered from the external review (e.g., summary of key findings) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)

Item 14 Updating Procedure: A procedure for updating the guideline is provided.
Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) A statement that the guideline will be updated (2');
b) Explicit time interval or explicit criteria to guide decisions about when an update will occur (2');
c) Methodology for the updating procedure is reported (2')

Related *Report Criteria* from *User's Manual*: • a statement that the guideline will be updated • explicit

time interval or explicit criteria to guide decisions about when an update will occur • methodology for the updating procedure is reported

Domain 4 Clarity of Presentation

Item 15 Specific and Unambiguous Recommendations: The recommendations are specific and unambiguous.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) If a recommendation is uncertain, the uncertainty should be reflected in the recommendation and also be explicitly stated (2')

b) Identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects, 2');

- *Clarification*: If the benefit for uric acid lowering in patients with CVD is not clearly stated, the score for this aspect should not be added.

c) Identification of the relevant population (e.g., patients, public, 1');

d) Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply, 1').

Note: if c) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • statement of the recommended action • identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) • identification of the relevant population (e.g., patients, public) • caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)

Item 16 Management Options: The different options for management of the condition or health issue are clearly presented.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) Description of options (3');

b) Description of population or clinical situation most appropriate to each option (3')

- *Note*: Please subtract 1' if only some options are provided with the most appropriate population or clinical situation.

Related *Report Criteria* from *User's Manual*: • description of options • description of population or clinical situation most appropriate to each option

Item 17 Identifiable Key Recommendations: Key recommendations are easily identifiable.

Instructions:

Reporting style should follow two criteria (add 3' for each aspect, 6' in total):

a) Description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms (3');

b) Specific recommendations are grouped together in one section (3')

- *Clarification*: If recommendations are summarised in the abstract, scores for aspect b) can also be given.

Related *Report Criteria* from *User's Manual*: • description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms • specific recommendations are grouped together in one section

Domain 5 Applicability

Item 18 Facilitators and Barriers to Application: The guideline describes facilitators and barriers to its application.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of facilitators and barriers that were considered (2');

- *Clarification*: Statements of that certain drugs are not available in certain regions can be considered as identification of the facilitators and barriers.

b) Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation, 2');

c) Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography, 1');

d) Description of how the information influenced the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of facilitators and barriers that were considered • methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) • information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) • description of how the information influenced the guideline development process and/or formation of the recommendations

Item 19 Implementation Advice or Tools: The guideline provides advice and/or tools on how the recommendations can be put into practice.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) An implementation section in the guideline (2');

b) Tools and resources to facilitate application (add 1' for each tool/resource, maximum 2'): guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned;

c) Directions on how users can access tools and resources (2')

Related *Report Criteria* from *User's Manual*: • an implementation section in the guideline • tools and resources to facilitate application: guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned • directions on how users can access

tools and resources

Item 20 Resource Implications: The potential resource implications of applying the recommendations have been considered.

- *Clarification*: The aim of this item is to the cost information considered by the guideline.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs, 2');

b) Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc., 2');

c) Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course, 1');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) • methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) • information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 21 Monitoring or Auditing Criteria: The guideline presents monitoring and/or auditing criteria.

- *Clarification*: The aim of this item is to evaluate the adherence to guidelines, but not to provide follow up parameters for diseases. *Monitoring* in this item refers to the action to monitor physicians' adherence to the guideline in daily practice by a group of investigators, but not to monitor the management of the disease in an individual patient. And the *auditing criteria* are the criteria to assess how well the guideline affects the practice in a region, but not how well the patients achieve the treatment target.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of criteria to assess guideline implementation or adherence to recommendations (2');

b) Criteria for assessing impact of implementing the recommendations (2');

c) Advice on the frequency and interval of measurement (1');

d) Descriptions or operational definitions of how the criteria should be measured (1')

Related *Report Criteria* from *User's Manual*: • identification of criteria to assess guideline implementation or adherence to recommendations • criteria for assessing impact of implementing the recommendations • advice on the frequency and interval of measurement • descriptions or operational definitions of how the criteria should be measured

Domain 6 Editorial Independence

Item 22 Funding Body: The views of the funding body have not influenced the content of the guideline.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) The name of the funding body or source of funding (or explicit statement of no funding, 3');
b) A statement that the funding body did not influence the content of the guideline (3')

Related *Report Criteria* from *User's Manual*: • the name of the funding body or source of funding (or explicit statement of no funding) • a statement that the funding body did not influence the content of the guideline

Item 23 Competing Interests: Competing interests of guideline development group members have been recorded and addressed.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the types of competing interests considered (2');
b) Methods by which potential competing interests were sought (1');
c) Description of the competing interests (1');
d) Description of how the competing interests influenced the guideline process and development of recommendations (2')

Related *Report Criteria* from *User's Manual*: • description of the types of competing interests considered • methods by which potential competing interests were sought • description of the competing interests • description of how the competing interests influenced the guideline process and development of recommendations

Overall Guideline Assessment

Question 1 Overall quality: Rate the overall quality of this guideline.

Instructions:

7' in total. Reviewer's impression on the overall quality of the guideline.

Question 2 Strength of recommendation: I would recommend this guideline for use.

Instructions:

Three options to choose from: a) Yes; b) Yes, with modifications; c) No
Reviewer's impression on whether the guideline is easy to be applied to clinical practice.

Related *Report Criteria* from *User's Manual*: The overall assessment requires the AGREE II user to make a judgment as to the quality of the guideline, taking into account the appraisal items considered in the assessment process.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported -on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21-22

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Keywords:	Clinical practice guideline, Hyperuricemia, Gout, Systematic review

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

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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ABSTRACT

Objectives

Despite the publication of hundreds of trials on gout and hyperuricemia, management of these conditions remains suboptimal. We aimed to assess the quality and consistency of guidance documents for gout and hyperuricemia.

Design

Systematic review and quality assessment using the Appraisal of Guidelines for Research and Evaluation (AGREE) II methodology.

Data Sources

PubMed and EMBASE (27 October 2016), two Chinese academic databases, eight guideline databases, and Google and Google scholar (July 2017).

Eligibility Criteria

We included the latest version of international and national/regional clinical practice guidelines and consensus statements for diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese.

Data Extraction and Synthesis

Two reviewers independently screened searched items and extracted data. Four reviewers independently scored documents using AGREE II. Recommendations from all documents were tabulated and visualized in a coloured grid.

Results

Twenty-four guidance documents (16 clinical practice guidelines and 8 consensus statements) published between 2003 and 2017 were included. Included documents performed well in the domains of scope and purpose (median 85.4%, range 66.7%-100.0%) and clarity of presentation (median 81.3%, range 48.6%-98.6%), but unsatisfied in applicability (median 9.9%, range 0.0%-66.7%) and editorial independence (median 28.1%, range 0.0%-83.3%). The 2017 British Society of Rheumatology guideline received the highest scores. Recommendations were concordant on the target serum uric acid level for long-term control, on some indications for urate-lowering

therapy, and on the first-line drugs for urate-lowering therapy and for acute attack. Substantially inconsistent recommendations were provided for many items, especially for the timing of initiation of urate-lowering therapy and for treatment for asymptomatic hyperuricemia.

Conclusions

Methodological quality needs improvement in guidance documents on gout and hyperuricemia. Evidence for certain clinical questions is lacking, despite numerous trials in this field. Promoting standard guidance development methods and synthesizing high-quality clinical evidence are potential approaches to reduce recommendation inconsistencies.

Study registration

PROSPERO (CRD42016046104).

Keywords

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The first systematic review to assess the quality of clinical practice guidelines and consensus statements on the diagnosis and treatment for both hyperuricemia and gout.
2. The first systematic review to summarise recommendations for best practice in hyperuricemia and gout.
3. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is an international, structured, validated, and rigorously developed tool.
4. Only guidance documents in English and Chinese were included.
5. Literature search was more than one year old at the time of publication.

BACKGROUND

Gout is an inflammatory arthritis occurring in response to monosodium urate (MSU) crystals formation, a common and necessary pathogenic factor of which is hyperuricemia. The prevalence of gout and hyperuricemia [1-4], as well as their disease burden [5, 6], are rising globally. However, although more than six hundred related clinical studies [7] have been published to date, the quality of care for gout and hyperuricemia remains suboptimal. The goal of treatment is to reduce the body's total uric acid pool [8, 9] and consequently to minimize the risk of acute flares, arthropathy, nephrolithiasis, and other complications [7, 10, 11]. A study in the United States found that only 22% of patients with gout received therapy adhering to all quality indicators [12]. A nationwide population study in the United Kingdom reported that only 48% of prevalent patients received proper consultation and only 27% of incident patients were provided with urate-lowering therapy (ULT) within one year of diagnosis [6].

High-quality guidance documents are important for improving the quality of care for gout and hyperuricemia at individual, community, and national levels [13]. Current guidance documents for gout and hyperuricemia have been developed by rheumatology, endocrinology, and cardiology groups, at regional, national or international levels. Among these documents, the American College of Rheumatology (ACR) guidelines [14, 15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16-18], updated in 2016, have the most substantial global influence. The most recent documents (released in 2017) are two national guidelines, from the American College of Physicians (ACP) [19, 20] and the British Society of Rheumatology (BSR) [21], and one consensus statement, from the Chinese Multi-disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases [22].

Despite the variety of documents, current guidelines and consensuses on gout and hyperuricemia provide inconsistent recommendations, even those released by highly respected professional organizations, such as the ACP and the ACR [23]. Some distinct differences lie in key aspects for patient care, such as the pharmacological treatment for asymptomatic hyperuricemic patients, the timing of initiation of ULT in patients with gout flare [24], and indications for ULT [25]. These discrepancies may result from ethnic and social differences, but can be a consequence of inconsistent guideline development [23]. Low-quality guidance documents put individual patients and communities at risk, and impede the application of guideline recommendations in clinical practice [26]. Hence, we conducted this study to systematically evaluate the quality of clinical practice guidelines and consensus statements on gout and hyperuricemia and to compare key recommendations on patient care from all included documents.

METHODS

Detailed methods of the study have been published previously [27] and this study was registered with PROSPERO (registration number: CRD42016046104).

Literature search and selection criteria

We systematically searched PubMed and EMBASE from inception to 27 October 2016 using a comprehensive search strategy (Supplementary Table 1 and Supplementary Table 2) to identify guidelines and consensus recommendations pertaining to the diagnosis and treatment of gout and hyperuricemia. We searched two academic databases for Chinese publications (the Chinese Biomedical Literature Database and the Wanfang Data) and eight guideline databases from inception to 24 July 2017 using search strategies tailored to different databases (Supplementary Table 3). We also searched Google and Google scholar in July 2017 for potentially eligible

guidelines and consensus recommendations that were not indexed in the aforementioned databases.

We included the latest versions of all international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of gout and hyperuricemia, published in English or Chinese. Two reviewers (Q.L., X.L.) independently screened all searched documents. Reasons for exclusion were provided for documents excluded during the full-text review (Supplementary Table 4). Disagreements were resolved through discussion with a third reviewer (S.L.).

Data extraction

We extracted the following data from each included document: document characteristics (e.g., year of publication, funding body, and evidence base), recommendations for diagnosis and monitoring of gout and hyperuricemia, and recommendations for management. Data were extracted by one investigator (Q.L.) and checked by another (X.L.).

Appraisal of guidance documents

All included documents were assessed by four reviewers (Q.L., X.L., J.W., and H.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [28]. AGREE II is an internationally developed and validated tool to evaluate the quality of clinical practice guidelines [29-31] and consensus statements [32, 33].

All reviewers completed an online training tutorial [34] before the commencement of appraisal to ensure standardization. We adapted detailed instructions for scoring from the AGREE II User's Manual [28] and provided objective scoring criteria for each item (Supplementary File 1). We selected four guidance documents for pilot scoring, during which we discussed and

clarified our objective scoring criteria. When scoring for all included documents was completed, a meeting was held among reviewers and every item with scores differed more than one point was discussed. After the meeting, reviewers were given the opportunity to revise their scores or to keep the original scores. We recorded all original scores, revised scores, and reasons for modifying scores for quality control purpose, and used the intra-class correlation coefficient (ICC) to test inter-rater reliability. The ICC was calculated via IBM SPSS (IBM Co., Armonk, New York, USA) and an ICC ≥ 0.7 was considered acceptable [35].

Recommendation synthesis

We manually extracted recommendations on key clinical questions from all included guidance documents and summarized them into four tables: a) the diagnosis of gout and hyperuricemia, b) the treatment of hyperuricemia, c) the treatment of acute gout, and d) the treatment of tophi. Recommendations were extracted by one investigator (Q.L.) and checked by another (X.L.). We further visualized these recommendations in a five-colour grid to illustrate inconsistencies. The most frequently recommended content was used as a reference. We used green to colour documents providing consistent recommendations, red to colour those providing contrary recommendations, and blue to colour those providing partially consistent recommendations. A partially consistent recommendation was defined as a recommendation that included but not the same as the reference content. Where recommendations were not given or were not applicable, the cell was coloured in yellow and in grey, respectively.

Patient involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

RESULTS

Search results

Overall, we identified 5811 items across academic databases, guideline databases, Google, and Google Scholar. After applying the inclusion and exclusion criteria, 24 guidance documents from 26 papers [14-22, 36-52] were included in the final appraisal and recommendation synthesis (Figure 1). Studies excluded after full-text review and reasons for exclusion were provided as Supplementary Table 4.

Characteristics of included guidelines and consensus statements

Table 1 summarized characteristics of included guidance documents, among which 16 were clinical practice guidelines [14-21, 38, 41, 44-46, 48-52] and eight were consensus statements [22, 36, 37, 39, 40, 42, 43, 47]. 16 national or regional organizations and three international groups (i.e., the 3e [Evidence, Expertise, Exchange] Initiative, the EULAR, and the development group for the Treat-to-target [T2T] recommendations) published these documents between 2003 to 2017. 16 documents [14-18, 21, 22, 36-38, 40, 42, 43, 45, 46, 49, 50] were issued by rheumatology organizations and seven [16-18, 36, 39, 42, 43] were developed by multinational development groups. 17 documents [14-18, 21, 22, 36, 38-41, 43-46, 49, 51] provided information on their guideline development group, among which 11 [14-17, 19-21, 36, 41-43, 45, 46] explicitly stated the involvement of a methodologist. 12 documents [14-18, 21, 22, 38-41, 43-46, 49, 51] provided information on their target audience, among which only three [16, 38, 44] considered patients as one of the target audiences. 18 documents [14-21, 36, 39-43, 45, 46, 48-52] conducted systematic literature review as part of their development process, among which 17 documents [14-21, 36, 39-41, 43, 45, 46, 48-52] reported the level of evidence supporting recommendations and 16 [16-21, 36, 39-41, 43, 45, 46, 48-52] graded the strength of recommendations. Ten documents [16, 19-21, 39, 42, 46, 48, 49, 51, 52] clearly stated being externally reviewed. Five [19-21,

46, 49, 50] provided a clear time of update plan. 12 documents [14, 15, 17-21, 36, 39, 42, 46, 49, 51, 52] provided information on their funding body, among which six [17, 36, 39, 46, 49, 51] were fully or partially funded by the pharmaceutical industry and the rest did not clearly declare their funding body.

Appraisal of guidelines and consensus statements

Standardized AGREE II domain scores for each guidance document were shown as Figure 2 and were provided in value as Supplementary Table 5. Scores for each AGREE II item were provided in mean as Supplementary Table 6 and in detail as Supplementary Table 7. The overall quality of guidance documents, as assessed by AGREE II, varied both between documents across domains and within documents between domains. The document with the highest domain scores was the gout management guideline published by the BSR in 2017 [21], with five domains scoring above the upper quartile, followed by the guidelines published by the ACP in 2017 [19, 20], and the 2015 gout classification criteria by the ACR and the EULAR jointly [42], both with four domains scoring above the upper quartile. Guidelines did not always score higher than consensus statements. No tendency of improvement in the quality score over time was observed (Supplementary Figure 1).

The AGREE II instrument evaluated guidelines and consensus statements in six domains, from the development, dissemination, to implementation. The scope and purpose (domain 1) of a document clarifies its clinical questions. Proper involvement of stakeholders (domain 2) balances individuals' biases. The rigour of development domain (domain 3) is most concerned by clinicians and ensures the validity of development methodology [53]. Clearly presented recommendations (domain 4) conveyed precise and accessible information from the development group to clinicians. Good performances in the applicability domain (domain 5) and the editorial independence domain (domain 6) guarantee the usefulness and the independence of documents.

Guidance documents received the highest scores for the scope and purpose domain (median 85.42%, range 66.67% to 100.00%) and the clarity of presentation domain (median 79.17%, range 48.61% to 98.61%), and the lowest scores for the applicability domain (median 10.94%, range 0.00% to 66.67%) and the editorial independence domain (median 28.13%, range 0.00% to 83.33%). The worst scored item was the monitoring or auditing criteria item (mean score 1.2, range 1.0-4.0), followed by the implementation advice or tools item (mean 1.7, range 1.0-4.8), the external review item (mean 2.1, range 1.0-6.0), and the updating procedure item (mean 2.1, range 1.0-6.5).

The ICC was 0.896. Group discussion modified 365/2208 (16.53%) of individual scores.

Synthesis of recommendations

Included guidance documents addressed four major themes: diagnosis of gout and hyperuricemia, treatment for hyperuricemia, treatment for acute gout attack, and treatment for tophi. Figure 3 showed key recommendations and their inconsistencies.

Approaches to diagnostic strategies for gout and hyperuricemia

Thirteen guidance documents [17-20, 22, 36, 38, 40-43, 46, 49, 51] covered the diagnosis of gout and 11 [17, 22, 37, 38, 45-51] covered that of hyperuricemia. Supplementary Table 8 showed key recommendations. The identification of MSU crystals in synovial fluid or tophi was a gold standard for definite diagnosis, as recommended by all included documents. In the absence of MSU crystals, three aspects were commonly evaluated for gout diagnosis, namely the clinical manifestation, considered by all documents; the laboratory result, considered by all but one document [49]; and the imaging

result, considered by all but four documents [17, 19, 20, 49, 51].

Guidance documents differed when recommending the cut-off serum uric acid (SUA) level to diagnose hyperuricemia. Four documents [38, 47, 48, 51] recommended 7.0 mg/dL (or 420 μmol/L) as the cut-off, while two [17, 45] preferred 6.8 mg/dL in the general population. Five documents [22, 37, 46, 49, 50] provided gender-specific cut-offs, recommending 6.0 mg/dL (or 360 μmol/L) in female and 7.0 mg/dL (or 420 μmol/L) in male. Asymptomatic hyperuricemia was defined in seven [36, 38, 46-50] documents, among which six [36, 38, 46-48, 50] excluded patients with gout and two [36, 48] excluded patients with tophi when making the diagnosis. Attitudes were inconsistent for renal diseases. Patients with renal diseases were not eligible for the diagnosis of asymptomatic hyperuricemia in the Japanese [48] and the Philippine [50] guidelines, but patients with pre-existing renal or cardiovascular diseases were eligible in the 3e initiative document [36].

Approaches to treatment for hyperuricemia

Twenty-two guidance documents [14-17, 19-22, 36-41, 43-52] covered the treatment for hyperuricemia and Supplementary Table 9 summarized key recommendations. All but three documents [19, 20, 44, 52] explicitly recommended target levels for long-term SUA control, most of which stated 6.0 mg/dL (or 360 μmol/L), except the South African guideline [51] which stated 5.0mg/dL (300 μmol/L). Two documents [16, 22] recommended a lower limit of 3.0 mg/dL (or 180 μmol/L) for long-term SUA management. Only the 2016 EULAR guideline [16] explained the reason for providing a lower limit was that low SUA might increase the risk of neurodegenerative diseases, but the level of evidence and the grade of recommendation were both low.

All but six guidance documents [36, 39, 40, 43, 44, 52] provided indications for long-term ULT. The most commonly recommended indications were recurrent

attacks [14-17, 19-22, 41, 45, 48-51], tophi [14-17, 19-22, 38, 41, 45, 48-51], urate nephrolithiasis [14-17, 19-22, 37, 38, 49, 50], arthropathy [16, 17, 21, 22, 38, 41, 45, 49], and comorbidities [14-16, 19-22, 37, 47, 49, 50]. The definition of recurrent attacks varied from at least once per year [17] to at least three times per year [49], while the majority of documents [14-16, 19-21, 41] recommended twice per year as the cut-off.

Regarding the timing to initiate ULT, the documents did not agree on whether to start pharmacological ULT after an acute attack [17, 21, 22, 36-38, 40, 48, 49, 51, 52] or during an attack [14, 15, 37]. When recommending to start ULT after an attack, the preferred time to wait since the attack resolved varied from two weeks [37, 48] to six weeks [52]. All guidance documents based this recommendation on expert opinions due to insufficient evidence. When recommending not to start ULT during an attack, guidance documents explained that ULT was better discussed when a patient was not painful [21], and that ULT initiation could prolong or worsen the acute attack [51]. Two documents [16, 39] explicitly presented the currently conflicting views and insufficient evidence and stated consequently no recommendation for this issue.

When pharmacological ULT options were provided with prioritization, allopurinol was recommended by all guidance documents [14-17, 21, 36, 40, 43, 45, 46, 48-50] to be the first-line drug, while febuxostat was recommended by three documents [14, 15, 17, 46] to be the first-line and by six documents [16, 21, 36, 40, 43, 45] to be the second-line. However, recommendations on the dosage of allopurinol varied largely. The maximum daily allopurinol dose recommended varied from 300 mg [51], 600 mg [22, 37, 47], 800 mg [14, 15, 17, 38, 45], to 900 mg [21, 43, 46], and the daily starting dose recommended in patients with normal renal function varied from 50 mg [19, 20, 22, 47, 48, 51] to 200 mg [21]. As for patients with impaired renal function, the cut-off to initiate

dose adjustment was provided diversely as creatinine clearance (CCr) 20-140 mL/min [37, 45, 46, 49, 51], or estimated glomerular filtration rate (eGFR) 130 ml/min/1.73m^2 [21]. One document preferred to depend allopurinol dose solely on eGFR by limiting the maximum daily dose to 1.5 mg/eGFR in patients with renal impairment [22]. HLA-B*5801 gene screening prior to allopurinol use was recommended by five guidance documents [14, 15, 21, 22, 37, 38].

For patients with asymptomatic hyperuricemia, 14 guidance documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52] commented on the option of pharmacological ULT, among which, five [17, 21, 38, 51, 52] explicitly recommended no treatment under any circumstances. Three documents [47-49] recommended pharmacological treatments in asymptomatic hyperuricemia patients with comorbidities [47, 48] or with very high SUA levels [40, 47-49], but their cut-off SUA level to indicate ULT varied from 8.0 mg/dL [47, 48] to 13.0 mg/dL [49]. The Portuguese consensus [40] was incoherent itself by recommending no pharmacological treatment in general, but recommending pharmacological ULT for patients with SUA higher than 9 mg/dL. No direct evidence was provided by any document to support pharmacological treatment for asymptomatic hyperuricemia, and such recommendations were only made in concern of the onset of gout [40] and the risk of cardiovascular events [47, 48].

Approaches to treatment for acute gout attack

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for acute gout attack and Supplementary Table 10 summarized their key recommendations. Non-steroidal anti-inflammatory drugs (NSAIDs) was recommended by all but three documents [19, 20, 39, 44] as the first line pharmacological treatment, while colchicine by 11 documents [14-17, 21, 22, 36, 37, 40, 43, 45, 48]. Colchicine was recommended to be given in a fixed dose by three documents [38, 40, 48] and in a loading dose followed by

different doses by six documents [14-17, 19, 20, 22, 38, 51, 52]. Seven documents [21, 36, 41, 43, 45, 49, 50] only recommended the total daily dose for colchicine, regardless of the regimen, and their doses recommended varied from 1 mg [21, 49, 50] to 2.4 mg [49]. One document [43] surprisingly recommended 1.8 g in 24 hours without any further explanation, which was likely a typo. Systemic steroids were recommended by all but three documents [37, 39, 44], among which six [14-17, 19, 20, 36, 43] recommended them as the first-line option and ten [21, 22, 38, 41, 45, 46, 48, 50-52] recommended them when NSAIDs and colchicine were contraindicated or intolerant. Intra-articular steroids injection was recommended by 14 documents [14-17, 21, 22, 36, 38, 40, 43, 45, 46, 49, 51, 52], among which five [14-16, 21, 36, 43] clearly recommended it as the first-line option.

Approaches to treatment for tophi

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered treatment for tophi and Supplementary Table 11 showed their key recommendations. Surgery was recommended by nine documents [22, 36, 38, 40, 43, 48, 49, 51], among which five [22, 36, 38, 43, 49] explicitly presented its indications, most commonly nerve compression [22, 36, 38, 43] and infection [36, 38, 43]. The risk for surgery was discussed by one document [51] and only the risk of delayed wound healing was stated. Long-term ULT was recommended by all but two documents [44, 52], but pharmacological treatment was only explicitly recommended by eight of them [15-17, 21, 37, 43, 46, 51].

DISCUSSION

Principal findings and interpretations

This systematic review, including 16 guidelines and eight consensus statements, found generally low methodological quality and inconsistent recommendations from guidance documents covering the diagnosis and

management of gout and hyperuricemia. During revision of our work, the English version of two documents, from the Chinese Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases [54] and the Taiwan Rheumatologist Association [55], respectively, were released. Despite increase in the number of guidance documents published between 2003 and 2017, the quality of documents in all domains did not seem to improve with time. To date, this is the first systematic appraisal for the quality of guidelines and consensus statements pertaining to both gout and hyperuricemia.

Comparison with existing research

Guidance documents assessed in our study performed well in the domains of scope and purpose (domain 1) and clarity of presentation (domain 4), but poorly in the domain of applicability (domain 5). These results were consistent with two previous reviews [56, 57], one of which systematically assessed the quality of all guidelines for gout and the other assessed three documents released respectively by the 3e initiative [36], the ACR [14, 15], and the EULAR [18, 58]. Our study systematically included both guidelines and consensus statements in the field of both gout and hyperuricemia, and the differential performance by domain was shared across both type of document.

This distribution of AGREE II domain scores has been observed by many previous guideline appraisal studies, in which documents scored higher in the scope and purpose domain and the clarity of presentation domain, and lower in the applicability domain and the editorial independence domain. This domain score distribution was not only shared by guidance documents for endocrinology diseases, such as diabetes [59, 60] and thyroid disorders [31, 61], and rheumatology diseases, such as rheumatoid arthritis [32, 62, 63] and systemic lupus erythematosus [64], but also shared by documents for diseases in other clinical specialities [33, 65-67]. Despite generally low and varied scores in the applicability domain, guidance documents for gout and

hyperuricemia performed obviously poorer comparing to documents for other conditions [31-33, 59-61, 63-67], suggesting that improving the usefulness of guidance being more challenging in gout and hyperuricemia. One major impediment to good applicability of guidance document is the time and cost to perform economic evaluations and pilot studies, and a stable and long-term task force of guideline development is required to conduct these evaluations and studies. Although forming such a task force is practically difficult in some regions and countries, guidance documents were suggested to at least inform audience the need to consider these issues [65]. Low scores in the editorial independence domain often resulted from lacking of detailed information on the influence of funding body and on the conflict of interests. We found that 50% of documents declaring funding sources were supported by the pharmaceutical industry, calling for awareness of the potential influence of pharmaceutical industry on the synthesis of clinical guidance and for the need of promoting transparency in financial declaration.

