



## ENDOCRINE SOCIETY GUIDELINE METHODOLOGY

THE ENDOCRINE SOCIETY IS DEDICATED TO PROVIDING THE FIELD OF ENDOCRINOLOGY WITH TIMELY, EVIDENCE-BASED RECOMMENDATIONS FOR CLINICAL CARE AND PRACTICE. WE CONTINUALLY DEVELOP NEW GUIDELINES AND UPDATE EXISTING GUIDELINES TO REFLECT EVOLVING CLINICAL SCIENCE AND MEET THE NEEDS OF PRACTICING PHYSICIANS. WE STRIVE TO ADHERE TO NATIONAL AND INTERNATIONAL QUALITY STANDARDS AND EMPLOY RIGOROUS METHODOLOGY. WE CONTINUALLY MAKE IMPROVEMENTS ON OUR PROTOCOLS TO ENSURE BEST PRACTICES. THE CLINICAL PRACTICE GUIDELINES DEVELOPMENT PROGRAM IS OVERSEEN BY THE CLINICAL GUIDELINES COMMITTEE (CGC).

### TOPIC SELECTION

During each topic selection cycle, the CGC analyzes specific criteria and makes a recommendation for guideline topics to the Board of Directors (BOD). The CGC selects new guideline topics using predefined, decision-making criteria which include environmental scanning of external clinical guidance documents, internal scanning of content being developed by the Endocrine Society, specific scientific criteria, and strategic importance to the Endocrine Society. Scientific criteria include the state of the scientific evidence underpinning the topic, the importance of the topic to practicing endocrinologist and other clinicians, any clinical controversies/uncertainties regarding the topic, and or any variations in current practice. Potential topics are identified through a survey of Endocrine Society membership, suggestion by CGC members, and annual surveillance of current Endocrine Society guidelines for topics to be updated. The comprehensive pool of potential topics goes through the above criteria filters and a curated list of topic candidates is established. The final curated list goes through a formal prioritization process by the CGC, and the highest-ranking topics are selected for recommendation to the BOD. The BOD formally approves all topics for guideline development.

### PANEL SELECTION AND COMPOSITION

Guideline Development Panel (GDP) nominees are identified by the Endocrine Society BOD, CGC, and any co-sponsoring organizations. To be considered for membership of a GDP, nominees are required to disclose all relationships with industry for the 12-month period prior to guideline and are vetted according to the Endocrine Society's [Conflict of Interest \(COI\) Policy](#), which is in adherence with national standards<sup>1</sup> (See Conflict of Interest section). The chair of the CGC reviews all disclosed relationships and determines whether they are relevant to the topic of the guideline and present a potentially relevant COI. The chair of the CGC selects GDP Chairs and Co-Chairs based on COI information, the individuals' clinical expertise, and other skills. The Endocrine Society BOD reviews and endorses the nominees or makes appropriate changes. The three Chairs then select and appoint GDP members based on the specific clinical or other expertise needed for the guideline. The Chairs also identify any potential co-sponsoring organizations based on the clinical topic, desired expertise, and intended audience of the guideline. Co-sponsoring organizations are also invited to appoint official representatives to the GDP. These representatives undergo COI review as well. The Endocrine Society strives to have multidisciplinary panels whenever appropriate, in

accordance with guideline standards.<sup>1</sup> Each guideline panel also includes a patient representative to ensure that the patient perspective is represented at all stages of guideline development.

An Endocrine Society Guideline Methodologist (ESGM) who is trained in the GRADE methodological framework is a member of the guideline panel and instructs the GDP on the application of the methodology. There is also a clinical practice guideline methodologist from the Mayo Evidence-based Practice Center who leads the team of comparative effectiveness researchers for the systematic reviews and meta-analyses for the guideline.

**GUIDELINE DEVELOPMENT PROCESS**

The Endocrine Society’s clinical practice guidelines are developed following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.<sup>2</sup> This methodology includes the use of Evidence-to-Decision (EtD) Frameworks to ensure all important criteria are considered when making recommendations.<sup>3,4</sup> The process is facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT).<sup>5</sup>

The GRADE process begins with a scoping process and the prioritization of clinical questions to be addressed in the guideline. The GDP compiles an extensive list of potential questions, which is narrowed down to the most important questions through a systematic prioritization process that includes discussion and survey. Through a similar prioritization process, the most important clinical outcomes for each question are identified. These will be the outcomes that are analyzed in the systematic review. The Mayo Evidence-based Practice Center external research team conducts a systematic review for each of the questions and produces evidence summaries and GRADE evidence profiles that summarize the body of evidence for each question and the certainty of the evidence. The certainty of evidence is graded as high, moderate, or low based on a number of criteria. These criteria include the quality of included studies, risk of bias of included studies, consistency of findings across studies, precision of estimated treatment effects, directness of the evidence to the question of interest, and potential for publication bias (Table 1 and 2).<sup>6,7</sup>

**TABLE 1. GRADE APPROACH TO RATING CERTAINTY OF EVIDENCE**

According to GRADE, certainty, quality, strength of the evidence or the confidence in the estimate of effect, is determined for each outcome based on a systematic review of the evidence for each outcome. For recommendations, the overall certainty is determined across outcomes based on the lowest quality outcome among those critical for decision-making for the specific context.

