

Rheumatology for the Internist: Why Are Gout Guidelines So Controversial?

Robert McLean, M.D., FACP

American College of Physicians, President 2019-20

Associate Clinical Professor, Yale School of Medicine

Medical Director of Clinical Quality, Northeast Medical Group, Yale New Haven Health System

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ACP Guidelines Definition

The goal of the ACP is to provide clinicians with clinical guidelines based on the best available evidence; to make recommendations on the basis of that evidence; to inform clinicians of when there is no evidence; and finally, to help clinicians deliver the best health care possible.

2 types of clinical recommendations:

clinical practice guidelines : Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances

clinical guidance statements: involve review and critique of available guidelines.

ACP Guideline process overview

- Key questions and scope for the evidence-review papers are developed with input from the Clinical Guidelines Committee.
- The evidence-review paper is a comprehensive systematic review or meta-analysis that addresses the clinical topic area under review.
- Quality of evidence is evaluated by using the ACP's Guideline Grading System, which is adopted from the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system
- Evidence reviews provide information about whether the studies included are reliable and accurate and provide reasonable assessments of potential adverse events.

Institute of Medicine reports 2011

Finding What Works in Health Care: Standards for Systematic Reviews

- Established optimal practice for systematic reviews and clearly distinguishes an systematic review of the evidence from other types of literature reviews.
- Systematic reviews are rigorous protocol-driven literature reviews that summarize evidence by identifying, selecting, assessing, and synthesizing the findings of similar but separate studies.
- Help clarify what is known and not known about the potential benefits and harms of drugs, devices, and other health care services.

Clinical Practice Guidelines We Can Trust

- Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options
- The new definition provides a clear distinction between the term “Clinical practice guidelines” and other forms of clinical guidance derived from widely disparate development processes:

*consensus statements, expert advice, appropriate use criteria

Standards for Developing Trustworthy Clinical Practice Guidelines

1. Establishing **Transparency**--processes by which a Clinical Practice Guideline is developed and funded should be detailed explicitly and publicly accessible.
2. Management of **Conflict of Interest**
3. Guideline Development Group Composition- should be **multidisciplinary** and balanced, comprising a variety of **methodological experts and clinicians**, and populations expected to be affected by the Guideline; **Patient and public involvement** should be facilitated by including a current or former patient, and a patient advocate or patient/consumer organization representative
4. Clinical Practice Guideline--**Systematic Review** Intersection

Standards for Developing Trustworthy Clinical Practice Guidelines

5. Establishing Evidence Foundations for and **Rating Strength of Recommendations**
6. Articulation of **Recommendations in a standardized form** detailing precisely what the recommended action is, and under what circumstances it should be performed.
7. **External Review-** should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.
8. **Updating-** publication date, date of pertinent systematic evidence review, and proposed date for future Guideline review should be documented in the Guideline; Literature should be monitored regularly following Guideline publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the Guideline.

The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Jennifer S. Lin, MD, MCR; Reem A. Mustafa, MD, MPH, PhD; and Timothy J. Wilt, MD, MPH; for the Clinical Guidelines Committee of the American College of Physicians*

The American College of Physicians (ACP) was one of the first organizations in the United States to develop evidence-based clinical guidelines and has been developing guidelines since 1981. ACP's Clinical Guidelines Committee (CGC), in collaboration with staff from the Clinical Policy department, develops clinical guidelines and guidance statements and continues to refine and enhance its methodology. This article presents an update of the CGC's 2010 paper outlining policies, methods, and presentation format of ACP's clinical guidelines and guidance statements. Updated methods include more stringent policies about disclosure of interests and conflict management; inclusion of

public perspective; full adoption of GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods; more standardized reporting formats that consider value of care, patient comorbid conditions, patient values and preferences, and costs; and further clarification of guidance statement methods.