Clinical implications and future research

Guidance documents were concordant and recommended a target for SUA < 6.0 mg/dL (or 360 μmol/L) for long-term control, to consider recurrent attacks as one of the indications for ULT (although the definitions for recurrent attacks differed), to consider allopurinol as the first-line ULT and NSAIDs as the first-line drug in acute attack, and to consider long-term ULT in patient with tophi. Despite these similarities, recommendations differed in the majority of items and these discrepancies might come from several sources, including ethnic difference, quality of documents, and lack of evidence.

Ethnical and social differences are important reasons why recommendations may vary between guidelines and consensus, and such diversity is to be encouraged in order to best meet the needs of local populations. Ethnicity differences explain the tendency for Asian guidance documents to positively

recommend HLA-B*5801 gene screening before prescribing allopurinol [22, 37, 38]. The risk of hypersensitivity reactions associated with allopurinol is significantly increased in individuals carrying the variant allele HLA-B*5801, the frequency of which in Han Chinese, Korean, and Tai people are higher than that in the Caucasian population [14, 15, 21]. Studies suggested that HLA-B*5801 gene screening prior to allopurinol initiation is cost-effective for Asians but not Caucasians [68, 69]. Providing ethnicity-specific recommendations or explicitly specifying the ethnicity of target audience helps clarify this source of inconsistency and improves the precision of recommendations.

However, low methodological quality of guidance documents may also lead to discrepant recommendations and consequent variability in application. Documents with high quality (i.e., scoring above the upper quartile in at least three out of the six AGREE II domains) [16, 19-21, 36, 42, 46], included ambiguous prioritization of ULT drugs for hyperuricemia and of steroid options for acute attack those with low quality (i.e., scoring below the lower quartile in at least three out of the six AGREE II domains) [22, 37, 38, 44, 47, 52] provided. Among all domains assessed by the AGREE II instrument, those pertaining to stakeholder involvement, rigor of development, applicability and editorial independence could be primarily improved by standardizing developing processes, which consequently improved the reliability of recommendations. These results reinforced that it is better for clinicians to refer to high-quality guidance documents instead of the low-quality ones. However, when high-quality documents are unavailable in local language, referring to low-quality local documents might mislead clinical practice in the region. Selecting appropriate guidance documents to follow in clinical practice is thus more challenging for non-English speaking countries, including China [13]. Moreover, the oldest document included in our study was the South African Medical Association guideline, published in 2003, and no guidance

document in either English or Chinese was released in South African in the past 16 years. This finding suggested that some old documents might still affect regional practice. Efforts to timely update or declare the withdrawal of existing guidance documents are also critical for clinical practice.

Guidance documents are considered as the starting point to identify evidence gaps and to prioritize research questions [70]. Evidence gaps were discussed in the recommendations of treatment for asymptomatic hyperuricemia, by five [14, 15, 36, 37, 39, 43] out of 14 documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52], and of timing to initiate ULT, by two [16, 39] out of 14 documents [14-17, 21, 22, 36-40, 48, 49, 51, 52]. Although the rest of documents provided explicit recommendations, they based their recommendations either on indirect evidence or expert opinions. As for gout and hyperuricemia, evidence synthesis is warranted for the effects of pharmacological ULT in patients with asymptomatic hyperuricemia and for the optimal timing to initiate ULT in patients with the acute attack.

Strengths and limitations

Strengths of our review included a systematic approach to identify guidance documents pertaining to the diagnosis and management of hyperuricemia and gout. Both guidelines and consensus statements were evaluated and compared. We used the AGREE II instrument, an international, validated and rigorously developed tool, to assess the quality of document development and we tailored the AGREE II instrument to point-by-point scoring criteria (Supplementary File 1) to improve the objectivity and reproducibility of our study. We summarized all key recommendations, and compared and visualized the inconsistencies among them, providing a concise but informative overview for clinicians and researchers.

Our study also has limitations. Firstly, we only included documents published

in English or Chinese, which could lead to a risk of neglecting essential documents from regions not using English or Chinese as the first language. We attempted to mitigate this risk by tailoring our search strategy to identify the English versions of guidance documents published from these regions. Secondly, unconscious bias from a subjective rating of documents was inevitable. We avoided inviting co-authors of guidance documents as reviewers to prevent subconscious competing interest, and conducted two rounds of group discussions to minimize subjective bias. Thirdly, the AGREE II instrument itself has weaknesses [31, 59, 67, 71], although it was the most commonly used tool to assess the quality of guidance documents. The AGREE system assigned equal weight to all six domains, regardless of their relative importance [72]. Although better methods of guideline development and greater transparency of reporting are associated with more reliable recommendations, they do not guarantee better patient outcomes. Hence, the quality scores assessed by the AGREE II should be interpreted with caution, especially when used to indicate which guidelines to follow in clinical practice. Moreover, the subjective interpretation of scoring criteria impeded the replicability of AGREE II studies and direct comparison of quality scores in guidance documents provided by different reviews. Fourthly, our literature search was over 12 months old when the study was ready to publish, affecting the timeliness of our study. However, we decided not to update the literature at a late stage of the study, because of the infeasibility of bringing together all reviewers with another round of centralized training and appraisal, and the risk of inconsistent scoring criteria for each reviewer after a long time since their previous scoring. Moreover, a quick review of publications in PubMed, using the same search strategy (Supplementary table 1) and limiting the publication date from 1 September 2016 to 21 January 2019, did not found any new relevant documents, reassuring us of the timeliness of our study.

CONCLUSIONS

The methodological quality needs to be improved in the current guidelines and consensuses on the diagnosis and management of gout and hyperuricemia, as assessed by the AGREE II. Inconsistent recommendations are common, even in some key aspects. Promoting standard methods for guidance documents development, and synthesizing high-quality clinical evidence to fill in evidence gaps, are warranted to improve the quality of guidance documents.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

HT and SL conceived this study. QL, JSWK, and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC, LL, and XS designed the appraisal strategy of each included guideline and consensus. QL and XL searched literature search and extracted data. QL, XL, JW, HL, and SL assessed the quality of each document. QL analysed and visualized the outcomes. SC, AS, YC, AZ, XS, and HH provided critical review. QL, XL, and SL drafted the manuscript. All authors discussed actively in the protocol of the study.

DATA AVAILABILITY

All data in this paper were obtained from published studies. No additional data are available from the authors.

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TABLES AND FIGURES

Table 1. Characteristics of included guidelines and consensus statements

3e: Evidence, Expertise, Exchange; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; CS: consensus statement; CVD: cardiovascular diseases; ER: external review; EULAR: European League Against Rheumatism; LOE: level of evidence; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; Multi: multidisciplinary development group; NG: not given; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; Phy: physicians; Pt: patients; Rheu: rheumatologists; SLR: systematic literature review; SOR: strength of recommendation.

Document	Issuing organization	Year of publication	Country	Funding body	Target population	Target audience	Guideline development	Guideline review	Guideline update	Evidence base	LOE	SOR
Guidelines												
SAMA_2003 [51]	South African Medical Association	2003	South Africa	Pharmaceutical company	Gout	Phy	Multi	ER	Intermittent	NG	-	-
EULAR_2006 [18]	EULAR	2006	Europe	EULAR	Gout	NG	Rheu	NG	NG	SLR	+	+
MOH_MSR_AMM_2008 [49]	MOH, MSR, AMM	2008	Malaysia	Pharmaceutical company	Adults (>16y) with gout	Phy	Multi	ER	2012 or sooner	SLR	+	+
PRA_2008 [50]	Philippine Rheumatology Association	2008	Philippine	NG	Gout	Phy	NG	NG	Three or more years	SLR	+	+
UTAustin_2009 [52]	University of Texas at Austin	2009	US	University of Texas at Austin	Adults with gout	Phy	NG	ER	NG	SLR	+	+
EULAR_2011 [17]	EULAR	2011	Multination	Pharmaceutical company, ASCR	Gout	Phy	Multi	NG	NG	SLR	+	+

JSGNAM_2011 [48]	Japanese Society of Gout and Nucleic Acid Metabolism	2011	Japan	NG	Hyperuricemia or gout	NG	NG	ER	NG	SLR	+	+
ACR_2012 [14, 15]	ACR	2012	US	ACR, NIAMS, NIH	Gout	Phy	Multi	NG	Intermittent	SLR	+	-
SER_2013 [46]	Spanish Society of Rheumatology	2013	Spain	Pharmaceutical company	Gout	Phy	Multi	ER	Four years	SLR	+	+
SIR_2013 [45]	Italian Society of Rheumatology	2013	Italy	NG	Gout	Phy	Multi	NG	NG	SLR	+	+
FMOH_2014 [44]	Federal Ministry of Health (Nigeria)	2014	Nigeria	NG	Gout	Phy, Pts in Nigeria	Multi	NG	NG	NG	-	-
CRA_2016 [41]	Chinese Rheumatology Association	2016	China	NG	Gout in China	Phy	Multi	NG	NG	SLR	+	+
EULAR_2016 [16]	EULAR	2016	Europe	NG	Gout	Phy, Pts	Multi	ER	Intermittent	SLR	+	+
TRA_2016 [38]	Taiwan Rheumatology Association	2016	Taiwan, China	NG	Hyperuricemia or gout	Phy, Pts	Multi	NG	NG	NG	-	-
ACP_2017 [19, 20]	ACP	2017	US	ACP	Acute and recurrent gout	Phy	NG	ER	Five years	SLR	+	+
BSR_2017 [21]	The British Society for Rheumatology	2017	UK	No specific funding.	Gout in the UK	Phy	Multi	ER	Planned in 2020	SLR	+	+
Consensus statements												
CCCP_2012 [47]	Chinese College of Cardiovascular Physicians	2012	China	NG	Asymptomatic hyperuricemia with CVD	NG	NG	NG	NG	CS	-	-
3e_2013 [36]	3e Initiative	2013	Multination	Pharmaceutical company	Gout	NG	Rheu	NG	NG	SLR	+	+
CSE_2013 [37]	Chinese Society of Endocrinology	2013	China	NG	Hyperuricemia or gout	NG	NG	NG	NG	CS	-	-
3e_PT_2014 [40]	Portuguese 3e Initiative	2014	Portugal	NG	Gout in Portuguese	NG	Rheu	NG	NG	SLR	+	+
3e_AU_NZ_2015 [43]	Australian and New Zealand 3e Initiative	2015	Multination	NG	Gout	NG	Rheu	NG	NG	SLR	+	+

ACR_EULAR_2015 [42]	ACR/EULAR	2015	Multination	ACR, EULAR	Gout	NG	NG	ER	Intermittent	SLR	-	-
T2T_2016 [39]	NG	2016	Multination	Pharmaceutical company	Gout	NG	Rheu	ER	NG	SLR	+	+
CRA_multi_2017 [22]	Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases	2017	China	NG	Hyperuricemia	Phy	Multi	NG	NG	CS	-	-

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.

Figure 2. Standardized domain scores for each guidance document

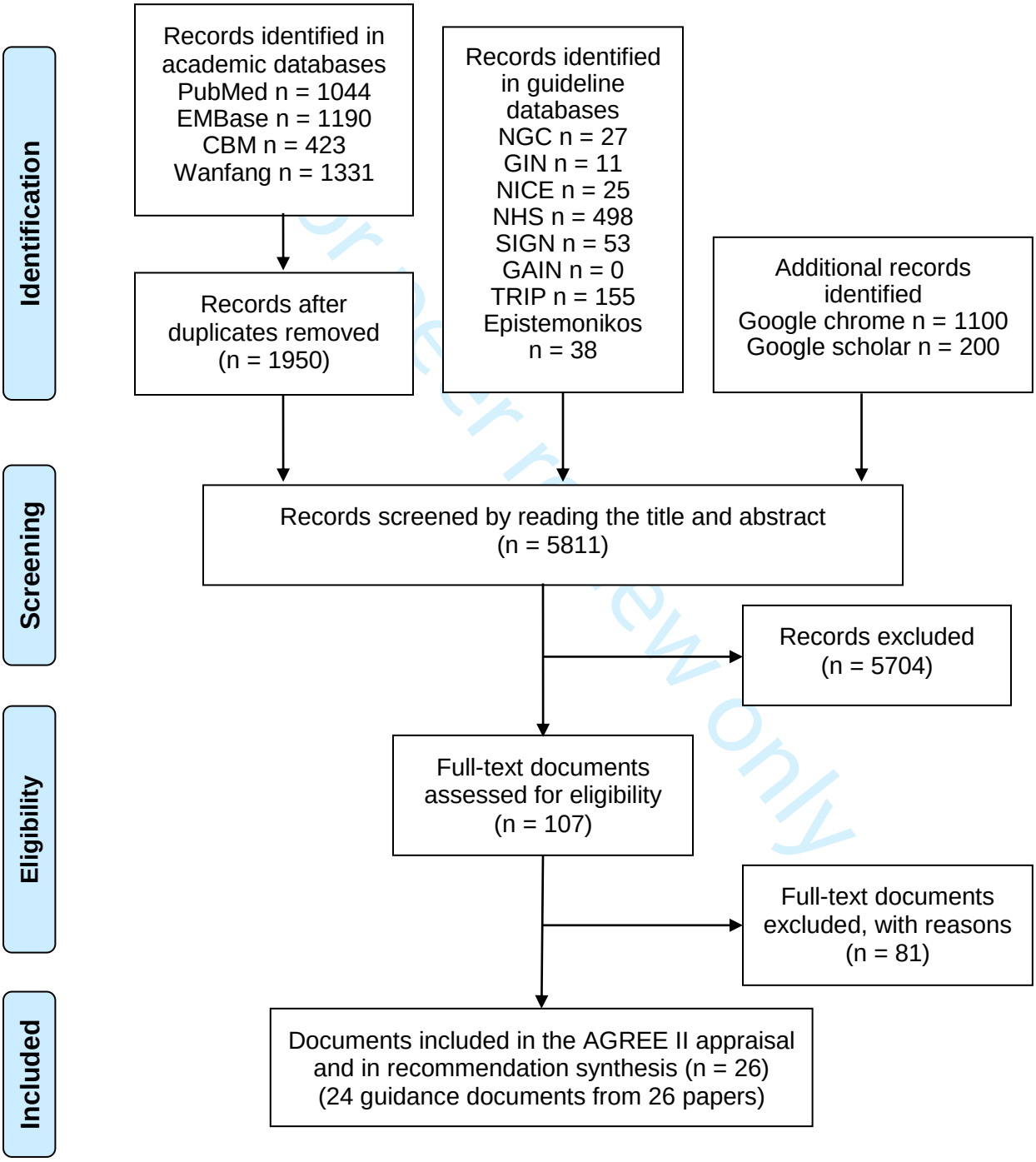
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia

3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

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.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

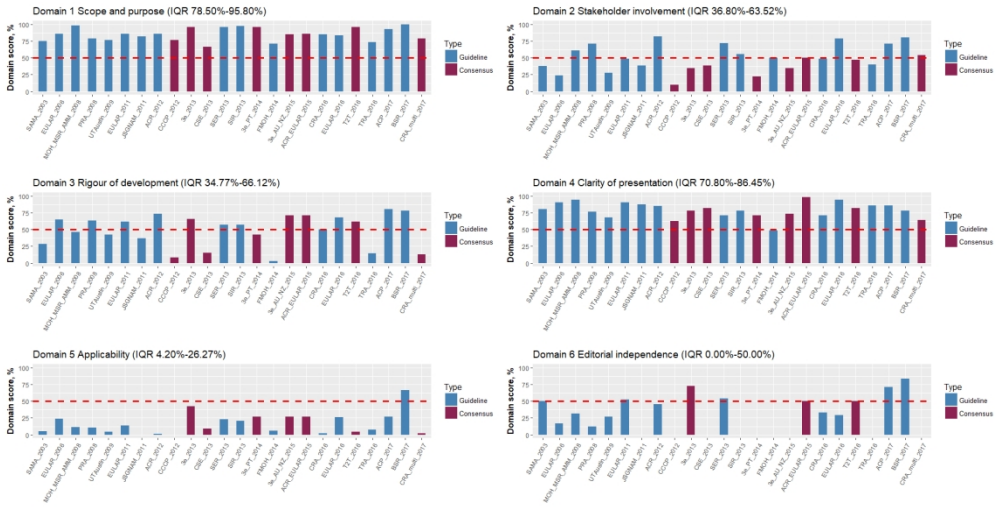


Figure 2. Standardized domain scores for each guidance document3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

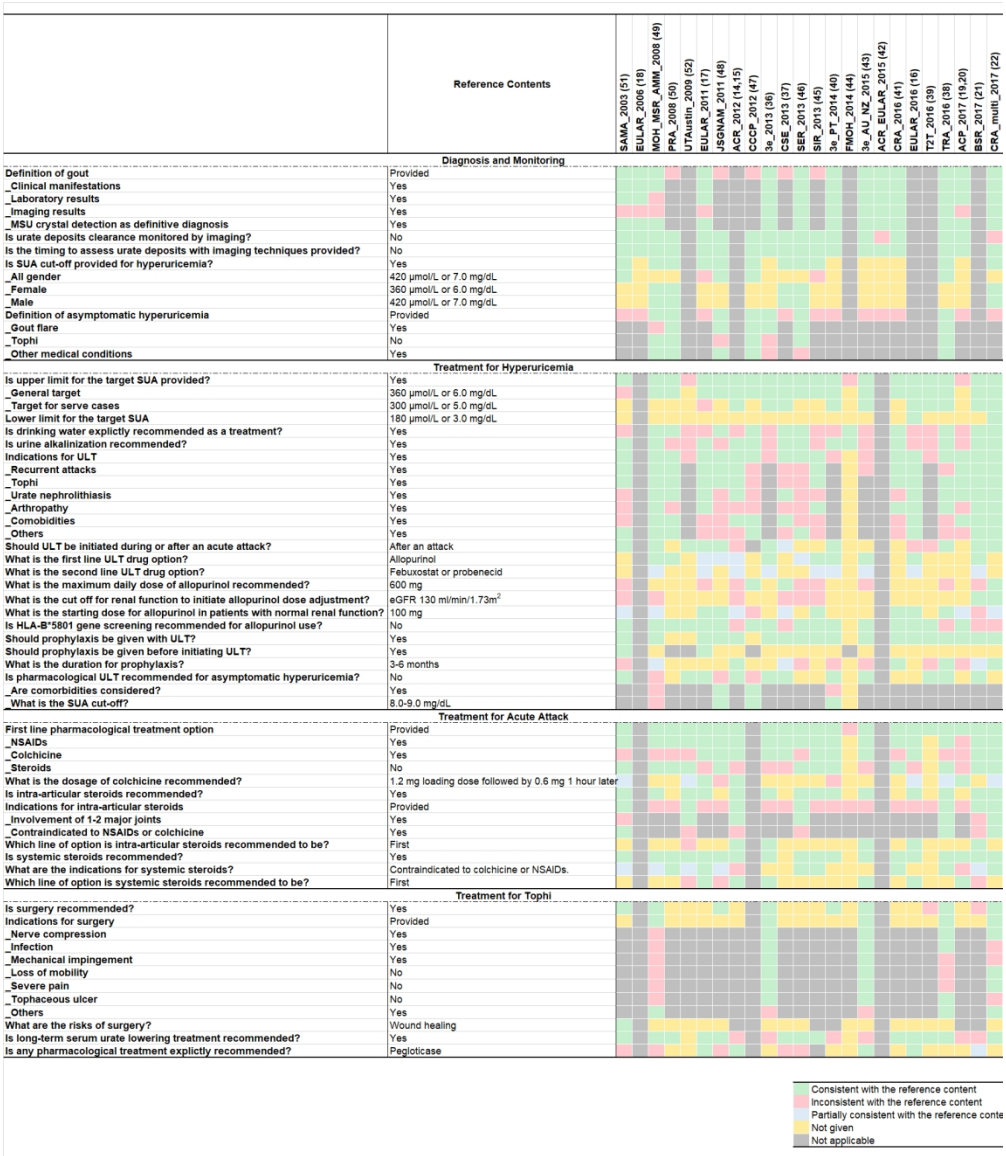


Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Supplementary Materials

Contents

Supplementary Table 1. Search strategy in PubMed

1	urate* OR uric acid OR gout OR hyperuricemia OR hyperuricaemia
2	guideline OR guideline* OR consensus OR policy OR polic* OR statement* OR recommendation*
3	1 AND 2

Supplementary Table 2. Search strategy in EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	gout.m_titl.
6	uric acid.m_titl.
7	urate$.m_titl.
8	hyperuric?emia.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.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

Supplementary Table 3. Searches in guideline databases

Databases	Date of search	Search strategy	Results found	Full text screened	Included documents	URL
National Guideline Clearinghouse	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	27	6	4	www.guideline.gov
Guidelines International Network	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, Search mode: Guidelines	11	5	5	www.g-i-n.net
National Institute for Health and Care Excellence	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	25	2	0	www.nice.org.uk
National Health Service	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter type: guidance and policy	498	5	3	www.evidence.nhs.uk
Scottish Intercollegiate Guidelines Network	2017/07/24	NA	53	0	0	www.sign.ac.uk/our-guidelines.html
Guidelines and Audit Implementation Network	2017/07/24	“hyperuricaemia” OR “hyperuricemia” OR “gout”	0	0	0	rqia.org.uk/search-result
Turning Research Into Practice Database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: all secondary evidence	155	9	3	www.tripdatabase.com
Epistemonikos database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: Broad syntheses OR Structured summaries	38	2	1	www.epistemonikos.org
Chinese Biomedical Literature Database	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	423	7	5	202.115.54.56/index.jsp
Wanfang Data	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	1331	19	4	www.wanfangdata.com.cn/

Abbreviations: NA: Not applicable.

Supplementary Table 4. Excluded studies and reasons for exclusion

First author	Year	Reason for exclusion
Wuthrich [68]	2016	Review
Ceriotti [69]	2016	Primary study
Liote [70]	2016	Editorial
de Lautour [71]	2016	Primary study
de Lautour [72]	2014	Conference abstract
Dalbeth [73]	2015	Review
Terslev [74]	2015	Primary study
Turk [75]	2016	Not providing specific recommendations for hyperuricemia or gout
Stewart Coats [76]	2016	Editorial
Sullivan [77]	2015	Review
Gutierrez [78]	2015	Primary study
Grainger [79]	2015	Primary study
Robinson [80]	2015	Review
Chaudhary [81]	2013	Review
Bakris [82]	2014	Multimedia section
Terkeltaub [83]	2013	Review
Lyseng-Williamson [84]	2013	Review
Deodhar [85]	2013	Review
Simao [86]	2012	Review
Stamp [87]	2011	Review
Jansen [88]	2010	Not produced by related professional associations, institutes, societies, or communities
Grainger [89]	2009	Review
Grainger [90]	2008	Review
Dalbeth [91]	2007	Review
Jordan [92]	2007	Replaced by updated versions from the same organization
Becker [93]	2007	Not providing specific recommendations for hyperuricemia or gout

Zhang [55]	2006	Replaced by updated versions from the same organization
Caramia [94]	2004	Review
Terkeltaub [95]	2003	Case report
Cleland [96]	1995	Review
Hande [97]	1984	Case series
Committee on the Review of Medicines [98]	1978	Not providing specific recommendations for hyperuricemia or gout
Mourgues [99]	2016	Conference abstract
Bakris [100]	1970	Not providing specific recommendations for hyperuricemia or gout
Pai [101]	2015	Review
Vargas-Santos [102]	2016	Review
Filiopoulos [103]	2016	Comment letter
Chinchilla [104]	2016	Review
Rimler [105]	2016	Review
Saito [106]	2016	Not providing specific recommendations for hyperuricemia or gout
Mody [107]	2015	Review
Richette [108]	2014	Conference abstract
Richette [109]	2014	Conference abstract
Gutierrez [110]	2014	Conference abstract
Furst [111]	2013	Not providing specific recommendations for hyperuricemia or gout
Hershfield [112]	2013	Not providing specific recommendations for hyperuricemia or gout
Andres [113]	2012	Conference abstract
Stevenson [114]	2011	Technology appraisal
Diaz-Borjon [115]	2009	Review
Furst [116]	2010	Not providing specific recommendations for hyperuricemia or gout
Taylor [117]	2009	Primary study
Taylor [118]	2008	Primary study
Bussieres [119]	2008	Not providing specific recommendations for hyperuricemia or gout
Brooks [120]	2007	Review

Bestermann [121]	2005	Not providing specific recommendations for hyperuricemia or gout
Schumacher Jr [122]	2004	Review
Bartlett [123]	2002	Not providing specific recommendations for hyperuricemia or gout
Furst [124]	2013	Not providing specific recommendations for hyperuricemia or gout
Newberry [125]	2017	Review
Shekelle [126]	2017	Review
Sandberg [127]	2015	Not providing specific recommendations for hyperuricemia or gout
Kallinich [128]	2007	Not providing specific recommendations for hyperuricemia or gout
Preminger [129]	2007	Not providing specific recommendations for hyperuricemia or gout
TA164 [130]	2008	Technology appraisal
Phoon [131]	2012	Not providing specific recommendations for hyperuricemia or gout
Li [132]	2011	Review
Zhang [133]	2013	Review
Deng [134]	2016	Primary study
Chinese Rheumatology Association [135]	2004	Replaced by updated versions from the same organization
Chinese College of Cardiovascular Physicians [136]	2010	Replaced by updated versions from the same organization
Chinese Rheumatology Association [137]	2011	Replaced by updated versions from the same organization
National Department of Health, Pretoria, South Africa [138]	2006	Not providing specific recommendations for hyperuricemia or gout
European Medicines Agency [139]	2012	Not providing specific recommendations for hyperuricemia or gout
Agency for Healthcare Research and Quality [140]	2017	Review
Agency for Healthcare Research and Quality [141]	2017	Review
National Institute for Health and Care Excellence [142]	2013	Technology appraisal
Agency for Healthcare Research and Quality [143]	2016	Review
National Health System, United Kingdom [144]	2013	Not providing specific recommendations for hyperuricemia or gout
Canadian Expert Drug Advisory Committee [145]	2011	Not providing specific recommendations for hyperuricemia or gout
CME Academic Detailing Service [146]	2013	Presented as a 'handout', not a clinical practice guideline.
Henderson [147]	2015	Not released by a professional association