1. Establish initial level of certainty (as implemented in current GRADE)		2. Consider lowering or raising level of certainty		3. Final level of certainty rating
<i>Study design</i>	<i>Initial certainty in the evidence</i>	<i>Reasons for considering lowering or raising certainty</i>		<i>Certainty in the evidence across those considerations</i>
<i>Randomized trials</i> →	High certainty	↓ Lower if	↑ Higher if*	High ⊕⊕⊕⊕
		Risk of Bias	Large effect	Moderate ⊕⊕⊕○
		Inconsistency	Dose response	Low ⊕⊕○○
<i>Observational studies</i> →	Low certainty	Indirectness	All plausible confounding and bias	Very low ⊕○○○
		Imprecision	• would reduce a demonstrated effect	
		Publication bias	or	
			• would suggest a spurious effect if no effect was observed	

\*Criteria for upgrading the quality are usually only applicable to observational studies without any reason for rating down.

Source: Schünemann HJ, Cuello C, Akl EA, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol.* 2019;111:105-114. doi:10.1016/j.jclinepi.2018.01.012<sup>6</sup>

In parallel to the development of the evidence summaries, the GDP members are assigned specific clinical questions for which to research the Evidence-to-Decision (EtD) criteria that are not included in the systematic reviews. The EtD framework provides a systematic and transparent approach for going from the evidence to the healthcare decision. EtD criteria include priority of the problem, patient values, resource use and cost-effectiveness, equity, acceptability, and feasibility. During a series of video conferences, or at an in-person meeting, the GDP judges the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of the recommendation (Table 3)<sup>8-10</sup>.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, we include Technical Remarks. These provide supplementary information such as timing, setting, dosing regimens, and necessary expertise. Some of the Society’s clinical practice guidelines also include ungraded Good Practice Statements.<sup>11,12</sup> Good practice statements are included when there is information necessary to health care practice, implementation which will result in large net positive consequences, collecting and summarizing the evidence would be a poor use of the panel’s limited resources, and there is a well-documented clear and explicit rationale.

In the guideline manuscript, all recommendations are followed by a summary of evidence, EtD factors, and the justification for the recommendation. Authors may also include a comment section including a minority report, alternative approaches, sub-group considerations, etc. The EtD tables for each recommendation are published as an appendix to the guideline manuscript. This is informational for the reader and ensures a transparent process of development of recommendations and making judgments on the evidence and criteria.

### INTERNAL AND EXTERNAL REVIEW

Approximately 18 months into the development process, Endocrine Society clinical practice guidelines undergo a review and public comment period when there is an opportunity for internal and external stakeholders to review the guideline draft and provide comments. These stakeholders include Endocrine Society members and members of the public; the CGC; representatives of any co-sponsoring organizations; a representative of the BOD; and an Expert Reviewer. Following revisions to the guideline manuscript in response to comments, it is returned to CGC, the Board of Directors Reviewer, and the Expert Reviewer for a second review and ballot for approval. Finally, the guideline manuscript is subject to JCEM Publisher’s Review prior to publication. This review is undertaken by an individual with expertise in the topic, without relevant conflicts of interest, and external to the GDP, CGC, and the BOD.

### CONFLICT OF INTEREST

The Endocrine Society’s [COI rules](#) for the development of clinical practice guidelines are summarized as follows:

To be considered for membership of a Guideline Development Panel (GDP), nominees are required to disclose all relationships (and all known immediate family members) for the 12-month period prior to GDP initiation. This is consistent with the reporting timeframe for the National Institutes of Health and the Food and Drug Administration.

Potential conflicts of interest that should be declared include all relationships with commercial, non-commercial, institutional, and patient/public organizations. This includes employment, consultancy, interests in start-up companies and/or in those where stock is not publicly traded, ownership interests in publicly-traded companies such as stock options (excluding indirect investments through mutual funds), research funding directly paid to the individual, research funding paid to employer

**TABLE 2. GRADE CERTAINTY OF EVIDENCE CLASSIFICATIONS**

CERTAINTY OF EVIDENCE	INTERPRETATION
<b>High</b> ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect
<b>Moderate</b> ⊕⊕⊕○	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
<b>Low</b> ⊕⊕○○	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
<b>Very Low</b> ⊕○○○	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Reprinted from Eds. Schünemann H, Brożek J, Guyatt G, and Oxman A. GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.<sup>7</sup>

organization or other research institution with whom the individual is involved, serving as a Principal and/or Co-Investigator, honoraria, royalties, paid or unpaid expert testimony, speaking engagements, speaker's bureaus, etc. Leadership positions and memberships of other entities (paid and unpaid) including Data Standards Monitoring Boards, non-profit or for-profit advisory boards and committees must also be disclosed.

