IDSA

Infectious Diseases Society of America

Handbook for Clinical Practice Guidelines Development

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1. Introduction

Purpose of this handbook

This handbook was developed by the IDSA Standards and Practice Guidelines Committee (SPGC) and the IDSA department of Clinical Affairs and Practice Guidelines (CAPG) to serve as a reference to IDSA-sponsored guideline panelists for the purpose of developing clinical practice guidelines (CPGs).

The primary objective of CPGs is to improve the quality of care provided to patients through rigorous, evidence-based recommendations. For this reason, IDSA believes that guidelines should be held to the highest standards of quality. The process by which guidelines are developed should be based on a uniform methodology that can be applied to diverse populations, diseases, and interventions.

This handbook provides a framework for guideline development by standardizing the methodological process to improve the rigor, transparency, robustness, and consistency of IDSA guidelines. This handbook includes detailed information on the various steps from guideline inception to completion and dissemination with expectations for panel members and IDSA staff, and timelines. All panelists should familiarize themselves thoroughly with this handbook and understand that IDSA considers the application of its content as mandatory at all levels of the guideline development process. This handbook thereby serves as a tacit agreement between the IDSA SPGC and panelists to comply with the guidance as set forth in this document.

This handbook is to be considered a living document and will be updated as needed at the discretion of the IDSA SPGC or IDSA Board of Directors. Updates will be conveyed to all guideline panel members and the living document will be maintained on the IDSA website.

Introduction to clinical practice guidelines

Definition

CPGs are defined as “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.”[1]

Objectives

Guidelines are written to improve the quality of care, to improve the appropriateness of care, to improve cost-effectiveness of interventions, to serve as educational guidance tools, and to identify pertinent research directions.

The goal is not to create standards of care; however, other organizations may choose to adopt these guidelines or components thereof for such purposes. Practice guidelines, however, are never a substitute for clinical judgment. Clinical discretion is of the utmost importance in the application of a guideline to individual patients, because no guideline can ever be specific enough to be applied in all situations.[2]

Methodology

Similar to many medical associations, the IDSA SPGC has adopted the 2011 standards of the Institute of Medicine (IOM) regarding the development of trustworthy CPGs.[3] The IOM had identified standards that need to be addressed appropriately such as:

- Selection of a multidisciplinary panel comprising content experts from a variety of relevant disciplines, methodological expert, clinicians and patients affected,
- Appropriate management of conflicts of interest (COI) of individuals considered for a panel (from selection, disclosure, divestment to exclusion),
- Performance of systematic reviews to identify the full scope of relevant body of evidence to inform the recommendations,
- Transparency on the reasoning underlying each recommendation (from the presentation and rating of the certainty in the evidence, the description of the balance of benefits/harms and patient values and preferences, to the standardization of articulation of recommendations and their final ratings), and
- Systematic external review and updating process.

IDSA has heightened its focus on a thorough appraisal of the evidence and extensive considerations related to COIs. Also in line with the IOM,[3] IDSA has integrated the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for the assessment of the quality of the evidence (QoE) and strength of recommendations (SoR).

The advantages of GRADE are numerous and include:

- Clear separation between judging confidence in the effect estimates and SoR
- Explicit evaluation of the importance of outcomes of alternative management strategies
- Explicit, comprehensive criteria for downgrading and upgrading QoE ratings
- Explicit acknowledgment of values and preferences
- Transparent process of moving from evidence to recommendations, and
- Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers.

The subsequent chapters of this handbook explain the IDSA guideline development process that aligns with the GRADE approach.

References

1. Clinical Practice Guidelines We Can Trust. In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds.: The National Academies Press, 2011:15.
2. Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001; 32:851-4.
3. Institute of Medicine: url: http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

2. Department of Clinical Affairs and Practice Guidelines and Standards and Practice Guidelines Committee

Roles and responsibilities

IDSA Governance		
BOD, Executive Committee		• Oversee all IDSA program activities • Reviews and approves the final selection of SPGC members, guideline chairs and panel members • Review guidelines for final approval or endorsement
BOD Liaison to the SPGC		Informs the BOD of all SPGC activities
SPGC Chair and Members		• Oversee all SPGC activities • Review and approve new proposed guideline topics and help prioritize guideline topics for development and update • Review and approve selection of chairs and the list of potential panel members • Identify a SPGC liaison to each guideline panel • Review guidelines for approval or endorsement
SPGC Liaison to the Guideline Panel		• Provides guidance to the panel on the development and review process • Monitors the guideline development and provides updates to the SPGC • Reviews and approves guideline manuscript prior to the review process
IDSA Staff (Department of Clinical Affairs and Practice Guidelines)		
Vice President		Oversees all CAPG activities and manages operations. Helps prioritize activities and allocates resources, as needed
Senior Director, Clinical Policy		Oversees the Guidelines Team within the Clinical Affairs & Guidelines Department. Leads the development, dissemination and implementation of IDSA clinical policy initiatives, including clinical practice guidelines, standards, and other resources designed to guide the provision of high quality, high value ID care and services.
Guideline Specialists/Methodologists		Responsible for designing and conducting systematic reviews of the literature, developing summaries of evidence, and producing clinical practice guidelines, endorsements and other guidance products in infectious diseases. Working with multi-disciplinary teams of content experts, participates in the development of guideline-related clinical tools and resources, algorithms, and other content to support the Clinical Affairs & Guidelines Department.
Program Staff	**Director, Practice Guideline Operations**	Provides direction and oversight of programmatic activities related to guideline development, dissemination and implementation, providing leadership and support to the Standards & Practice Guidelines Committee, expert panels and staff in the development of guidelines and related resources designed to guide the provision of high quality, high value ID care and services.
	Program Coordinator	Supports the Standards & Practice Guidelines Committee, expert panels and staff in developing clinical guidelines and related resources designed to guide the provision of high quality, high value ID care and services.
	Program Assistant	Provide administrative and programmatic support to the Guidelines Team of the Clinical Affairs & Guidelines Department, clinical practice guideline expert panels, and the Standards & Clinical Practice Guidelines Committee.

3. Guideline Topic Proposal

The CPG development program falls under the auspices of the SPGC. While the SPGC is charged with the review and approval of guideline topics and guideline drafts, actual guideline development is performed by content experts with the support of IDSA methods experts.

The SPGC will consider topic proposals from any IDSA member. Proposed topics will be chosen based upon the anticipated impact that the guideline will have on the prevention, diagnosis and/or treatment of infectious diseases.

Requirements for a guideline topic proposal

IDSA members who submit a topic proposal are required to submit a compelling narrative that provides responses to the following series of questions/considerations:

1. What is the topic under consideration for this guideline?
    a. What is the title of the proposed guideline?
    b. What is the scope of the guideline? Of note, proposals with well-defined limited scope are preferred (see section on “Defining the scope” of the Handbook).
    c. What is the target population (e.g., pediatric and/or adults, outpatients, and/or hospitalized)?
    d. Who is the target audience/end-users (i.e., the type of physicians for which the guideline is intended, such as infectious diseases specialists, general practitioners, and/or other specialists; US only, North American/European, or international)?
    e. What perspective will the proposed guideline take (individual patients or public healthcare perspective)?
    f. Are there existing CPGs on the same topic? And if so, how is this proposal different from existing documents? Of note, it is critical that the SPGC be aware of existing guidelines on the same topic to avoid duplication of efforts. Other associations’ CGPs, if judged to be methodologically sound by the SPGC, can be submitted for consideration of endorsement by the SPGC and subsequently the IDSA Board of Directors (BOD).

2. Why is the topic under consideration a priority?
    a. Is the burden/importance of the condition/intervention large enough to warrant the development of a document (prevalence and/or incidence of the condition should be included)?
    b. Are the consequences of the problem serious (i.e., severe or important in terms of the potential clinical benefits or savings)?
    c. Is the problem urgent?
    d. Is it a recognized priority (e.g., based on a political or public health policy decision(s))?

3. What body of evidence is expected to support the recommendations?
    a. For the main clinical questions potentially under consideration, what is the expected supporting body of evidence?
    b. If the supporting body of evidence is limited, please outline how an IDSA document will still be of significant utility to IDSA members.

4. What is the expected impact of the guideline?
    a. Is there uncertainty/controversy about the relative effectiveness of the available clinical strategies (i.e., creating considerable variation in current practice)?

b. Is there a need to confirm the appropriateness of a specific practice management and/or to discourage certain clinical strategies?
c. Assuming appropriate dissemination, what would be the expected impact of this proposed CPG on clinical decision-making and clinical outcomes?

Review process for approval

After a topic proposal has been submitted, it will be considered for approval by the SPGC, which meets at regular intervals. The committee must come to consensus on whether to develop this specific guideline according to the following criteria:

Criteria for Setting Priorities[1]	Source of Data
Burden of disease (health or economic)	National data; review articles
Costs of care	National data; review articles
Variability in practice	Quality measurement; surveys; expert opinion
Potential impact of guideline or recommendation	Expert opinion and stakeholder input
Importance to clinicians	Survey, consultation, and *ad hoc* stakeholder input
Importance to patients	Survey, consultation, and *ad hoc* stakeholder input
Availability of evidence	Existing reviews; preliminary literature search
Uncertainty or controversy	Literature search for editorials,
Emerging issues	Meetings, drug/device approvals, policy experts

If the proposed guideline topic is approved, the committee will prioritize its development relative to other ongoing and upcoming guidelines. This prioritization will be decided by consensus utilizing input from the SPGC, and the IDSA BOD. If the proposed guideline topic is not approved, the SPGC might suggest that the group consider doing a structured review that could be partially supported by IDSA.

References

1. Atkins D, Perez-Padilla R, MacNee W, Buist AS, and Cruz AA; on behalf of the ATS/ERS Ad Hoc Committee on Integrating and Coordinating Efforts in COPD. Priority Setting in Guideline Development. Article 2 in Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report. Proc Am Thorac Soc 2012; 9 (5): 225-228.

4. Overview of Guideline Development Process and Expected Timeline

Steps		Actions	Timeline
Pre-development phase			
	Topic proposal	Submission and approval by SPGC	**SPGC meeting**
	Panel composition	1. SPGC selects chairs with IDSA BOD approval 2. Chairs propose panel members to SPGC 3. Chairs ensure involvement of all relevant stakeholders	**4-8 weeks**
	Conflicts of interest	1. Chairs and panel members declare COI 2. SPGC and Executive Committee of the BOD review and manage COI	
	Contract of agreement	All SPGC-approved chairs/panelists sign contract of agreement	
Development phase			
First stage	Defining the scope	1. Chairs discuss scope of the guideline 2. Panel approves by consensus the selected scope	**Within 4 weeks**
	Framing clinical questions	1. Panel identifies clinical problems requiring guidance 2. Chairs with assigned subgroups develop clinical questions in PICO format, including defining subgroups 3. Panel prioritizes the final set of clinical questions, either by consensus or anonymous online voting	**8-12 weeks**
	Selection of patient-important outcomes	Panel: selects patient-important outcomes for each PICO clinical question, ranking them either by consensus or anonymous online voting	**2-4 weeks**
Second stage	Literature search	For each selected PICO clinical question, chairs and subgroups: 1. Identify high-quality up-to-date systematic reviews and meta-analyses 2. If not available, perform a systematic review and/or meta-analysis and select eligible articles	**12-24 weeks**
	Supplementary literature searches	Chairs and subgroups provide input on the need for complementary information such as: 1. Stratification for subpopulations 2. Values & preferences 3. Resourcing 4. Others (feasibility, acceptability and equity)	**4-8 weeks**
	Evidence synthesis and grading	Generation of "Evidence profile" and "Summary of findings" tables with the quality of evidence grading per patient-important outcome	**4-8 weeks**
	Preparation for development of recommendations	Generation of "Evidence to Decision" framework in preparation for development of recommendations	**4-8 weeks**
Third stage	Recommendations development and grading	Panel: development of recommendations using "Evidence to Decision" framework (during a face-to-face meeting or by teleconference)	**1-2 days**
Post-development phase			
	Writing manuscript	Panel subgroups: development of manuscript for each clinical question following the standard IDSA format Chairs: periodic monitoring of subgroups by chairs	**12-16 weeks**
	Review process and approval	1. Simultaneous review by external peer reviewers, by relevant stakeholders (2 weeks review, 2 weeks in-office) 2. SPGC review and approval (1 week review, 2 weeks in-office) 3. BOD review and final approval (1 week review, 2 weeks in-office)	**≤ 10 weeks**
	Dissemination and implementation	1. Publication of guideline in *CID* 2. Presentation at conferences and development of derivatives	**Rapid online availability**
	Updating	Monitoring of literature and identification of practice changing evidence	**Ongoing**
Total projected time for the development of a new CPG			**~1 to 2 years**

5. Panel Composition

The success of producing a high-quality guideline is dependent on the composition, selection, energy, and work ethic of the panel.