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The American College of Physicians (ACP) officially initiated its guideline development program in 1981 but has participated in the development of evidence-based clinical recommendations since the late 1970s, making it one of the oldest guideline programs in the United States (1). The founding principle of ACP's guideline development program is that its clinical guidelines should be based on scientific evidence. As the arena of clinical guidelines grows and matures, guideline developers face increasingly rigorous standards to ensure the production of trustworthy, high-quality, and useful products (2, 3). Red flags that are raised to question the trustworthiness of a clinical guideline include but are not limited to sponsoring by a

methods; and reporting formats that consider value of care, patient comorbid conditions, patient values and preferences, and costs. ACP develops clinical guidelines in accordance with standards set forth by the Guidelines International Network and National Academy of Medicine (previously called the Institute of Medicine), and it voluntarily completes and posts standard reporting forms with each guideline in the Guidelines International Network library and on ACP's Web site (2, 3). This article describes ACP's current methods for developing clinical guidelines and guidance statements and serves as an update to the 2010 methods paper (Table) (4). The updated methods have been included in Clinical Guidelines Committee (CGC) publications

Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians

Amir Qaseem, MD, PhD, MHA, and Timothy J. Wilt, MD, MPH; for the Clinical Guidelines Committee of the American College of Physicians*

One of the hallmarks of a trustworthy clinical guideline or guidance statement is a comprehensive process for disclosure of interests (DOI) and management of conflicts of interest (COIs). The American College of Physicians (ACP) Clinical Guidelines Committee (CGC) aims to disclose all health care-related interests and manage conflicts in a manner that is transparent, proportional, and consistent. Any person involved in the development of an ACP clinical guideline or guidance statement must disclose all financial and intellectual interests related to health care from the previous 3 years. Persons complete disclosures at the start of their participation and are required to update them over the course of their involvement with the CGC, including before each

CGC meeting. A DOI-COI Review and Management Panel reviews the disclosures, flags potential conflicts, grades the COI as low-, moderate-, or high-level, and manages the person's participation accordingly. A high-level COI results in recusal from authorship, voting, and all committee discussions. Participants with a moderate-level COI are recused from authorship and voting for clinically relevant topics but may participate in all discussions. A low-level COI results in no role restrictions. All disclosures and COI management decisions are publicly reported.

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A rigorous process for disclosure of interests (DOI) and management of conflicts of interest (COIs) is essential for the development of high-quality clinical guidelines and guidance statements. National and international organizations, such as the National Academy of Medicine (formerly the Institute of Medicine) (1, 2) and the Guidelines International Network (3), have called for adoption of high-quality standards for the development of trustworthy guidelines and stress the im-

any actual bias during clinical guideline development and to ensure credibility and public trust in ACP clinical guidelines by reducing the potential for perceived bias. Some subjectivity is inherent to the development of any guideline or guidance statement. Systematic reviewers make judgments when assessing the quality of studies, as do guideline developers when balancing benefits against harms and costs to make recommendations (6). The threat of COIs influencing these judgments war-

Table. Additions and Changes in the 2019 CGC Methods Paper Compared With the 2010 CGC Methods Paper

Enhanced and more stringent DOI and COI policies and management

Inclusion of public perspective in clinical guideline development

Full adoption of GRADE methods, including evidence-to-decision tables

Standardized reporting formats that consider value of care, patient comorbid conditions, patient values and preferences, and costs