Supplementary Table 5. Domain score for each included guidance document

Document	Domain 1, %	Domain 2, %	Domain 3, %	Domain 4, %	Domain 5, %	Domain 6, %
3e_2013 [36]	95.8	34.7	65.6	77.8	42.7	72.9
3e_AU_NZ_2015 [43]	84.7	34.7	71.4	73.6	27.1	0.0
3e_PT_2014 [40]	95.8	22.2	42.7	70.8	27.1	0.0
ACP_2017 [19, 20]	93.1	70.8	80.2	86.1	27.1	70.8
ACR_2012 [14, 15]	86.1	81.9	73.4	84.7	1.0	45.8
ACR_EULAR_2015 [42]	86.1	50.0	71.4	98.6	27.1	50.0
BSR_2017 [21]	100.0	80.6	78.1	77.8	66.7	83.3
CCCP_2012 [47]	76.4	9.7	8.3	62.5	0.0	0.0
CRA_2016 [41]	84.7	48.6	50.5	70.8	2.1	33.3
CRA_multi_2017 [22]	79.2	54.2	13.0	63.9	2.1	0.0
CSE_2013 [37]	66.7	38.9	15.6	81.9	9.4	0.0
EULAR_2006 [18]	86.1	23.6	65.1	90.3	24.0	16.7
EULAR_2011 [17]	86.1	48.6	61.5	90.3	13.5	52.1
EULAR_2016 [16]	83.3	79.2	67.7	94.4	26.0	29.2
FMOH_2014 [44]	70.8	50.0	3.1	48.6	6.3	0.0
JSGNAM_2011 [48]	81.9	38.9	37.0	87.5	0.0	0.0
MOH_MSR_AMM_2008 [49]	98.6	61.1	46.4	94.4	11.5	31.3
PRA_2008 [50]	79.2	70.8	63.5	76.4	10.4	12.5
SAMA_2003 [51]	75.0	37.5	28.1	80.6	5.2	50.0
SER_2013 [46]	95.8	72.2	56.8	70.8	22.9	54.2
SIR_2013 [45]	97.2	55.6	56.8	77.8	20.8	0.0
T2T_2016 [39]	95.8	47.2	61.5	81.9	4.2	50.0
TRA_2016 [38]	73.6	40.3	14.1	86.1	7.3	0.0
UTAustin_2009 [52]	76.4	27.8	42.2	68.1	4.2	27.1
Median	85.4	48.6	56.8	79.2	10.9	28.1
Minimum	66.7	9.7	3.1	48.6	0.0	0.0
Maximum	100.0	81.9	80.2	98.6	66.7	83.3

Supplementary Table 6. Mean scores across reviewers for the individual AGREE II domain items

Document	Domain 1			Domain 2			Domain 3								Domain 4			Domain 5				Domain 6	
Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3e_2013 [36]	6.8	6.5	7.0	7.0	1.3	1.0	6.3	3.8	6.3	5.8	5.8	6.8	4.0	1.0	6.0	7.0	4.0	6.8	1.0	5.3	1.3	7.0	3.8
3e_AU_NZ_2015 [43]	6.0	5.5	6.8	5.8	1.0	2.5	6.5	6.8	7.0	6.5	6.5	6.8	1.3	1.0	5.8	6.0	4.5	5.8	1.0	2.8	1.0	1.0	1.0
3e_PT_2014 [40]	6.5	7.0	6.8	4.8	1.3	1.0	2.8	2.3	5.5	3.5	5.5	6.8	1.3	1.0	5.5	6.3	4.0	4.5	1.3	2.8	2.0	1.0	1.0
ACP_2017 [19, 20]	6.0	6.8	7.0	6.3	5.3	4.3	6.8	6.8	6.5	5.0	6.5	5.3	4.8	5.0	5.3	6.8	6.5	2.5	1.8	5.3	1.0	4.0	6.5
ACR_2012 [14, 15]	6.5	5.5	6.5	7.0	5.3	5.5	7.0	7.0	6.8	6.0	5.8	6.0	1.5	3.3	5.8	7.0	5.5	1.0	1.0	1.0	1.3	3.3	4.3
ACR_EULAR_2015 [42]	6.5	5.0	7.0	5.3	4.8	2.0	7.0	6.8	5.3	6.0	7.0	5.5	1.8	3.0	6.8	7.0	7.0	3.8	4.0	1.8	1.0	3.8	4.3
BSR_2017 [21]	7.0	7.0	7.0	5.5	5.3	6.8	7.0	6.0	6.5	6.8	6.3	6.0	5.0	2.0	6.8	6.8	3.5	4.8	4.8	6.5	4.0	7.0	5.0
CCCP_2012 [47]	6.8	3.0	7.0	2.0	1.0	1.8	1.0	1.0	1.0	1.0	3.8	2.0	1.3	1.0	4.5	5.8	4.0	1.0	1.0	1.0	1.0	1.0	1.0
CRA_2016 [41]	6.3	5.0	7.0	5.5	1.0	5.3	5.0	3.3	6.3	3.5	6.0	5.5	1.8	1.0	5.3	6.5	4.0	1.3	1.0	1.3	1.0	1.0	5.0
CRA_multi_2017 [22]	7.0	3.5	6.8	4.8	1.3	6.8	1.0	1.0	1.0	1.3	5.0	2.8	1.3	1.0	5.0	6.5	3.0	1.0	1.3	1.0	1.3	1.0	1.0
CSE_2013 [37]	7.0	1.8	6.3	3.0	1.0	6.0	1.0	1.0	2.0	1.0	5.0	3.5	1.0	1.0	5.5	5.5	6.8	3.0	1.0	1.0	1.3	1.0	1.0
EULAR_2006 [18]	6.0	5.5	7.0	5.0	1.0	1.3	7.0	7.0	5.8	4.3	6.0	5.8	1.3	2.3	6.0	6.8	6.5	1.0	2.5	5.3	1.0	3.0	1.0
EULAR_2011 [17]	6.5	5.0	7.0	5.0	1.0	5.8	4.0	4.5	6.8	6.0	7.0	7.0	1.3	1.0	5.8	6.8	6.8	1.3	1.3	3.8	1.0	3.8	4.5
EULAR_2016 [16]	6.3	4.8	7.0	5.8	5.0	6.5	5.0	2.0	6.3	6.8	6.0	6.5	6.0	2.0	6.5	6.8	6.8	3.0	1.3	5.0	1.0	1.5	4.0
FMOH_2014 [44]	6.5	2.8	6.5	5.3	1.0	5.8	1.0	1.0	1.0	1.0	2.0	1.5	1.0	1.0	3.0	4.5	4.3	1.0	1.3	2.3	1.0	1.0	1.0
JSGNAM_2011 [48]	5.3	5.5	7.0	1.8	4.3	4.0	1.3	1.0	6.8	3.3	6.3	3.8	2.5	1.0	6.8	6.3	5.8	1.0	1.0	1.0	1.0	1.0	1.0
MOH_MSR_AMM_2008 [49]	6.8	7.0	7.0	5.5	1.5	7.0	4.3	1.0	5.8	1.5	5.8	4.8	2.5	4.8	6.5	6.8	6.8	1.8	3.0	1.0	1.0	4.0	1.8
PRA_2008 [50]	6.5	5.5	5.3	3.8	5.0	7.0	5.0	4.3	7.0	4.8	6.5	4.8	1.3	5.0	5.3	6.5	5.0	1.8	1.3	2.5	1.0	1.0	2.5
SAMA_2003 [51]	6.5	3.0	7.0	4.0	1.3	4.5	1.0	1.0	1.0	4.0	6.5	2.8	2.5	2.8	5.0	6.5	6.0	1.0	2.0	1.3	1.0	7.0	1.0
SER_2013 [46]	7.0	6.3	7.0	6.8	5.0	4.3	3.3	1.0	7.0	4.0	6.8	4.8	2.0	6.5	5.8	6.8	4.3	3.5	2.3	2.8	1.0	6.5	2.0
SIR_2013 [45]	6.8	6.8	7.0	6.3	1.0	5.8	4.0	6.8	6.3	4.3	6.3	5.5	1.3	1.0	6.3	6.8	4.0	2.5	1.0	4.5	1.0	1.0	1.0
T2T_2016 [39]	6.3	7.0	7.0	5.3	5.0	1.3	7.0	6.5	6.5	6.5	3.3	4.0	1.8	2.0	5.0	6.3	6.5	2.0	1.0	1.0	1.0	3.5	4.5
TRA_2016 [38]	5.8	3.5	7.0	5.0	1.5	3.8	1.0	1.3	1.0	1.3	5.5	2.5	1.3	1.0	5.5	6.5	6.5	1.0	1.5	2.3	1.0	1.0	1.0
UTAustin_2009 [52]	7.0	2.8	7.0	3.0	1.0	4.0	4.3	2.0	7.0	2.5	4.3	5.3	2.0	1.0	4.8	5.3	5.3	1.3	1.5	1.3	1.0	4.0	1.3

Supplementary Table 7. Scores for each individual AGREE II domain items by each reviewer

	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14	Item15	Item16	Item17	Item18	Item19	Item20	Item21	Item22	Item23
3e_2013 [36]																							
Rev1	7	7	7	7	1	1	6	4	4	5	7	7	2	1	6	7	4	7	1	5	1	7	4
Rev2	6	7	7	7	1	1	6	2	7	5	6	7	4	1	6	7	4	7	1	6	1	7	4
Rev3	7	5	7	7	2	1	7	5	7	6	5	6	5	1	5	7	4	7	1	5	2	7	3
Rev4	7	7	7	7	1	1	6	4	7	7	5	7	5	1	7	7	4	6	1	5	1	7	4
3e_AU_NZ_2015 [43]																							
Rev1	5	5	7	7	1	2	7	7	7	7	7	7	2	1	5	6	4	6	1	2	1	1	1
Rev2	7	5	7	7	1	1	5	7	7	6	6	7	1	1	6	7	4	6	1	4	1	1	1
Rev3	5	7	7	4	1	4	7	7	7	7	7	7	1	1	6	5	6	6	1	2	1	1	1
Rev4	7	5	6	5	1	3	7	6	7	6	6	6	1	1	6	6	4	5	1	3	1	1	1
3e_PT_2014 [40]																							
Rev1	6	7	7	5	1	1	3	1	7	3	6	7	2	1	5	6	4	4	1	5	1	1	1
Rev2	6	7	7	5	1	1	3	1	7	3	6	7	1	1	6	7	4	6	1	3	1	1	1
Rev3	7	7	6	5	2	1	2	1	6	5	4	6	1	1	5	6	4	4	2	2	5	1	1
Rev4	7	7	7	4	1	1	3	6	2	3	6	7	1	1	6	6	4	4	1	1	1	1	1
ACP_2017 [19, 20]																							
Rev1	6	7	7	6	5	4	7	7	7	5	7	5	5	5	5	7	7	2	2	4	1	4	7
Rev2	6	7	7	6	5	4	7	7	7	5	7	5	5	4	6	7	7	4	3	7	1	4	7
Rev3	6	7	7	6	6	3	6	6	6	6	6	5	4	5	5	6	6	2	1	5	1	4	6
Rev4	6	6	7	7	5	6	7	7	6	4	6	6	5	6	5	7	6	2	1	5	1	4	6
ACR_2012 [14, 15]																							
Rev1	6	5	7	7	5	7	7	7	6	6	6	5	2	3	5	7	4	1	1	1	1	3	4
Rev2	6	7	7	7	7	4	7	7	7	6	6	5	2	3	6	7	7	1	1	1	1	4	4
Rev3	7	5	7	7	5	7	7	7	7	6	5	7	1	3	5	7	7	1	1	1	2	3	4
Rev4	7	5	5	7	4	4	7	7	7	6	6	7	1	4	7	7	4	1	1	1	1	3	5
ACR_EULAR_2015 [42]																							
Rev1	6	5	7	6	6	2	7	7	7	7	7	5	2	3	7	7	7	3	3	1	1	4	4

Rev2	6	5	7	5	6	1	7	7	6	6	7	5	2	3	7	7	7	5	7	1	1	4	4
Rev3	7	5	7	5	6	2	7	7	7	6	7	5	2	3	7	7	7	3	3	1	1	3	4
Rev4	7	5	7	5	1	3	7	6	1	5	7	7	1	3	6	7	7	4	3	4	1	4	5
BSR_2017 [21]																							
Rev1	7	7	7	6	5	7	7	6	6	7	6	6	5	2	7	7	4	5	4	7	2	7	5
Rev2	7	7	7	6	5	7	7	6	6	6	7	5	5	2	7	7	3	5	5	7	5	7	5
Rev3	7	7	7	4	5	6	7	7	7	7	5	6	5	1	6	6	3	4	5	6	2	7	5
Rev4	7	7	7	6	6	7	7	5	7	7	7	7	5	3	7	7	4	5	5	6	2	7	5
CCCP_2012 [47]																							
Rev1	6	3	7	2	1	2	1	1	1	1	3	1	2	1	3	6	4	1	1	1	1	1	1
Rev2	7	3	7	2	1	1	1	1	1	1	4	3	1	1	4	5	4	1	1	1	1	1	1
Rev3	7	3	7	2	1	1	1	1	1	1	4	2	1	1	6	6	4	1	1	1	1	1	1
Rev4	7	3	7	2	1	3	1	1	1	1	4	2	1	1	5	6	4	1	1	1	1	1	1
CRA_2016 [41]																							
Rev1	5	5	7	6	1	4	5	3	7	3	7	5	2	1	5	7	4	1	1	1	1	1	4
Rev2	7	5	7	6	1	5	4	3	6	4	6	5	3	1	6	7	4	1	1	1	1	1	4
Rev3	7	5	7	5	1	6	5	3	6	1	5	6	1	1	5	6	4	1	1	2	1	1	6
Rev4	6	5	7	5	1	6	6	4	6	6	6	6	1	1	5	6	4	2	1	1	1	1	6
CRA_multi_2017 [22]																							
Rev1	7	3	7	5	1	7	1	1	1	1	5	3	2	1	5	7	2	1	1	1	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	2	5	2	1	1	5	7	3	1	1	1	1	1	1
Rev3	7	3	7	4	2	6	1	1	1	1	5	5	1	1	5	5	3	1	1	1	2	1	1
Rev4	7	5	6	5	1	7	1	1	1	1	5	1	1	1	5	7	4	1	2	1	1	1	1
CSE_2013 [37]																							
Rev1	7	1	6	3	1	6	1	1	2	1	5	5	1	1	5	6	7	3	1	1	1	1	1
Rev2	7	3	6	4	1	6	1	1	3	1	5	3	1	1	6	6	7	3	1	1	1	1	1
Rev3	7	1	7	2	1	7	1	1	2	1	5	3	1	1	6	6	6	3	1	1	2	1	1
Rev4	7	2	6	3	1	5	1	1	1	1	5	3	1	1	5	4	7	3	1	1	1	1	1
EULAR_2006 [18]																							
Rev1	5	5	7	5	1	1	7	7	5	3	6	5	2	1	5	7	7	1	2	5	1	4	1

Rev2	6	5	7	5	1	1	7	7	6	5	6	6	1	1	6	7	6	1	4	6	1	4	1
Rev3	7	7	7	5	1	1	7	7	6	5	7	6	1	1	7	7	7	1	1	5	1	1	1
Rev4	6	5	7	5	1	2	7	7	6	4	5	6	1	6	6	6	6	1	3	5	1	3	1
EULAR_2011 [17]																							
Rev1	6	5	7	4	1	7	4	1	7	7	7	7	2	1	5	7	7	2	1	2	1	4	4
Rev2	6	5	7	5	1	3	4	7	7	4	7	7	1	1	6	7	7	1	1	5	1	4	4
Rev3	7	5	7	6	1	7	4	4	7	7	7	7	1	1	6	7	7	1	1	4	1	4	6
Rev4	7	5	7	5	1	6	4	6	6	6	7	7	1	1	6	6	6	1	2	4	1	3	4
EULAR_2016 [16]																							
Rev1	7	7	7	6	5	7	5	2	7	7	7	7	6	1	7	7	7	2	2	5	1	1	4
Rev2	7	1	7	6	5	7	5	2	7	7	6	7	6	3	7	7	7	4	1	6	1	1	4
Rev3	5	5	7	5	5	5	5	1	6	6	5	6	6	2	5	6	6	4	1	4	1	1	4
Rev4	6	6	7	6	5	7	5	3	5	7	6	6	6	2	7	7	7	2	1	5	1	3	4
FMOH_2014 [44]																							
Rev1	7	3	7	6	1	4	1	1	1	1	2	1	1	1	3	1	4	1	1	2	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	1	2	1	1	1	4	4	4	1	2	3	1	1	1
Rev3	6	2	5	5	1	6	1	1	1	1	1	2	1	1	2	7	6	1	1	1	1	1	1
Rev4	6	3	7	5	1	6	1	1	1	1	3	2	1	1	3	6	3	1	1	3	1	1	1
JSGNAM_2011 [48]																							
Rev1	5	5	7	2	4	4	1	1	6	3	6	3	2	1	7	7	4	1	1	1	1	1	1
Rev2	6	5	7	2	4	4	1	1	7	4	6	4	3	1	7	6	7	1	1	1	1	1	1
Rev3	5	7	7	1	4	4	1	1	7	1	7	4	2	1	7	6	7	1	1	1	1	1	1
Rev4	5	5	7	2	5	4	2	1	7	5	6	4	3	1	6	6	5	1	1	1	1	1	1
MOH_MSR_AMM_2008 [49]																							
Rev1	6	7	7	5	1	7	4	1	5	1	6	5	2	4	7	7	7	2	3	1	1	4	1
Rev2	7	7	7	5	3	7	4	1	6	2	6	4	3	5	6	7	7	3	5	1	1	4	2
Rev3	7	7	7	7	1	7	4	1	6	1	6	5	2	5	7	7	7	1	1	1	1	4	2
Rev4	7	7	7	5	1	7	5	1	6	2	5	5	3	5	6	6	6	1	3	1	1	4	2
PRA_2008 [50]																							
Rev1	5	3	5	4	5	7	5	1	7	4	7	5	1	5	5	7	4	2	1	2	1	1	2

Rev2	7	7	4	3	5	7	5	6	7	4	6	4	2	5	5	6	7	3	2	3	1	1	4
Rev3	7	7	7	4	5	7	5	5	7	6	7	5	1	5	6	7	5	1	1	2	1	1	2
Rev4	7	5	5	4	5	7	5	5	7	5	6	5	1	5	5	6	4	1	1	3	1	1	2
SAMA_2003 [51]																							
Rev1	6	3	7	5	1	4	1	1	1	5	7	3	2	3	3	6	7	1	1	2	1	7	1
Rev2	7	3	7	4	1	5	1	1	1	5	7	2	4	2	5	7	4	1	5	1	1	7	1
Rev3	7	3	7	2	1	5	1	1	1	1	7	3	1	1	6	7	7	1	1	1	1	7	1
Rev4	6	3	7	5	2	4	1	1	1	5	5	3	3	5	6	6	6	1	1	1	1	7	1
SER_2013 [46]																							
Rev1	7	6	7	7	5	4	3	1	7	3	7	5	2	5	5	6	4	2	2	2	1	7	2
Rev2	7	6	7	6	5	3	3	1	7	5	6	4	2	7	6	7	4	4	5	3	1	5	2
Rev3	7	7	7	7	5	5	3	1	7	3	7	6	2	7	7	7	4	4	1	4	1	7	2
Rev4	7	6	7	7	5	5	4	1	7	5	7	4	2	7	5	7	5	4	1	2	1	7	2
SIR_2013 [45]																							
Rev1	7	7	7	6	1	7	4	7	5	3	7	5	2	1	7	7	4	2	1	4	1	1	1
Rev2	7	7	7	6	1	4	4	7	7	5	6	5	1	1	6	7	4	4	1	6	1	1	1
Rev3	7	7	7	6	1	6	4	7	7	6	7	6	1	1	6	7	4	1	1	4	1	1	1
Rev4	6	6	7	7	1	6	4	6	6	3	5	6	1	1	6	6	4	3	1	4	1	1	1
T2T_2016 [39]																							
Rev1	6	7	7	5	5	1	7	7	7	7	3	3	2	1	4	6	7	3	1	1	1	4	2
Rev2	7	7	7	6	5	1	7	7	7	7	4	5	2	5	6	7	7	1	1	1	1	4	4
Rev3	5	7	7	5	5	2	7	6	6	6	2	3	2	1	5	6	6	3	1	1	1	3	6
Rev4	7	7	7	5	5	1	7	6	6	6	4	5	1	1	5	6	6	1	1	1	1	3	6
TRA_2016 [38]																							
Rev1	5	3	7	5	1	4	1	1	1	1	6	2	2	1	6	7	7	1	1	2	1	1	1
Rev2	6	3	7	5	1	7	1	1	1	2	6	2	1	1	6	7	7	1	3	3	1	1	1
Rev3	6	3	7	5	3	1	1	2	1	1	5	4	1	1	5	6	6	1	1	2	1	1	1
Rev4	6	5	7	5	1	3	1	1	1	1	5	2	1	1	5	6	6	1	1	2	1	1	1
UTAustin_2009 [52]																							
Rev1	7	3	7	4	1	4	4	1	7	3	4	5	2	1	3	4	4	1	1	1	1	4	2

Rev2	7	3	7	2	1	4	4	1	7	2	4	5	2	1	5	6	7	2	3	1	1	4	1
Rev3	7	2	7	2	1	4	4	1	7	1	6	5	2	1	6	6	7	1	1	1	1	4	1
Rev4	7	3	7	4	1	4	5	5	7	4	3	6	2	1	5	5	3	1	1	2	1	4	1

Supplementary Table 8. Summary of recommendations for the diagnosis of gout and hyperuricemia by included guidance document

IE: insufficient evidence; MSU: monosodium urate; NA: not applicable; NG: not given; SUA: serum uric acid.

	SAMA_2003 [51]	EULAR_2006 [18]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	EULAR_2011 [17]	JSGNAM_2011 [48]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	3e_AU_NZ_2015 [43]	ACR_EULAR_2015 [42]	CRA_2016 [41]	TRA_2016 [38]	ACP_2017 [19, 20]	CRA_multi_2017 [22]
Diagnosis of gout	+	+	+	NG	+	NG	NG	+	NG	+	NG	+	+	+	+	+	+	+
_Clinical manifestations	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Laboratory results	+	+	-	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Imaging results	-	+*	-	NA	-	NA	NA	+	NA	+	NA	+	+	+	+	+	IE	+
_MSU crystal as definitive diagnosis	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
Monitor urate deposits clearance by imaging	-	-	-	-	-	-	-	-	-	IE	-	-	-	+	-	-	-	+
Is the timing to assess urate deposits with imaging techniques provided?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUA for hyperuricemia, µmol/L [mg/dL]	+	NG	+	+	+	+	+	NG	+	+	+	NG	NG	NG	NG	+	NG	+
_All gender	420	NG	NG	NG	[6.8]	[7.0]	420 [7.0]	NG	NG	NG	404 [6.8]	NG	NG	NG	NG	[7.0]	NG	NG
_Female	NG	NG	360 [6.0]	357 [6.0]	NG	NG	NG	NG	360	[6.0]	NG	NG	NG	NG	NG	NG	NG	360
_Male	NG	NG	420 [7.0]	416 [7.0]	NG	NG	NG	NG	420	[7.0]	NG	NG	NG	NG	NG	NG	NG	420
Diagnosis of asymptomatic hyperuricemia	NG	NG	+	+	NG	+	+	+.	NG	+	NG	NG	NG	NG	NG	+	NG	NG
_Gout flare	NA	NA	-	+	NA	+	+	+	NA	+	NA	NA	NA	NA	NA	+	NA	NA
_Tophi	NA	NA	-	-	NA	+	-	+	NA	-	NA	NA	NA	NA	NA	-	NA	NA
_Additional medical conditions†	NA	NA	+	+	NA	+	+	-	NA	-	NA	NA	NA	NA	NA	+	NA	NA

*Imaging results are considered for chronic gout, but not for early/acute gout.

†Additional medical conditions considered in the definition of asymptomatic hyperuricemia included complications of gout [47], renal disorder [48], signs or symptoms of

urate deposition [49], and uric acid nephrolithiasis [50]. One document provided a general statement of any clinical presentations [38]. One document explicitly stated that the inclusion of patients with pre-existing renal or cardiovascular disease was allowed [36].

Supplementary Table 9. Summary of recommendations for the treatment of hyperuricemia by included guidance documents

A: allopurinol; Aft: (to initiate ULT) after an acute attack; B: benzbromarone; CCr: creatinine clearance rate; Cr: serum creatinine; CKD: chronic kidney disease; D: (to initiate ULT) during an acute attack; eGFR: estimated glomerular filtration rate; F: febuxostat; IE: insufficient evidence; m: month(s); NA: not applicable; NG: not given; P: probenecid; RF: renal function; SUA: serum uric acid; U: uricosurics without specification; ULT: urate lowering therapy; w: week(s); y: year.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Upper limit for target SUA, μmol/L [mg/dL]																						
_General target*	300	360 [6.0]	[6.0]	NG	[6.0]	[6.0]	[6.0]	357 [6.0]	360 [6.0]	360	[6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]	360 [6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]
_Target for serve cases†	NG	NG	NG	NG	[4.0]	NG	[5.0]	NG	300	300	NG	NG	300 [5.0]	NG	300	NG	300 [5.0]	300 [5.0]	300 [5.0]	NG	300	300 [5.0]
Lower limit for target SUA, μmol/L [mg/dL]	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	[3.0]	NG	NG	NG	NG	180
Drinking water	-	+	+	-	-	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+
Urine alkalinisation	+	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	+	+
Indications for ULT	+	+	+	-	+	+	+	+	-	+	+	+	-	NG	-	+	+	-	+	+	+	+
_Recurrent attacks	+, >2	+, >3/y	+	NA	+, >1/y	+	+, ≥2/y	-	NA	-	-	+	NA	NG	-	+, >2/y	+, ≥2/y	NA	-	+, ≥2/y	+, ≥2/y	+
_Tophi	+	+	+	NA	+	+	+	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	+	+	+
_Urate nephrolithiasis	-	+	+	NA	+	-	+	-	NA	+	-	-	NA	NG	NA	-	+	NA	+	+	+	+
_Arthropathy	-	+	-	NA	+	-	-	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	-	+	+
_Comorbidities‡	-	+	+	NA	-	-	+	+	NA	+	-	-	NA	NG	NA	-	+	NA	-	+	+	+
_Others§	+	+	+	NA	-	-	-	+	NA	-	+	-	NA	NG	NA	-	+	NA	-	-	+	+
Initiate ULT during or after an acute attack (Aft[time after attack])	Aft	Aft	NG	Aft (4-6 w)	Aft	Aft (2w)	D	NA	Aft	D/ Aft (2w)	NG	NG	Aft	NG	NG	NG	IE	IE	Aft	NG	Aft	Aft
First line ULT drug(s)	NG	A	A	NG	A, F	A, B	A, F	NG	A	NG	A, F,	A	A	NG	A	NG	A	NG	NG	NG	A	NG

											B										
Second line ULT drug(s)	NG	P	NG	NG	P	NG	P	NG	U, F	NG	NG	F, P, B	F, B, P, U	NG	P, B, F	NG	F, U	NG	NG	NG	F	NG
Allopurinol use																						
_Maximum dose (mg/d)	300	NG	NG	NG	800	NG	800	600	NG	600	800-900	800	NG	NG	900	NG	NG	NG	800	NG	900	600
_RF to initiate dose adjustment (eGFR in ml/min/1.73m^2, CCr in mL/min)	CCr 60	CCr 80	NG	NG	NG	NG	CK D4	NG	NG	CCr 60	CCr 140	CCr 20	NG	NG	NG	NG	NG	NG	NG	NG	eGFR 130	1.5mg/ eGFR‖
_Starting dose in normal RF (mg/d)	50-100	100-150	NG	NG	100	50	≤100	50	NG	100-150	NG	100	NG	NG	NG	100	100	NG	100	50-100	200	50-100
_HLA-B*5801 gene screening	-	-	-	-	-	-	+	-	-	+	-	-	-	NG	-	-	-	-	+	-	+	+
Prophylaxis before ULT	+	NG	NG	NG	+	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Prophylaxis with ULT	+	+	NG	NG	+	+	+	NG	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Duration for prophylaxis	1-3 m¶	1-6 m**	NG	NG	NG	NG	3-6 m††	NG	Un-clear	6m	>6m	NG	>6m	NG	Vari-ed‡‡	3-6 m	NG	>6m	3-6 m	>8w	<6m	3-6m
Pharmacological ULT for asymptomatic hyperuricemia?	-	+	NG	-	-	+	IE	+	IE	IE	NG	NG	-§§	NG	IE	NG	NG	IE	-	NG	-	NG
_Comorbidities	NA	-	NA	NA	NA	+	NA	+	NA	NA	NA	NA	-	NG	NA	NA	NA	NA	NA	NA	NA	NA
_SUA cut-offs, µmol/L [mg/dL]	NA	[10-13]‖‖	NA	NA	NA	[8.0-9.0] ¶¶	NA	[8.0-9.0] ***	NA	NA	NA	NA	[9.0]	NG	NA	NA	NA	NA	NA	NA	NA	NA

* The general target was the target serum uric acid level for long term control recommended for all patients on pharmacological urate lowering therapy.