Chair(s)

Because of the crucial importance of the chair's function towards timely guideline development, the chair/co-chairs should possess the following qualities:

1) Strong diplomatic and organizational skills
    a. The chair should be experienced in group facilitation and able to maintain a constructive dynamic throughout the process, providing each panel member an equal opportunity to contribute. This requires giving appropriate consideration to different arguments as well as being objective and responsive to the viewpoint of each panel member.
    b. The chair should have tools to identify, address, and resolve potential conflicts by mediating disagreements and facilitating compromise.
2) Strong project management skills
    a. The chair should lead from example and guide/motivate the panel members to meet deadlines and ensure tasks are completed successfully.
    b. The chair should ideally have some expertise in guideline methodology and be in regular communication with the methods experts and professional technical support team.
    c. The chair must be able to effectively delegate work and responsibility to the panel members.
    d. The chair must be accountable for the work completed by the workgroup.
3) Adept skills of persuasion and emotional intelligence
    a. The chair should be recognized prior to the work, not only as someone who has prominence in the field but more importantly as someone who is accepted by their peers as a leader.
    b. The chair should be capable of exercising authority if problems arise, even excluding a panel member if he/she is not fulfilling the requirements as agreed upon.
4) Availability and Flexibility
    a. The chair should confirm that he/she can dedicate ample time to commit to the responsibilities required for the entire guideline development process.
    b. The chair should confirm that he/she will commit to the structured post-publication process of prospectively following the literature, evaluating the validity of the guideline and assessing the need for updates.

In many cases, selection of one or more additional co-chairs may be advisable; this ensures seamless continuation in the process if one co-chair cannot perform their functions appropriately (e.g., clinical duties, sickness). If this strategy is selected, complementary skills among co-chairs is preferable, such as having both a content expert and a methodologist or to have both a senior and a junior member. Co-chairing may also resolve issues regarding COI requirements for chairs (see section on "COI" of the Handbook).

The SPGC chair, with the assistance of the methods experts, will recommend a list of 6-7 potential chair/co-chairs with a ranking of preferences and a rationale for considering their candidacy. To enhance the chair selection process, the SPGC reserves the right to formalize the process by various means, including but not limited to job postings and/or interviews. Once identified, the Executive Committee of the BOD will review the list of candidates and approve the final chair/co-chairs

selection. The BOD will be kept informed of the selection process and final choices. The SPGC chair and/or the BOD have the full authority to remove a chair if he/she is not fulfilling the requirements listed above.

Panel members

A CPG panel usually consists of 10 to 20 individuals (fewer than 10 panel members might impede representativeness and more than 20 can become unmanageable). The panel should be multidisciplinary to optimise the **diversity of relevant stakeholders**. Thus, the following members should be included:

1. Clinicians
    a. Experts in the field
        i. From diverse backgrounds (e.g., different geographical locations)
        ii. With different types of practice (public vs. private practice, hospitalists vs. consultants)
        iii. SPGC encourages junior faculty members/experts to become panel members
    b. Primary care physicians
    c. Relevant specialists
        i. Pediatrics (at least one pediatrician should be included whenever the management of children is within the scope of a guideline; the PIDS liaison to the SPGC will help identify potential panel members)
        ii. HIV specialists (HIVMA representative to the SPGC will help identify potential panel members)
        iii. Microbiology (as needed, to address diagnostic testing issues)
        iv. Any other subspecialties having a unique interest in the specific field (usually from other stakeholder organizations)
    d. Pharmacology/Pharmacy expert
    e. Representatives from related disciplines (e.g., nursing, epidemiology, etc.)
2. Researchers
3. Patients or patient advocates
4. Other collaborators or healthcare organizations, if relevant

The panel members, in collaboration with the chair/co-chairs and method experts, are responsible for selecting the final scope of the guideline, identifying the most important and relevant clinical questions, framing these questions into the PICO format (see chapter 8: “Framing the Clinical Questions”), selecting the patient-important outcomes, guiding the review of literature and assessment of the literature, and developing the recommendations and drafting of the manuscript. All panel members will be required to participate in and adhere to the principles of IDSA-provided formal training on guideline development and to be compliant with the IDSA Handbook for Clinical Practice Guidelines Development at all steps. Panel members are required to meet regularly via conference calls and, if possible, via at least one face-to-face meeting (such as during **ID**Week).

The chair/co-chairs with the assistance of methods experts will develop a list of potential guideline development panel members. Once identified, the SPGC chair will review and approve the list of potential panel members, and then inform the Executive Committee of the BOD of the final selection. Prospective panel members will then receive an e-mail invitation to participate and be asked to complete a COI disclosure form. Final participation will be only be confirmed following review of potential COIs. Chairs/co-chairs have the full authority to remove a panel member if he/she is not fulfilling the requirements listed above.

Stakeholder organizations

The SPGC encourages panels, at the earliest convenience, to invite stakeholder organizations to participate during the guideline development process (e.g., PIDS, HIVMA, SHEA, CDC, ATS, SIDP, ASHP, SIS, ACEP, SAEM, AAFP). It is recommended and preferable to reach out to societies **prior to the guideline work** to identify and define the type of association.

This might take two forms:

1) **Partnership:** This form of association leads to the development of a joint guideline and entails having co-chairs from each organization combined with equal representation on the panel. In such cases, the development process should be defined and agreed upon prior to the work, with a memo of understanding from the onset.
2) **Endorsement:** This form of association is possible by requesting the endorsement of a guideline by another society who may request to delegate a representative to the process.

Methods experts

One or more members of the IDSA methods expert team and possibly other method expert designees will participate in all steps of the guideline development from inception to publication. The methods experts have experience in performing systematic reviews and applying the GRADE approach and will assist the chair/co-chairs at every step of the process.

If feasible, a technical review team, composed of 2-3 content experts (ideally one of these experts should be chair or co-chair of the guideline), 2-3 methods experts and a librarian will be assigned. Their work will be to evaluate the body of evidence that will support the PICOs from the literature search, screening and selection of studies, synthesis of the evidence, assessment of the QoE and the production of evidence tables. Regular calls are mandatory to make this process efficient. The technical review team does not have any responsibility towards generating the recommendations, but the results will be presented to the panel members who will develop the recommendations and draft the manuscript.

Liaison to the SPGC

The SPGC Chair will also identify an SPGC member to serve as the liaison-advisor to any panel of a guideline for which IDSA is leading the development or jointly developing. The liaison-advisor will provide guidance to the panel on the development, formatting, and approval process of the guideline as well as monitor the progress for purposes of keeping the SPGC and IDSA BOD informed.

References

1. Kunz R, Fretheim A, Cluzeau F, Wilt TJ, Qaseem A, Lelgemann M, et al; on behalf of the ATS/ERS Ad Hoc Committee on Integrating and Coordinating Efforts in COPD Guideline Development. Guideline Group Composition and Group Processes. Article 3 in Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report. Proc Am Thorac Soc 2012; 9 (5): 229-233.

6. Conflicts of Interest

General principles

All guideline chairs and panel members should act in the best interest of IDSA, its membership, and the public. Decisions that lead to guideline recommendations should not be influenced by personal financial interests or by other extraneous considerations. Each guideline panel member has a high duty and obligation to disclose any potential COI and to abstain from any decision where a potential COI exists. A potential COI exists if a panel member has a financial or other interest that might bias his or her decisions or actions concerning matters before the guideline panel. In the interest of full disclosure, **any** relationship with a pharmaceutical, biotechnology, medical device, health insurer, or health-related company or venture that may result in financial benefit to the member should be disclosed to IDSA. If uncertain about whether a particular financial or other interest constitutes a COI, chairs and panel members as well as SPGC committee members, IDSA BOD members, guideline reviewers, or any other participant involved in the guideline development process should report for review any financial or other interest that an independent observer might reasonably consider a COI.

In June, 2017, IDSA adopted the "Council on Medical Specialty Societies (CMSS) Code of Interactions with Companies" which provides principles for interactions with companies as they relate to CPG development (**Table 1**), as well as defining prohibited relationships (**Table 2**)**.** Furthermore, **Table 3** defines allowed relationships for participation in IDSA's guideline process. Aspects of the implementation of the updated IDSA ethics and COI guidelines are in progress. This document will be updated as additional specific processes are operationalized. For all COI determinations, the IDSA Executive Committee of the BOD has final authority in decisions.

Reporting time-frame

All disclosures should be for activities and financial relationships/investments that are current, planned, and present in the preceding two years. COI disclosure forms will be completed annually by guideline participants until completion. For chairs or panel members involved in the post-publication review and update process, COI disclosure forms will continue to be required annually. Current or prior relationships will not exclude candidates. However, guideline panel participation is contingent on the candidates' termination of such relationship(s) prior to their assignment to a guideline development panel. In some cases, IDSA may agree to allow for current commitments (e.g., speaking engagements) to be honored.

Table 1. Principles for Interactions with Companies on Clinical Practice Guidelines (Abstracted from the CMSS Code, Section 7)[1]

7.1. Societies will base Clinical Practice Guidelines on scientific evidence.
7.2. Societies will follow a transparent Guideline development process that is not subject to Company influence. For Guidelines and Guideline Updates published after adoption of the Code, Societies will publish a description of their Guideline development process, including their process for identifying and managing conflicts of interest, in Society Journals or on Society websites.
7.3 Societies will not permit direct Company support of the development of Clinical Practice Guidelines or Guideline Updates.
7.4 Societies will not permit direct Company support for the initial printing, publication, and distribution of Clinical Practice Guidelines or Guideline Updates. After initial development, printing, publication and distribution is complete, it is permissible for Societies to accept Company support for the Society's further distribution of the Guideline or Guideline Update, translation of the Guideline or Guideline Update, or repurposing of the Guideline content.
7.5. Societies will require all Guideline development panel members to disclose relevant relationships prior to panel deliberations, and to update their disclosure throughout the Guideline development process.
7.6. Societies will develop procedures for determining whether financial or other relationships between Guideline development panel members and Companies constitute conflicts of interest relevant to the subject matter of the guideline, as well as management strategies that minimize the risk of actual and perceived bias if panel members do have conflicts.
7.7. Societies will require that a majority of Guideline development panel members are free of conflicts of interest relevant to the subject matter of the Guideline.
7.8. Societies will require the panel chair (or at least one chair if there are co-chairs) to be free of conflicts of interest relevant to the subject matter of the Guideline, and to remain free of such conflicts of interest for at least one year after Guideline publication.
7.9. Societies will require that Guideline recommendations be subject to multiple levels of review, including rigorous peer-review by a range of experts. Societies will not select as reviewers individuals employed by or engaged to represent a Company.
7.10. Societies' Guideline recommendations will be reviewed and approved before submission for publication by at least one Society body beyond the Guideline development panel, such as a committee or the Board of Directors.
7.12. Societies will publish Guideline development panel members' disclosure information in connection with each Guideline and may choose to identify abstentions from voting.
7.13. Societies will require all external reviewers who are not officially part of a Guideline development panel, to disclose financial or other substantive relationships that may constitute conflicts of interest.
7.14. Societies will recommend that Guideline development panel members decline offers from affected Companies to speak about the Guideline on behalf of the Company for a reasonable period after publication.[2]
7.15. Societies will not permit Guideline development panel members or staff to discuss a Guideline's development with Company employees or representatives, will not accept unpublished data from Companies, and will not permit Companies to review Guidelines in draft form, except if a Society permits public or member comment on draft Guidelines as a part of the Society's published Guideline development process.

1 Clause 7.11 in the original Code that stated 'guideline manuscripts will be subject to independent editorial review by a journal or other publication where they are first published/ was deleted for use in the IDSA guideline process because of the IDSA in-place, multi-tiered review process prior to submission for journal publication.
2 A reasonable period of time is defined as at least one year by the IDSA.

Table 2. Relationships Prohibited

1. Royalties, licensing fees, patents from any product or device related to the topic under consideration. This includes patents, the rights for which have been turned over to an institution but from which the individual benefits.
2. Serving as an officer, board of directors member or employee of any device, insurance, pharmaceutical or diagnostic product or commercial entity with a product or device related to the topic under consideration.
3. Representation of any commercial healthcare-related entity (with a product or device related to the topic under consideration) before FDA advisory committees or in any other interactions such an entity may have with FDA.
4. Any honoraria, gifts, or other payments (includes funds for travel/hotel) directly received from any relevant commercial healthcare-related entity (US and International). This includes participation in speakers bureaus labeled as promotional and/or when any associated presentation is: a. content-restricted in any way, including, but not limited to, the requirement to use only company-provided material; paid for by any mechanism other than an unrestricted educational grant to a CME-approved (or other educational) entity; and/or product-specific.
5. Any activity not sponsored by the research arm of the company will **NOT** be allowed. For example, an advisory board sponsored by the marketing division, even if concentrating on "future research directions," will **NOT** be allowed. In addition, consulting on post-research regulatory issues will **NOT** be allowed.
6. Stock or equity in any commercial healthcare-related entities (excludes diversified funds).

Table 3. Relationships Allowed

1. Advisory/consultancies when research-related will be considered as a research activity, even if the company with which you have the relationship, has products related to the guideline. Thus, work with a pharmaceutical or device company involving study design or service on a Data Safety Monitoring Board **WILL** be allowed. ***Exception, Chair(s)***
2. Serving as an investigator on a company-supported or company-sponsored research study. If you are a panel chair and conduct research, IDSA will require a co-chair with no relationships.
3. Presentations at national or international meetings provided that: a. Presentations are non-promotional and there should be no involvement of industry in presentation content. There should be complete intellectual independence with regard to presentation content. b. There is NO direct payment by industry to an individual for his/her participation (any industry support of speaker expenses must be through a third-party organization (e.g, IDSA, ICAAC, ATS, etc), institution, CME, or other educational provider. ***Exception, Chair(s)***

Process for disclosure

All participants in the IDSA guideline process will complete the IDSA COI form and be approved for specific roles within the guideline process prior to participating. Until individual disclosures are reviewed and approved by the chair of the SPGC, SPGC liaison to the panel, the IDSA BOD liaison to the SPGC, and, if necessary, the IDSA Executive Committee of the BOD, participation in the guideline panel is prohibited. Assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). All potential or perceived COI of members of the guideline development process will be disclosed in the guideline publication.