Further details on methods for guidance statement development

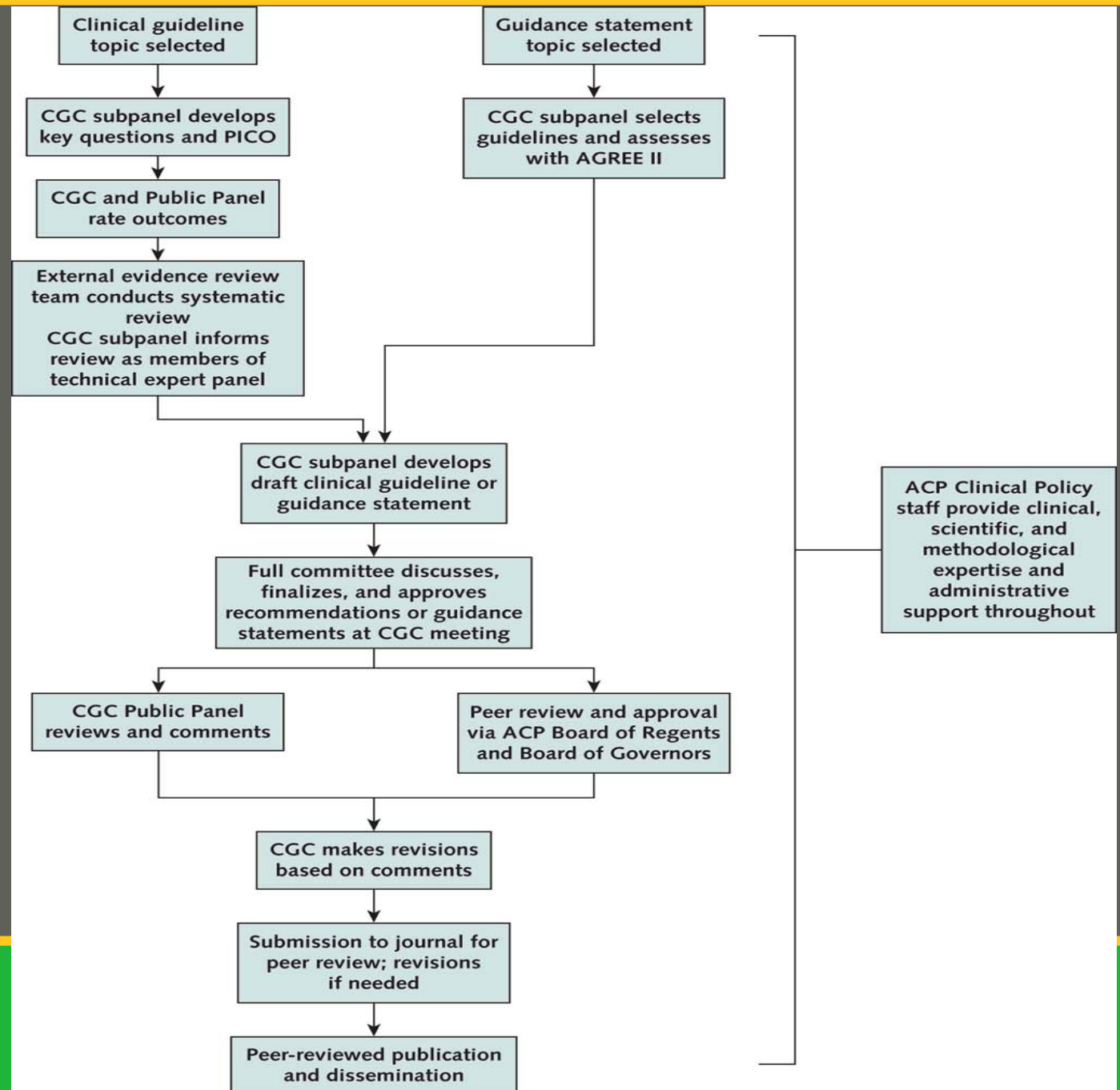
CGC = Clinical Guidelines Committee; COI = conflict of interest; DOI = disclosure of interest; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Overview of ACP development and approval process

AGREE II = Appraisal of Guidelines for Research and Evaluation II;

CGC = Clinical Guidelines Committee;

PICO = population, interventions, comparators, and outcomes.



GRADE = Grading of Recommendations Assessment, Development, and Evaluation

Grading Certainty of Evidence				
High	Confident that the true effect is close to the estimated effect.			
Moderate	Moderately confident in the effect estimate: The true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different.			
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimated effect.			
Grading Recommendations				
Strength	Certainty of Evidence	Balance of Benefits and Harms	Applicable Patient Population	Policy Implication
Strong	High or moderate Low only in very rare circumstances	Confidence that benefits clearly outweigh risks and burden or vice versa.	Applies to most patients in most circumstances.	Only strong recommendations could be considered for use as performance measures.
<i>Example from ACP's guideline on treatment of major depressive disorder: "ACP recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder after discussing treatment effects, adverse effect profiles, cost, accessibility, and preferences with the patient (Grade: strong recommendation, moderate-quality evidence)" (7).</i>				
Conditional	High, moderate, or low	Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.	Applies to many patients but may differ depending on circumstances or patients' values and preferences.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.
<i>Example from ACP's guideline on noninvasive treatments of acute, subacute, and chronic low back pain: "In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)" (8).</i>				

ACP Guideline Process Example

Key questions: Management of Gout

Key Question 1- Acute Gout Treatment

- a. What are the benefits and harms of different pharmacologic therapies?
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics & comorbid conditions (including renal function)?
- c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement & time since start of flare) and laboratory values (serum uric acid)?

ACP Guideline Process Example

Key questions: Management of Gout

Key Question 2- *Dietary and Lifestyle Management of Gout*

- a. What are the benefits and harms of different dietary therapies and lifestyle measures on intermediate (serum uric acid levels) and final health outcomes (including recurrence of gout episodes and progression, development of tophi)?
- b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum uric acid level), underlying mechanisms of hyperuricemia, or baseline demographic and comorbid characteristics?