† The intensive target the intensive target was the target serum uric acid level for long term control recommended for patients with tophi [16, 17, 22, 36, 38, 40, 43], with recurrent attacks [16, 21, 22], or with chronic gouty arthritis [16, 22], or to prevent crystal formation [21], or to improve gout signs and symptoms [14, 15]. One document provided stricter target for any patient with gout [37], and one for patients with severe gout without clear definition [39].

‡ Comorbidities considered as the indication for ULT include renal impairment [14-16, 19-22, 37, 49, 50], cardiovascular risk or cardiovascular diseases [16, 22, 47], glucose intolerance or DM, lipid disorder, and obesity [22].

§ Others indications considered for pharmacological ULT include joint damage [21], diuretic therapy use [21], young age [16, 21, 22] with some documents defined as less than 40 years old [16, 22], high SUA level defined as >8mg/dL (480 umol/L) [16] or >13mg/dl [50], impending cytotoxic chemotherapy or radiotherapy for lymphoma or

leukaemia [49], persistently raised uric acid levels and willingness to continue lifelong therapy [51]. Some documents evaluated SUA levels in patients after lifestyle modification and indicated pharmacological ULT in individuals with SUA above 6 mg/dL [46], or with SUA above 8mg/dl with CV risk or CVD and above 9mg/dl without CV risk or CVD [47].

|| The starting dose of allopurinol in patients with renal impairment should not exceed 1.5mg/eGFR.

¶ Prophylaxis should be continued until the serum urate is normal and the patient has not had any attacks for 1-3 months.

** Prophylaxis should be continued until 6 months free of acute attacks or until 1 month with target serum urate level achieved.

†† Prophylaxis should be continued for 1) 6 months' duration, 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination, or 3) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination.

‡‡ The during for prophylaxis varied and depends on the presence of tophi and comorbidities and on serum urate response. But prophylaxis should be continued until the target SUA is reached or until the tophi has resolved.

§§ The recommendations provided were conflict within the same document.

|||| Pharmacological urate lowering therapy is recommended in male patients with serum uric acid >13 mg/dL and in female patients with serum uric acid >10 mg/dL.

¶¶ Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with complications or >9 mg/dL in all patients.

*** Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with cardiovascular disease or cardiovascular risk factors or >9 mg/dL if without cardiovascular disease or cardiovascular risk factors.

Supplementary Table 10. Summary of recommendations for the treatment of acute gout by included guidance documents

NG: not given; NSAIDs: non-steroidal anti-inflammatory drugs.

	What is the first line pharmacological treatment option?	Is colchicine recommended to be given as a fixed dose or as a loading dose + followed doses?	Is intra-articular steroids recommended?	What are the indications for intra-articular steroids?	Which line is intra-articular steroids recommended to be?	Is systemic steroids recommended?	What are the indications for systemic steroids?	Which line of option is systemic steroids recommended to be?
SAMA_2003 [51]	NSAIDs	Loading dose + followed doses	Yes	Contraindicated to NSAIDs and joint accessible	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	NG
MOH_MSR_AMM_2008 [49]	NSAIDs	NG	Yes	NG	NG	Yes	Elderly people, renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease, and hypersensitivity to NSAIDs	NG
PRA_2008 [50]	NSAIDs	NG	NG	NG	NG	Yes	Contraindicated to NSAIDs	NG
UTAustin_2009 [52]	NSAIDs	Loading dose + followed doses	Yes	Only 1-2 joints is involved	Third	Yes	Contraindicated or not responding to NSAIDs and colchicine and polyarthritis	Third
EULAR_2011 [17]	Colchicine, NSAIDs, glucocorticoids	Loading dose + followed doses	Yes	NG	NG	Yes	Contraindications to NSAIDs and colchicine	First
JSGNAM_2011 [48]	Colchicine, NSAIDs	Fixed	NG	NG	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	Second
ACR_2012 [14, 15]	NSAIDs, corticosteroids, colchicine	Loading dose + followed doses	Yes	Involvement of 1 or 2 large joints	First	Yes	Oral steroids for involvement of 1 or 2 joints or when intra-articular joint injection is impractical. Intravenous steroids for the nothing by mouth patients.	First
3e_2013 [36]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CSE_2013 [37]	NSAIDs, colchicine,	NG	NG	NG	NG	NG	NG	NG

	corticosteroids							
SER_2013 [46]	NSAIDs	NG	Yes	Monoarthritis	NG	Yes	Contraindicated to NSAIDs	NG
SIR_2013 [45]	NSAIDs, colchicine	NG	Yes	NG	NG	Yes	Intolerance or contraindications to NSAIDs and colchicine	NG
3e_PT_2014 [40]	Colchicine, NSAIDs	Fixed low dose	Yes	NG	NG	Yes	NG	NG
FMOH_2014 [44]	NG	NG	NG	NG	NG	NG	NG	NG
3e_AU_NZ_2015 [43]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CRA_2016 [41]	NSAIDs	NG	NG	NG	NG	Yes	Contraindications to NSAIDs and colchicine	NG
EULAR_2016 [16]	Colchicine, NSAIDs, corticosteroid	Loading dose + followed doses	Yes	NG	First	Yes	NG	First
T2T_2016 [39]	Anti-inflammatory medications	NG	NG	NG	NG	NG	NG	NG
TRA_2016 [38]	NSAIDs	Fixed or Loading dose + followed doses	Yes	Involvement of 1-2 major joints, contraindications to both colchicine and NSAIDs	NG	Yes	Contraindications to NSAIDs and colchicine	NG
ACP_2017 [19, 20]	Corticosteroids	Loading dose + followed doses	NG	NG	NG	Yes	If not contraindicated.	First
BSR_2017 [21]	NSAIDs, colchicine	NG	Yes	Patients with acute illness and comorbidity	First	Yes	Intolerance to NSAIDs and colchicine and intra-articular injection is not feasible.	Second
CRA_multi_2017 [22]	NSAIDs, colchicine	Loading dose + followed doses	Yes	Involvement of 1-2 major joints and not responding to systemic treatment	NG	Yes	Contraindicated to or not responding to NSAIDs and colchicine	NG

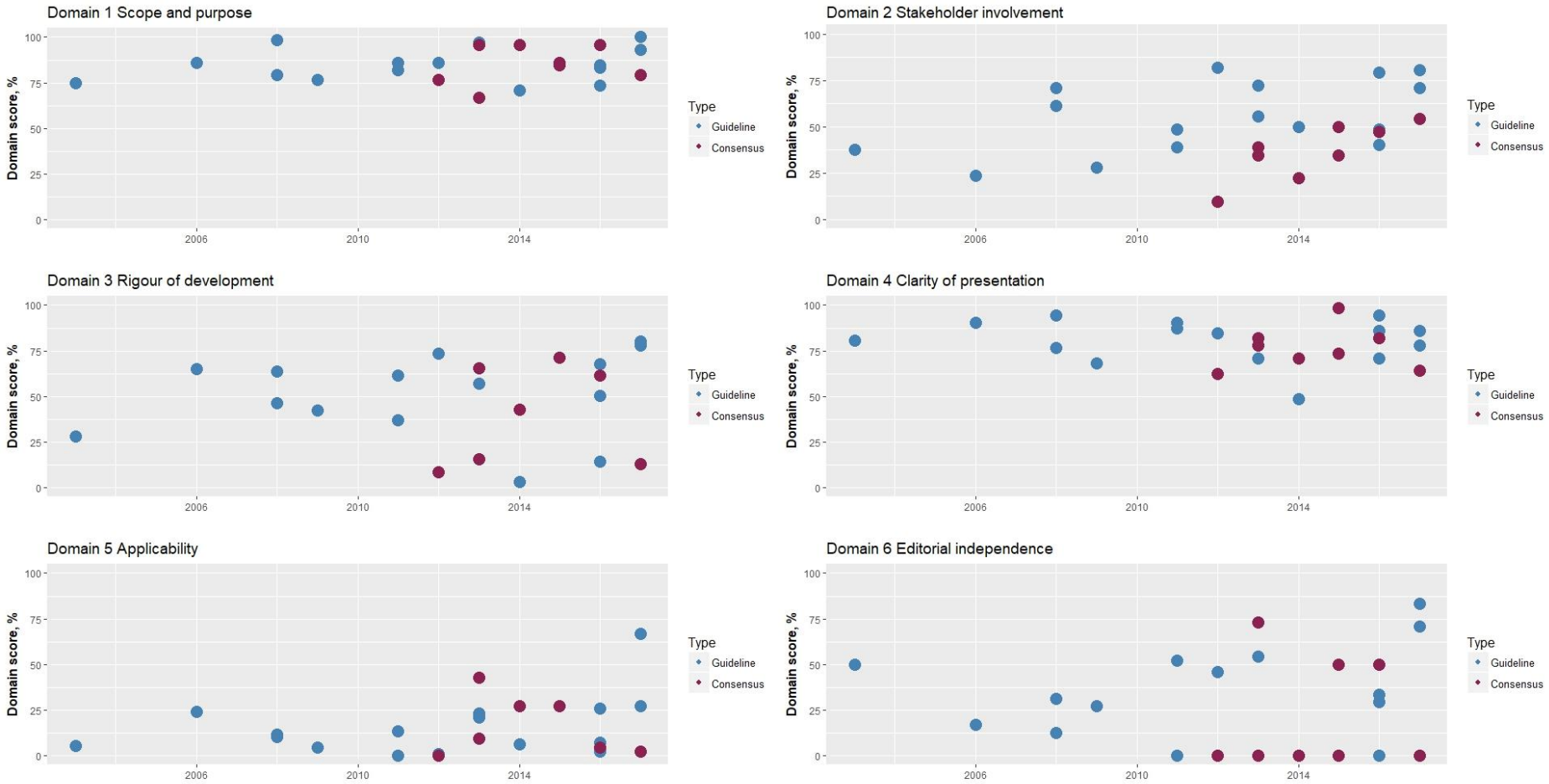
Supplementary Table 11. Summary of recommendations for the treatment of tophi by included guidance documents

A: allopurinol; B: benzbromarone; F: febuxostat; NA: not applicable; NG: not given; P: pegloticase; R: rasburicase; ULT: urate lowering therapy; WH: wound healing.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Is surgery recommended?	+	+	NG	NG	NG	+	NG	+	NG	NG	NG	+	NG	+	NG	NG	IE	+	NG	-	+
Indications for surgery	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	+	NG	NG	+
_Nerve compression	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	+
_Infection	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	-
_Mechanical impingement	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	-	NA	NA	-
_Loss of mobility	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Severe pain	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Tophaceous ulcer	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	-	NA	NA	+
_Others*	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	+
Risks of surgery	WH	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Is long-term ULT recommended?	+	+	+	NG	+	+	+	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Is any ULT drug recommended?	A	-	-	-	P	-	P	-	B	F	NA	-	-	P	-	P	-	-	-	P, R	-

* Other indications for surgery include large tophi [22], persistent tophi [22], joint deformation [38], major joint destruction [49], pressure symptoms [49], and cosmetic [49].

Supplementary Figure 1. Standardized domain scores by the year of publication



Supplementary File 1. Instructions for Guideline Appraisal Using the AGREE II Instrument

TRAINING MATERIALS

- Online tutorial: http://www.agreetrust.org/resource-centre/agree-ii-training-tools/
- User's Manual: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

PROLOGUE

- The Appraisal of Guidelines for REsearch & Evaluation (AGREE) Instrument is an international, validated and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements.
- The AGREE II instrument was published in 2010 and consists of 23 key items organized within 6 domains followed by 2 global rating items ("Overall Assessment"). Each domain captures a unique dimension of guideline quality.
  - Scope and purpose
  - Stakeholder involvement
  - Rigour of development
  - Clarity of presentation
  - Applicability
  - Editorial independence.
- Reviewers score each item on a 7-point Likert Scale.
  - 1 - Strongly disagree
  - 7 - Strongly agree
  - For the majority of items, we use an 'add-up' strategy to score, that is, corresponding scores will be added to 1' if information on predefined aspects is provided. For only one item, we subtract scores from 7'.
- Domain scores will be calculated as: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)

DETAILED INSTRUCTIONS FOR SCORING

(adapted from AGREE II User's Manual [28])

Domain 1 Scope and Purpose

Item 1 Objectives: The overall objective(s) of the guideline is (are) specifically described.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Health intent, i.e., prevention, screening, diagnosis, treatment, etc. (2');

b) Expected benefit or outcome (2');

- *Clarification*: If gout epidemiology is provided as background information (i.e., the importance or significance of the diagnosis and management of gout/hyperuricemia is stated), 1' will be given. If clear statements, such as "to prevent (long term) complications of patients with diabetes mellitus" "to lower the risk of subsequent vascular events in patients with previous myocardial infarction", are provided, 2' will be given.

c) Target, e.g., patient population, society (1').

Performance: Is the item well written and is the content easy to find? (1')

Related *Report Criteria* from *User's Manual*: • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) • expected benefit or outcome • target(s) (e.g., patient population, society)

Item 2 Questions: The health question(s) covered by the guideline is (are) specifically described.

Instructions:

Information on five aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Target population (2');

b) Intervention or exposure (if appropriate, 1');

c) Comparisons (if appropriate, 1');

d) Outcome (1');

e) Health care setting or context (1').

Performance: Is the item well written and is the content easy to find? (1')

Note:

1) If c) is not appropriate, no score will be subtracted.
2) It is not necessary to have this information provided in questions. Reviewers can try to paraphrase 2-3 key recommendations into questions to see the information above is provided and score based on paraphrased questions.

Related *Report Criteria* from *User's Manual*: • target population • intervention(s) or exposure(s) • comparisons (if appropriate) • outcome(s) • health care setting or context

Item 3 Population: The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Instructions:

A default full score (7') should be considered. Subtract 1-2 points where the population is not clearly described or where the descriptions in the guideline is contradictory (e.g., a guideline stating "to treat asymptomatic hyperuricaemia" in the introduction, while stating "to treat hyperuricaemia and gout" in the title and providing no specific definition of patients' condition in recommendations).

Related *Report Criteria* from *User's Manual*: • target population, gender and age • clinical condition (if relevant) • severity/stage of disease (if relevant) • comorbidities (if relevant) • excluded populations (if relevant)

Domain 2 Stakeholder Involvement

Item 4 Group Membership: The guideline development group includes individuals from all relevant professional groups.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) The guideline development group is stated (1');

b) For each member of the guideline development group, the following information is included (1' each): name (1'), discipline/content expertise (e.g., neurosurgeon, methodologist, 1'), institution (e.g., St. Peter's hospital, 1'), a description of the member's role in the guideline development group (1')

- *Clarification*: Please subtract 1' if no methodologist (i.e., epidemiologist) is inferred from the discipline/content expertise.

Performance: Is the item well written and is the content easy to find? (1')

Note: Where the relation between the guideline development group and the authors is unclear, the authors of the guidance document will be considered as equivalent to the guideline development group.

Related *Report Criteria* from *User's Manual*: • For each member of the guideline development group, the following information is included: name, discipline/content expertise (e.g., neurosurgeon, methodologist), institution (e.g., St. Peter's hospital), geographical location (e.g., Seattle, WA), a description of the member's role in the guideline development group

Item 5 Target Population Preferences and Views: The views and preferences of the target population (patients, public, etc.) have been sought.

Instructions:

Information the following four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences, 2');

b) Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups, 1');

c) Outcomes/information gathered on patient/public information (2');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

- *Clarification*: If a patient representative is included in the guideline development panel, scores on aspects a), b), and d) will be given as default.

Related *Report Criteria* from *User's Manual*: • statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) • methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) • outcomes/information gathered on patient/public information • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 6 Target Users: The target users of the guideline are clearly defined.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators, 3');

b) Description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care, 3')

Related *Report Criteria* from *User's Manual*: • clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) • description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)

Domain 3 Rigour of Development

Item 7 Search Methods: Systematic methods were used to search for evidence.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL, 2');
b) Time periods searched (e.g., January 1, 2004 to March 31, 2008, 1');
c) Search terms used (e.g., text words, indexing terms, subheadings, 1');
d) Full search strategy included (e.g., possibly located in appendix, 2')

Related *Report Criteria* from *User's Manual*: • named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) • time periods searched (e.g., January 1, 2004 to March 31, 2008) • search terms used (e.g., text words, indexing terms, subheadings) • full search strategy included (e.g., possibly located in appendix)

Item 8 Evidence Selection Criteria: The criteria for selecting the evidence are clearly described.
Instructions:
Information on both inclusion and exclusion criteria should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the inclusion criteria:
a1) target population (patient, public, etc.) characteristics (2'),
a2) study design (2),
a4) outcomes (1'),
b) Description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement, 1').
Note: if a3), a5), a6), b) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • description of the inclusion criteria, including: target population (patient, public, etc.) characteristics, study design, comparisons (if relevant), outcomes, language (if relevant), context (if relevant) • description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement)

Item 9 Strengths and Limitations of The Evidence: The strengths and limitations of the body of evidence are clearly described.
Instructions:
For each evidence, information on two aspects should be provided. If only some of the evidences report the following information, please first calculate the score based on the most informative evidence (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').
For each evidence, both a general statement of the method and detailed descriptions should be provided:
a) A statement of the method used to evaluate the strengths and limitations of the evidence should be provided (3').
b) The stated method should evaluate at least three of the following aspects (add 1' for each aspect, maximum 3'):
b1) Study design(s);
b2) Study methodology limitations (e.g., sampling, blinding, allocation concealment, analytical methods);
b3) Appropriateness/relevance of primary and secondary outcomes considered;
b4) Consistency of results across studies;
b5) Direction of results across studies;
b6) Magnitude of benefit versus magnitude of harm;

b7) Applicability to practice context

Related *Report Criteria* from *User's Manual*: • descriptions of how the body of evidence was evaluated for bias and how it was interpreted by members of the guideline development group • aspects upon which to frame descriptions include: study design(s) included in body of evidence, study methodology limitations (sampling, blinding, allocation concealment, analytical methods), appropriateness/relevance of primary and secondary outcomes considered, consistency of results across studies, direction of results across studies, magnitude of benefit versus magnitude of harm, applicability to practice context

Item 10 Formulation of Recommendations: The methods for formulating the recommendations are clearly described.

Instructions:

Information on three aspects should be provide (add 2' for each aspect, 6' in total):

a) Description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered, 2');

b) Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures, 2');

c) Description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote, 2')

Related *Report Criteria* from *User's Manual*: • description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) • outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) • description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)

Item 11 Consideration of Benefits and Harms: The health benefits, side effects, and risks have been considered in formulating the recommendations.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Supporting data and report of benefits (2'); b) Supporting data and report of harms/side effects/risks (2');

- *Clarification*: Data on a) and b) can be provided as references.

c) Reporting of the balance/trade-off between benefits and harms/side effects/risks (1');

d) Recommendations reflect considerations of both benefits and harms/side effects/risks (1')

Related *Report Criteria* from *User's Manual*: • supporting data and report of benefits • supporting data and report of harms/side effects/risks • reporting of the balance/trade-off between benefits and harms/side effects/risks • recommendations reflect considerations of both benefits and harms/side effects/risks

Item 12 Link Between Recommendations and Evidence: There is an explicit link between the recommendations and the supporting evidence.

Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) The guideline describes how the guideline development group linked and used the evidence to inform recommendations (2');
- *Clarification*: Can be provided as narrative summaries and/or discussions of evidences.
b) Each recommendation is linked to a key evidence description/paragraph and/or reference list (2');
- *Note*: Please subtract 1' if only some recommendations meet criterium b).
c) Recommendations linked to evidence summaries, evidence tables in the results section of the guideline (2')

Related *Report Criteria* from *User's Manual*: • the guideline describes how the guideline development group linked and used the evidence to inform recommendations • each recommendation is linked to a key evidence description/paragraph and/or reference list • recommendations linked to evidence summaries, evidence tables in the results section of the guideline

Item 13 External Review: The guideline has been externally reviewed by experts prior to its publication.
Instructions:
Information on five aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence, 1');
b) Methods taken to undertake the external review (e.g., rating scale, open-ended questions, 1');
c) Description of the external reviewers (e.g., number, type of reviewers, affiliations, 1');
d) Outcomes/information gathered from the external review (e.g., summary of key findings, 1');
e) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations, 2')
- *Clarification*: Publication through a peer-reviewed journal can be considered as externally reviewed. Note: If dates of revision and acceptance is provided on the document, it is also considered externally reviewed.

Related *Report Criteria* from *User's Manual*: • purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) • methods taken to undertake the external review (e.g., rating scale, open-ended questions) • description of the external reviewers (e.g., number, type of reviewers, affiliations) • outcomes/information gathered from the external review (e.g., summary of key findings) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)

Item 14 Updating Procedure: A procedure for updating the guideline is provided.
Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) A statement that the guideline will be updated (2');
b) Explicit time interval or explicit criteria to guide decisions about when an update will occur (2');
c) Methodology for the updating procedure is reported (2')

Related *Report Criteria* from *User's Manual*: • a statement that the guideline will be updated • explicit

time interval or explicit criteria to guide decisions about when an update will occur • methodology for the updating procedure is reported

Domain 4 Clarity of Presentation

Item 15 Specific and Unambiguous Recommendations: The recommendations are specific and unambiguous.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) If a recommendation is uncertain, the uncertainty should be reflected in the recommendation and also be explicitly stated (2')

b) Identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects, 2');

- *Clarification*: If the benefit for uric acid lowering in patients with CVD is not clearly stated, the score for this aspect should not be added.

c) Identification of the relevant population (e.g., patients, public, 1');

d) Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply, 1').

Note: if c) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • statement of the recommended action • identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) • identification of the relevant population (e.g., patients, public) • caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)

Item 16 Management Options: The different options for management of the condition or health issue are clearly presented.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) Description of options (3');

b) Description of population or clinical situation most appropriate to each option (3')

- *Note*: Please subtract 1' if only some options are provided with the most appropriate population or clinical situation.

Related *Report Criteria* from *User's Manual*: • description of options • description of population or clinical situation most appropriate to each option

Item 17 Identifiable Key Recommendations: Key recommendations are easily identifiable.

Instructions:

Reporting style should follow two criteria (add 3' for each aspect, 6' in total):

a) Description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms (3');

b) Specific recommendations are grouped together in one section (3')

- *Clarification*: If recommendations are summarised in the abstract, scores for aspect b) can also be given.

Related *Report Criteria* from *User's Manual*: • description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms • specific recommendations are grouped together in one section

Domain 5 Applicability

Item 18 Facilitators and Barriers to Application: The guideline describes facilitators and barriers to its application.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of facilitators and barriers that were considered (2');

- *Clarification*: Statements of that certain drugs are not available in certain regions can be considered as identification of the facilitators and barriers.

b) Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation, 2');

c) Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography, 1');

d) Description of how the information influenced the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of facilitators and barriers that were considered • methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) • information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) • description of how the information influenced the guideline development process and/or formation of the recommendations

Item 19 Implementation Advice or Tools: The guideline provides advice and/or tools on how the recommendations can be put into practice.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) An implementation section in the guideline (2');

b) Tools and resources to facilitate application (add 1' for each tool/resource, maximum 2'): guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned;

c) Directions on how users can access tools and resources (2')

Related *Report Criteria* from *User's Manual*: • an implementation section in the guideline • tools and resources to facilitate application: guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned • directions on how users can access

tools and resources

Item 20 Resource Implications: The potential resource implications of applying the recommendations have been considered.

- *Clarification*: The aim of this item is to the cost information considered by the guideline.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs, 2');

b) Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc., 2');

c) Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course, 1');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) • methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) • information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 21 Monitoring or Auditing Criteria: The guideline presents monitoring and/or auditing criteria.

- *Clarification*: The aim of this item is to evaluate the adherence to guidelines, but not to provide follow up parameters for diseases. *Monitoring* in this item refers to the action to monitor physicians' adherence to the guideline in daily practice by a group of investigators, but not to monitor the management of the disease in an individual patient. And the *auditing criteria* are the criteria to assess how well the guideline affects the practice in a region, but not how well the patients achieve the treatment target.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of criteria to assess guideline implementation or adherence to recommendations (2');

b) Criteria for assessing impact of implementing the recommendations (2');

c) Advice on the frequency and interval of measurement (1');

d) Descriptions or operational definitions of how the criteria should be measured (1')

Related *Report Criteria* from *User's Manual*: • identification of criteria to assess guideline implementation or adherence to recommendations • criteria for assessing impact of implementing the recommendations • advice on the frequency and interval of measurement • descriptions or operational definitions of how the criteria should be measured

Domain 6 Editorial Independence

Item 22 Funding Body: The views of the funding body have not influenced the content of the guideline.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) The name of the funding body or source of funding (or explicit statement of no funding, 3');
b) A statement that the funding body did not influence the content of the guideline (3')

Related *Report Criteria* from *User's Manual*: • the name of the funding body or source of funding (or explicit statement of no funding) • a statement that the funding body did not influence the content of the guideline

Item 23 Competing Interests: Competing interests of guideline development group members have been recorded and addressed.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the types of competing interests considered (2');
b) Methods by which potential competing interests were sought (1');
c) Description of the competing interests (1');
d) Description of how the competing interests influenced the guideline process and development of recommendations (2')

Related *Report Criteria* from *User's Manual*: • description of the types of competing interests considered • methods by which potential competing interests were sought • description of the competing interests • description of how the competing interests influenced the guideline process and development of recommendations

Overall Guideline Assessment

Question 1 Overall quality: Rate the overall quality of this guideline.

Instructions:

7' in total. Reviewer's impression on the overall quality of the guideline.

Question 2 Strength of recommendation: I would recommend this guideline for use.

Instructions:

Three options to choose from: a) Yes; b) Yes, with modifications; c) No
Reviewer's impression on whether the guideline is easy to be applied to clinical practice.

Related *Report Criteria* from *User's Manual*: The overall assessment requires the AGREE II user to make a judgment as to the quality of the guideline, taking into account the appraisal items considered in the assessment process.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported -on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21-22

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

Running title: AGREE II assessment for hyperuricemia and gout guidelines

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ABSTRACT

Objectives

Despite the publication of hundreds of trials on gout and hyperuricemia, management of these conditions remains suboptimal. We aimed to assess the quality and consistency of guidance documents for gout and hyperuricemia.