COI disclosure is initiated by IDSA staff who are responsible for sending the COI disclosure form to all participants in the development of a guideline in a stratified process as follows. COI disclosure is **first** obtained from the prospective chair of a guideline panel. The COI disclosure for the prospective panel chair will be reviewed by the chair of the SPGC, the BOD liaison to the SPGC, and the BOD Executive Committee. COI approval for the prospective panel chair will precede final approval of the prospective chair by the BOD Executive Committee. If a prospective chair is not approved, additional candidates for the chair will be reviewed using the same process. Once the chair is approved by the BOD Executive Committee, IDSA staff will initiate obtaining COI disclosure from all proposed panel members, methodologists, SPGC liaison to the panel, and other anticipated participants in the specific guideline development process. These COI disclosures will be reviewed by the SPGC chair and the BOD liaison to the SPGC. At the discretion of the SPGC chair, a request may be made to the Executive Committee of the BOD for review.

Partnership in guideline development or guideline endorsement

IDSA participates in or endorses guidelines developed by other organizations with established processes for disclosure. The administrative management of the guideline, including disclosure and management of COIs, shall be the responsibility of the collaborating organization. IDSA does not participate in guidelines developed with funding from commercial entities.

Types of COI and requirements

Criteria for panel chair(s)

Chairs will be free from all financial or other interests that might bias his or her decisions or actions concerning matters before the panel. Relationships potentially allowed for panel members are not allowed for chairs (Table 3). COI review for chairs will precede and be finalized prior to selection and COI review of potential panel members. A prospective chair should disclose, if known, whether an affected commercial entity has provided financial support to the division, or department within which the individual conducts research and patient care. The existence of such support does not necessarily disqualify the individual from service as a chair, but will be taken into consideration.

Because IDSA guidelines are subject to regular revision or updating, chairs must complete and sign the IDSA Panel Chair Agreement acknowledging their commitment not to become involved in prohibited financial interests for an additional period of one year after publication of the guideline (see General Principles section). If current financial interests preclude continuing as chair, these individuals may be considered for service as members of the panel for the update (with full disclosure of their current financial or beneficial interests).

Potential Exceptions. Generally, chairs will not be appointed that have financial interests in or relationships with affected companies or products. In rare circumstances, exceptions may be approved such as a chair receives research funding from an affected company that is usual and customary for the efforts needed to conduct the study and if the expertise the chair brings because of his/her work is assessed to ultimately help the panel develop a better quality guideline. In this instance, the chair will be unable to vote on guideline recommendations that are specifically related to the product about which his/her research is being conducted. In addition, a co-chair that has no financial or other beneficial interests must also be selected.

Occasionally, a chair may have a relevant financial interest or relationship that is not covered by IDSA's formal disclosure process (e.g., an intellectual property, as opposed to financial conflict). In these situations, the panel chair should disclose this interest to the chair of the SPGC for review prior to accepting the panel chair portion.

Criteria for panel members

In April 2009, the IOM released its report on "Conflict of Interest in Medical Research, Education, and Practice." Among its recommendations were that groups that develop CPGs "should generally exclude as panel members individuals with conflicts of interest." It further recommends that "in the exceptional situation in which avoidance of panel members with conflicts of interest is impossible because of the critical need for their expertise, then groups should limit members with conflicting interests to a distinct minority of the panel." IDSA supports this goal and, with rare exception, all IDSA guideline panels will have ≤30% of panel members with potential or perceived COIs and >30% will be free of any COIs related to the subject matter under consideration. For those with potential COI, it may be determined that an individual is not eligible to serve as part of the panel because of the nature and extent/intensity of his or her relationship with an affected company.

Information regarding the interests of a panel candidate's spouse and dependents is gathered as part of the disclosure process. Candidates should report, to the best of their ability, any known interests of his/her immediate family that may be related to the guideline topic under consideration. The extent of the family members' relationship will be considered as part of the evaluation of the candidate.

Criteria for other participants involved in the guideline development process

- **Methodologists and technical review team.** All participants involved in the methodological aspects of the guideline development or technical review of the literature (e.g., methodologists (either IDSA staff or appointed), librarians, systematic review specialists, and data extractors) will complete the IDSA COI form. Only individuals free of perceived or potential COI relevant to the subject matter of the guideline will be allowed to participate.
- **SPGC members and SPGC liaison to guideline panel**. Members of the SPGC serve in a liaison capacity to guideline development panels. In rare cases, these liaisons may serve as full members of the development panels. Liaisons who serve in this capacity are required to meet all criteria set forth above. Members of the SPGC are also charged with the review and approval of all IDSA guidelines. As with all IDSA Committees, SPGC members are required to disclose any relationship with a pharmaceutical, biotechnology, medical device, or health-related company or venture that may result in financial benefit to the member.
- **Guideline reviewers.** All potential guideline reviewers (e.g., SPGC members, BOD liaison to SPGC, SPGC liaison to guideline panels, external reviewers, and BOD reviewers) will complete the IDSA COI form. Only guideline reviewers free of perceived or potential COI relevant to the subject matter of the guideline will serve as guideline reviewers.

Recusals

Financial COI

- **Panel members**. The SPGC will require that, in the rare instance of inclusion in a guideline panel, members with a product-specific financial interest recuse themselves from specific discussions or votes. The SPGC liaison to the guideline panel and chair(s) will be responsible for determining the need for recusal for these specific discussions and votes, as well as to ensure that the recusal is respected throughout the whole guideline development process. If there is a dispute regarding the necessity of recusal, the chair of the SPGC, the BOD liaison to the SPGC, and, if necessary, the Executive Committee of the BOD will determine subsequent resolution.
- **Reviewers, SPGC and BOD members**. To underscore the independence and integrity of the guideline adoption process, guidelines will be approved only by reviewers, SPGC members, and IDSA BOD members who do not have financial relationships with affected companies or products. Disclosure of any financial relationship with an affected company or product will be cause for recusal from the decision on approval of a guideline.

Non-financial COI

Rarely, relationships may be disclosed that, though not financial in nature, could undermine public confidence in the guideline process. This concept applies to any stage of the guideline process and to any person involved in the guideline process, as such, may be relevant from IDSA BOD members to panel members. If there is a question as to whether a particular relationship warrants recusal, a determination will be made by the appropriate oversight group that could be the IDSA Executive Committee of the BOD, SPGC chair, panel chair, or IDSA BOD liaison to the panel.

Publication of disclosure information

When IDSA publishes a guideline in one of its journals, all disclosures of panel members will be published concurrently. The following language will accompany the list of disclosures within the "Acknowledgements" section:

> ***"Potential Conflict of Interest:*** The following list is a reflection of what has been reported to the IDSA. In order to provide thorough transparency, IDSA requires **full** disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential COIs is determined by a review process which includes assessment by the SPGC chair, the BOD liaison to the SPGC, the SPGC liaison to the panel, and, if necessary, the Executive Committee of the BOD. This assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed."

Potential exceptions

IDSA's goal is to assemble a diverse and well-qualified group of experts to develop, approve, and adopt guideline recommendations. If required to achieve this goal, the above procedures may be modified by the Executive Committee of the BOD on a case-by-case basis.

References

1. Council on Medical Specialty Societies (CMSS) Code of Interactions with Companies, April 2015: url: https://cmss.org/wp-content/uploads/2016/02/CMSS-Code-for-Interactions-with-Companies-Approved-Revised-Version-4.13.15-with-Annotations.pdf

7. Defining the Scope

After the panel is convened, the guideline topic proposal will be reviewed, and the scope of the guideline should be agreed upon by consensus. Frequently, refinement of the scope of the guideline may be needed prior to the development of the clinical questions.

The initial step requires the panel to define and agree on the **target audience** (end-users) for the guideline and the patient populations to which the guideline will apply, ensuring thereby that the scope will address the most common problems for this specific target audience.[1]

The second step is to identify more specific topics within the broad subject potentially covered by the guideline. Usually, the development of candidate topics is left to the panel after consideration of health burden, variability in practice, potential impact of a recommendation, uncertainty or controversy, importance to clinicians, importance to patients, costs of care, availability of evidence, or emerging issues.

Topics selection within the guideline may also be informed from the following:

- Review of previous guidelines with a similar scope to evaluate potential recommendations change;
- Review of other guidelines to create a list of potential topics of interest while avoiding redundancy and ensuring coordination and harmonization of existing guidelines;
- Consultation with end-users and stakeholders. This input can be collected by:
    - Surveying clinicians (e.g., IDSA members), experts, and patients for candidate topics
    - Contacting individual representatives of these groups
    - Consulting the general public for input on priorities, via formal or informal group processes (e.g., website, formal consultation)
- Identification of new and emerging technologies and treatments, current policy controversies, or evolving practice from abstracts, major research meetings, editorials, and recent drug approvals.

These steps should help identify topics for which clinical questions should be further developed.

References

1. Atkins D, Perez-Padilla R, MacNee W, Buist AS, and Cruz AA; on behalf of the ATS/ERS Ad Hoc Committee on Integrating and Coordinating Efforts in COPD. Priority Setting in Guideline Development. Article 2 in Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report. Proc Am Thorac Soc 2012; 9 (5): 225-228.

8. Framing the Clinical Questions

CPGs are defined by the IOM as "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." Thus, each recommendation within a CPG should answer a focused and sensible clinical question that is immediately **actionable**. Guidelines are **NOT** a narrative review and should never attempt to replace a textbook.

Prioritizing clinical questions

Prioritizing clinical questions to answer is the first step in developing a guideline. Important questions should be **driven by practice** rather than evidence. These questions should be commonly encountered in clinical practice and/or apply to a large proportion of patients. Such questions typically arise when trying to decide how to **diagnose** or **manage** a patient or a group of patients.

A question should also be prioritized when:

1) There is controversy around the answer (i.e., there is considerable variation in practice)
2) There is doubt around the answer (e.g., there are uncertainty if current practice is appropriate)
3) There is a need to reinforce current standard-of-care (e.g., discourage a specific practice that is still being performed)
4) The existing body of evidence is probably sufficient to support a recommendation or will help determine research in future

Types of questions (foreground and background)

When developing clinical questions, the information needed can lead to two types of questions: foreground and background questions.

Foreground questions

Foreground questions address the effectiveness of an intervention that the guideline development group is considering evaluating. This type of question will provide information on the balance of desirable and undesirable effects of an intervention vs. its comparator (such as medical or surgical treatments, a prophylaxis, an infection control measure, or a diagnostic test). The foreground questions will directly lead to an **actionable** recommendation to "use" or "not to use" an intervention vs. its comparator in a certain predefined population.

Questions about management (treatment, prophylaxis, or infection control measures) should be formulated as: "In [health problem and/or population], should [intervention] vs. [comparison] be used to improve [outcomes]?"

Example of foreground question:

Clinical question: *In patients with recurrent furunculosis, should systemic antistaphylococcal antibiotics be used rather than topical antibiotics?*

- **P** **Population** = patients with recurrent furunculosis
- **I** **Intervention** = systemic antistaphylococcal antibiotics
- **C** **Comparison** = topical antibiotics
- **O** **Outcomes** = progression to abscess, frequency of recurrence, side effects of antibiotics, costs

Final recommendation: In patients with recurrent furunculosis, we suggest using systemic antistaphylococcal antibiotics over topical antibiotics.

Foreground questions are the most important ones for a guideline since the answer will directly become a recommendation. These questions should be framed using the PICO format to enable an effective systematic search of the literature, and by doing this, will allow for a quality assessment of the evidence using the GRADE approach and inform the recommendations.

Background questions

Background questions are important considerations for making recommendations on the foreground questions, but are not meant to become recommendations in themselves. These include questions on definitions, pathophysiology, etiology, clinical presentation, epidemiology, risk factors, and prognosis. This background information may help define health problems, populations, interventions, comparators, or outcomes.

Examples of background questions:

- **Definition**: How do we define recurrent furunculosis?
- **Etiology**: Which pathogens can cause recurrent furunculosis?
- **Epidemiology (baseline risk)**: What is the prevalence of recurrent furunculosis caused by MRSA?
- **Risk factor**: Who is at increased risk of recurrent furunculosis caused by MRSA?
- **Clinical presentation**: Do pediatric patients differ from adults in clinical presentation?
- **Prognosis**: What is the frequency of recurrence in immunocompromised patients?

Importance of framing foreground questions into the PICO format

The question formulation should be considered as one of the most **critical steps** and requires that all panel members participate in their development. Each clinical question will be formulated in the **PICO** (P=population, I=intervention, C=comparison, O=outcome) format which is a standardized way to structure each question; this ensures that the question includes the minimum components to translate it into an actionable recommendation.

A clinical question formulated in a PICO format:

1) Helps develop clear, well-defined, and focused recommendations;
2) Determines the next steps in guiding a systematic search, appraisal, grading, and summarization of the evidence;
3) Forms the basis of the final recommendation (i.e., either the intervention or the comparator will be recommended in the population of interest).