ACP Guideline Process Example

Key questions: Management of Gout

Key Question 3- *Pharmacologic Management of Hyperuricemia in Patients With Gout*

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

ACP Guideline Process Example

Key questions: Management of Gout

Key Question 4- *Treatment Monitoring of Patients With Gout*

- a. Does monitoring serum uric acid levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., adherence) improve treatment outcomes?
- b. Is achieving lower subsequent serum uric acid levels (<5 vs. 5-7 mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

ACP Guideline Process Example

Key questions: Management of Gout

Key Question 5- Discontinuation of Pharmaceutical Management for Patients Receiving Acute or Chronic Gout Medications

Are there criteria that can identify patients who are candidates for discontinuing:

- i. Urate-lowering therapy?
- ii. Anti-inflammatory prophylaxis against acute gout attack, for patients receiving urate-lowering therapy after an acute gout attack?

ACP Recommendations

Recommendation 1: ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout.

(Grade: strong recommendation, high-quality evidence)

Recommendation 2: ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout.

(Grade: strong recommendation, moderate-quality evidence)

ACP Recommendations

Recommendation 3: *ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks.*

(Grade: strong recommendation, moderate-quality evidence)

Recommendation 4: *ACP recommends that clinicians discuss benefits, harms, costs, and individual preferences with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patients with recurrent gout attacks.*

(Grade: strong recommendation, moderate-quality evidence)

The Challenge with “Recommendations”

A Clinical Practice Guideline by definition is supposed to tell you:

“what does good evidence suggest or support we should do for a given condition or clinical situation?”

But what we actually want to know is:

“what should we do for a given condition or clinical situation?”

The Challenges and Why Guidelines might differ

- What if the Systematic Review does not find answers to the Key Questions?
- What if studies that other guidelines quote are not felt adequate for consideration?
- What if other guideline-developing entities rely on “expert opinion” in their process rather than pure evidence review?
- What if other entities do not have stringent DOI/COI policies?

What did ACP say for Gout management?

Following a treat-to-target approach is wrong.

OR

ACP cannot endorse the Treat-to-target approach because there is not strong enough evidence to tell us it is the right thing to do.

Of course,

Treating the pain of acute gout (Treat-to-avoid-symptoms) is appropriate, in ways that have proven effective

What ACP Gout Guideline did NOT say

- Treat only to avoid symptoms and do not use urate-lowering therapy
- Do not base any treatment decisions based on serum uric acid levels
- BUT, those were conclusions attributed to ACP guidelines

Stating “there is not evidence to clearly endorse” is NOT the same as saying “do not do that”

ACP stated need for additional evidence

Key questions from ACP Process could not be answered due to areas of inconclusive evidence

***Treatment Strategy for Patients With Gout Receiving Urate-Lowering Therapy: No study has compared a Treat-to-Target strategy to a Treat-to-avoid-symptoms strategy**

*Effect of Urate-Lowering Treatment on Adverse Health Outcomes Beyond Acute Gout

*Duration of Urate-Lowering Treatment

*Treatment in Different Patient Groups

*Effect of Dietary Treatments

*Long Term effects of Febuxostat

So When Guideline Controversy Seems to Occur

The questions to ask:

- **Is there a Systematic Review and how was it constructed?**
- **Is the same evidence being evaluated?**
- **Is expert opinion being given a role?**
- **Is stringent DOI/COI process present, for participants as well as sponsoring entity?**

The Official Quiz

1. Which one of the following statements accurately represents a conclusions from the ACP gout guidelines?

A.	Treat only to avoid symptoms and do not use urate-lowering therapy
B.	A Treat-to-target approach cannot be endorsed because there is not strong enough evidence that it is the right thing to do
C.	Do not make any treatment decision based on serum uric acid levels
D.	Following a treat-to-target approach is wrong and should never be used

Official Quiz cont'd

2. Which of the following therapeutic options does the ACP recommend that clinicians choose to treat acute gout?

A.	Corticosteroids or allopurinol
B.	Nonsteroidal anti-inflammatory drugs (NSAIDs) only
C.	Colchicine or allopurinol
D.	Corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine
E.	Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen

Thank you!

Live neither in the past nor in the future, but let each day absorb all your interest, energy, and enthusiasm. The best preparation for tomorrow is to live today superbly well.

- Sir William Osler

rmmclean@optonline.net

Twitter: @rmmclean84