Design

Systematic review and quality assessment using the Appraisal of Guidelines for Research and Evaluation (AGREE) II methodology.

Data Sources

PubMed and EMBASE (27 October 2016), two Chinese academic databases, eight guideline databases, and Google and Google scholar (July 2017).

Eligibility Criteria

We included the latest version of international and national/regional clinical practice guidelines and consensus statements for diagnosis and/or treatment of hyperuricemia and gout, published in English or Chinese.

Data Extraction and Synthesis

Two reviewers independently screened searched items and extracted data. Four reviewers independently scored documents using AGREE II. Recommendations from all documents were tabulated and visualized in a coloured grid.

Results

Twenty-four guidance documents (16 clinical practice guidelines and 8 consensus statements) published between 2003 and 2017 were included. Included documents performed well in the domains of scope and purpose (median 85.4%, range 66.7%-100.0%) and clarity of presentation (median 79.2%, range 48.6%-98.6%), but unsatisfactory in applicability (median 10.9%, range 0.0%-66.7%) and editorial independence (median 28.1%, range 0.0%-83.3%). The 2017 British Society of Rheumatology guideline received the highest scores. Recommendations were concordant on the target serum uric acid level for long-term control, on some indications for urate-lowering

therapy, and on the first-line drugs for urate-lowering therapy and for acute attack. Substantially inconsistent recommendations were provided for many items, especially for the timing of initiation of urate-lowering therapy and for treatment for asymptomatic hyperuricemia.

Conclusions

Methodological quality needs improvement in guidance documents on gout and hyperuricemia. Evidence for certain clinical questions is lacking, despite numerous trials in this field. Promoting standard guidance development methods and synthesizing high-quality clinical evidence are potential approaches to reduce recommendation inconsistencies.

Study registration

PROSPERO (CRD42016046104).

Keywords

Clinical practice guideline, Hyperuricemia, Gout, Systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The first systematic review to assess the quality of clinical practice guidelines and consensus statements on the diagnosis and treatment for both hyperuricemia and gout.
2. The first systematic review to summarise recommendations for best practice in hyperuricemia and gout.
3. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument is an international, structured, validated, and rigorously developed tool.
4. Only guidance documents in English and Chinese were included.
5. Literature search was more than one year old at the time of publication.

BACKGROUND

Gout is an inflammatory arthritis occurring in response to monosodium urate (MSU) crystals formation, a common and necessary pathogenic factor of which is hyperuricemia. The prevalence of gout and hyperuricemia [1-4], as well as their disease burden [5, 6], are rising globally. However, although more than six hundred related clinical studies [7] have been published to date, the quality of care for gout and hyperuricemia remains suboptimal. The goal of treatment is to reduce the body's total uric acid pool [8, 9] and consequently to minimize the risk of acute flares, arthropathy, nephrolithiasis, and other complications [7, 10, 11]. A study in the United States found that only 22% of patients with gout received therapy adhering to all quality indicators [12]. A nationwide population study in the United Kingdom reported that only 48% of prevalent patients received proper consultation and only 27% of incident patients were provided with urate-lowering therapy (ULT) within one year of diagnosis [6].

High-quality guidance documents are important for improving the quality of care for gout and hyperuricemia at individual, community, and national levels [13]. Current guidance documents for gout and hyperuricemia have been developed by rheumatology, endocrinology, and cardiology groups, at regional, national or international levels. Among these documents, the American College of Rheumatology (ACR) guidelines [14, 15], updated in 2012, and the European League Against Rheumatism (EULAR) guidelines [16-18], updated in 2016, have the most substantial global influence. Besides, the most recent documents (released in 2017) are two national guidelines, from the American College of Physicians (ACP) [19, 20] and the British Society of Rheumatology (BSR) [21], respectively, and one consensus statement, from the Chinese Multi-disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases [22].

Despite the variety of documents, current guidelines and consensuses on gout and hyperuricemia provide inconsistent recommendations, even those released by highly respected professional organizations, such as the ACP and the ACR [23]. Some distinct differences lie in key aspects for patient care, such as the pharmacological treatment for asymptomatic hyperuricemic patients, the timing of initiation of ULT in patients with gout flare [24], and indications for ULT [25]. These discrepancies may result from ethnic and social differences, but can be a consequence of inconsistent guideline development [23]. Low-quality guidance documents put individual patients and communities at risk, and impede the application of guideline recommendations in clinical practice [26]. Hence, we conducted this study to systematically evaluate the quality of clinical practice guidelines and consensus statements on gout and hyperuricemia and to compare key recommendations on patient care from all included documents.

METHODS

Detailed methods of the study have been published previously [27] and this study was registered with PROSPERO (registration number: CRD42016046104).

Literature search and selection criteria

We systematically searched PubMed and EMBASE from inception to 27 October 2016 using a comprehensive search strategy (Supplementary Table 1 and Supplementary Table 2) to identify guidelines and consensus recommendations pertaining to the diagnosis and treatment of gout and hyperuricemia. We searched two academic databases for Chinese publications (the Chinese Biomedical Literature Database and the Wanfang Data) and eight guideline databases from inception to 24 July 2017 using search strategies tailored to different databases (Supplementary Table 3). We also searched Google and Google scholar in July 2017 for potentially eligible

guidelines and consensus recommendations that were not indexed in the aforementioned databases.

We included the latest versions of all international and national/regional clinical practice guidelines and consensus statements for the diagnosis and/or treatment of gout and hyperuricemia, published in English or Chinese. Two reviewers (Q.L., X.L.) independently screened all searched documents. Reasons for exclusion were provided for documents excluded during the full-text review (Supplementary Table 4). Disagreements were resolved through discussion with a third reviewer (S.L.).

Data extraction

We extracted the following data from each included document: document characteristics (e.g., year of publication, funding body, and evidence base), recommendations for diagnosis and monitoring of gout and hyperuricemia, and recommendations for management. Data were extracted by one investigator (Q.L.) and checked by another (X.L.).

Appraisal of guidance documents

All included documents were assessed by four reviewers (Q.L., X.L., J.W., and H.L.) independently using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [28]. AGREE II is an internationally developed and validated tool to evaluate the quality of clinical practice guidelines [29-31] and consensus statements [32, 33].

All reviewers completed an online training tutorial [34] before the commencement of appraisal to ensure standardization. We adapted detailed instructions for scoring from the AGREE II User's Manual [28] and provided objective scoring criteria for each item (Supplementary File 1). We selected four guidance documents for pilot scoring, during which we discussed and

clarified our objective scoring criteria. When scoring for all included documents was completed, a meeting was held among reviewers and every item with scores differed more than one point was discussed. After the meeting, reviewers were given the opportunity to revise their scores or to keep the original scores. We recorded all original scores, revised scores, and reasons for modifying scores for quality control purpose, and used the intra-class correlation coefficient (ICC) to test inter-rater reliability. The ICC was calculated via IBM SPSS (IBM Co., Armonk, New York, USA) and an ICC ≥ 0.7 was considered acceptable [35].

Recommendation synthesis

We manually extracted recommendations on key clinical questions from all included guidance documents and summarized them into four tables: a) the diagnosis of gout and hyperuricemia, b) the treatment of hyperuricemia, c) the treatment of acute gout, and d) the treatment of tophi. Recommendations were extracted by one investigator (Q.L.) and checked by another (X.L.). We further visualized these recommendations in a five-colour grid to illustrate inconsistencies. The most frequently recommended content was used as a reference. We used green to colour documents providing consistent recommendations, red to colour those providing contrary recommendations, and blue to colour those providing partially consistent recommendations. A partially consistent recommendation was defined as a recommendation that included but not the same as the reference content. Where recommendations were not given or were not applicable, the cell was coloured in yellow and in grey, respectively.

Patient involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

RESULTS

Search results

Overall, we identified 5811 items across academic databases, guideline databases, Google, and Google Scholar. After applying the inclusion and exclusion criteria, 24 guidance documents from 26 papers [14-22, 36-52] were included in the final appraisal and recommendation synthesis (Figure 1). Studies excluded after full-text review and reasons for exclusion were provided as Supplementary Table 4.

Characteristics of included guidelines and consensus statements

Table 1 summarized characteristics of included guidance documents, among which 16 were clinical practice guidelines [14-21, 38, 41, 44-46, 48-52] and eight were consensus statements [22, 36, 37, 39, 40, 42, 43, 47]. 16 national or regional organizations and three international groups (i.e., the 3e [Evidence, Expertise, Exchange] Initiative, the EULAR, and the development group for the Treat-to-target [T2T] recommendations) published these documents between 2003 to 2017. 16 documents [14-18, 21, 22, 36-38, 40, 42, 43, 45, 46, 49, 50] were issued by rheumatology organizations and seven [16-18, 36, 39, 42, 43] were developed by multinational development groups. 17 documents [14-18, 21, 22, 36, 38-41, 43-46, 49, 51] provided information on their guideline development group, among which 11 [14-17, 19-21, 36, 41-43, 45, 46] explicitly stated the involvement of a methodologist. 12 documents [14-18, 21, 22, 38-41, 43-46, 49, 51] provided information on their target audience, among which only three [16, 38, 44] considered patients as one of the target audiences. 18 documents [14-21, 36, 39-43, 45, 46, 48-52] conducted systematic literature review as part of their development process, among which 17 documents [14-21, 36, 39-41, 43, 45, 46, 48-52] reported the level of evidence supporting recommendations and 16 [16-21, 36, 39-41, 43, 45, 46, 48-52] graded the strength of recommendations. Ten documents [16, 19-21, 39, 42, 46, 48, 49, 51, 52] clearly stated being externally reviewed. Five [19-21,

46, 49, 50] provided a clear time of update plan. 12 documents [14, 15, 17-21, 36, 39, 42, 46, 49, 51, 52] provided information on their funding body, among which six [17, 36, 39, 46, 49, 51] were fully or partially funded by the pharmaceutical industry and the rest did not clearly declare their funding body.

Appraisal of guidelines and consensus statements

Standardized AGREE II domain scores for each guidance document were shown as Figure 2 and were provided in value as Supplementary Table 5. Scores for each AGREE II item were provided in mean as Supplementary Table 6 and in detail as Supplementary Table 7. The overall quality of guidance documents, as assessed by AGREE II, varied both between documents across domains and within documents between domains. The document with the highest domain scores was the gout management guideline published by the BSR in 2017 [21], with five domains scoring above the upper quartile, followed by the guidelines published by the ACP in 2017 [19, 20], and the 2015 gout classification criteria by the ACR and the EULAR jointly [42], both with four domains scoring above the upper quartile. Guidelines did not always score higher than consensus statements. No tendency of improvement in the quality score over time was observed (Supplementary Figure 1).

The AGREE II instrument evaluated guidelines and consensus statements in six domains, from the development, dissemination, to implementation. The scope and purpose (domain 1) of a document clarifies its clinical questions. Proper involvement of stakeholders (domain 2) balances individuals' biases. The rigour of development domain (domain 3) is most concerned by clinicians and ensures the validity of development methodology [53]. Clearly presented recommendations (domain 4) conveyed precise and accessible information from the development group to clinicians. Good performances in the applicability domain (domain 5) and the editorial independence domain (domain 6) guarantee the usefulness and the independence of documents.

Guidance documents received the highest scores for the scope and purpose domain (median 85.4%, range 66.7% to 100.0%) and the clarity of presentation domain (median 79.2%, range 48.6% to 98.6%), and the lowest scores for the applicability domain (median 10.9%, range 0.0% to 66.7%) and the editorial independence domain (median 28.1%, range 0.0% to 83.3%). The worst scored item was the monitoring or auditing criteria item (mean score 1.2, range 1.0-4.0), followed by the implementation advice or tools item (mean 1.7, range 1.0-4.8), the external review item (mean 2.1, range 1.0-6.0), and the updating procedure item (mean 2.1, range 1.0-6.5).

The ICC was 0.896. Group discussion modified 365/2208 (16.53%) of individual scores.

Synthesis of recommendations

Included guidance documents addressed four major themes: diagnosis of gout and hyperuricemia, treatment for hyperuricemia, treatment for acute gout attack, and treatment for tophi. Figure 3 showed key recommendations and their inconsistencies.

Approaches to diagnostic strategies for gout and hyperuricemia

Thirteen guidance documents [17-20, 22, 36, 38, 40-43, 46, 49, 51] covered the diagnosis of gout and 11 [17, 22, 37, 38, 45-51] covered that of hyperuricemia. Supplementary Table 8 showed key recommendations. The identification of MSU crystals in synovial fluid or tophi was a gold standard for definite diagnosis, as recommended by all included documents. In the absence of MSU crystals, three aspects were commonly evaluated for gout diagnosis, namely the clinical manifestation, considered by all documents; the laboratory result, considered by all but one document [49]; and the imaging result, considered by all but four documents [17, 19, 20, 49, 51].

Guidance documents differed when recommending the cut-off serum uric acid (SUA) level to diagnose hyperuricemia. For the patient population in general, four documents [38, 47, 48, 51] recommended 7.0 mg/dL (or 420 μmol/L) as the cut-off, while two [17, 45] preferred 6.8 mg/dL. Five documents [22, 37, 46, 49, 50] provided gender-specific cut-offs, recommending 6.0 mg/dL (or approximately 360 μmol/L) in female and 7.0 mg/dL (or approximately 420 μmol/L) in male. Asymptomatic hyperuricemia was defined in seven documents [36, 38, 46-50], among which six [36, 38, 46-48, 50] excluded patients with gout and two [36, 48] excluded patients with tophi when making the diagnosis. Attitudes were inconsistent for whether or not patients with renal diseases can be diagnosed with asymptomatic hyperuricemia. Patients with renal diseases were not eligible for the diagnosis in the Japanese [48] and the Philippine [50] guidelines, but patients with pre-existing renal or cardiovascular diseases can receive this diagnosis in the 3e initiative document [36].

Approaches to treatment for hyperuricemia

Twenty-two guidance documents [14-17, 19-22, 36-41, 43-52] covered the treatment for hyperuricemia and Supplementary Table 9 summarized key recommendations. All but three documents [19, 20, 44, 52] explicitly provided target levels for long-term SUA control, most of which recommended 6.0 mg/dL (or 360 μmol/L), except the South African guideline [51] which recommended 5.0mg/dL (300 μmol/L). Two documents [16, 22] recommended a lower limit of 3.0 mg/dL (or 180 μmol/L) for long-term SUA management. Among these two documents, only the 2016 EULAR guideline [16] explained the reason for providing a lower limit was that low SUA might increase the risk of neurodegenerative diseases, but the level of evidence and the grade of recommendation were both low.

All but six guidance documents [36, 39, 40, 43, 44, 52] provided explicitly

indications for long-term ULT. The most commonly recommended indications were recurrent attacks [14-17, 19-22, 41, 45, 48-51], tophi [14-17, 19-22, 38, 41, 45, 48-51], urate nephrolithiasis [14-17, 19-22, 37, 38, 49, 50], arthropathy [16, 17, 21, 22, 38, 41, 45, 49], and comorbidities [14-16, 19-22, 37, 47, 49, 50]. The definition of recurrent attacks varied from at least once per year [17] to at least three times per year [49], while the majority of documents [14-16, 19-21, 41] recommended twice per year as the cut-off.

Regarding the timing to initiate ULT, the documents did not agree on whether to start pharmacological ULT after an acute attack [17, 21, 22, 36-38, 40, 48, 49, 51, 52] or during an attack [14, 15, 37]. When recommending to start ULT after an attack, the preferred time to wait since the attack resolved varied from two weeks [37, 48] to six weeks [52]. All guidance documents based their recommendation for this question on expert opinions, due to insufficient evidence. The explanations provided for starting ULT after an attack were that ULT was better discussed when a patient was not painful [21], and that ULT initiation could prolong or worsen the acute attack [51]. Two documents [16, 39] explicitly presented the currently conflicting views and insufficient evidence and stated consequently no recommendation for this issue.

When pharmacological ULT options were explicitly provided, allopurinol was recommended by all guidance documents [14-17, 21, 36, 40, 43, 45, 46, 48-50] to be the first-line drug, while febuxostat was recommended by three documents [14, 15, 17, 46] to be the first-line and by six documents [16, 21, 36, 40, 43, 45] to be the second-line. However, recommendations on the dosage of allopurinol varied largely. The maximum daily allopurinol dose recommended varied from 300 mg [51], 600 mg [22, 37, 47], 800 mg [14, 15, 17, 38, 45], to 900 mg [21, 43, 46], and the daily starting dose recommended in patients with normal renal function varied from 50 mg [19, 20, 22, 47, 48, 51] to 200 mg [21]. As for patients with impaired renal function, the cut-off renal

function to initiate dose adjustment was provided diversely as creatinine clearance (CCr) 20-140 mL/min [37, 45, 46, 49, 51], or estimated glomerular filtration rate (eGFR) 130 ml/min/1.73m^2 [21]. One document preferred to depend allopurinol dosage solely on eGFR by limiting the maximum daily dose to 1.5 mg/eGFR in patients with renal impairment [22]. HLA-B*5801 gene screening prior to allopurinol use was recommended by five guidance documents [14, 15, 21, 22, 37, 38].

For patients with asymptomatic hyperuricemia, 14 guidance documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52] commented on the option of pharmacological ULT, among which, five [17, 21, 38, 51, 52] explicitly recommended no treatment under any circumstances. Three documents [47-49] recommended pharmacological treatments in asymptomatic hyperuricemia patients with comorbidities [47, 48] or with very high SUA levels [40, 47-49], but their cut-off SUA level to indicate ULT varied from 8.0 mg/dL [47, 48] to 13.0 mg/dL [49]. We also found that the Portuguese consensus [40] was incoherent itself by stating that no pharmacological ULT was recommended as a general principle, but also stating that pharmacological ULT was recommended for patients with SUA higher than 9 mg/dL. No direct evidence was provided by any document to support pharmacological treatment for asymptomatic hyperuricemia, and such recommendations were only made in concern of the onset of gout [40] and the risk of cardiovascular events [47, 48].

Approaches to treatment for acute gout attack

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered the treatment for acute gout attack and Supplementary Table 10 summarized their key recommendations. Non-steroidal anti-inflammatory drugs (NSAIDs) was recommended by all but three documents [19, 20, 39, 44] as the first line pharmacological treatment, while colchicine by 11 documents [14-17, 21, 22,

36, 37, 40, 43, 45, 48]. Colchicine was recommended to be given in a fixed dose by three documents [38, 40, 48] and in a loading dose followed by different doses by six documents [14-17, 19, 20, 22, 38, 51, 52]. Seven documents [21, 36, 41, 43, 45, 49, 50] only recommended the total daily dose for colchicine, regardless of the regimen, and their doses recommended varied from 1 mg [21, 49, 50] to 2.4 mg [49]. Suprisingly, one document [43] recommended 1.8 g colchicine in 24 hours without any further explanation, which was likely a typo. Systemic steroids were recommended by all but three documents [37, 39, 44], among which six [14-17, 19, 20, 36, 43] recommended them as the first-line option and ten [21, 22, 38, 41, 45, 46, 48, 50-52] recommended them when NSAIDs and colchicine were contraindicated or intolerant. Intra-articular steroids injection was recommended by 14 documents [14-17, 21, 22, 36, 38, 40, 43, 45, 46, 49, 51, 52], among which five [14-16, 21, 36, 43] clearly recommended it as the first-line option.

Approaches to treatment for tophi

Twenty-one guidance documents [14-17, 19-22, 36-41, 43-46, 48-52] covered treatment for tophi and Supplementary Table 11 showed their key recommendations. Surgery was recommended by nine documents [22, 36, 38, 40, 43, 48, 49, 51], among which five [22, 36, 38, 43, 49] explicitly presented its indications, most commonly nerve compression [22, 36, 38, 43] and infection [36, 38, 43]. The risk for surgery was only discussed by one document [51] and only the risk of delayed wound healing was stated. Long-term ULT was recommended by all but two documents [44, 52], but the drugs used for pharmacological treatment was only explicitly recommended by eight of them [15-17, 21, 37, 43, 46, 51].

DISCUSSION

Principal findings and interpretations

This systematic review, including 16 guidelines and eight consensus

statements, found generally low methodological quality and inconsistent recommendations from guidance documents covering the diagnosis and management of gout and hyperuricemia. During revision of our work, the English version of two documents, from the Chinese Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases [54] and the Taiwan Rheumatologist Association [55], respectively, were released. Despite increase in the number of guidance documents published between 2003 and 2017, the quality of documents in all domains did not seem to improve with time. To date, this is the first systematic appraisal for the quality of guidelines and consensus statements pertaining to both gout and hyperuricemia.

Comparison with existing research

Guidance documents assessed in our study performed well in the domains of scope and purpose (domain 1) and clarity of presentation (domain 4), but poorly in the domain of applicability (domain 5). These results were consistent with two previous reviews [56, 57], one of which systematically assessed the quality of all guidelines for gout and the other assessed three documents released respectively by the 3e initiative [36], the ACR [14, 15], and the EULAR [18, 58]. Our study systematically included both guidelines and consensus statements in the field of both gout and hyperuricemia, and the diverse performance by different AGREE II domains was shared across both types of document.

This distribution of AGREE II domain scores has been observed by many previous guideline appraisal studies, in which documents scored higher in the scope and purpose domain and the clarity of presentation domain, and lower in the applicability domain and the editorial independence domain. This domain score distribution was not only shared by guidance documents for endocrinology diseases, such as diabetes [59, 60] and thyroid disorders [31, 61], and rheumatology diseases, such as rheumatoid arthritis [32, 62, 63] and

systemic lupus erythematosus [64], but also shared by documents for diseases in other clinical specialities [33, 65-67]. Despite generally low and varied scores in the applicability domain, guidance documents for gout and hyperuricemia performed obviously poorer comparing with documents for other conditions [31-33, 59-61, 63-67], suggesting that improving the usefulness of guidance being more challenging in gout and hyperuricemia. One major impediment to good applicability of guidance document is the time and cost to perform economic evaluations and pilot studies, and a stable and long-term task force of guideline development is required to conduct these evaluations and studies. Although forming such a task force is practically difficult in some regions and countries, guidance documents were suggested to at least inform audience the need to consider these issues [65]. Low scores in the editorial independence domain often resulted from lacking of detailed information on the influence of funding body and on the conflict of interests. We found that 50% of documents declaring funding sources were supported by the pharmaceutical industry, calling for awareness of the potential influence of pharmaceutical industry on the synthesis of clinical guidance and for the need of promoting transparency in financial declaration.

Clinical implications and future research

Guidance documents were concordant and recommended a target for SUA < 6.0 mg/dL (or 360 μmol/L) for long-term control, to consider recurrent attacks as one of the indications for ULT (although the definitions for recurrent attacks differed), to consider allopurinol as the first-line ULT and NSAIDs as the first-line drug in acute attack, and to consider long-term ULT in patient with tophi. Despite these similarities, recommendations differed in the majority of items and these discrepancies might come from several sources, including ethnic difference, quality of documents, and lack of evidence.

Ethnical and social differences are important reasons why recommendations

may vary between guidelines and consensus, and such diversity is to be encouraged, in order to best meet the needs of local populations. One example was that Asian guidance documents were more likely to recommend HLA-B*5801 gene screening before prescribing allopurinol [22, 37, 38]. HLA-B*5801 gene screening was promoted because the risk of hypersensitivity reactions associated with allopurinol is significantly increased in individuals carrying the variant allele HLA-B*5801. Studies suggested that the frequency of this variant allele are higher in Han Chinese, Korean, and Tai people than that in the Caucasian population [14, 15, 21], and that that HLA-B*5801 gene screening prior to allopurinol initiation is cost-effective for Asians but not Caucasians [68, 69]. These findings are consistent with the preferences of Asian documents. Providing ethnicity-specific recommendations or explicitly specifying the ethnicity of target audience helps clarify this source of inconsistency and improves the precision of recommendations.

However, it is worrying that low methodological quality of guidance documents may also lead to discrepant recommendations and consequent variability in application. Our study suggested that comparing to high-quality documents [16, 19-21, 36, 42, 46], low-quality ones [22, 37, 38, 44, 47, 52] were more likely to provide ambiguous prioritization of both a) ULT drugs for hyperuricemia and b) steroid options for acute attack. A quick notice was that when making this rough summary, we considered a document to be high-quality when it scored above the upper quartile in at least three out of the six AGREE II domains, and to be low-quality when it scored below the lower quartile in at least three out of the six AGREE II domains. Among all AGREE II domains, those pertaining to stakeholder involvement, rigor of development, applicability and editorial independence could be improved by standardizing developing processes, which consequently improved the reliability of recommendations. These results reinforced that it is better for clinicians to

refer to high-quality guidance documents instead of the low-quality ones. However, when high-quality documents are unavailable in local language, referring to low-quality local documents might mislead clinical practice in the region. Selecting appropriate guidance documents to follow in clinical practice is thus more challenging for non-English speaking countries, including China [13]. Moreover, the oldest document included in our study was the South African Medical Association guideline, published in 2003, and no guidance document in either English or Chinese was released in South African in the past 16 years. This finding suggested that some old documents might still affect regional practice. Efforts to timely update or declare the withdrawal of existing guidance documents are also critical for clinical practice.

Guidance documents are considered as the starting point to identify evidence gaps and to prioritize research questions [70]. Evidence gaps were discussed in the recommendations of both a) treatment for asymptomatic hyperuricemia, by five [14, 15, 36, 37, 39, 43] out of 14 documents [14, 15, 17, 21, 36-40, 43, 47-49, 51, 52], and b) timing to initiate ULT, by two [16, 39] out of 14 documents [14-17, 21, 22, 36-40, 48, 49, 51, 52]. Although the rest of documents provided explicit recommendations, they based their recommendations either on indirect evidence or expert opinions. As for gout and hyperuricemia, evidence synthesis is warranted for the effects of pharmacological ULT in patients with asymptomatic hyperuricemia and for the optimal timing to initiate ULT in patients with the acute attack.

Strengths and limitations

Strengths of our review included a systematic approach to identify guidance documents pertaining to the diagnosis and management of hyperuricemia and gout. Both guidelines and consensus statements were evaluated and compared. We used the AGREE II instrument, an international, validated and rigorously developed tool, to assess the quality of document development and

we tailored the AGREE II instrument to point-by-point scoring criteria (Supplementary File 1) to improve the objectivity and reproducibility of our study. We summarized all key recommendations, and compared and visualized the inconsistencies among them, providing a concise but informative overview for clinicians and researchers.