Defining each element of the PICO format

The final scope of each clinical question will be determined by the broadness/narrowness of each PICO element. A broader question may permit a summary of a larger body of evidence and more generalizable findings, while a narrow question may yield less heterogenous evidence and a better interpretation of variations between subgroups. Depending on the scope of the guideline and the availability of information, a broad question might be further split into a number of narrower questions later in the process.

Defining the population (P)

The most challenging decision in framing the question is how broadly the population should be defined. For a defined population, if it seems plausible that the balance of absolute benefits and harms of an intervention is similar across the range of patients, then no further stratification is needed. But if that is not the case, estimates might be misleading for some subpopulations of patients. These subpopulations should, therefore, be defined separately. For example, if the effect

of systemic antibiotics on the frequency of recurrence in patients with recurrent furuncles is different in children than it is in adults, a single estimate across the range of all patients will not optimally serve the decision-making needs of patients and clinicians. Often, experts might speculate that the effects will be different in certain subpopulations but there is only limited data to support that conclusion. The panel must therefore decide how broadly the evidence can be applied – a term that GRADE calls "indirectness." For example, the guideline can restrict the scope by defining the population as outpatients presenting with recurrent furunculosis rather than also including hospitalized patients.

For example:

- **Clinical question**: In patients with recurrent furunculosis, should systemic antistaphylococcal antibiotics be used rather than no antibiotic therapy?
    - **Prognosis** question: What is the frequency of recurrence in immunocompromised patients?
        - **Stratification:** Reviewing evidence might show that immunocompromised patients are at high risk of poor outcomes (more frequent progression to abscess and higher number of recurrences per year) as well as a larger beneficial effect of systemic antistaphylococcal antibiotics in this subpopulation.
    - **Risk factor** question: Who is at increased risk of recurrent furunculosis caused by *Pseudomonas aeruginosa*?
        - **Stratification:** Reviewing evidence might show that patients visiting hot tubs are at high-risk of *Pseudomonas* furunculosis as well as that patients with *Pseudomonas* furunculosis experience no beneficial effect of systemic antistaphylococcal antibiotics as compared to topical antibiotics and do experience a beneficial effect when the systemic antibiotics include antipseudomonal coverage.
- **Final recommendations can then be nuanced such as**:
    - In patients with recurrent furunculosis, we suggest using systemic antistaphylococcal antibiotics over topical antibiotics.
        - For immunocompromised patients, we recommend using systemic antistaphylococcal antibiotics.
        - For patients with risk factors for *Pseudomonas aeruginosa*, we suggest using systemic antibiotics with antipseudomonal coverage.

Here are examples of questions that can be helpful to better define the population targeted by the action being recommended:

- How can the population be best described?
- What are the relevant demographic factors (e.g., age, presence of immunosuppression, risk factor of multi-resistant pathogens, severity of infection)?
- What is the setting (e.g., community-acquired vs. healthcare-associated, outpatient vs. hospitalized)?
- Are there any subgroups that might need to be considered?
- Are there subgroups that should be excluded?

Defining the intervention (I)

Another challenge in framing the question is how broadly the intervention should be defined. Interventions may consist of a treatment (medical or surgical), a prophylaxis (or individual preventive measure), an infection control measure (population preventive measure), or a diagnostic test. For a defined intervention, if it seems plausible that the effect of a range of interventions is similar for a population, then no further stratification is needed. But if that is not the case, estimates might be

misleading for at least some interventions. These interventions should, therefore, be defined separately. For example, if systemic antibiotics differ in effectiveness depending on the class of antibiotics used, then a single estimate for all classes of antibiotics will not be optimal for the decision-making needs of patients and clinicians.

Here are examples of questions that can be helpful to better define the action that is being considered:

- What exactly is being evaluated? Treatment, surgical procedure, prophylaxis, diagnostic test, or preventive measure?
- Is there a variation or specificity of the above which may have clinical relevance (dosage, frequency, delivery or administration, timing and duration)?

Defining the comparator (C)

Finally, another aspect in framing the question is how broadly should the comparator be defined. Comparators may consist of alternative(s), which are often the control group(s) used in studies and can include not performing the action or intervention. The same concepts that were used to define the population or the interventions apply here. Although the comparator is often obvious, it should always be explicitly specified in the recommendation. Comparisons may be made to placebo, no intervention, standard care, current standard diagnostic, variations of the intervention (coverage, timing or duration), or another alternative.

There may be multiple comparators for a given intervention. For example, when multiple antimicrobial agents are implicated, the formulated recommendation should clearly state if the comparison includes:

a) Using antibiotics XYZ vs. no antibiotic (antibiotics XYZ could either be all types of antibiotics or a prespecified set of antibiotics, where all antibiotics would be considered as equally recommendable)
b) using antibiotics XYZ vs. antibiotics QRS (preference of a group of antibiotics over another group or a rank of preference)

It is acknowledged, moreover, that the estimate of effect for each agent may come from evidence of varying quality (e.g., high-quality evidence for one agent, low-quality evidence for another).

Defining the outcomes (O) *(see next chapter)*

Framing diagnostic questions

Diagnostic questions can address diverse types of diagnostic tests such as clinical presentation, biochemistry, microbiology, imaging, or pathology testing. These diagnostic tests can also be used in different contexts such as screening, diagnosis, monitoring illness and treatment response, or establishing prognosis.

Questions about diagnosis would be formulated as: “In [health problem and/or population], should [intervention i.e., diagnostic test or strategy] vs. [comparison i.e., another diagnostic test or strategy] be used to diagnose [target condition] to improve [outcomes]?”
The **role or purpose** of the index test or test strategy needs to be clearly established to identify relevant clinical questions. The role of the index test can differ:

1) Replacement: A new test might replace an old one because it is more accurate, less invasive or risky for patients, easier to perform or interpret, quicker, or cheaper. For example, in patients with recurrent furunculosis, should a PCR method be used as a replacement for standard culture to diagnose MRSA carrier state?
2) Triage: A new test might be added before the current existing diagnostic pathway. A triage test implies that only patients with a specific result would continue through the diagnostic

pathway. A triage (screening) test is usually easier to perform or interpret, quicker, or cheaper (but not necessarily more accurate). For example, in patients with fluctuating mass, should a quick ultrasound be used to screen for deep abscess prior to standard imaging?

3) Add-on: A new test might be added after the current existing diagnostic pathway. The purpose of an add-on test is usually to limit the number of false positive or false negative results. An add-on test is thus usually more accurate (but lacking other advantages). For example, in patients with necrotising lesions, should skin biopsy be used to confirm the clinical and microbiological diagnosis of furunculosis?

Defining the PICO elements

- **Population** refers to group of patients having a specific pre-test probability (prevalence) of the target condition.
- **Intervention** (index test or new test) consists of a single diagnostic test or test strategy (composed of several tests).
- **Comparator** can either be another diagnostic test or test strategy, or a control group (not tested).
- **Reference standard** refers to the current best and accepted approach to making a diagnosis (previously called "gold standard") to which the intervention and the comparator will be compared to assess diagnostic test accuracy (e.g., sensitivity and specificity).
- **Outcomes** *(see next chapter)*

Selecting the final set of questions

CPGs should have a restricted number of clinical questions; thus, the panel should prioritize questions. Clinical questions may be selected either by consensus or by anonymous online vote. A maximum number of clinical questions will be set *a priori* depending of the scope of the guideline. Ideally, full coverage of a topic would include 15-20 questions. The breakdown is as follows:

- Diagnostics: 5 questions
- Management: 10 questions
- Infection control: 5 questions

Panel members should be involved at all steps to:

1) Discuss questions
2) Compile questions that are relevant within the scope of the guideline (in PICO format)
3) Anonymously rank the relative importance of questions by following these steps:
    a) Each clinical question is submitted in the PICO format
    b) Each panellist will rate the importance of each question on a 9-point Likert scale (1 being an unimportant question and 9 being a crucial question)
    c) For each question, the median of votes will be computed and the questions will be ranked by importance
    d) Questions ranking as the most important will be selected for further analysis
4) Discuss the results and agree on final questions

References

1. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. JCE 2011; 64:395-400.
2. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence-indirectness. Journal of Clinical Epidemiology 2011; 64:1303-1310.
3. GRADE handbook. url: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html
4. WHO Handbook for guideline development. World Health Organization 2012.
5. Cochrane Handbook (chapter 5, 11 and 12). url: http://handbook-5-1.cochrane.org/

9. Selecting Important Outcomes

Importance of selecting and rating outcomes

The purpose of any recommendation is to provide guidance on the optimal course of action according to a careful weighing of desirable and undesirable consequences. Thus, to make sensible recommendations, all outcomes that are important to patients (individual benefits and harms of an intervention) or to others (e.g., public health impact of an intervention on antibiotic resistance or transmission of infection) need to be considered.

Although all outcomes require consideration, they are **not equally important in the decision-making process** and should be ranked in order of relative importance. Ranking the outcomes by importance will help focus on those considered important for decision making as well as determine the overall QoE for a specific recommendation.

Determining the relative importance of outcomes

First step: Generation of a list of outcomes

The first step is to identify *a priori* all potential patient-important outcomes which can be identified from literature; from the panel members based on their experience, expertise, and interpretation of the medical literature; from clinical experts; and/or from patient groups.

Important outcomes should be **driven by practice** rather than evidence. Although experts might focus on what they know from research studies (i.e., outcomes typically measured and for which evidence is available), they must base the choice of outcomes on what is important for decision making. If evidence is lacking for an important outcome, this should be acknowledged, rather than ignoring the outcome since 1) a surrogate outcome may be reported and could serve as an indirect outcome, or 2) this lack of evidence can be informative in that it identifies research gaps.

When identifying all important outcomes, the panel should always consider benefits as well as harms to provide a full assessment of the decision-making process. Furthermore, outcomes should always be clearly defined (for example, a rash can be defined as mild or life-threatening, or an outcome can be measured at different points in time or on different scales).

Here are examples of questions that can be helpful to better define the outcomes that need to be identified:

- What is the purpose of the recommendation?
- What will it achieve?
- What harms could it lead to?

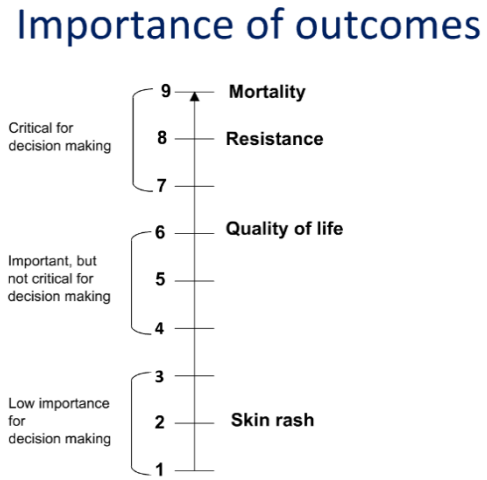
For example

- **Clinical question**: *In patients with recurrent furunculosis, should systemic antistaphylococcal antibiotics be used rather than topical antibiotics?*
    - **Outcomes**: recurrence of furunculosis, progression to abscess, secondary transmission**, duration of disease, contact dermatitis, quality of life, side effects related to systemic antibiotics, *Clostridium difficile* disease, costs/cost-effectiveness related to systemic antibiotics, allergic reaction, antibiotic resistance
- **Here, the primary outcome reported in the literature is the “recurrence of furunculosis,” but the panel could decide to include “secondary transmission” if patients identified this outcome as important when deciding to use or not to use systemic antibiotics.

Second step: Ranking the importance of outcomes

Often there will be many outcomes listed by the panel members for a PICO question and thus the panel will be asked to anonymously rank the importance of outcomes on a scale from 1 to 9 according to their importance for decision making (1 being not important and 9 being critical).

These judgments are ideally informed by a systematic review of the literature focusing on what the target population considers as critical or important outcomes for decision making (literature about values, preferences, or utilities). Alternatively (often in absence of such evidence), the collective experience of the panel members, patients, and members of the public can be used to assume patients' values and preferences surrounding the importance of outcomes.



The final selection of outcomes will depend on the mean/median for each outcome. Panel should agree on the final ranking of outcomes (large variability in ratings usually means that the outcome needs further clarification, such as the skin rash example). Only critical and important outcomes will be included for searching, summarizing, and grading the evidence.

Example

- The ranking of patient-important outcomes could be:
  - Critical outcomes:
    - Recurrence of furunculosis (median = 7)
  - Important outcomes:
    - *Clostridium difficile* disease (median = 6)
    - Progression to abscess (median = 5)
    - Duration of disease (median = 4)
    - Side effects related to systemic antibiotics (median = 4)
    - Allergic reaction (median = 4)
  - Less important outcomes:
    - Secondary transmission (median = 3)
    - Quality of life (median = 3)
    - Costs related to systemic antibiotics (median = 3)
    - Contact dermatitis (median = 2)
    - Increased risk of antibiotic resistance (median = 2)

The critical and important outcomes (rankings from 4 to 9) will appear in the evidence tables to assess the balance of benefits and harms of alternative courses of action. The overall quality of

evidence will be determined by the critical outcomes only (ranking from 7 to 9). Less important outcomes (ranking from 1 to 3) will not be further considered.

Third step: Reassessment

A preliminary classification should always occur before the development of the systematic review. Nevertheless, a reassessment can be necessary after evidence becomes available when:

1) Review of evidence identifies important outcomes that were not initially considered (i.e., unknown serious adverse effect),
2) Review of evidence questions the ranking of the relative importance of outcomes (i.e., patient views and preferences),
3) Review of evidence shows that there is no association between an outcome and an intervention of interest.