Review of COI information is conducted as follows:

**GDP CHAIRS:** The CGC Chair reviews all COI information and determines whether any relationship represents a potentially relevant conflict of interest. The CGC Chair's final recommendations are submitted to Endocrine Society Council for approval.

**GDP MEMBERS:** The GDP Chairs review all COI information and determine whether any relationship represents a potentially

relevant conflict of interest. Decisions on the relevance of relationships/conflicts to each guideline topic/section—in addition to the overall acceptability of a candidate's COI—will be made by the GDP Chairs in collaboration with the CGC Chair, who will have veto power.

Optimally, the Society's GDPs would only include members who are free of COIs relevant to the topic of the guideline. The Society strives to achieve this ideal whenever possible. The Chair and Co-Chair of the Guideline Development Panel must be free of any COI or other biases that could undermine the integrity or credibility of the work. A majority (>50%) of the Guideline Development Panel members must be free of relevant COI.

GDP members with relevant COI are required to declare the situation and recuse themselves from any relevant discussions, votes, and from drafting recommendations. GDP members with relevant COI cannot be assigned to a clinical question for

**TABLE 3. GRADE STRENGTH OF RECOMMENDATION CLASSIFICATIONS AND INTERPRETATION**

STRENGTH OF RECOMMENDATION	CRITERIA	INTERPRETATION BY PATIENTS	INTERPRETATION BY HEALTH CARE PROVIDERS	INTERPRETATION BY POLICY MAKERS
1 - Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa)	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should receive the recommended course of action.  Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.  Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations.  Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2 - Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa)	The majority of individuals in this situation would want the suggested course of action, but many would not.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences.  Decision aids may be useful to help individuals make decisions consistent with their individual risks, values and preferences.	Policy-making will require substantial debate and involvement of various stakeholders.  Performance measures should assess whether decision making is appropriate.

Adapted from Schünemann HJ et al. Blood Adv, 2018; 2(22) © by The American Society of Hematology.<sup>9</sup>

which they have a conflict. All GDP members are prohibited from adding new relevant industry relationships throughout the guideline development process, until publication. Before any new relationship is added, it is encouraged for GDP members to contact the GDP chairs, in consultation with the CGC Chair, to determine whether the relationship represents a relevant COI. If a GDP member accepts a new relationship and is determined to represent a relevant COI, the CGC chair and GDP chairs must determine how that COI should be managed.

If a relevant COI exists, it will be managed as follows:

1. Disclosure:
  - a. Following initiation of the committee, members are asked to disclose relationships with industry at every in-person meeting, on most conference calls, and on annual COI questionnaires.
  - b. If a member is aware of another person who might have a conflict and has not declared it for some reason, they are obliged to bring this to the GDP Chair's attention.
2. Divestment:
  - a. Members of the GDP (and their immediate family members) must divest themselves of direct financial investments with entities that may have a potential financial interest in the contents of the guideline.
  - b. GDP members must also refrain from participating in the marketing activities or advisory boards of such entities.
3. Recusal:
  - a. GDP members are prohibited from drafting guideline sections directly related to her/his COI.
  - b. GDP members are prohibited from determining the strength and direction of a recommendation directly related to her/his COI.
  - c. GDP members are prohibited from voting on matters directly related to her/his COI.
4. Transparency:
  - a. The Society will include details of all relevant conflicts of interest of members of the GDP in a detailed appendix within the published guideline.
  - b. More detailed COI documentation will be made available as needed in the form of supplemental materials (available online).

## UPDATING

The CGC continually surveils the portfolio of published clinical practice guidelines for potential updates to make sure we are providing timely, evidence-based recommendations for clinical care and practice. The chairs and/or panel members of the guideline are asked to complete a survey and assess if there is new evidence that materially changes expected benefits and/or potential harms of treatments, approaches or interventions included in a recommendation; new evidence of outcomes that has since changed practice substantially; new treatments or interventions that would change an existing recommendation. They are also asked to provide an overall assessment to the CGC as to whether the guideline requires an update and how that update should be prioritized (high, medium, low). The CGC analyzes the results of these surveys and decides whether the guideline needs to go into the queue for update. If a guideline is deemed in need of update, and an update cannot be immediately initiated, that guideline may be retired, either permanently or temporarily until an update can occur.

## FUNDING

Funding for the development of Endocrine Society clinical practice guidelines is provided by the Endocrine Society. No other entities provide financial support.

## DISCLAIMER

The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered as an all-encompassing approach to patient care and not inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgement of healthcare providers and each patient's individual circumstances.

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This document applies to guidelines with a publication date of 2022 or later.

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- <sup>6</sup> Schünemann HJ, Cuello C, Akl EA, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol*. 2019;111:105-114. doi:10.1016/j.jclinepi.2018.01.012
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