Our study also has limitations. Firstly, we only included documents published in English or Chinese, which could lead to a risk of neglecting essential documents from regions not using English or Chinese as the first language. We attempted to mitigate this risk by tailoring our search strategy to identify the English versions of guidance documents published from these regions. Secondly, unconscious bias from a subjective rating of documents was inevitable. We avoided inviting co-authors of guidance documents as reviewers to prevent subconscious competing interest, and conducted two rounds of group discussions to minimize subjective bias. Thirdly, the AGREE II instrument itself has weaknesses [31, 59, 67, 71], although it was the most commonly used tool to assess the quality of guidance documents. The AGREE system assigned equal weight to all six domains, regardless of their relative importance [72]. Although better methods of guideline development and greater transparency of reporting are associated with more reliable recommendations, they do not guarantee better patient outcomes. Hence, the quality scores assessed by the AGREE II should be interpreted with caution, especially when used to indicate which guidelines to follow in clinical practice. Moreover, the subjective interpretation of scoring criteria impeded the replicability of AGREE II studies and direct comparison of quality scores in guidance documents provided by different reviews. Fourthly, our literature search was over 12 months old when the study was ready to publish, affecting the timeliness of our study. However, we eventually decided not to update the literature at a late stage of the study, because of the infeasibility of bringing together all reviewers with another round of centralized training and appraisal,

and the risk of inconsistent scoring criteria for each reviewer after a long time since their previous scoring. Moreover, a quick review of publications in PubMed, using the same search strategy (Supplementary table 1) and limiting the publication date from 1 September 2016 to 21 January 2019, did not found any new relevant documents, reassuring us of the timeliness of our study.

CONCLUSIONS

The methodological quality needs to be improved in the current guidelines and consensuses on the diagnosis and management of gout and hyperuricemia, as assessed by the AGREE II. Inconsistent recommendations are common, even in some key aspects. Promoting standard methods for guidance documents development, and synthesizing high-quality clinical evidence to fill in evidence gaps, are warranted to improve the quality of guidance documents.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

HT and SL conceived this study. QL, JSWK, and SL designed the inclusion/exclusion criteria and the searching resource and strategy. QL, JSWK, HC, LL, and XS designed the appraisal strategy of each included guideline and consensus. QL and XL searched literature search and extracted data. QL, XL, JW, HL, and SL assessed the quality of each document. QL analysed and visualized the outcomes. SC, AS, YC, AZ, XS, and HH provided critical review. QL, XL, and SL drafted the manuscript. All authors discussed actively in the protocol of the study.

DATA AVAILABILITY

All data in this paper were obtained from published studies. No additional data are available from the authors.

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TABLES AND FIGURES

Table 1. Characteristics of included guidelines and consensus statements

3e: Evidence, Expertise, Exchange; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; CS: consensus statement; CVD: cardiovascular diseases; ER: external review; EULAR: European League Against Rheumatism; LOE: level of evidence; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; Multi: multidisciplinary development group; NG: not given; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; Phy: physicians; Pt: patients; Rheu: rheumatologists; SLR: systematic literature review; SOR: strength of recommendation.

Document	Issuing organization	Year of publication	Country	Funding body	Target population	Target audience	Guideline development	Guideline review	Guideline update	Evidence base	LOE	SOR
Guidelines												
SAMA_2003 [51]	South African Medical Association	2003	South Africa	Pharmaceutical company	Gout	Phy	Multi	ER	Intermittent	NG	-	-
EULAR_2006 [18]	EULAR	2006	Europe	EULAR	Gout	NG	Rheu	NG	NG	SLR	+	+
MOH_MSR_AMM_2008 [49]	MOH, MSR, AMM	2008	Malaysia	Pharmaceutical company	Adults (>16y) with gout	Phy	Multi	ER	2012 or sooner	SLR	+	+
PRA_2008 [50]	Philippine Rheumatology Association	2008	Philippine	NG	Gout	Phy	NG	NG	Three or more years	SLR	+	+
UTAustin_2009 [52]	University of Texas at Austin	2009	US	University of Texas at Austin	Adults with gout	Phy	NG	ER	NG	SLR	+	+
EULAR_2011 [17]	EULAR	2011	Multination	Pharmaceutical company, ASCR	Gout	Phy	Multi	NG	NG	SLR	+	+

JSGNAM_2011 [48]	Japanese Society of Gout and Nucleic Acid Metabolism	2011	Japan	NG	Hyperuricemia or gout	NG	NG	ER	NG	SLR	+	+
ACR_2012 [14, 15]	ACR	2012	US	ACR, NIAMS, NIH	Gout	Phy	Multi	NG	Intermittent	SLR	+	-
SER_2013 [46]	Spanish Society of Rheumatology	2013	Spain	Pharmaceutical company	Gout	Phy	Multi	ER	Four years	SLR	+	+
SIR_2013 [45]	Italian Society of Rheumatology	2013	Italy	NG	Gout	Phy	Multi	NG	NG	SLR	+	+
FMOH_2014 [44]	Federal Ministry of Health (Nigeria)	2014	Nigeria	NG	Gout	Phy, Pts in Nigeria	Multi	NG	NG	NG	-	-
CRA_2016 [41]	Chinese Rheumatology Association	2016	China	NG	Gout in China	Phy	Multi	NG	NG	SLR	+	+
EULAR_2016 [16]	EULAR	2016	Europe	NG	Gout	Phy, Pts	Multi	ER	Intermittent	SLR	+	+
TRA_2016 [38]	Taiwan Rheumatology Association	2016	Taiwan, China	NG	Hyperuricemia or gout	Phy, Pts	Multi	NG	NG	NG	-	-
ACP_2017 [19, 20]	ACP	2017	US	ACP	Acute and recurrent gout	Phy	NG	ER	Five years	SLR	+	+
BSR_2017 [21]	The British Society for Rheumatology	2017	UK	No specific funding.	Gout in the UK	Phy	Multi	ER	Planned in 2020	SLR	+	+
Consensus statements												
CCCP_2012 [47]	Chinese College of Cardiovascular Physicians	2012	China	NG	Asymptomatic hyperuricemia with CVD	NG	NG	NG	NG	CS	-	-
3e_2013 [36]	3e Initiative	2013	Multination	Pharmaceutical company	Gout	NG	Rheu	NG	NG	SLR	+	+
CSE_2013 [37]	Chinese Society of Endocrinology	2013	China	NG	Hyperuricemia or gout	NG	NG	NG	NG	CS	-	-
3e_PT_2014 [40]	Portuguese 3e Initiative	2014	Portugal	NG	Gout in Portuguese	NG	Rheu	NG	NG	SLR	+	+
3e_AU_NZ_2015 [43]	Australian and New Zealand 3e Initiative	2015	Multination	NG	Gout	NG	Rheu	NG	NG	SLR	+	+

ACR_EULAR_2015 [42]	ACR/EULAR	2015	Multination	ACR, EULAR	Gout	NG	NG	ER	Intermittent	SLR	-	-
T2T_2016 [39]	NG	2016	Multination	Pharmaceutical company	Gout	NG	Rheu	ER	NG	SLR	+	+
CRA_multi_2017 [22]	Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases	2017	China	NG	Hyperuricemia	Phy	Multi	NG	NG	CS	-	-

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.

Figure 2. Standardized domain scores for each guidance document

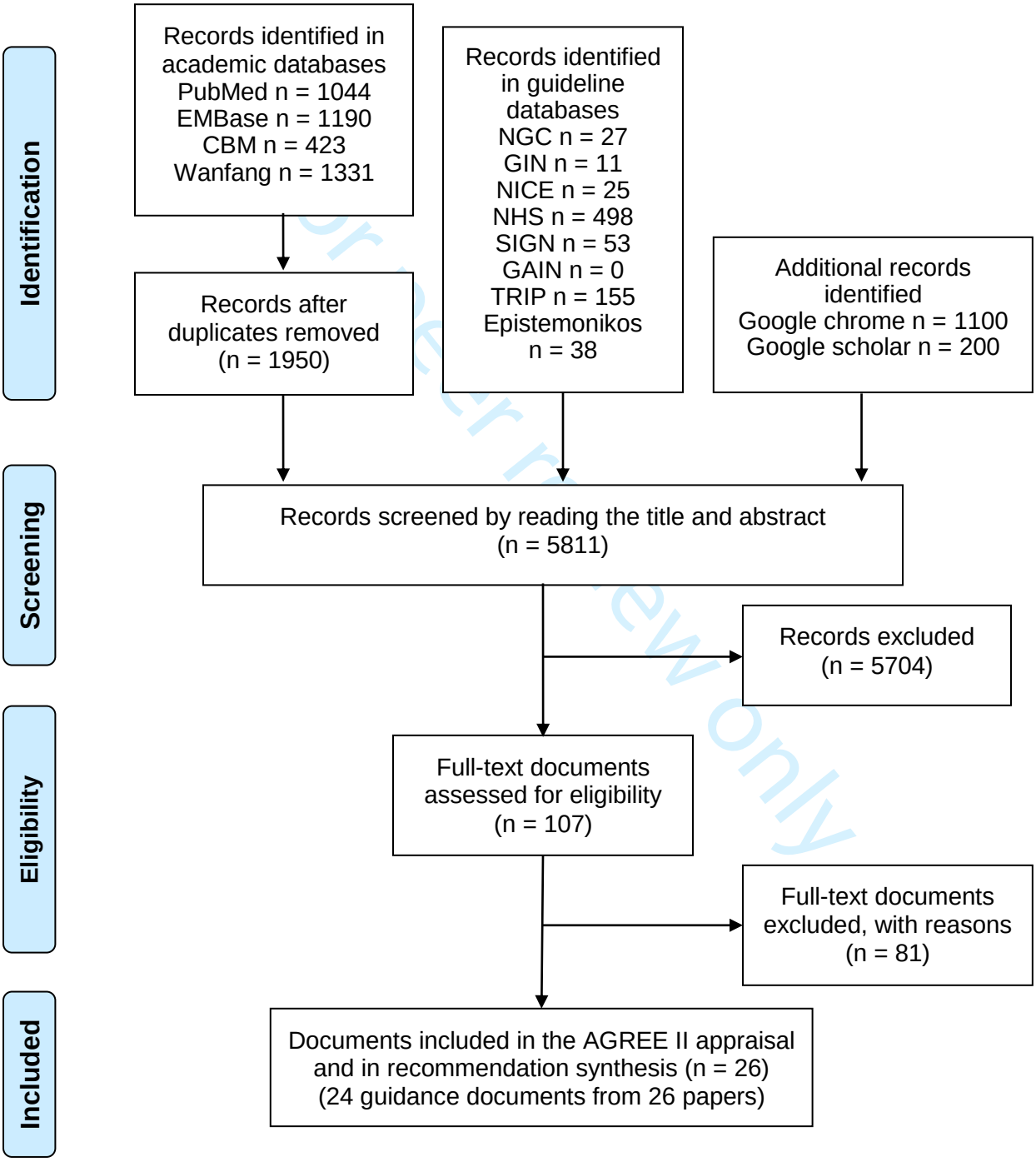
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia

3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

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.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

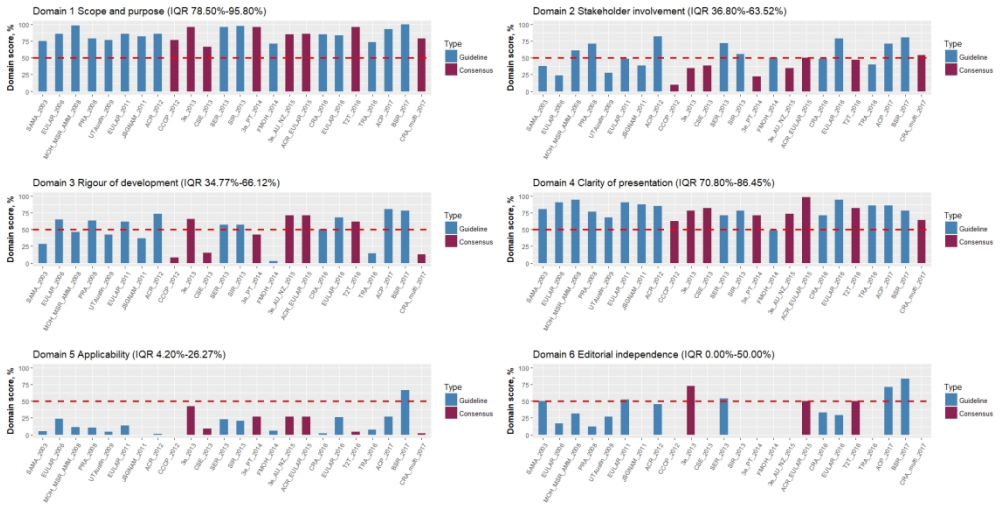


Figure 2. Standardized domain scores for each guidance document3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); IQR: interquartile range; JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

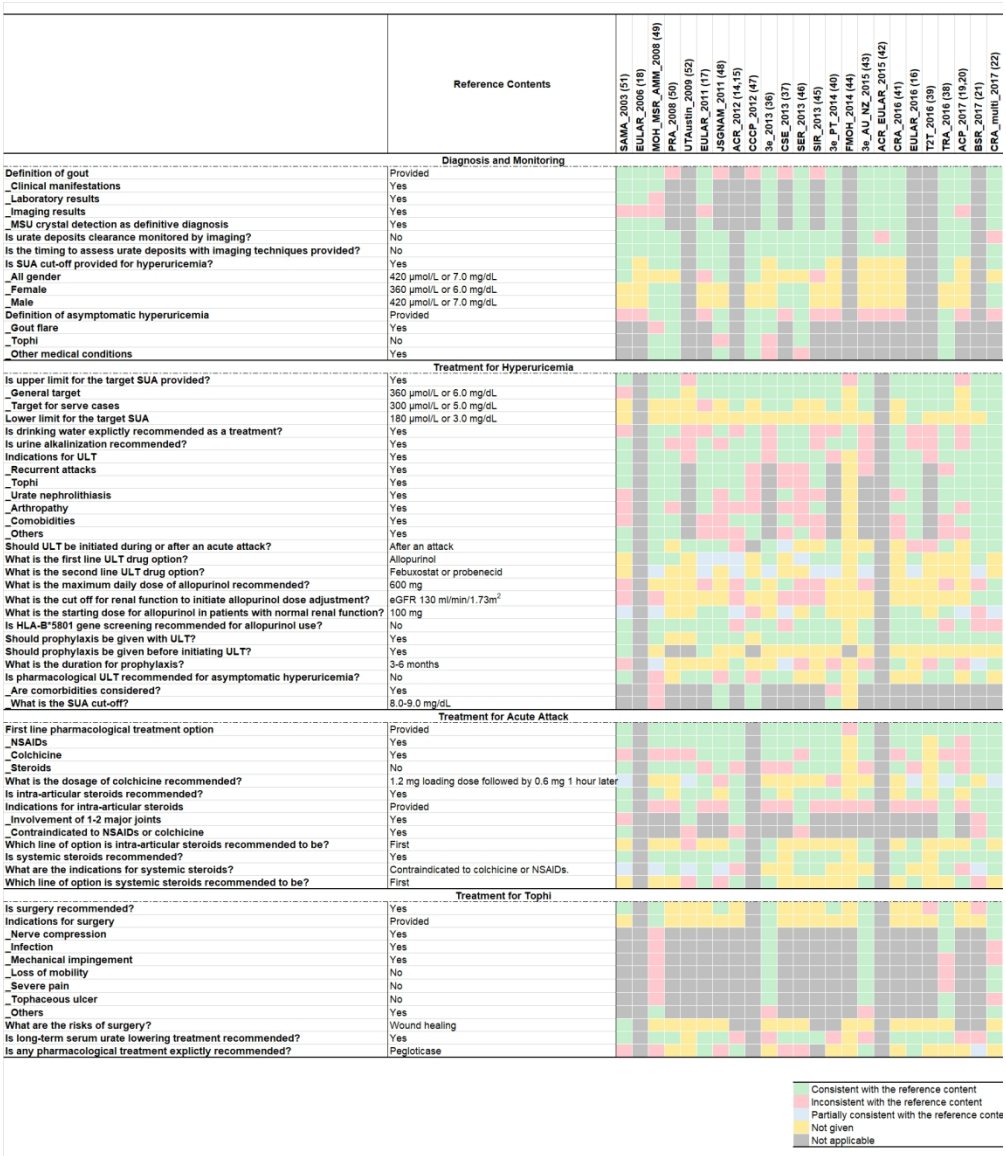


Figure 3. Summary of key recommendations for the diagnosis and treatment of gout and hyperuricemia
3e: Evidence, Expertise, Exchange Initiative; 3e_AU_NZ: Australian and New Zealand 3e Initiative; 3e_PT: Portuguese 3e Initiative; ACP: American College of Physicians; ACR: American College of Rheumatology; AMM: Academy of Medicine of Malaysia; ASCR: American Society of Clinical Rheumatologists; BSR: British Society for Rheumatology; CCCP: Chinese College of Cardiovascular Physicians; CRA: Chinese Rheumatology Association; CRA_multi: Chinese multi-disciplinary expert task force on hyperuricemia and its related diseases; CSE: Chinese Society of Endocrinology; EULAR: European League Against Rheumatism; FMOH: Federal Ministry of Health (Nigeria); JSGNAM: Japanese Society of Gout and Nucleic Acid Metabolism; MOH: Ministry of Health Malaysia; MSR: Malaysian Society of Rheumatology; NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH: National Institutes of Health; PRA: Philippine Rheumatology Association; SAMA: South African Medical Association; SER: Spanish Society of Rheumatology; SIR: Italian Society of Rheumatology; SUA: serum uric acid; T2T: Treat-to-target recommendations; TRA: Taiwan Rheumatology Association; UTAustin: University of Texas at Austin.

Supplementary Materials

Contents

Supplementary Table 1. Search strategy in PubMed

1	urate* OR uric acid OR gout OR hyperuricemia OR hyperuricaemia
2	guideline OR guideline* OR consensus OR policy OR polic* OR statement* OR recommendation*
3	1 AND 2

Supplementary Table 2. Search strategy in EMBASE using the OVID interface

1	exp hyperuricemia/
2	exp gout/
3	exp uric acid/
4	exp urate/
5	gout.m_titl.
6	uric acid.m_titl.
7	urate$.m_titl.
8	hyperuric?emia.m_titl.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp practice guideline/
11	guideline$.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

Supplementary Table 3. Searches in guideline databases

Databases	Date of search	Search strategy	Results found	Full text screened	Included documents	URL
National Guideline Clearinghouse	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	27	6	4	www.guideline.gov
Guidelines International Network	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, Search mode: Guidelines	11	5	5	www.g-i-n.net
National Institute for Health and Care Excellence	2017/07/24	hyperuricaemia OR hyperuricemia OR gout	25	2	0	www.nice.org.uk
National Health Service	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter type: guidance and policy	498	5	3	www.evidence.nhs.uk
Scottish Intercollegiate Guidelines Network	2017/07/24	NA	53	0	0	www.sign.ac.uk/our-guidelines.html
Guidelines and Audit Implementation Network	2017/07/24	“hyperuricaemia” OR “hyperuricemia” OR “gout”	0	0	0	rqia.org.uk/search-result
Turning Research Into Practice Database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: all secondary evidence	155	9	3	www.tripdatabase.com
Epistemonikos database	2017/07/24	hyperuricaemia OR hyperuricemia OR gout, filter: Broad syntheses OR Structured summaries	38	2	1	www.epistemonikos.org
Chinese Biomedical Literature Database	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	423	7	5	202.115.54.56/index.jsp
Wanfang Data	2017/07/22	[Original search term in Chinese] (hyperuricaemia OR gout) AND (guideline OR consensus OR statement OR recommendation)	1331	19	4	www.wanfangdata.com.cn/

Abbreviations: NA: Not applicable.

Supplementary Table 4. Excluded studies and reasons for exclusion

First author	Year	Reason for exclusion
Wuthrich [68]	2016	Review
Ceriotti [69]	2016	Primary study
Liote [70]	2016	Editorial
de Lautour [71]	2016	Primary study
de Lautour [72]	2014	Conference abstract
Dalbeth [73]	2015	Review
Terslev [74]	2015	Primary study
Turk [75]	2016	Not providing specific recommendations for hyperuricemia or gout
Stewart Coats [76]	2016	Editorial
Sullivan [77]	2015	Review
Gutierrez [78]	2015	Primary study
Grainger [79]	2015	Primary study
Robinson [80]	2015	Review
Chaudhary [81]	2013	Review
Bakris [82]	2014	Multimedia section
Terkeltaub [83]	2013	Review
Lyseng-Williamson [84]	2013	Review
Deodhar [85]	2013	Review
Simao [86]	2012	Review
Stamp [87]	2011	Review
Jansen [88]	2010	Not produced by related professional associations, institutes, societies, or communities
Grainger [89]	2009	Review
Grainger [90]	2008	Review
Dalbeth [91]	2007	Review
Jordan [92]	2007	Replaced by updated versions from the same organization
Becker [93]	2007	Not providing specific recommendations for hyperuricemia or gout

Zhang [55]	2006	Replaced by updated versions from the same organization
Caramia [94]	2004	Review
Terkeltaub [95]	2003	Case report
Cleland [96]	1995	Review
Hande [97]	1984	Case series
Committee on the Review of Medicines [98]	1978	Not providing specific recommendations for hyperuricemia or gout
Mourgues [99]	2016	Conference abstract
Bakris [100]	1970	Not providing specific recommendations for hyperuricemia or gout
Pai [101]	2015	Review
Vargas-Santos [102]	2016	Review
Filiopoulos [103]	2016	Comment letter
Chinchilla [104]	2016	Review
Rimler [105]	2016	Review
Saito [106]	2016	Not providing specific recommendations for hyperuricemia or gout
Mody [107]	2015	Review
Richette [108]	2014	Conference abstract
Richette [109]	2014	Conference abstract
Gutierrez [110]	2014	Conference abstract
Furst [111]	2013	Not providing specific recommendations for hyperuricemia or gout
Hershfield [112]	2013	Not providing specific recommendations for hyperuricemia or gout
Andres [113]	2012	Conference abstract
Stevenson [114]	2011	Technology appraisal
Diaz-Borjon [115]	2009	Review
Furst [116]	2010	Not providing specific recommendations for hyperuricemia or gout
Taylor [117]	2009	Primary study
Taylor [118]	2008	Primary study
Bussieres [119]	2008	Not providing specific recommendations for hyperuricemia or gout
Brooks [120]	2007	Review

Bestermann [121]	2005	Not providing specific recommendations for hyperuricemia or gout
Schumacher Jr [122]	2004	Review
Bartlett [123]	2002	Not providing specific recommendations for hyperuricemia or gout
Furst [124]	2013	Not providing specific recommendations for hyperuricemia or gout
Newberry [125]	2017	Review
Shekelle [126]	2017	Review
Sandberg [127]	2015	Not providing specific recommendations for hyperuricemia or gout
Kallinich [128]	2007	Not providing specific recommendations for hyperuricemia or gout
Preminger [129]	2007	Not providing specific recommendations for hyperuricemia or gout
TA164 [130]	2008	Technology appraisal
Phoon [131]	2012	Not providing specific recommendations for hyperuricemia or gout
Li [132]	2011	Review
Zhang [133]	2013	Review
Deng [134]	2016	Primary study
Chinese Rheumatology Association [135]	2004	Replaced by updated versions from the same organization
Chinese College of Cardiovascular Physicians [136]	2010	Replaced by updated versions from the same organization
Chinese Rheumatology Association [137]	2011	Replaced by updated versions from the same organization
National Department of Health, Pretoria, South Africa [138]	2006	Not providing specific recommendations for hyperuricemia or gout
European Medicines Agency [139]	2012	Not providing specific recommendations for hyperuricemia or gout
Agency for Healthcare Research and Quality [140]	2017	Review
Agency for Healthcare Research and Quality [141]	2017	Review
National Institute for Health and Care Excellence [142]	2013	Technology appraisal
Agency for Healthcare Research and Quality [143]	2016	Review
National Health System, United Kingdom [144]	2013	Not providing specific recommendations for hyperuricemia or gout
Canadian Expert Drug Advisory Committee [145]	2011	Not providing specific recommendations for hyperuricemia or gout
CME Academic Detailing Service [146]	2013	Presented as a 'handout', not a clinical practice guideline.
Henderson [147]	2015	Not released by a professional association

Supplementary Table 5. Domain score for each included guidance document

Document	Domain 1, %	Domain 2, %	Domain 3, %	Domain 4, %	Domain 5, %	Domain 6, %
3e_2013 [36]	95.8	34.7	65.6	77.8	42.7	72.9
3e_AU_NZ_2015 [43]	84.7	34.7	71.4	73.6	27.1	0.0
3e_PT_2014 [40]	95.8	22.2	42.7	70.8	27.1	0.0
ACP_2017 [19, 20]	93.1	70.8	80.2	86.1	27.1	70.8
ACR_2012 [14, 15]	86.1	81.9	73.4	84.7	1.0	45.8
ACR_EULAR_2015 [42]	86.1	50.0	71.4	98.6	27.1	50.0
BSR_2017 [21]	100.0	80.6	78.1	77.8	66.7	83.3
CCCP_2012 [47]	76.4	9.7	8.3	62.5	0.0	0.0
CRA_2016 [41]	84.7	48.6	50.5	70.8	2.1	33.3
CRA_multi_2017 [22]	79.2	54.2	13.0	63.9	2.1	0.0
CSE_2013 [37]	66.7	38.9	15.6	81.9	9.4	0.0
EULAR_2006 [18]	86.1	23.6	65.1	90.3	24.0	16.7
EULAR_2011 [17]	86.1	48.6	61.5	90.3	13.5	52.1
EULAR_2016 [16]	83.3	79.2	67.7	94.4	26.0	29.2
FMOH_2014 [44]	70.8	50.0	3.1	48.6	6.3	0.0
JSGNAM_2011 [48]	81.9	38.9	37.0	87.5	0.0	0.0
MOH_MSR_AMM_2008 [49]	98.6	61.1	46.4	94.4	11.5	31.3
PRA_2008 [50]	79.2	70.8	63.5	76.4	10.4	12.5
SAMA_2003 [51]	75.0	37.5	28.1	80.6	5.2	50.0
SER_2013 [46]	95.8	72.2	56.8	70.8	22.9	54.2
SIR_2013 [45]	97.2	55.6	56.8	77.8	20.8	0.0
T2T_2016 [39]	95.8	47.2	61.5	81.9	4.2	50.0
TRA_2016 [38]	73.6	40.3	14.1	86.1	7.3	0.0
UTAustin_2009 [52]	76.4	27.8	42.2	68.1	4.2	27.1
Median	85.4	48.6	56.8	79.2	10.9	28.1
Minimum	66.7	9.7	3.1	48.6	0.0	0.0
Maximum	100.0	81.9	80.2	98.6	66.7	83.3

Supplementary Table 6. Mean scores across reviewers for the individual AGREE II domain items