Importance of outcomes for diagnostic questions

Two different situations may present when considering diagnostic questions:

1) Rarely, "diagnostic intervention studies" are available (randomized comparative). These studies are designed to measure the direct impact of alternative diagnostic strategies on patient-important outcomes. If these are available, patient-important outcomes should be selected as previously explained.
2) More frequently, "diagnostic test accuracy studies" are the only studies available. These studies are designed to measure the diagnostic accuracy (e.g., sensitivity and specificity) of alternative diagnostic strategies rather than the impact of testing on patient-important outcomes. In this situation, diagnostic test accuracy is then considered a **surrogate outcome** for patient-important outcomes. In order words, patient-important outcomes will focus on the "consequences" of each test result (e.g., the consequences of a false positive result, or being falsely diagnosed as having a disease).

Example

- **Diagnostic question**: *In patients with suspected deep abscess, should quick ultrasound be used as a replacement to computerized tomography?*
- **Surrogate outcomes:**
  - True positives, false positives, true negatives, and false negatives
- **Patient-important outcomes:**
  - **Direct consequences of testing** such as associated time to diagnosis, costs, and direct complications of testing such as risk associated with radiation.
  - **Downstream consequences of test results** (focusing mainly on the impact of misdiagnosed patients, i.e., FP and FN) such as recurrence of abscess, duration of disease, bleeding due to surgical intervention, costs, and side effects related to prolonged antibiotics.

References

1. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. JCE 2011; 64:395-400.
2. GRADE handbook. url: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

10. Literature Search

At this stage of the process, the following steps should have been performed: 1) the questions must have already been prioritized (since each question may require its own literature search), and 2) the questions must have been formulated and structured in PICO format.[1] It must be re-emphasized that putting questions in PICO format facilitates the subsequent literature search.

From clinical question to search strategy

The final set of prioritized PICO questions[2] are submitted to the medical librarian. This handover can be via the IDSA methods experts or by the chairs, although it is understood that the chairs, the panel members, IDSA methods experts, and the librarian will communicate regularly as needed during the commission of the search.

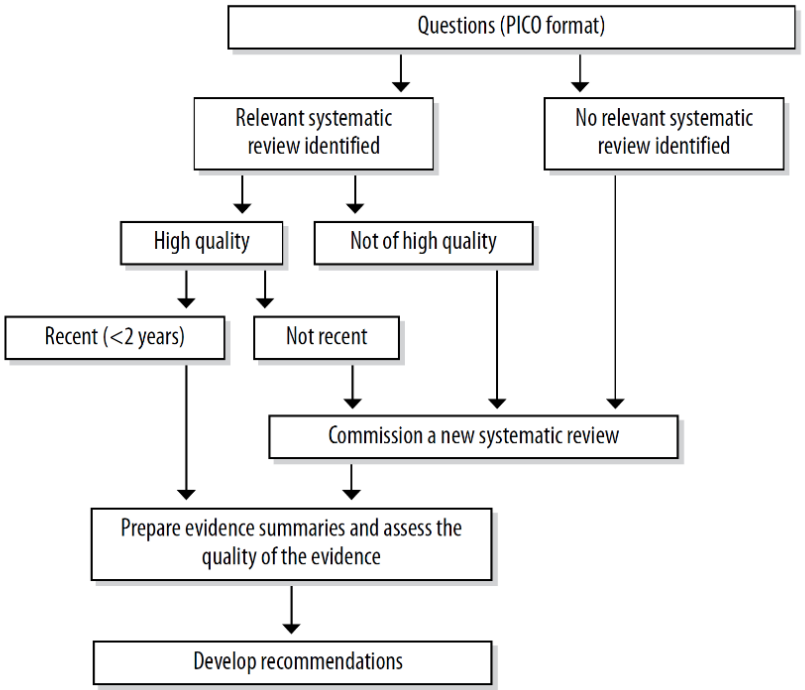
Identifying relevant systematic reviews

For each prioritized PICO question, the panel subgroup members responsible for the specific PICO question (with the assistance of methods experts) will conduct a cursory search of at least two electronic databases (e.g., PubMed/MEDLINE, Cochrane Database of Systematic Reviews) to ascertain whether there is any relevant systematic review that:

1) Appropriately answers the PICO question,
2) Is of high methodological quality,
3) Is recently published and up-to-date.

This first step is necessary to avoid conducting a new systematic review when such existing studies can be updated and adopted instead. If the panel, in collaboration with the IDSA methods experts, are satisfied that a pre-existing systematic review addresses and informs the PICO question, then a new search might not be necessary.

Evidence retrieval decision diagram[1]



Conducting new systematic reviews

With the guidance of IDSA methods experts, the panel can decide to conduct new systematic reviews if:

1) There is no pre-existing systematic review that addresses the PICO question
2) There is a pre-existing systematic review but newly published studies (randomized controlled trials (RCTs) or observational cohort type studies) could be added to the existing body of evidence to improve precision around summary estimates (i.e., meta-analysis) or change the strength or direction of a recommendation.

Search strategies

The panel subgroup members should provide a list of relevant keywords and search terms with synonyms, and the years of search coverage.

The panel subgroup members should also provide the librarian with:

1) Studies that they expect to be included in the result of the search (e.g., RCTs addressing the PICO question under evaluation)
2) Relevant Cochrane Reviews or meta-analyses (as these typically include comprehensive search strategies in the Appendix of optimal quality)
3) Any additional references they think could help with search development (e.g., seminal but unsystematic reviews).

For this full search, the librarian will typically search at least three databases including MEDLINE, EMBASE, and Cochrane Database for Clinical Trials. Additional databases can be searched as warranted by the librarian to ensure an optimal search. The librarian's search can be sensitive (very broad and inclusive) or specific (narrow and tailored). Finding the right balance requires ongoing communication between the librarian, IDSA methods experts, and the panel content experts. To supplement the electronic searches, panel members also have the option of contacting experts and manually searching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles.

Selection of articles

The librarian will save the search strategies and de-duplicated citations (titles/abstracts) that emerge from the searching. The librarian will then place the citations in a reference management database such as EndNote, which will be shared with the chairs, panel members, and methods experts.

Once the citations emerging from the initial search are placed in the reference manager database, panel subgroup members will conduct the various rounds of screening for final eligibility. The IDSA methods experts will assist the panel members in devising a systematic process for conducting the screening. The objective of the screenings is to arrive at the final and 'optimal' set of manuscripts that inform the PICO question.

The steps that the panel subgroup members are responsible for include:

a) **Inclusion/exclusion criteria**: Prior to the screening steps, IDSA methods experts in conjunction with the panel subgroup members will develop a list of inclusion/exclusion criteria for study selection.
b) **First screen (title and abstracts)**: Titles and abstracts will be screened in duplicate and independently to identify and include all potentially eligible studies.
c) **Second screen (full texts)**: Selected citations will be screened in duplicate and independently (with consensus agreement or third-party adjudication, as required) to select

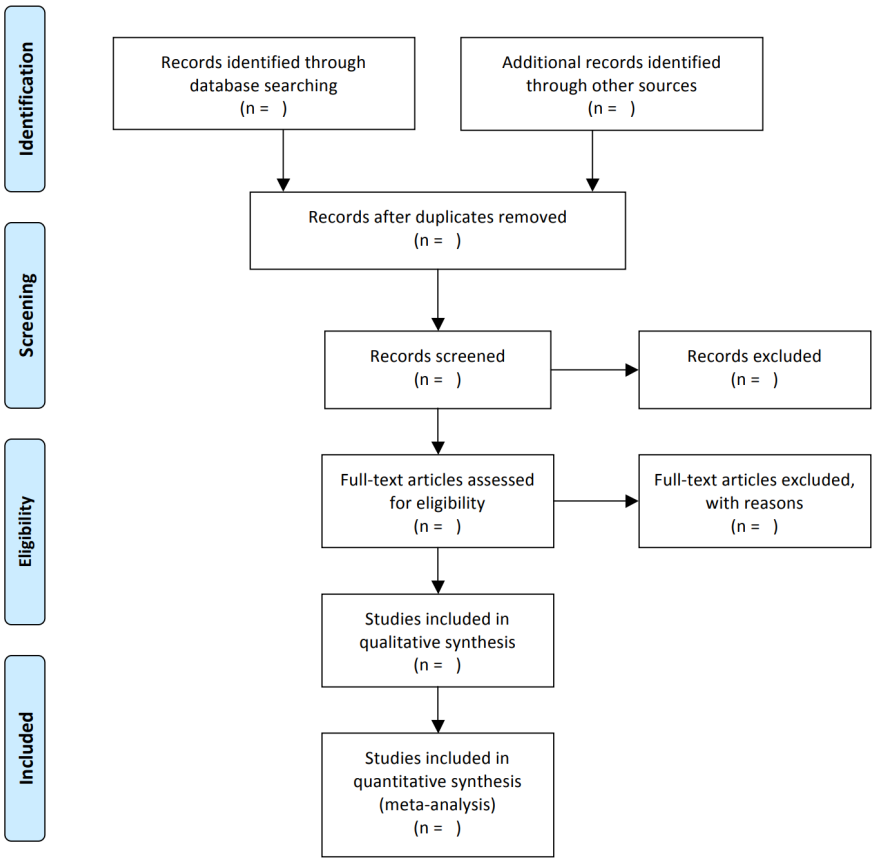
eligible studies. Panel subgroup members and chairs are responsible to obtain PDFs of full texts and, if not available to them, IDSA staff will provide further assistance.

d) **Final selection**: Once the eligible studies are selected, the panel subgroup members, in conjunction with the chairs and the methodologists team, will decide if a qualitative and/or a quantitative analysis is appropriate. The final set of selected studies will be placed into an online storage system with access available to all panel members and will be provided to the IDSA methods experts in charge of conducting the systematic review/meta-analysis.

Flow diagram

PRISMA flow diagrams will be included in the supplementary materials section accompanying the clinical practice guideline. Thus, a flow diagram of the literature search and screening process will be developed by the panel subgroup members in collaboration with the librarian. For each question, the flow diagram will list the number of citations identified via database and other searching, the total number of records following removal of duplicates, the number of records excluded after screening by title and abstract, the number of articles excluded after full text screening, the number of articles included in qualitative narrative review(s), and the number included in quantitative review(s). The flow diagram details should be documented per PICO question searched, to be subsequently collated based on the publication rules.

PRISMA flow diagram[2]



Supplementary searches

Even though the initial literature search often focuses on comparative effectiveness of an intervention over a comparator, other considerations might add value in developing sensitive recommendations such as values and preferences, cost and cost-effectiveness, feasibility, acceptability, accessibility, and equity. The librarian should be advised by the panel and/or IDSA methods experts if there may be a need to develop specific searches regarding any of these considerations.

References

1. WHO Handbook for guideline development. World Health Organization 2012.
2. PRISMA Flow Diagram. url: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx.

11. Evidence Synthesis

In circumstances where no recent high-quality systematic review can inform a specific clinical question, the panel and IDSA methods experts may decide to conduct a systematic review. This chapter will outline the different steps involved in the conduct of a systematic review and meta-analysis as well as the presentation of the results (summary of the estimates of effect(s) and QoE per outcome) in evidence tables. It is not expected that the panelists would perform these steps alone, but rather in close collaboration with methods experts.

Data abstraction and risk of bias assessment

At this stage of the guideline development process, the panel should have selected studies for final review inclusion amongst those initially identified from the literature search and screening process.

In preparation for data abstraction, the IDSA methods experts in collaboration with the panelists will identify all important variables to be collected (e.g., PICO elements as well as methodological elements to assess risk of bias). Of note, the risk of bias will be assessed using the Cochrane Risk of Bias tool[1] for RCTs and equivalents for observational studies, e.g., ROBINS tool or Newcastle-Ottawa Scale (NOS).[2] Finally, these variables will be compiled on spreadsheet tools which will be calibrated and pilot tested prior to any data abstraction.

When spreadsheet tools are finalized, IDSA methods experts with the assistance of trained IDSA membership and/or other trained abstractors (referred to as the technical review team) will conduct data abstraction and risk of bias assessment of the individual studies in duplicate and independently.

Evidence synthesis

Heterogeneity

Once the data abstraction and risk of bias assessment are completed, the IDSA methods experts will evaluate the heterogeneity of the included studies for each outcome to decide if the results can be pooled in a meta-analysis (*evidence synthesis*).

- If the studies are sufficiently homogeneous across the PICO and methods elements, study results will be pooled in meta-analyses. Summary estimates of effect will be presented using the outcome measure: relative risk (RR), odds-ratio (OR), risk difference (RD), Hazard ratio (HR), mean difference (MD), or standardized mean difference (SMD). Results will be presented in Forest plots. All pooling analyses will be performed using RevMan software.
- If the studies cannot be pooled due to heterogeneity (appreciable differences) between the PICO or methods elements, then they will be summarized in narrative format.
- If the studies cannot be pooled due to heterogeneity between outcomes, then the focus should be on the most important outcomes that were identified *a priori* by the panel.
- If there is only one study (thus no possible pooling), the study's estimates will be reported as such.

Quality of evidence

Whereby data was either pooled or summarized in narrative format, IDSA methods experts and panel members will use the GRADE framework to assess quality of the evidence (also known as certainty of evidence) for each critical and important outcome for decision-making. GRADE provides explicit criteria for rating the QoE per patient-important outcome that include five domains: study

design/limitations/risk of bias, imprecision, inconsistency, indirectness, and publication bias. [3] The following chapter will cover additional information on how to apply the GRADE framework. The rating of QoE should be performed by at least two persons with training in GRADE methods.

Evidence tables

An evidence table is a key tool in evidence synthesis and the preferred method for presenting the absolute and relative effects of an intervention as compared to an alternative strategy for each outcome of interest as well as the quality of the evidence using the GRADE approach[3-5]. Evidence tables allow the judgments that bear on the quality rating to be clearer to the reader and thus offer clinicians, patients, the public, guideline developers, and policy-makers an explicit, succinct, and transparent summary to support their decisions.

Two types of evidence tables exist, both of which serve different purposes and are intended for different audiences: evidence profile (EP) and summary of findings (SoF) tables[5]. Both iterations will include outcomes considered important or critical for clinical decision-making.

In general, no more than seven outcomes per evidence table should be included. Of note, available studies do not always provide evidence for all important outcomes. For each PICO question, a set of EP/SoF tables should synthesize the evidence. In situations where more than one comparison of alternative interventions is evaluated (e.g., intervention group vs. comparative group or control group), a set of EP/SoF tables should be presented for each comparison.

The Guideline Development Tool (GRADEpro GDT) is used to produce both EP and SoF tables. After populating the tables, the relative and absolute effects are computed by the GRADEpro software based on the data the user inputs. All inputs will be stored online and tables will be updatable at any time (either during the initial phase of development or later when an update will be required).

Evidence profile table

The EP table is the more thorough and explicit of the two evidence tables proposed by GRADE[5]. The EP table includes detailed information about the body of evidence, the judgments about the underlying QoE, key statistical results, and the QoE rating for each outcome. This table permits a presentation of data systematically and transparently and helps panel members by ensuring that they agree about the judgments underlying the quality assessments.

An EP table should include:

- A listing of the patient-important outcomes (critical and important) with the number of studies and study design, and the judgments about each of the QoE factors assessed,
- Assumed risk (control group risk/baseline risk which represents a measure of the burden of the outcomes when the intervention is not applied) and corresponding risk (risk in the intervention group, which represents a measure of the burden of the outcomes after the intervention is applied),
- Relative effect (for dichotomous outcomes, the relative risk ratio, odds ratio, risk difference, or hazard ratio) and absolute effect (for dichotomous outcomes, the number of fewer or more events in treated/exposed group as compared to the control group; for continuous outcomes, the mean difference, or standardized mean difference),
- Rating of the overall QoE for each outcome
- Classification of the importance of each outcome.

Example of evidence profile table

In patient with recurrent furunculosis, should systemic antistaphylococcal antibiotics be used over topical antibiotics?

Patient or population: ***Patients with recurrent furunculosis***
Intervention: ***systemic antistaphylococcal antibiotics***
Comparison: ***topical antibiotics***
Outcomes: ***progression to abscess, recurrence, side effects of antibiotics (diarrhea)***

		Quality assessment					№ of patients		Effect		Quality of evidence	Impo
№ of studies	Study design	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider ations	With systemic anti-staph antibiotics	With topical antibiotics	Relative (95% CI)	Absolute (95% CI)		
Progression to abscess (at 1 month)												
11	RCT	not serious [a]	serious [b]	not serious [c]	not serious [d]	none	278/2678 (10.4%)	492/2990 (16.5%)	**RR 0.63** (0.49 to 0.89)	**61 fewer per 1,000** (from 86 to 17 fewer)	⊕⊕⊕◯ MODERATE	CRIT
Recurrence (at 3 months)												
4	RCT	serious [f]	serious [e]	not serious [c]	not serious [d]	none	605/1958 (30.9%)	568/1982 (28.7%)	**RR 1.07** (0.97 to 1.19)	**22 more per 1,000** (from 1 fewer to 49 more)	⊕⊕◯◯ LOW	IMPO
Side effects of antibiotics (diarrhea)												
7	RCT	serious [g]	not serious [h]	serious [i]	serious [j]	none	124/1581 (7.8%)	148/2890 (5.1%)	**RR 1.53** (1.22 to 1.93)	**27 more per 1,000** (from 11 to 48 more)	⊕◯◯◯ VERY LOW	CRIT

Footnotes:
a. no serious risk of bias as all studies had adequate randomization, concealment of allocation, blinding, baseline balance, low attrition, no selective outcome reporting, etc.
b. high significant Cochran's Q and I^2 (differences beyond chance), study estimates are not visually similar, some CIs not overlapping
c. trial patients and interventions etc. applicable/similar to study PICO
d. CI upper and lower limits of harms and benefits fall on one side of the no effect line and sample size and number of events moderate/large
e. Cochran's Q significant and I^2 level 50%
f. 2 trials revealed severe concerns with randomization and allocation concealment of randomization
g. 1 trial revealed severe concerns with randomization, allocation concealment of randomization, and blinding
h. no concerning inconsistency or heterogeneity of point estimates/95% confidence intervals
i. some trial patients and interventions, etc. not directly applicable/similar to study PICO e.g., differences in age-groups
j. CI upper and lower limits of harms and benefits suggest potentially different treatment decisions; benefit vs. harmful effect of treatment and thus uncertainty (e.g., marginal 3% reduced risk vs. 19% increased risk of side effects)

Summary of Findings table

The SoF table provides a summary of the information presented in the EP table, except for the judgments about the underlying QoE[4]. This condensed table is intended for a broader audience, including the end users of the guideline, and provides them with a succinct summary of the key information needed to explain the decision-making process underlying the recommendation.

A SoF table should include:

- Patient-important outcomes, with the respective number of participants and studies per outcome,
- Relative effect and absolute effect (with assumed risk and corresponding risk),
- Rating of the overall QoE for each outcome,
- Plain language summary[5]: standardized narrative statement to express in words the direction of the effects and the certainty in the estimate of effects/QoE.

Example of summary of findings table

In patient with recurrent furunculosis, should systemic antistaphylococcal antibiotics be used over topical antibiotics?

Patient or population: ***Patients with recurrent furunculosis***
Intervention: ***systemic antistaphylococcal antibiotics***
Comparison: ***topical antibiotics***
Outcomes: ***progression to abscess, recurrence, side effects of antibiotics (diarrhea)***

Outcomes, no of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Quality of the evidence (GRADE)	What happens
		With systemic anti-staph antibiotics	With topical antibiotics	Difference		
Progression to abscess (at 1 month), 5668 (11 studies)	**RR 0.63** (0.49 to 0.89)	104 per 1,000 (65 to 143)	165 per 1,000	**61 fewer per 1,000** (from 86 to 17 fewer)	⊕⊕⊕◯ MODERATE [a,b,c,d]	Probably reduces the incidence of progression to abscess at one month
Recurrence (at 3 months), 3940 (4 studies)	**RR 1.07** (0.97 to 1.19)	309 per 1,000 (277 to 348) 00	287 per 1,0	**22 more per 1,000** (from 1 fewer to 49 more)	⊕⊕◯◯ LOW [c,d,e,f]	It is very uncertain if there is absence of difference of recurrence at 3 months
Side effects of antibiotics (diarrhea), 4471 (7 studies)	**RR 1.53** (1.22 to 1.93)	78 per 1,000 (62 to 99)	51 per 1,000	**27 more per 1,000** (from 11 to 48 more)	⊕◯◯◯ VERY LOW [g,h,I,j]	May increase the incidence of side effects of antibiotics (diarrhea)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Footnotes:

a. no serious risk of bias as all studies had adequate randomization, concealment of allocation, blinding, baseline balance, low attrition, no selective outcome reporting, etc.
b. high significant Cochran's Q and I^2, study estimates are not visually similar, some CIs not overlapping
c. trial patients and interventions etc. applicable to study PICO
d. CI upper and lower limits of harms and benefits on one side of line of no effect and sample size and number of events moderate/large
e. Cochran's Q significant and I^2 level 50%
f. 2 trials revealed severe concerns with randomization and allocation concealment of randomization
g. 1 trial revealed severe concerns with randomization, allocation concealment of randomization, and blinding
h. no concerning inconsistency or heterogeneity of point estimates/95% confidence intervals
i. some trial patients and interventions etc. not directly applicable/similar to study PICO e.g., differences in age-groups
j. CI upper and lower limits of harms and benefits suggest potentially different treatment decision; benefit vs. harmful effect of treatment/thus uncertainty (e.g., marginal 3% reduced risk vs. 15% increased risk of side effects)

Evidence tables for diagnostic questions

Evidence tables need to be adapted depending on the body of evidence identified:

1) If the body of evidence consists of "diagnostic intervention studies," (randomized comparative studies), the evidence tables need to be presented in the same way as above since these studies are directly reporting patient-important outcomes.
2) If the body of evidence only consists of "diagnostic test accuracy studies," the evidence tables need to be modified since there are no "patient-important outcomes"; diagnostic accuracy results should be considered and presented as "surrogate outcomes," i.e., the test results (true positive, false positive, true negative, false negative) and the absolute effect will be estimated based on the pre-test probability (prevalence) of the disease.

For more information, see online tutorials at: cebgrade.mcmaster.ca

References

1. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing the risk of bias in randomised trials. BMJ. 2011 Oct 18;343.
2. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. url: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
3. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. JCE. 2013 Feb;66(2):151-7.
4. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: Introduction-GRADE evidence profiles and summary of findings tables. JCE. 2011 Apr; 64(4):383-94.
5. Carrasco-Labra A, Brignardello-Petersen R, Santesso N, Neumann I, Mustafa RA, Mbuagbaw L, et al. Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. JCE. 2016 Jun;74:7-18.

12. Quality of Evidence

IDSA requires that guideline developers follow the GRADE methodology to assess the quality of the evidence. The GRADE methodology was selected since it is well-recognized, widely used, and preferred as it is explicit, transparent, and reproducible. This chapter will introduce the general principles underlying this process, but is not intended to be exhaustive. Supplementary resources are proposed at the end of the chapter. It is not expected that the panelists would perform these steps alone, but rather in close collaboration with methods experts.

General concepts

In the context of guideline development, the *quality of evidence* (also known as the *certainty in the evidence*) indicates the "extent to which our confidence in the estimate of the effect is adequate to support a particular recommendation."[1] The QoE is always assessed relative to the specific context in which the evidence is used.

For each PICO question developed, the following **two steps** are required to rate the QoE regarding a particular recommendation:

1) **For each patient-important outcome**, the identified body of evidence will be assessed and a QoE rating will be determined for each critical and important outcome for decision-making ("outcome-centric"),
2) **For each recommendation**, the overall QoE will be determined by the lowest QoE of the critical outcomes for decision-making.

The QoE is categorized in **4 different grades with interpretation[1]:**

Grade	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	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. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. We are very uncertain about the estimate.

Determining the quality of evidence per patient-important outcome

The initial level of evidence will be first determined by the **study design** of the body of evidence, and then, the level of evidence will be further modified after evaluating **factors that may reduce or increase our certainty** in the evidence[2].

Study design

The study design determines the **initial** level of evidence:

- RCTs: high quality evidence

- Non-randomized experimental trials (quasi-RCT): moderate quality evidence, due to lack of concealment of allocation
- Observational studies: low quality evidence, due to inherent risk of bias associated with the study design (i.e., selection bias and unadjusted confounding factors due to the lack of randomization)
- Uncontrolled case series and case reports: very low-quality evidence, due to the lack of a control group.

Expert opinion is not categorized in any of the above classification (i.e., not a level of QoE), but may be critical to interpret studies included in the systematic review.

Factors that can decrease the quality of evidence

Factors influencing the QoE are[1]:

Factors influencing the QoE	Impact on the QoE*
5 factors that can decrease the QoE	
Risk of bias	↓ by 1 or 2 level(s)
Inconsistency of results	↓ by 1 or 2 level(s)
Indirectness	↓ by 1 or 2 level(s)
Imprecision	↓ by 1 or 2 level(s)
Publication bias	↓ by 1 or 2 level(s)
3 factors that can increase the QoE	
Large magnitude of effect	↑ by 1 or 2 level(s)
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ by 1 level
Dose-response gradient	↑ by 1 level

*When identifying the presence of a specific factor potentially influencing the QoE, its impact on the QoE needs to be graded as "not serious" (no modification), "serious" (modifying by one level) or "very serious" (modifying by two levels). Although the impact of these factors is additive, this grading still remains a continuum and requires the reviewers to make judgments on the body of evidence and to make these judgments explicit and transparent to the end-users.

Risk of bias

Risk of bias refers to the limitations in study design or execution that may bias the estimate of the measured effect, and thus lower our certainty in the evidence.[1] Both randomized trials and observational studies can be rated down (a decrease in quality by one or two levels); the more severe the limitations, the more likely the QoE will be downgraded.