Document	Domain 1			Domain 2			Domain 3								Domain 4			Domain 5				Domain 6	
Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3e_2013 [36]	6.8	6.5	7.0	7.0	1.3	1.0	6.3	3.8	6.3	5.8	5.8	6.8	4.0	1.0	6.0	7.0	4.0	6.8	1.0	5.3	1.3	7.0	3.8
3e_AU_NZ_2015 [43]	6.0	5.5	6.8	5.8	1.0	2.5	6.5	6.8	7.0	6.5	6.5	6.8	1.3	1.0	5.8	6.0	4.5	5.8	1.0	2.8	1.0	1.0	1.0
3e_PT_2014 [40]	6.5	7.0	6.8	4.8	1.3	1.0	2.8	2.3	5.5	3.5	5.5	6.8	1.3	1.0	5.5	6.3	4.0	4.5	1.3	2.8	2.0	1.0	1.0
ACP_2017 [19, 20]	6.0	6.8	7.0	6.3	5.3	4.3	6.8	6.8	6.5	5.0	6.5	5.3	4.8	5.0	5.3	6.8	6.5	2.5	1.8	5.3	1.0	4.0	6.5
ACR_2012 [14, 15]	6.5	5.5	6.5	7.0	5.3	5.5	7.0	7.0	6.8	6.0	5.8	6.0	1.5	3.3	5.8	7.0	5.5	1.0	1.0	1.0	1.3	3.3	4.3
ACR_EULAR_2015 [42]	6.5	5.0	7.0	5.3	4.8	2.0	7.0	6.8	5.3	6.0	7.0	5.5	1.8	3.0	6.8	7.0	7.0	3.8	4.0	1.8	1.0	3.8	4.3
BSR_2017 [21]	7.0	7.0	7.0	5.5	5.3	6.8	7.0	6.0	6.5	6.8	6.3	6.0	5.0	2.0	6.8	6.8	3.5	4.8	4.8	6.5	4.0	7.0	5.0
CCCP_2012 [47]	6.8	3.0	7.0	2.0	1.0	1.8	1.0	1.0	1.0	1.0	3.8	2.0	1.3	1.0	4.5	5.8	4.0	1.0	1.0	1.0	1.0	1.0	1.0
CRA_2016 [41]	6.3	5.0	7.0	5.5	1.0	5.3	5.0	3.3	6.3	3.5	6.0	5.5	1.8	1.0	5.3	6.5	4.0	1.3	1.0	1.3	1.0	1.0	5.0
CRA_multi_2017 [22]	7.0	3.5	6.8	4.8	1.3	6.8	1.0	1.0	1.0	1.3	5.0	2.8	1.3	1.0	5.0	6.5	3.0	1.0	1.3	1.0	1.3	1.0	1.0
CSE_2013 [37]	7.0	1.8	6.3	3.0	1.0	6.0	1.0	1.0	2.0	1.0	5.0	3.5	1.0	1.0	5.5	5.5	6.8	3.0	1.0	1.0	1.3	1.0	1.0
EULAR_2006 [18]	6.0	5.5	7.0	5.0	1.0	1.3	7.0	7.0	5.8	4.3	6.0	5.8	1.3	2.3	6.0	6.8	6.5	1.0	2.5	5.3	1.0	3.0	1.0
EULAR_2011 [17]	6.5	5.0	7.0	5.0	1.0	5.8	4.0	4.5	6.8	6.0	7.0	7.0	1.3	1.0	5.8	6.8	6.8	1.3	1.3	3.8	1.0	3.8	4.5
EULAR_2016 [16]	6.3	4.8	7.0	5.8	5.0	6.5	5.0	2.0	6.3	6.8	6.0	6.5	6.0	2.0	6.5	6.8	6.8	3.0	1.3	5.0	1.0	1.5	4.0
FMOH_2014 [44]	6.5	2.8	6.5	5.3	1.0	5.8	1.0	1.0	1.0	1.0	2.0	1.5	1.0	1.0	3.0	4.5	4.3	1.0	1.3	2.3	1.0	1.0	1.0
JSGNAM_2011 [48]	5.3	5.5	7.0	1.8	4.3	4.0	1.3	1.0	6.8	3.3	6.3	3.8	2.5	1.0	6.8	6.3	5.8	1.0	1.0	1.0	1.0	1.0	1.0
MOH_MSR_AMM_2008 [49]	6.8	7.0	7.0	5.5	1.5	7.0	4.3	1.0	5.8	1.5	5.8	4.8	2.5	4.8	6.5	6.8	6.8	1.8	3.0	1.0	1.0	4.0	1.8
PRA_2008 [50]	6.5	5.5	5.3	3.8	5.0	7.0	5.0	4.3	7.0	4.8	6.5	4.8	1.3	5.0	5.3	6.5	5.0	1.8	1.3	2.5	1.0	1.0	2.5
SAMA_2003 [51]	6.5	3.0	7.0	4.0	1.3	4.5	1.0	1.0	1.0	4.0	6.5	2.8	2.5	2.8	5.0	6.5	6.0	1.0	2.0	1.3	1.0	7.0	1.0
SER_2013 [46]	7.0	6.3	7.0	6.8	5.0	4.3	3.3	1.0	7.0	4.0	6.8	4.8	2.0	6.5	5.8	6.8	4.3	3.5	2.3	2.8	1.0	6.5	2.0
SIR_2013 [45]	6.8	6.8	7.0	6.3	1.0	5.8	4.0	6.8	6.3	4.3	6.3	5.5	1.3	1.0	6.3	6.8	4.0	2.5	1.0	4.5	1.0	1.0	1.0
T2T_2016 [39]	6.3	7.0	7.0	5.3	5.0	1.3	7.0	6.5	6.5	6.5	3.3	4.0	1.8	2.0	5.0	6.3	6.5	2.0	1.0	1.0	1.0	3.5	4.5
TRA_2016 [38]	5.8	3.5	7.0	5.0	1.5	3.8	1.0	1.3	1.0	1.3	5.5	2.5	1.3	1.0	5.5	6.5	6.5	1.0	1.5	2.3	1.0	1.0	1.0
UTAustin_2009 [52]	7.0	2.8	7.0	3.0	1.0	4.0	4.3	2.0	7.0	2.5	4.3	5.3	2.0	1.0	4.8	5.3	5.3	1.3	1.5	1.3	1.0	4.0	1.3

Supplementary Table 7. Scores for each individual AGREE II domain items by each reviewer

	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14	Item15	Item16	Item17	Item18	Item19	Item20	Item21	Item22	Item23
3e_2013 [36]																							
Rev1	7	7	7	7	1	1	6	4	4	5	7	7	2	1	6	7	4	7	1	5	1	7	4
Rev2	6	7	7	7	1	1	6	2	7	5	6	7	4	1	6	7	4	7	1	6	1	7	4
Rev3	7	5	7	7	2	1	7	5	7	6	5	6	5	1	5	7	4	7	1	5	2	7	3
Rev4	7	7	7	7	1	1	6	4	7	7	5	7	5	1	7	7	4	6	1	5	1	7	4
3e_AU_NZ_2015 [43]																							
Rev1	5	5	7	7	1	2	7	7	7	7	7	7	2	1	5	6	4	6	1	2	1	1	1
Rev2	7	5	7	7	1	1	5	7	7	6	6	7	1	1	6	7	4	6	1	4	1	1	1
Rev3	5	7	7	4	1	4	7	7	7	7	7	7	1	1	6	5	6	6	1	2	1	1	1
Rev4	7	5	6	5	1	3	7	6	7	6	6	6	1	1	6	6	4	5	1	3	1	1	1
3e_PT_2014 [40]																							
Rev1	6	7	7	5	1	1	3	1	7	3	6	7	2	1	5	6	4	4	1	5	1	1	1
Rev2	6	7	7	5	1	1	3	1	7	3	6	7	1	1	6	7	4	6	1	3	1	1	1
Rev3	7	7	6	5	2	1	2	1	6	5	4	6	1	1	5	6	4	4	2	2	5	1	1
Rev4	7	7	7	4	1	1	3	6	2	3	6	7	1	1	6	6	4	4	1	1	1	1	1
ACP_2017 [19, 20]																							
Rev1	6	7	7	6	5	4	7	7	7	5	7	5	5	5	5	7	7	2	2	4	1	4	7
Rev2	6	7	7	6	5	4	7	7	7	5	7	5	5	4	6	7	7	4	3	7	1	4	7
Rev3	6	7	7	6	6	3	6	6	6	6	6	5	4	5	5	6	6	2	1	5	1	4	6
Rev4	6	6	7	7	5	6	7	7	6	4	6	6	5	6	5	7	6	2	1	5	1	4	6
ACR_2012 [14, 15]																							
Rev1	6	5	7	7	5	7	7	7	6	6	6	5	2	3	5	7	4	1	1	1	1	3	4
Rev2	6	7	7	7	7	4	7	7	7	6	6	5	2	3	6	7	7	1	1	1	1	4	4
Rev3	7	5	7	7	5	7	7	7	7	6	5	7	1	3	5	7	7	1	1	1	2	3	4
Rev4	7	5	5	7	4	4	7	7	7	6	6	7	1	4	7	7	4	1	1	1	1	3	5
ACR_EULAR_2015 [42]																							
Rev1	6	5	7	6	6	2	7	7	7	7	7	5	2	3	7	7	7	3	3	1	1	4	4

Rev2	6	5	7	5	6	1	7	7	6	6	7	5	2	3	7	7	7	5	7	1	1	4	4
Rev3	7	5	7	5	6	2	7	7	7	6	7	5	2	3	7	7	7	3	3	1	1	3	4
Rev4	7	5	7	5	1	3	7	6	1	5	7	7	1	3	6	7	7	4	3	4	1	4	5
BSR_2017 [21]																							
Rev1	7	7	7	6	5	7	7	6	6	7	6	6	5	2	7	7	4	5	4	7	2	7	5
Rev2	7	7	7	6	5	7	7	6	6	6	7	5	5	2	7	7	3	5	5	7	5	7	5
Rev3	7	7	7	4	5	6	7	7	7	7	5	6	5	1	6	6	3	4	5	6	2	7	5
Rev4	7	7	7	6	6	7	7	5	7	7	7	7	5	3	7	7	4	5	5	6	2	7	5
CCCP_2012 [47]																							
Rev1	6	3	7	2	1	2	1	1	1	1	3	1	2	1	3	6	4	1	1	1	1	1	1
Rev2	7	3	7	2	1	1	1	1	1	1	4	3	1	1	4	5	4	1	1	1	1	1	1
Rev3	7	3	7	2	1	1	1	1	1	1	4	2	1	1	6	6	4	1	1	1	1	1	1
Rev4	7	3	7	2	1	3	1	1	1	1	4	2	1	1	5	6	4	1	1	1	1	1	1
CRA_2016 [41]																							
Rev1	5	5	7	6	1	4	5	3	7	3	7	5	2	1	5	7	4	1	1	1	1	1	4
Rev2	7	5	7	6	1	5	4	3	6	4	6	5	3	1	6	7	4	1	1	1	1	1	4
Rev3	7	5	7	5	1	6	5	3	6	1	5	6	1	1	5	6	4	1	1	2	1	1	6
Rev4	6	5	7	5	1	6	6	4	6	6	6	6	1	1	5	6	4	2	1	1	1	1	6
CRA_multi_2017 [22]																							
Rev1	7	3	7	5	1	7	1	1	1	1	5	3	2	1	5	7	2	1	1	1	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	2	5	2	1	1	5	7	3	1	1	1	1	1	1
Rev3	7	3	7	4	2	6	1	1	1	1	5	5	1	1	5	5	3	1	1	1	2	1	1
Rev4	7	5	6	5	1	7	1	1	1	1	5	1	1	1	5	7	4	1	2	1	1	1	1
CSE_2013 [37]																							
Rev1	7	1	6	3	1	6	1	1	2	1	5	5	1	1	5	6	7	3	1	1	1	1	1
Rev2	7	3	6	4	1	6	1	1	3	1	5	3	1	1	6	6	7	3	1	1	1	1	1
Rev3	7	1	7	2	1	7	1	1	2	1	5	3	1	1	6	6	6	3	1	1	2	1	1
Rev4	7	2	6	3	1	5	1	1	1	1	5	3	1	1	5	4	7	3	1	1	1	1	1
EULAR_2006 [18]																							
Rev1	5	5	7	5	1	1	7	7	5	3	6	5	2	1	5	7	7	1	2	5	1	4	1

Rev2	6	5	7	5	1	1	7	7	6	5	6	6	1	1	6	7	6	1	4	6	1	4	1
Rev3	7	7	7	5	1	1	7	7	6	5	7	6	1	1	7	7	7	1	1	5	1	1	1
Rev4	6	5	7	5	1	2	7	7	6	4	5	6	1	6	6	6	6	1	3	5	1	3	1
EULAR_2011 [17]																							
Rev1	6	5	7	4	1	7	4	1	7	7	7	7	2	1	5	7	7	2	1	2	1	4	4
Rev2	6	5	7	5	1	3	4	7	7	4	7	7	1	1	6	7	7	1	1	5	1	4	4
Rev3	7	5	7	6	1	7	4	4	7	7	7	7	1	1	6	7	7	1	1	4	1	4	6
Rev4	7	5	7	5	1	6	4	6	6	6	7	7	1	1	6	6	6	1	2	4	1	3	4
EULAR_2016 [16]																							
Rev1	7	7	7	6	5	7	5	2	7	7	7	7	6	1	7	7	7	2	2	5	1	1	4
Rev2	7	1	7	6	5	7	5	2	7	7	6	7	6	3	7	7	7	4	1	6	1	1	4
Rev3	5	5	7	5	5	5	5	1	6	6	5	6	6	2	5	6	6	4	1	4	1	1	4
Rev4	6	6	7	6	5	7	5	3	5	7	6	6	6	2	7	7	7	2	1	5	1	3	4
FMOH_2014 [44]																							
Rev1	7	3	7	6	1	4	1	1	1	1	2	1	1	1	3	1	4	1	1	2	1	1	1
Rev2	7	3	7	5	1	7	1	1	1	1	2	1	1	1	4	4	4	1	2	3	1	1	1
Rev3	6	2	5	5	1	6	1	1	1	1	1	2	1	1	2	7	6	1	1	1	1	1	1
Rev4	6	3	7	5	1	6	1	1	1	1	3	2	1	1	3	6	3	1	1	3	1	1	1
JSGNAM_2011 [48]																							
Rev1	5	5	7	2	4	4	1	1	6	3	6	3	2	1	7	7	4	1	1	1	1	1	1
Rev2	6	5	7	2	4	4	1	1	7	4	6	4	3	1	7	6	7	1	1	1	1	1	1
Rev3	5	7	7	1	4	4	1	1	7	1	7	4	2	1	7	6	7	1	1	1	1	1	1
Rev4	5	5	7	2	5	4	2	1	7	5	6	4	3	1	6	6	5	1	1	1	1	1	1
MOH_MSR_AMM_2008 [49]																							
Rev1	6	7	7	5	1	7	4	1	5	1	6	5	2	4	7	7	7	2	3	1	1	4	1
Rev2	7	7	7	5	3	7	4	1	6	2	6	4	3	5	6	7	7	3	5	1	1	4	2
Rev3	7	7	7	7	1	7	4	1	6	1	6	5	2	5	7	7	7	1	1	1	1	4	2
Rev4	7	7	7	5	1	7	5	1	6	2	5	5	3	5	6	6	6	1	3	1	1	4	2
PRA_2008 [50]																							
Rev1	5	3	5	4	5	7	5	1	7	4	7	5	1	5	5	7	4	2	1	2	1	1	2

Rev2	7	7	4	3	5	7	5	6	7	4	6	4	2	5	5	6	7	3	2	3	1	1	4
Rev3	7	7	7	4	5	7	5	5	7	6	7	5	1	5	6	7	5	1	1	2	1	1	2
Rev4	7	5	5	4	5	7	5	5	7	5	6	5	1	5	5	6	4	1	1	3	1	1	2
SAMA_2003 [51]																							
Rev1	6	3	7	5	1	4	1	1	1	5	7	3	2	3	3	6	7	1	1	2	1	7	1
Rev2	7	3	7	4	1	5	1	1	1	5	7	2	4	2	5	7	4	1	5	1	1	7	1
Rev3	7	3	7	2	1	5	1	1	1	1	7	3	1	1	6	7	7	1	1	1	1	7	1
Rev4	6	3	7	5	2	4	1	1	1	5	5	3	3	5	6	6	6	1	1	1	1	7	1
SER_2013 [46]																							
Rev1	7	6	7	7	5	4	3	1	7	3	7	5	2	5	5	6	4	2	2	2	1	7	2
Rev2	7	6	7	6	5	3	3	1	7	5	6	4	2	7	6	7	4	4	5	3	1	5	2
Rev3	7	7	7	7	5	5	3	1	7	3	7	6	2	7	7	7	4	4	1	4	1	7	2
Rev4	7	6	7	7	5	5	4	1	7	5	7	4	2	7	5	7	5	4	1	2	1	7	2
SIR_2013 [45]																							
Rev1	7	7	7	6	1	7	4	7	5	3	7	5	2	1	7	7	4	2	1	4	1	1	1
Rev2	7	7	7	6	1	4	4	7	7	5	6	5	1	1	6	7	4	4	1	6	1	1	1
Rev3	7	7	7	6	1	6	4	7	7	6	7	6	1	1	6	7	4	1	1	4	1	1	1
Rev4	6	6	7	7	1	6	4	6	6	3	5	6	1	1	6	6	4	3	1	4	1	1	1
T2T_2016 [39]																							
Rev1	6	7	7	5	5	1	7	7	7	7	3	3	2	1	4	6	7	3	1	1	1	4	2
Rev2	7	7	7	6	5	1	7	7	7	7	4	5	2	5	6	7	7	1	1	1	1	4	4
Rev3	5	7	7	5	5	2	7	6	6	6	2	3	2	1	5	6	6	3	1	1	1	3	6
Rev4	7	7	7	5	5	1	7	6	6	6	4	5	1	1	5	6	6	1	1	1	1	3	6
TRA_2016 [38]																							
Rev1	5	3	7	5	1	4	1	1	1	1	6	2	2	1	6	7	7	1	1	2	1	1	1
Rev2	6	3	7	5	1	7	1	1	1	2	6	2	1	1	6	7	7	1	3	3	1	1	1
Rev3	6	3	7	5	3	1	1	2	1	1	5	4	1	1	5	6	6	1	1	2	1	1	1
Rev4	6	5	7	5	1	3	1	1	1	1	5	2	1	1	5	6	6	1	1	2	1	1	1
UTAustin_2009 [52]																							
Rev1	7	3	7	4	1	4	4	1	7	3	4	5	2	1	3	4	4	1	1	1	1	4	2

Rev2	7	3	7	2	1	4	4	1	7	2	4	5	2	1	5	6	7	2	3	1	1	4	1
Rev3	7	2	7	2	1	4	4	1	7	1	6	5	2	1	6	6	7	1	1	1	1	4	1
Rev4	7	3	7	4	1	4	5	5	7	4	3	6	2	1	5	5	3	1	1	2	1	4	1

Supplementary Table 8. Summary of recommendations for the diagnosis of gout and hyperuricemia by included guidance document

IE: insufficient evidence; MSU: monosodium urate; NA: not applicable; NG: not given; SUA: serum uric acid.

	SAMA_2003 [51]	EULAR_2006 [18]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	EULAR_2011 [17]	JSGNAM_2011 [48]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	3e_AU_NZ_2015 [43]	ACR_EULAR_2015 [42]	CRA_2016 [41]	TRA_2016 [38]	ACP_2017 [19, 20]	CRA_multi_2017 [22]
Diagnosis of gout	+	+	+	NG	+	NG	NG	+	NG	+	NG	+	+	+	+	+	+	+
_Clinical manifestations	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Laboratory results	+	+	-	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
_Imaging results	-	+*	-	NA	-	NA	NA	+	NA	+	NA	+	+	+	+	+	IE	+
_MSU crystal as definitive diagnosis	+	+	+	NA	+	NA	NA	+	NA	+	NA	+	+	+	+	+	+	+
Monitor urate deposits clearance by imaging	-	-	-	-	-	-	-	-	-	IE	-	-	-	+	-	-	-	+
Is the timing to assess urate deposits with imaging techniques provided?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SUA for hyperuricemia, µmol/L [mg/dL]	+	NG	+	+	+	+	+	NG	+	+	+	NG	NG	NG	NG	+	NG	+
_All gender	420	NG	NG	NG	[6.8]	[7.0]	420 [7.0]	NG	NG	NG	404 [6.8]	NG	NG	NG	NG	[7.0]	NG	NG
_Female	NG	NG	360 [6.0]	357 [6.0]	NG	NG	NG	NG	360	[6.0]	NG	NG	NG	NG	NG	NG	NG	360
_Male	NG	NG	420 [7.0]	416 [7.0]	NG	NG	NG	NG	420	[7.0]	NG	NG	NG	NG	NG	NG	NG	420
Diagnosis of asymptomatic hyperuricemia	NG	NG	+	+	NG	+	+	+.	NG	+	NG	NG	NG	NG	NG	+	NG	NG
_Gout flare	NA	NA	-	+	NA	+	+	+	NA	+	NA	NA	NA	NA	NA	+	NA	NA
_Tophi	NA	NA	-	-	NA	+	-	+	NA	-	NA	NA	NA	NA	NA	-	NA	NA
_Additional medical conditions†	NA	NA	+	+	NA	+	+	-	NA	-	NA	NA	NA	NA	NA	+	NA	NA

*Imaging results are considered for chronic gout, but not for early/acute gout.

†Additional medical conditions considered in the definition of asymptomatic hyperuricemia included complications of gout [47], renal disorder [48], signs or symptoms of

urate deposition [49], and uric acid nephrolithiasis [50]. One document provided a general statement of any clinical presentations [38]. One document explicitly stated that the inclusion of patients with pre-existing renal or cardiovascular disease was allowed [36].

Supplementary Table 9. Summary of recommendations for the treatment of hyperuricemia by included guidance documents

A: allopurinol; Aft: (to initiate ULT) after an acute attack; B: benzbromarone; CCr: creatinine clearance rate; Cr: serum creatinine; CKD: chronic kidney disease; D: (to initiate ULT) during an acute attack; eGFR: estimated glomerular filtration rate; F: febuxostat; IE: insufficient evidence; m: month(s); NA: not applicable; NG: not given; P: probenecid; RF: renal function; SUA: serum uric acid; U: uricosurics without specification; ULT: urate lowering therapy; w: week(s); y: year.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	CCCP_2012 [47]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Upper limit for target SUA, μmol/L [mg/dL]																						
_General target*	300	360 [6.0]	[6.0]	NG	[6.0]	[6.0]	[6.0]	357 [6.0]	360 [6.0]	360	[6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]	360 [6.0]	360 [6.0]	360 [6.0]	NG	360	360 [6.0]
_Target for serve cases†	NG	NG	NG	NG	[4.0]	NG	[5.0]	NG	300	300	NG	NG	300 [5.0]	NG	300	NG	300 [5.0]	300 [5.0]	300 [5.0]	NG	300	300 [5.0]
Lower limit for target SUA, μmol/L [mg/dL]	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	[3.0]	NG	NG	NG	NG	180
Drinking water	-	+	+	-	-	+	-	+	-	+	+	-	-	+	-	+	-	-	+	-	+	+
Urine alkalinisation	+	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	-	-	+	-	+	+
Indications for ULT	+	+	+	-	+	+	+	+	-	+	+	+	-	NG	-	+	+	-	+	+	+	+
_Recurrent attacks	+, >2	+, >3/y	+	NA	+, >1/y	+	+, ≥2/y	-	NA	-	-	+	NA	NG	-	+, >2/y	+, ≥2/y	NA	-	+, ≥2/y	+, ≥2/y	+
_Tophi	+	+	+	NA	+	+	+	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	+	+	+
_Urate nephrolithiasis	-	+	+	NA	+	-	+	-	NA	+	-	-	NA	NG	NA	-	+	NA	+	+	+	+
_Arthropathy	-	+	-	NA	+	-	-	-	NA	-	-	+	NA	NG	NA	+	+	NA	+	-	+	+
_Comorbidities‡	-	+	+	NA	-	-	+	+	NA	+	-	-	NA	NG	NA	-	+	NA	-	+	+	+
_Others§	+	+	+	NA	-	-	-	+	NA	-	+	-	NA	NG	NA	-	+	NA	-	-	+	+
Initiate ULT during or after an acute attack (Aft[time after attack])	Aft	Aft	NG	Aft (4-6 w)	Aft	Aft (2w)	D	NA	Aft	D/ Aft (2w)	NG	NG	Aft	NG	NG	NG	IE	IE	Aft	NG	Aft	Aft
First line ULT drug(s)	NG	A	A	NG	A, F	A, B	A, F	NG	A	NG	A, F,	A	A	NG	A	NG	A	NG	NG	NG	A	NG

											B										
Second line ULT drug(s)	NG	P	NG	NG	P	NG	P	NG	U, F	NG	NG	F, P, B	F, B, P, U	NG	P, B, F	NG	F, U	NG	NG	NG	F	NG
Allopurinol use																						
_Maximum dose (mg/d)	300	NG	NG	NG	800	NG	800	600	NG	600	800-900	800	NG	NG	900	NG	NG	NG	800	NG	900	600
_RF to initiate dose adjustment (eGFR in ml/min/1.73m^2, CCr in mL/min)	CCr 60	CCr 80	NG	NG	NG	NG	CK D4	NG	NG	CCr 60	CCr 140	CCr 20	NG	NG	NG	NG	NG	NG	NG	NG	eGFR 130	1.5mg/ eGFR‖
_Starting dose in normal RF (mg/d)	50-100	100-150	NG	NG	100	50	≤100	50	NG	100-150	NG	100	NG	NG	NG	100	100	NG	100	50-100	200	50-100
_HLA-B*5801 gene screening	-	-	-	-	-	-	+	-	-	+	-	-	-	NG	-	-	-	-	+	-	+	+
Prophylaxis before ULT	+	NG	NG	NG	+	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Prophylaxis with ULT	+	+	NG	NG	+	+	+	NG	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Duration for prophylaxis	1-3 m¶	1-6 m**	NG	NG	NG	NG	3-6 m††	NG	Un-clear	6m	>6m	NG	>6m	NG	Vari-ed‡‡	3-6 m	NG	>6m	3-6 m	>8w	<6m	3-6m
Pharmacological ULT for asymptomatic hyperuricemia?	-	+	NG	-	-	+	IE	+	IE	IE	NG	NG	-§§	NG	IE	NG	NG	IE	-	NG	-	NG
_Comorbidities	NA	-	NA	NA	NA	+	NA	+	NA	NA	NA	NA	-	NG	NA	NA	NA	NA	NA	NA	NA	NA
_SUA cut-offs, µmol/L [mg/dL]	NA	[10-13]‖‖	NA	NA	NA	[8.0-9.0] ¶¶	NA	[8.0-9.0] ***	NA	NA	NA	NA	[9.0]	NG	NA	NA	NA	NA	NA	NA	NA	NA

* The general target was the target serum uric acid level for long term control recommended for all patients on pharmacological urate lowering therapy.

† The intensive target the intensive target was the target serum uric acid level for long term control recommended for patients with tophi [16, 17, 22, 36, 38, 40, 43], with recurrent attacks [16, 21, 22], or with chronic gouty arthritis [16, 22], or to prevent crystal formation [21], or to improve gout signs and symptoms [14, 15]. One document provided stricter target for any patient with gout [37], and one for patients with severe gout without clear definition [39].

‡ Comorbidities considered as the indication for ULT include renal impairment [14-16, 19-22, 37, 49, 50], cardiovascular risk or cardiovascular diseases [16, 22, 47], glucose intolerance or DM, lipid disorder, and obesity [22].

§ Others indications considered for pharmacological ULT include joint damage [21], diuretic therapy use [21], young age [16, 21, 22] with some documents defined as less than 40 years old [16, 22], high SUA level defined as >8mg/dL (480 umol/L) [16] or >13mg/dl [50], impending cytotoxic chemotherapy or radiotherapy for lymphoma or

leukaemia [49], persistently raised uric acid levels and willingness to continue lifelong therapy [51]. Some documents evaluated SUA levels in patients after lifestyle modification and indicated pharmacological ULT in individuals with SUA above 6 mg/dL [46], or with SUA above 8mg/dl with CV risk or CVD and above 9mg/dl without CV risk or CVD [47].

|| The starting dose of allopurinol in patients with renal impairment should not exceed 1.5mg/eGFR.