For **randomized controlled trials**, study limitations can result from lack of or inadequate randomization to treatment groups or sequence generation, allocation concealment of the randomization sequence, blinding (patients, caregivers, investigators recording the outcomes or adjudicating outcomes, or data analysts), accounting of patients and outcome events (lost to follow-up or failure to adhere to the intention-to-treat), and outcome reporting (selective reporting), as well as other concerns, such as severe baseline imbalance, early stoppage for benefit, use of unvalidated outcome measures, or carryover effects in crossover trials. These potential sources of risk of bias in RCTs can be assessed using the Cochrane Risk of Bias tool.[3]

For **observational study designs** (non-randomized studies), the study limitations can result from lack of or inadequate development and application of eligibility criteria (inclusion of control population), measurement of exposure(s) and outcome(s), control of confounding factors, and follow-up.[1] These potential sources of risk of bias in observational studies can be assessed using ROBINS-i tool[4] or the Newcastle-Ottawa scale.[5]

For **diagnostic test accuracy studies** (observational studies), the study limitations can related to patient selection, index test, reference standard, or flow and timing of testing. These potential sources of risk of bias can be assessed using the QUADAS-2 tool.[6]

In the given example on the effect of systemic antistaphylococcal antibiotics vs. topical antibiotics for recurrent furunculosis, our systematic review includes mainly RCTs where patients were not blinded to the intervention. The initial QoE is therefore: "High." However, as mentioned, the body of evidence is assessed per outcome; reviewers may judge that the impact of patients not being blinded is not serious for objective outcomes such as progression to abscess or recurrence, but serious for self-reported side effects such as diarrhea. Thus, the reviewers could decide not to downgrade the QoE for the first outcome ("no serious limitation"), but to rate down by one level for the latter ("serious limitation").

Inconsistency

Inconsistency refers to **unexplained heterogeneity** of the results. Heterogeneity alludes to the variability (differences) in estimates of the treatment effect across studies. Obviously, more than one study is needed to assess consistency.

After generating the meta-analytical Forest Plot, the presence of heterogeneity can be assessed by different techniques (evaluating relative measures such as RR, HR or OR) such as:

1) Visual inspection
    a. Wide variance of point estimates across studies (without focusing on the direction of the effect),
    b. Minimal or no overlap of confidence intervals (CI) (more variation than expected by chance alone),
2) Statistical methods
    a. Cochran's Q test (test of heterogeneity where a p-value less than 0.10 means that studies are not homogenous),
    b. I^2 statistic (% of variation between studies that is due to heterogeneity rather than chance or sampling error: < 40% may be low, 30-60% may be moderate, 50-90% may be substantial, and 75-100% may be considerable).

In presence of heterogeneity, reviewers should evaluate the results and search for **explanations of the observed heterogeneity.**

Sources of heterogeneity can be explored by analyzing the effects by subgroup (*subgroup or sensitivity analysis*). True differences in the underlying treatment effect may exist and can be explained by differences in populations (e.g., larger relative effects in sicker patients), in interventions (e.g., larger effects with higher doses), in outcomes (e.g., duration of follow-up), or in study methods (e.g., RCTs with higher and lower risk of bias):

1) If heterogeneity can be explained (either by difference in populations, interventions or outcomes), then different estimates across subgroups should be presented. In this situation, there is likely no downgrade for inconsistency and guideline panels are likely to develop different recommendations for different subgroups.
2) If heterogeneity can be explained by difference in study methods, reviewers should consider presenting estimates from studies with a lower risk of bias only.
3) If no plausible explanation for the observed heterogeneity can be identified, then the quality of evidence should be downgraded for inconsistency, by one or two levels according to the severity of the inconsistency.

In the same given example, the systematic review suggests increase in antibiotic-induced diarrhea, but also shows significant observed heterogeneity. After performing a subgroup analysis for different

subgroup of interventions (i.e., class of antibiotics), the subgroup of patients treated with clindamycin shows a higher risk of antibiotic-induced diarrhea than those treated with another class of antibiotics. Because no residual heterogeneity was observed within the subgroups and the plausible source of heterogeneity identified, the reviewers decided not to downgrade for inconsistency (although different recommendations for clindamycin may apply).

Indirectness

Indirectness refers to the degree of confidence regarding how the body of evidence *directly* answers the PICO question (generalizability). Direct evidence consists of studies that directly compare the intervention and comparator of interest, in the population of interest, and measure the patient-important outcomes.[1]

Different sources of indirectness exist, and the impact of indirectness may vary according to different contexts:

1) Differences in populations (e.g., effects in adults might not necessarily be applicable to children, or effects in animals may not be applicable to humans),
2) Difference in interventions (e.g., parenteral vs. oral formulation of the same antimicrobial therapy may or may not necessarily be interchangeable, as the duration of coverage),
3) Difference in outcomes measures, including surrogate outcomes (e.g., infection recurrence measured at 6 months might not be interchangeable with measuring it at one month, or using increasing level of CRP as a surrogate for infection recurrence),
4) Indirect comparisons (e.g., if no direct comparison of clindamycin to cloxacillin is available, but there is available comparison of clindamycin to vancomycin and cloxacillin to vancomycin, vancomycin is then a common comparator for an indirect comparison).

The QoE might be downgraded for indirectness (a decrease in quality by one or two levels) after considering the extent to which they are uncertain about the applicability/generalizability of the evidence to their relevant question.

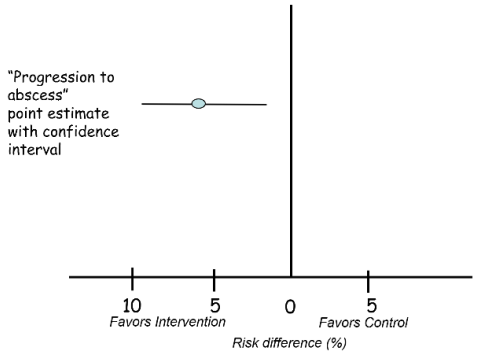
Imprecision

Imprecision usually refers to uncertainty of the results due to sparse data secondary to relatively few patients or number of events, or wide confidence interval (CI) around the pooled estimate of effect. In the context of guideline development, the assessment of imprecision will require that guideline panels evaluate if the results for a specific outcome is sufficiently precise to support that recommendation.

To judge imprecision in the context of a recommendation, guideline panels will need:

1) To focus on the 95% CI around the effect between the intervention and the comparator (in absolute effect),
2) To determine a clinical decision threshold that represents the trade-off between recommending or not to recommending the intervention over the comparator, after considering desirable and undesirable consequences (determining the acceptable threshold inevitably involves judgment that must be made explicit),
3) To determine if the recommendation would differ or not if the 95% CI boundaries are on the same side of the threshold or not:
    a. If both the upper and lower boundaries of the CI are on the same side of the threshold (i.e., the CI is not crossing the threshold), then we are confident that our recommendation would not differ and thus that it is precise.
    b. If the upper and lower boundaries lie on both sides of the threshold (i.e., the CI is crossing the threshold), then the recommendation would differ, and the QoE needs to be downgraded for imprecision.

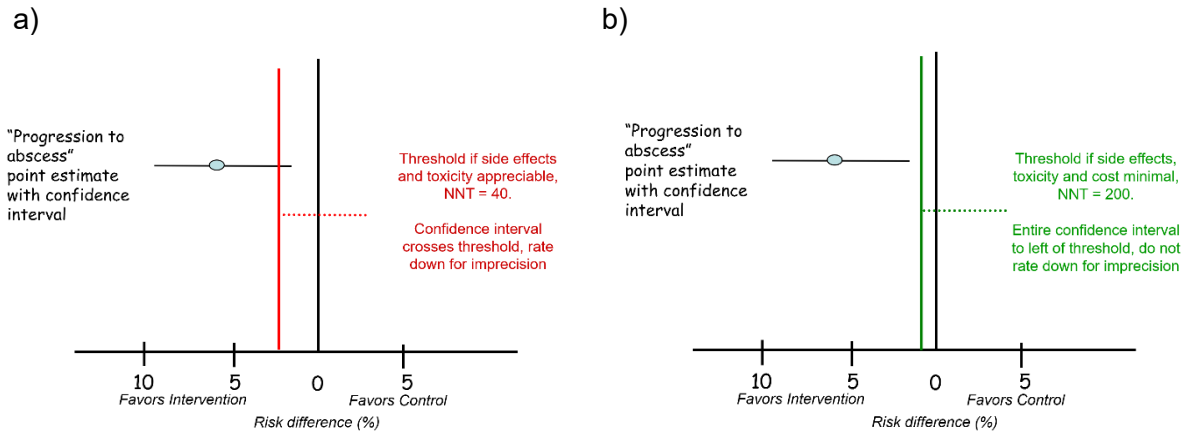
In the given example on the effect of systemic antistaphylococcal antibiotics vs. topical antibiotics for recurrent furunculosis (see Evidence Profile table in Chapter 11), the absolute effect between the intervention and the comparator for progression to abscess at 1 month was 165 abscesses per 1000 treated with topical antibiotics vs. 104 abscesses per 1000 treated with systemic antibiotics or, a 6.1% risk difference in favor of the intervention with 95% CI (1.7%-8.6%).



For the purpose of the example, the panel could have considered two different thresholds:

a) First, the panel decides to set the threshold to recommend/not recommend the intervention over the comparator based on the trade-off between desirable and undesirable consequences (i.e., effect of systemic antistaphylococcal antibiotics on progression to abscess vs. side effects). Thus, if we assume that the risk difference in side effects of antibiotics is 2.7% (NNT=40), as shown in the EP Table, the panel may set the threshold of benefit for systemic antibiotics at 2.7%.

   As represented on the graph a), the point estimate (6.1%) lies to the left of the threshold (2.7%), suggesting that a recommendation for the use of systemic antistaphylococcal antibiotics would be appropriate; however the lower boundary of benefit for systemic antibiotics from the 95% CI boundaries is 1.7% which is to the right of the given threshold of 2.7%.This results in imprecision about the treatment effect, particularly when considering the harmful effects, and the certainty would need to be downgraded for imprecision.



b) After discussion, the panel may decide that only the risk of *severe* side effects of antibiotics should determine the threshold. The risk difference of *severe* side effects was reported to be at 0.5% (NNT=200).

   As represented on the graph b), the point estimate (6.1%) lies to the left of the threshold (0.5%), suggesting that a recommendation for the use of systemic antistaphylococcal

antibiotics may be appropriate; in this case, the entire 95% CI (1.7%-8.6%) is to the left of the threshold (0.5%) (does not cross the threshold). Therefore, the recommendation would NOT differ within the range of the 95% CI and there is no imprecision about the treatment effect when considering the harmful effects. No downgrade of the certainty for imprecision is required here.

Nevertheless, CIs may appear satisfactorily narrow when an effect is large, even in the context of a small total sample size and/or number of events. In this circumstance, the QoE may need to be downgraded for imprecision.

To inform this decision, the following guidance is offered by GRADE[1] :

- Does the CI cross the clinical decision threshold between recommending and not recommending treatment? If the CI crosses the threshold, rate down for imprecision irrespective of where the point estimate and CI lie.
- If the threshold is not crossed, are criteria for an optimal information size (OIS) met? The criteria for an OIS are not met if the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial. If OIS criteria is not met, consider rating down for imprecision.
- Is the event rate very low and the sample size very large (at least 2000, and perhaps 4000, patients)? If yes, rate down for imprecision.

The QoE may be downgraded for imprecision by one or two levels according to the severity of the imprecision. For example, if there are very few events (one imprecision issue to consider) and CI of treatment effect crosses the threshold of undesirable consequences (a second imprecision issue to consider), then reviewers should consider rating down the QoE by two levels.

Publication bias

Publication bias refers to selective publication of research studies, usually related to a lack of reporting of statistically insignificant findings or “negative studies” and often resulting in a systematic bias to overestimate the underlying beneficial effect.

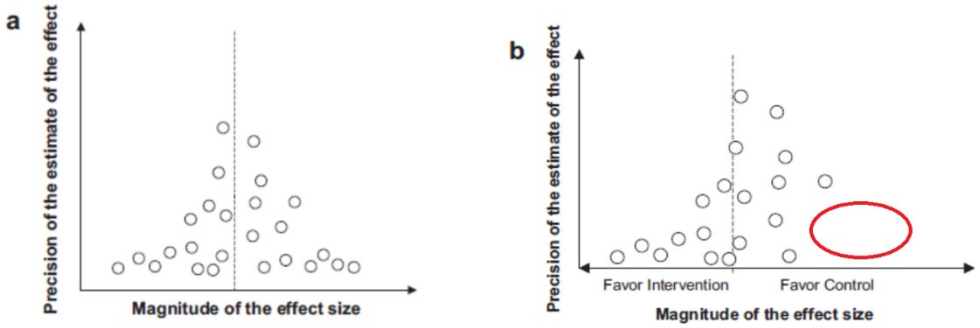
Publication bias can occur due the study design (risk of publication bias may be higher for systematic reviews of observational studies), to lack of completion (e.g., small studies are more likely to give non-significant results and thus to be uncompleted), to journal selection (non-indexed or non-English), and other editorial/peer review considerations (rejection and delay in resubmission/publication). Publication bias can also occur when reviewers fail to identify studies; thus, rigorous and comprehensive search techniques need to be applied to reduce this risk of bias.

Publication bias can be assessed by different techniques, such as

1) Funnel plot (when more than 10 studies are included)
    a. Visual inspection for asymmetry
    b. Tests for asymmetry (Egger’s statistical test)
2) “Trim and fill” method or “Fail-safe N”

The funnel plot is a graph plotting all studies included in the meta-analysis in relation to the magnitude of effect on the x-axis and to the measure of precision (inversely proportional to the sample size) on the y-axis. The expected graph shape is an inverted funnel since as sample size increases, precision also increases and variation in magnitude of effect decreases (small studies will be scattered across the base of the plot while the large studies will be regrouped at its top).

a) As shown on graph a), a symmetrical plot shows that even small negative studies were reported and included in the meta-analysis. Thus, there is no publication bias.
b) As shown on graph b), an asymmetrical plot shows that small negative studies were not reported, thus suggesting publication bias and thus, that we are less certain in the evidence.