¶ Prophylaxis should be continued until the serum urate is normal and the patient has not had any attacks for 1-3 months.

** Prophylaxis should be continued until 6 months free of acute attacks or until 1 month with target serum urate level achieved.

†† Prophylaxis should be continued for 1) 6 months' duration, 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination, or 3) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination.

‡‡ The during for prophylaxis varied and depends on the presence of tophi and comorbidities and on serum urate response. But prophylaxis should be continued until the target SUA is reached or until the tophi has resolved.

§§ The recommendations provided were conflict within the same document.

|||| Pharmacological urate lowering therapy is recommended in male patients with serum uric acid >13 mg/dL and in female patients with serum uric acid >10 mg/dL.

¶¶ Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with complications or >9 mg/dL in all patients.

*** Pharmacological urate lowering therapy is recommended in patients with serum uric acid >8 mg/dL if with cardiovascular disease or cardiovascular risk factors or >9 mg/dL if without cardiovascular disease or cardiovascular risk factors.

Supplementary Table 10. Summary of recommendations for the treatment of acute gout by included guidance documents

NG: not given; NSAIDs: non-steroidal anti-inflammatory drugs.

	What is the first line pharmacological treatment option?	Is colchicine recommended to be given as a fixed dose or as a loading dose + followed doses?	Is intra-articular steroids recommended?	What are the indications for intra-articular steroids?	Which line is intra-articular steroids recommended to be?	Is systemic steroids recommended?	What are the indications for systemic steroids?	Which line of option is systemic steroids recommended to be?
SAMA_2003 [51]	NSAIDs	Loading dose + followed doses	Yes	Contraindicated to NSAIDs and joint accessible	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	NG
MOH_MSR_AMM_2008 [49]	NSAIDs	NG	Yes	NG	NG	Yes	Elderly people, renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease, and hypersensitivity to NSAIDs	NG
PRA_2008 [50]	NSAIDs	NG	NG	NG	NG	Yes	Contraindicated to NSAIDs	NG
UTAustin_2009 [52]	NSAIDs	Loading dose + followed doses	Yes	Only 1-2 joints is involved	Third	Yes	Contraindicated or not responding to NSAIDs and colchicine and polyarthritis	Third
EULAR_2011 [17]	Colchicine, NSAIDs, glucocorticoids	Loading dose + followed doses	Yes	NG	NG	Yes	Contraindications to NSAIDs and colchicine	First
JSGNAM_2011 [48]	Colchicine, NSAIDs	Fixed	NG	NG	NG	Yes	Contraindicated or not responding to NSAIDs or polyarthritis	Second
ACR_2012 [14, 15]	NSAIDs, corticosteroids, colchicine	Loading dose + followed doses	Yes	Involvement of 1 or 2 large joints	First	Yes	Oral steroids for involvement of 1 or 2 joints or when intra-articular joint injection is impractical. Intravenous steroids for the nothing by mouth patients.	First
3e_2013 [36]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CSE_2013 [37]	NSAIDs, colchicine,	NG	NG	NG	NG	NG	NG	NG

	corticosteroids							
SER_2013 [46]	NSAIDs	NG	Yes	Monoarthritis	NG	Yes	Contraindicated to NSAIDs	NG
SIR_2013 [45]	NSAIDs, colchicine	NG	Yes	NG	NG	Yes	Intolerance or contraindications to NSAIDs and colchicine	NG
3e_PT_2014 [40]	Colchicine, NSAIDs	Fixed low dose	Yes	NG	NG	Yes	NG	NG
FMOH_2014 [44]	NG	NG	NG	NG	NG	NG	NG	NG
3e_AU_NZ_2015 [43]	NSAIDs, colchicine, glucocorticoids	NG	Yes	NG	First	Yes	NG	First
CRA_2016 [41]	NSAIDs	NG	NG	NG	NG	Yes	Contraindications to NSAIDs and colchicine	NG
EULAR_2016 [16]	Colchicine, NSAIDs, corticosteroid	Loading dose + followed doses	Yes	NG	First	Yes	NG	First
T2T_2016 [39]	Anti-inflammatory medications	NG	NG	NG	NG	NG	NG	NG
TRA_2016 [38]	NSAIDs	Fixed or Loading dose + followed doses	Yes	Involvement of 1-2 major joints, contraindications to both colchicine and NSAIDs	NG	Yes	Contraindications to NSAIDs and colchicine	NG
ACP_2017 [19, 20]	Corticosteroids	Loading dose + followed doses	NG	NG	NG	Yes	If not contraindicated.	First
BSR_2017 [21]	NSAIDs, colchicine	NG	Yes	Patients with acute illness and comorbidity	First	Yes	Intolerance to NSAIDs and colchicine and intra-articular injection is not feasible.	Second
CRA_multi_2017 [22]	NSAIDs, colchicine	Loading dose + followed doses	Yes	Involvement of 1-2 major joints and not responding to systemic treatment	NG	Yes	Contraindicated to or not responding to NSAIDs and colchicine	NG

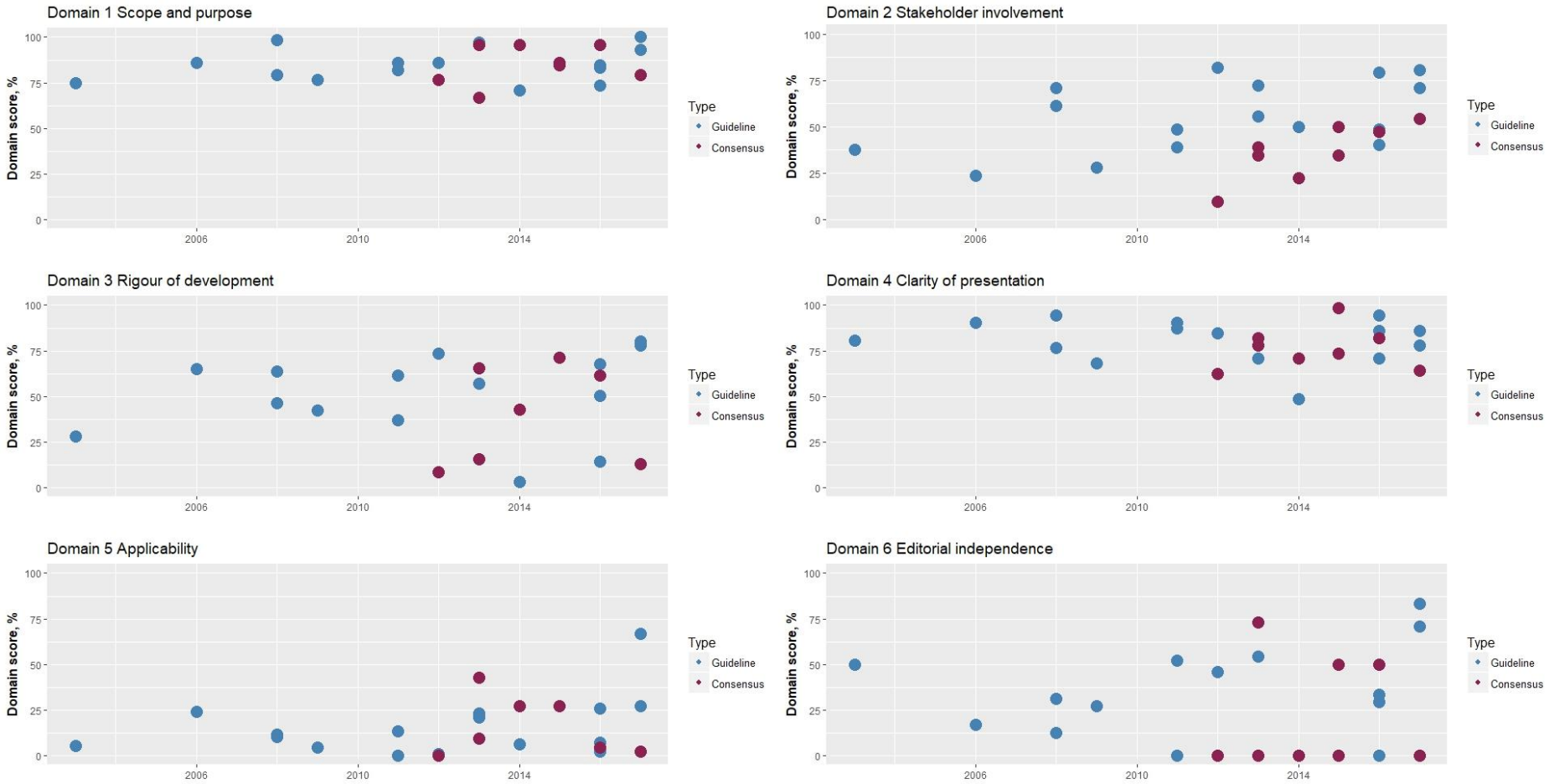
Supplementary Table 11. Summary of recommendations for the treatment of tophi by included guidance documents

A: allopurinol; B: benzbromarone; F: febuxostat; NA: not applicable; NG: not given; P: pegloticase; R: rasburicase; ULT: urate lowering therapy; WH: wound healing.

	SAMA_2003 [51]	MOH_MSR_AMM_2008 [49]	PRA_2008 [50]	UTAustin_2009 [52]	EULAR_2011 [17]	JSGNAM_2011 [48]	ACR_2012 [14, 15]	3e_2013 [36]	CSE_2013 [37]	SER_2013 [46]	SIR_2013 [45]	3e_PT_2014 [40]	FMOH_2014 [44]	3e_AU_NZ_2015 [43]	CRA_2016 [41]	EULAR_2016 [16]	T2T_2016 [39]	TRA_2016 [38]	ACP_2017 [19, 20]	BSR_2017 [21]	CRA_multi_2017 [22]
Is surgery recommended?	+	+	NG	NG	NG	+	NG	+	NG	NG	NG	+	NG	+	NG	NG	IE	+	NG	-	+
Indications for surgery	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	NG	NG	+	NG	NG	NG	+	NG	NG	+
_Nerve compression	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	+
_Infection	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	+	NA	NA	-
_Mechanical impingement	NA	-	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	+	NA	NA	NA	-	NA	NA	-
_Loss of mobility	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Severe pain	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	-
_Tophaceous ulcer	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	-	NA	NA	+
_Others*	NA	+	NA	NA	NA	NA	NA	-	NA	NA	NA	NA	NA	-	NA	NA	NA	+	NA	NA	+
Risks of surgery	WH	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
Is long-term ULT recommended?	+	+	+	NG	+	+	+	+	+	+	+	+	NG	+	+	+	+	+	+	+	+
Is any ULT drug recommended?	A	-	-	-	P	-	P	-	B	F	NA	-	-	P	-	P	-	-	-	P, R	-

* Other indications for surgery include large tophi [22], persistent tophi [22], joint deformation [38], major joint destruction [49], pressure symptoms [49], and cosmetic [49].

Supplementary Figure 1. Standardized domain scores by the year of publication



Supplementary File 1. Instructions for Guideline Appraisal Using the AGREE II Instrument

TRAINING MATERIALS

- Online tutorial: http://www.agreetrust.org/resource-centre/agree-ii-training-tools/
- User's Manual: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

PROLOGUE

- The Appraisal of Guidelines for REsearch & Evaluation (AGREE) Instrument is an international, validated and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements.
- The AGREE II instrument was published in 2010 and consists of 23 key items organized within 6 domains followed by 2 global rating items ("Overall Assessment"). Each domain captures a unique dimension of guideline quality.
  - Scope and purpose
  - Stakeholder involvement
  - Rigour of development
  - Clarity of presentation
  - Applicability
  - Editorial independence.
- Reviewers score each item on a 7-point Likert Scale.
  - 1 - Strongly disagree
  - 7 - Strongly agree
  - For the majority of items, we use an 'add-up' strategy to score, that is, corresponding scores will be added to 1' if information on predefined aspects is provided. For only one item, we subtract scores from 7'.
- Domain scores will be calculated as: (obtained score-minimal possible score)/(maximal possible score-minimal possible score)

DETAILED INSTRUCTIONS FOR SCORING

(adapted from AGREE II User's Manual [28])

Domain 1 Scope and Purpose

Item 1 Objectives: The overall objective(s) of the guideline is (are) specifically described.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Health intent, i.e., prevention, screening, diagnosis, treatment, etc. (2');

b) Expected benefit or outcome (2');

- *Clarification*: If gout epidemiology is provided as background information (i.e., the importance or significance of the diagnosis and management of gout/hyperuricemia is stated), 1' will be given. If clear statements, such as "to prevent (long term) complications of patients with diabetes mellitus" "to lower the risk of subsequent vascular events in patients with previous myocardial infarction", are provided, 2' will be given.

c) Target, e.g., patient population, society (1').

Performance: Is the item well written and is the content easy to find? (1')

Related *Report Criteria* from *User's Manual*: • health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) • expected benefit or outcome • target(s) (e.g., patient population, society)

Item 2 Questions: The health question(s) covered by the guideline is (are) specifically described.

Instructions:

Information on five aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) Target population (2');

b) Intervention or exposure (if appropriate, 1');

c) Comparisons (if appropriate, 1');

d) Outcome (1');

e) Health care setting or context (1').

Performance: Is the item well written and is the content easy to find? (1')

Note:

1) If c) is not appropriate, no score will be subtracted.
2) It is not necessary to have this information provided in questions. Reviewers can try to paraphrase 2-3 key recommendations into questions to see the information above is provided and score based on paraphrased questions.

Related *Report Criteria* from *User's Manual*: • target population • intervention(s) or exposure(s) • comparisons (if appropriate) • outcome(s) • health care setting or context

Item 3 Population: The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Instructions:

A default full score (7') should be considered. Subtract 1-2 points where the population is not clearly described or where the descriptions in the guideline is contradictory (e.g., a guideline stating "to treat asymptomatic hyperuricaemia" in the introduction, while stating "to treat hyperuricaemia and gout" in the title and providing no specific definition of patients' condition in recommendations).

Related *Report Criteria* from *User's Manual*: • target population, gender and age • clinical condition (if relevant) • severity/stage of disease (if relevant) • comorbidities (if relevant) • excluded populations (if relevant)

Domain 2 Stakeholder Involvement

Item 4 Group Membership: The guideline development group includes individuals from all relevant professional groups.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 5' in total):

a) The guideline development group is stated (1');

b) For each member of the guideline development group, the following information is included (1' each): name (1'), discipline/content expertise (e.g., neurosurgeon, methodologist, 1'), institution (e.g., St. Peter's hospital, 1'), a description of the member's role in the guideline development group (1')

- *Clarification*: Please subtract 1' if no methodologist (i.e., epidemiologist) is inferred from the discipline/content expertise.

Performance: Is the item well written and is the content easy to find? (1')

Note: Where the relation between the guideline development group and the authors is unclear, the authors of the guidance document will be considered as equivalent to the guideline development group.

Related *Report Criteria* from *User's Manual*: • For each member of the guideline development group, the following information is included: name, discipline/content expertise (e.g., neurosurgeon, methodologist), institution (e.g., St. Peter's hospital), geographical location (e.g., Seattle, WA), a description of the member's role in the guideline development group

Item 5 Target Population Preferences and Views: The views and preferences of the target population (patients, public, etc.) have been sought.

Instructions:

Information the following four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences, 2');

b) Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups, 1');

c) Outcomes/information gathered on patient/public information (2');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

- *Clarification*: If a patient representative is included in the guideline development panel, scores on aspects a), b), and d) will be given as default.

Related *Report Criteria* from *User's Manual*: • statement of type of strategy used to capture patients'/public's' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) • methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) • outcomes/information gathered on patient/public information • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 6 Target Users: The target users of the guideline are clearly defined.

Instructions:

Information on two aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators, 3');

b) Description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care, 3')

Related *Report Criteria* from *User's Manual*: • clear description of intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) • description of how the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)

Domain 3 Rigour of Development

Item 7 Search Methods: Systematic methods were used to search for evidence.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL, 2');
b) Time periods searched (e.g., January 1, 2004 to March 31, 2008, 1');
c) Search terms used (e.g., text words, indexing terms, subheadings, 1');
d) Full search strategy included (e.g., possibly located in appendix, 2')

Related *Report Criteria* from *User's Manual*: • named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) • time periods searched (e.g., January 1, 2004 to March 31, 2008) • search terms used (e.g., text words, indexing terms, subheadings) • full search strategy included (e.g., possibly located in appendix)

Item 8 Evidence Selection Criteria: The criteria for selecting the evidence are clearly described.
Instructions:
Information on both inclusion and exclusion criteria should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the inclusion criteria:
a1) target population (patient, public, etc.) characteristics (2'),
a2) study design (2),
a4) outcomes (1'),
b) Description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement, 1').
Note: if a3), a5), a6), b) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • description of the inclusion criteria, including: target population (patient, public, etc.) characteristics, study design, comparisons (if relevant), outcomes, language (if relevant), context (if relevant) • description of the exclusion criteria (if relevant; e.g., French only listed in the inclusion criteria statement could logically preclude non-French listed in the exclusion criteria statement)

Item 9 Strengths and Limitations of The Evidence: The strengths and limitations of the body of evidence are clearly described.
Instructions:
For each evidence, information on two aspects should be provided. If only some of the evidences report the following information, please first calculate the score based on the most informative evidence (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').
For each evidence, both a general statement of the method and detailed descriptions should be provided:
a) A statement of the method used to evaluate the strengths and limitations of the evidence should be provided (3').
b) The stated method should evaluate at least three of the following aspects (add 1' for each aspect, maximum 3'):
b1) Study design(s);
b2) Study methodology limitations (e.g., sampling, blinding, allocation concealment, analytical methods);
b3) Appropriateness/relevance of primary and secondary outcomes considered;
b4) Consistency of results across studies;
b5) Direction of results across studies;
b6) Magnitude of benefit versus magnitude of harm;

b7) Applicability to practice context

Related *Report Criteria* from *User's Manual*: • descriptions of how the body of evidence was evaluated for bias and how it was interpreted by members of the guideline development group • aspects upon which to frame descriptions include: study design(s) included in body of evidence, study methodology limitations (sampling, blinding, allocation concealment, analytical methods), appropriateness/relevance of primary and secondary outcomes considered, consistency of results across studies, direction of results across studies, magnitude of benefit versus magnitude of harm, applicability to practice context

Item 10 Formulation of Recommendations: The methods for formulating the recommendations are clearly described.

Instructions:

Information on three aspects should be provide (add 2' for each aspect, 6' in total):

a) Description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered, 2');

b) Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures, 2');

c) Description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote, 2')

Related *Report Criteria* from *User's Manual*: • description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) • outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) • description of how the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)

Item 11 Consideration of Benefits and Harms: The health benefits, side effects, and risks have been considered in formulating the recommendations.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Supporting data and report of benefits (2'); b) Supporting data and report of harms/side effects/risks (2');

- *Clarification*: Data on a) and b) can be provided as references.

c) Reporting of the balance/trade-off between benefits and harms/side effects/risks (1');

d) Recommendations reflect considerations of both benefits and harms/side effects/risks (1')

Related *Report Criteria* from *User's Manual*: • supporting data and report of benefits • supporting data and report of harms/side effects/risks • reporting of the balance/trade-off between benefits and harms/side effects/risks • recommendations reflect considerations of both benefits and harms/side effects/risks

Item 12 Link Between Recommendations and Evidence: There is an explicit link between the recommendations and the supporting evidence.

Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) The guideline describes how the guideline development group linked and used the evidence to inform recommendations (2');
- *Clarification*: Can be provided as narrative summaries and/or discussions of evidences.
b) Each recommendation is linked to a key evidence description/paragraph and/or reference list (2');
- *Note*: Please subtract 1' if only some recommendations meet criterium b).
c) Recommendations linked to evidence summaries, evidence tables in the results section of the guideline (2')

Related *Report Criteria* from *User's Manual*: • the guideline describes how the guideline development group linked and used the evidence to inform recommendations • each recommendation is linked to a key evidence description/paragraph and/or reference list • recommendations linked to evidence summaries, evidence tables in the results section of the guideline

Item 13 External Review: The guideline has been externally reviewed by experts prior to its publication.
Instructions:
Information on five aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence, 1');
b) Methods taken to undertake the external review (e.g., rating scale, open-ended questions, 1');
c) Description of the external reviewers (e.g., number, type of reviewers, affiliations, 1');
d) Outcomes/information gathered from the external review (e.g., summary of key findings, 1');
e) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations, 2')
- *Clarification*: Publication through a peer-reviewed journal can be considered as externally reviewed. Note: If dates of revision and acceptance is provided on the document, it is also considered externally reviewed.

Related *Report Criteria* from *User's Manual*: • purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) • methods taken to undertake the external review (e.g., rating scale, open-ended questions) • description of the external reviewers (e.g., number, type of reviewers, affiliations) • outcomes/information gathered from the external review (e.g., summary of key findings) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)

Item 14 Updating Procedure: A procedure for updating the guideline is provided.
Instructions:
Information on three aspects should be provided (add 2' for each aspect, 6' in total):
a) A statement that the guideline will be updated (2');
b) Explicit time interval or explicit criteria to guide decisions about when an update will occur (2');
c) Methodology for the updating procedure is reported (2')

Related *Report Criteria* from *User's Manual*: • a statement that the guideline will be updated • explicit

time interval or explicit criteria to guide decisions about when an update will occur • methodology for the updating procedure is reported

Domain 4 Clarity of Presentation

Item 15 Specific and Unambiguous Recommendations: The recommendations are specific and unambiguous.

Instructions:

For each recommendation, information on four aspects should be provided. If only some of the recommendations report the following information, please first calculate the score based on the most informative recommendation (e.g., scored 5'), and then subtract 1' to get the final score (e.g., 5'-1'=4').

For each recommendation, information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) If a recommendation is uncertain, the uncertainty should be reflected in the recommendation and also be explicitly stated (2')

b) Identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects, 2');

- *Clarification*: If the benefit for uric acid lowering in patients with CVD is not clearly stated, the score for this aspect should not be added.

c) Identification of the relevant population (e.g., patients, public, 1');

d) Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply, 1').

Note: if c) is not relevant, no score will be subtracted.

Related *Report Criteria* from *User's Manual*: • statement of the recommended action • identification of the intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) • identification of the relevant population (e.g., patients, public) • caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply)

Item 16 Management Options: The different options for management of the condition or health issue are clearly presented.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) Description of options (3');

b) Description of population or clinical situation most appropriate to each option (3')

- *Note*: Please subtract 1' if only some options are provided with the most appropriate population or clinical situation.

Related *Report Criteria* from *User's Manual*: • description of options • description of population or clinical situation most appropriate to each option

Item 17 Identifiable Key Recommendations: Key recommendations are easily identifiable.

Instructions:

Reporting style should follow two criteria (add 3' for each aspect, 6' in total):

a) Description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms (3');

b) Specific recommendations are grouped together in one section (3')

- *Clarification*: If recommendations are summarised in the abstract, scores for aspect b) can also be given.

Related *Report Criteria* from *User's Manual*: • description of recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms • specific recommendations are grouped together in one section

Domain 5 Applicability

Item 18 Facilitators and Barriers to Application: The guideline describes facilitators and barriers to its application.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of facilitators and barriers that were considered (2');

- *Clarification*: Statements of that certain drugs are not available in certain regions can be considered as identification of the facilitators and barriers.

b) Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation, 2');

c) Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography, 1');

d) Description of how the information influenced the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of facilitators and barriers that were considered • methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) • information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) • description of how the information influenced the guideline development process and/or formation of the recommendations

Item 19 Implementation Advice or Tools: The guideline provides advice and/or tools on how the recommendations can be put into practice.

Instructions:

Information on three aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) An implementation section in the guideline (2');

b) Tools and resources to facilitate application (add 1' for each tool/resource, maximum 2'): guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned;

c) Directions on how users can access tools and resources (2')

Related *Report Criteria* from *User's Manual*: • an implementation section in the guideline • tools and resources to facilitate application: guideline summary documents, links to check lists/algorithms, links to how-to manuals, solutions linked to barrier analysis (see Item 18), tools to capitalize on guideline facilitators (see Item 18), outcome of pilot test and lessons learned • directions on how users can access

tools and resources

Item 20 Resource Implications: The potential resource implications of applying the recommendations have been considered.

- *Clarification*: The aim of this item is to the cost information considered by the guideline.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs, 2');

b) Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc., 2');

c) Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course, 1');

d) Description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations (1')

Related *Report Criteria* from *User's Manual*: • identification of the types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) • methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) • information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) • description of how the information gathered was used to inform the guideline development process and/or formation of the recommendations

Item 21 Monitoring or Auditing Criteria: The guideline presents monitoring and/or auditing criteria.

- *Clarification*: The aim of this item is to evaluate the adherence to guidelines, but not to provide follow up parameters for diseases. *Monitoring* in this item refers to the action to monitor physicians' adherence to the guideline in daily practice by a group of investigators, but not to monitor the management of the disease in an individual patient. And the *auditing criteria* are the criteria to assess how well the guideline affects the practice in a region, but not how well the patients achieve the treatment target.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):

a) Identification of criteria to assess guideline implementation or adherence to recommendations (2');

b) Criteria for assessing impact of implementing the recommendations (2');

c) Advice on the frequency and interval of measurement (1');

d) Descriptions or operational definitions of how the criteria should be measured (1')

Related *Report Criteria* from *User's Manual*: • identification of criteria to assess guideline implementation or adherence to recommendations • criteria for assessing impact of implementing the recommendations • advice on the frequency and interval of measurement • descriptions or operational definitions of how the criteria should be measured

Domain 6 Editorial Independence

Item 22 Funding Body: The views of the funding body have not influenced the content of the guideline.

Instructions:

Information on two aspects should be provided (add 3' for each aspect, 6' in total):

a) The name of the funding body or source of funding (or explicit statement of no funding, 3');
b) A statement that the funding body did not influence the content of the guideline (3')

Related *Report Criteria* from *User's Manual*: • the name of the funding body or source of funding (or explicit statement of no funding) • a statement that the funding body did not influence the content of the guideline

Item 23 Competing Interests: Competing interests of guideline development group members have been recorded and addressed.

Instructions:

Information on four aspects should be provided (add corresponding scores for each aspect, 6' in total):
a) Description of the types of competing interests considered (2');
b) Methods by which potential competing interests were sought (1');
c) Description of the competing interests (1');
d) Description of how the competing interests influenced the guideline process and development of recommendations (2')

Related *Report Criteria* from *User's Manual*: • description of the types of competing interests considered • methods by which potential competing interests were sought • description of the competing interests • description of how the competing interests influenced the guideline process and development of recommendations

Overall Guideline Assessment

Question 1 Overall quality: Rate the overall quality of this guideline.

Instructions:

7' in total. Reviewer's impression on the overall quality of the guideline.

Question 2 Strength of recommendation: I would recommend this guideline for use.

Instructions:

Three options to choose from: a) Yes; b) Yes, with modifications; c) No
Reviewer's impression on whether the guideline is easy to be applied to clinical practice.

Related *Report Criteria* from *User's Manual*: The overall assessment requires the AGREE II user to make a judgment as to the quality of the guideline, taking into account the appraisal items considered in the assessment process.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported -on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22-23

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