(modified from GRADE handbook[1])

In deciding whether to downgrade for publication bias (a decrease in quality by one or two levels is possible), reviewers should consider how uncertain they are about the magnitude of the effect due to selective publication of studies.

Factors that can increase the quality of evidence

There are three recognized factors that can increase our confidence in the QoE. Before evaluating these, previously mentioned **factors that can potentially decrease the QoE** (*risk of bias, imprecision, inconsistency, indirectness, and publication bias*) should have been evaluated and **none rated down** for limitations.[1] Factors that can increase the confidence in the body of evidence usually apply to well-conducted observational studies.

Large magnitude of an effect

This factor refers to instances when a body of evidence from observational study designs demonstrates large or very large estimates of the magnitude of an intervention effect. Observational studies frequently overestimate the true effect of an intervention; however, it is possible to rate up the QoE of an observational study if the biases related to the study design are unlikely to explain the apparent magnitude of effect; additionally, the CI around the estimate should be precise. Other considerations may also influence the decision to rate up the QoE, such as the rapidity of the effect, consistency of the effect across different populations, reversal of the previously expected trajectory of disease, or a large magnitude of effect underpinned by indirect evidence. Magnitude of effect can be quantified as such:

1) Large effect = RR >2 or <0.5, based on direct evidence with no plausible confounders (may increase by one level)
2) Very large effect = RR >5 or <0.2, based on direct evidence with no serious risk of bias or imprecision (may increase by two levels).

Dose-response gradient

A dose-response gradient refers to the relationship between cause and effect. When there is a dose-response gradient in observational studies, the findings usually increase our confidence in the estimates. A classic example is the intimate dose-response gradient associated with the onset of antibiotic administration in patients with suspected meningitis (i.e., each hour's delay increases

meningitis related mortality). This dose-response relationship increases our confidence in the estimate and requires rating up of the QoE by one level.

Effect of plausible residual confounding

In certain circumstances, all plausible residual confounding may reduce the demonstrated effect or increase the effect, if no effect was observed.

Ideally, well-conducted observational studies should measure prognostic factors associated with the outcomes of interest and adjust for potentially known confounders, i.e., differences in the distribution of prognostic factors between intervention and control groups. Unfortunately, unmeasured or unknown determinants of outcome are often unaccounted for in the adjusted analysis and thus likely to be distributed unequally, i.e., residual confounding.

The presence of residual confounding can bias the estimates in any direction and, occasionally, plausible residual confounders may cause an underestimation of an apparent treatment effect. For example, in the hypothetical study on necrotizing fasciitis where the sicker patients receive a treatment of IV immunoglobulins: if this group has a better outcome compared to the control group (not receiving the intervention), then it is possible that the actual effect of the intervention is even greater than what the data suggests (because the treated group was sicker to begin with). This type of situation may require rating up the QoE by one level.[1]

Determining the overall quality of evidence

When making a recommendation for a certain course of action over an alternative, guideline panels are required to consider all outcomes critical for decision-making. Thus, the overall QoE will be based on the combination of the QoE for each of these critical outcomes. Logically, our confidence will be limited by the lowest QoE of these outcomes for decision-making.

In the given example on the effect of systemic antistaphylococcal antibiotics vs. topical antibiotics for recurrent furunculosis, only two outcomes were considered critical for decision-making: "progression to abscess" which was graded as "moderate QoE," and "side effects of antibiotics (diarrhea)" which was graded as "very low QoE." As mentioned, the overall QoE will be limited by the lowest QoE of critical outcomes, thus a "very low QoE" rating.

Of note, occasionally an outcome can cease to be considered critical if it turns out to be either irrelevant (e.g., very rare occurrence of the outcome) or unnecessary (e.g., other critical outcomes with higher QoE can support the same recommendation).

Supplementary resources on grading the QoE

For more information on how to downgrade/upgrade the QoE, see the GRADE handbook[1], the JCE GRADE series[2], and free online training modules available at cebgrade.mcmaster.ca.

References

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13. Developing recommendations

Similar to the QoE, IDSA also requires that guideline developers follow the GRADE methodology to determine the SoR. This chapter will introduce the general principles underlying this process, but is not intended to be exhaustive. Supplementary resources are proposed at the end of the chapter. It is not expected that the panelists would perform these steps alone, but rather in close collaboration with methods experts.

General concepts

In the context of guideline development, the SoR indicates the "extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects (or vice versa), across the range of patients for whom the recommendation is intended."[1]

When developing a recommendation, two distinct elements need to be addressed:

1) **Direction** of recommendation (i.e., **for** or **against** a specific course of action).
2) **Strength** of recommendation (i.e., **strongly** or **weakly** confident in the balance of all desirable and undesirable effects regarding a specific course of action).
    a. A **strong** recommendation means that the balance is **clearly** in favor of specific course of action AND no uncertainty exists around this balance.
    b. A **weak** (conditional) recommendation means that the balance is **probably** in favor of specific course of action, either because the balance is slightly in favor of that option OR uncertainty exists around this balance.

These two levels of strengths of recommendation translate into the following interpretations for the different end-users of the recommendation: [1]

	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline 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.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making 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.

Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should **never view recommendations as dictates**. Even strong recommendations based on high-quality evidence will not apply to all circumstances and all patients. Users of guidelines may reasonably conclude that following some strong recommendations based on the high-quality evidence will be a mistake for some patients.

Factors influencing the direction and strength of recommendations

When developing a recommendation, the following factors need to be considered to adequately decide the direction and strength of the recommendation:[1]

4 key factors	Comments
Benefits and harms	The smaller the net benefit between important desirable and undesirable outcomes, the less likely a strong recommendation is warranted
Quality of evidence	The lower the overall quality of evidence, the less likely a strong recommendation is warranted
Values and preferences	The greater the variability in patients' values and preferences, or uncertainty about typical values and preferences, the less likely a strong recommendation is warranted
Resource use	The higher the costs of an intervention, the less likely a strong recommendation is warranted
3 other considerations	
Equity	The greater impact an intervention has on health inequities, the less likely a strong recommendation is warranted
Acceptability	The less acceptable an intervention is for the stakeholders, the less likely a strong recommendation is warranted
Feasibility	The less feasible an intervention, the less likely a strong recommendation is warranted

Benefits and harms

When considering the direction and the SoR, the first step is to decide on the net balance desirable and undesirable outcomes. In the light of the SoF table, the panel needs to consider the following factors:

1) Magnitude of effects of benefits and harms
    a. Is the net balance trivial, small, moderate, or large?
    b. Is the net balance consistent between outcomes (are all outcomes pointing in the same direction or not)?
2) Relative importance of outcomes
    a. How is the balance of the magnitude of effects of benefits and harms when weighing the importance of these desirable and undesirable outcomes (based on typical patients' values and preferences)?

Typically, a strong recommendation will require that the net balance is large AND consistent between critical outcomes. Occasionally, the magnitude of net balance can vary between subgroups with different baseline risk (high- vs low-risk groups) and stratification will be required to develop appropriate recommendations for each subgroup (with potentially different directions and/or strengths).

For example, in the consideration of systemic antibiotics for furunculosis, it is well known that immunocompromised patients are at higher risk of abscess progression than immunocompetent patients.

1) In immunocompromised patients:
    a. Large desirable effects of antibiotics on abscess progression and recurrence
    b. Minimal undesirable effects i.e., side effects (diarrhea) and low costs
    c. =Net positive and large gradient in favor of systemic antibiotics
    d. =Strong recommendation
2) In immunocompetent patients:

a. Small desirable effects of antibiotics on abscess progression and recurrence
b. Minimal undesirable effects i.e., side effects (diarrhea) and low costs
c. =Net positive but small gradient in favor of systemic antibiotics
d. =Weak recommendation

Quality of evidence

The QoE or the confidence in the best estimates of the magnitude of effects is only **ONE of the key factors** influencing the SoR. This is contrary to many previous grading systems where QoE was directly influencing the SoR (See the chapter on "QoE" for more information).

Typically, a strong recommendation is associated with high or moderate QoE for **all critical outcomes**. In situations where there is a high QoE for some critical outcomes (often benefits) but low QoE for others (often harms), a weak recommendation is usually preferred since there are uncertainties around the estimate for some critical outcomes. This remains true even when a large gradient exists in the balance of desirable and undesirable outcomes.

In general, "**GRADE discourages guideline panels from making strong recommendations when their confidence in estimates of effect for critical outcomes is low or very low,**", except in the following five situations where a "discordant recommendation" is acceptable:

		Quality of Evidence				
Situations	**Meaning**	**Benefits**	**Harms**	**SoR**	**Examples**	**Rationale**
Life-threatening situation	Intervention with potential benefits in life-threatening situation	Low or very low	Immaterial (very low to high)	Strongly in favor for the intervention	*In life threatening disseminated blastomycosis, should amphotericin B be used rather than itraconazole?* [1]	-Low-quality evidence suggests that amphotericin B probably reduces mortality in this context -High-quality evidence suggests that amphotericin B is certainly more toxic than itraconazole = Strongly in favor of using amphotericin B rather than itraconazole in this life-threatening condition.
Uncertain benefit, certain harm	Intervention with potential benefits, but clearly harmful or very costly	Low or very low	High to moderate	Strongly against the intervention	*In uncomplicated Staphylococcus aureus bacteraemia, should gentamicin be added to standard therapy?*	-Low-quality evidence suggests that gentamicin probably reduces the duration of positive blood cultures -High-quality evidence suggests that gentamicin certainly increases the risk of nephrotoxicity = Strongly against adding gentamicin to standard therapy in *Staphylococcus aureus* bacteraemia
Uncertain equivalent benefits, but certain harm/cost in one alternative	Alternatives potentially equivalent regarding benefits, but one option is clearly more harmful or costly	Low or very low	High to moderate	Strongly against the more harmful or costly alternative	*In patients with early stage gastric MALT lymphoma with H. pylori positive, should H. pylori be eradicated rather than the alternatives of radiation therapy or gastrectomy?* [1]	-Low-quality evidence suggests that initial *H. pylori* eradication probably results in similar rates of complete response in comparison with the alternatives -High-quality evidence suggests that initial *H. pylori* eradication by antibiotics is certainly less harmful and morbid than radiation or gastrectomy =Strongly for initial *H. pylori* eradication rather than the alternatives

Certain equivalent benefits, but uncertain harm/cost in one alternative	Alternatives clearly equivalent regarding benefits, but one option is potentially more harmful or costly	High to moderate	Low or very low	Strongly in favor of the less harmful or costly alternative	*In HIV patients with positive HLA-B*5701, should treatment be initiated with TDF-FTC-Efavirenz rather than ABC-FTC-Efavirenz?*	-High-quality evidence suggests that both therapies certainly result in similar virologic response -Low-quality evidence suggests that ABC-FTC-Efavirenz probably results in more hypersensitivity reaction = Strongly against using ABC-FTC-Efavirenz in positive HLA-B*5701 patients
Potential catastrophic harm	Intervention with potential catastrophic harms	Immaterial (very low to high)	Low or very low	Strongly against the intervention	*In children with pulmonary tuberculosis and confirmed HIV infection, should intermittent regimes be used rather than standard therapies?* [2]	High-quality evidence suggests that intermittent regimens certainly result in better compliance to therapy Low-quality evidence suggests that intermittent regimens probably result in treatment failure, relapse and death = strongly against using intermittent regimens in this context

Values and preferences

Typical patient values and preferences should be informed either by systematic reviews or by direct consultation with patients. If not possible, the panel must rely on unsystematic reviews of the available literature and their experience from their interactions with patients.

When deciding the direction and the SoR, an important step is to assess our confidence in the assumed patients' values and preferences. Two factors need to be considered:

1) **Variability among patients' values and preferences**:
   In situations where there is a large variability in values and preferences, it is less likely that a single recommendation would apply uniformly across all patients. If this is so, a weak recommendation is likely warranted.
2) **Certainty concerning values and preferences**:
   The greater the uncertainty around the patients' values and preferences, the more likely a weak recommendation is preferred. On occasion, panels will, on the basis of clinical experience, be confident regarding typical patients' values and preferences despite a lack of systematic study.

Resource use (costs)

Depending on the context, a panel may decide to consider resource use to determine the direction and SoR.

If resource use is not considered, a guideline panel should be explicit about their decision and transparent about the reason for their decision. Many reasons can justify not considering resource use such as:

- Lack of reliable data
- The intervention is not useful thus, calculating resource use would not add any information
- The desirable effects so greatly outweigh undesirable effects that resource considerations would not alter the final judgment
- A guideline panel is asked to leave resource considerations up to other decision makers.

If resource use is considered, cost can be considered similarly to other patient-important outcomes (and presented with other relevant outcomes in EP and SoF tables).

Other considerations

Depending on the context, a panel may decide to consider other factors that may influence the direction and strength of recommendation, such as:

1) **Equity**: impact of the proposed course of action on health inequities
2) **Acceptability**: likelihood that the key stakeholders find the proposed course of action acceptable (based on their own value and preferences on desirable and undesirable outcomes, the timing of the benefits, harms and costs, and their moral values)
3) **Feasibility**: likelihood that the proposed course of action can be accomplished or implemented.

Other types of recommendations

To help the guideline end-users, a panel should always make recommendations, even if faced with uncertainty. Exceptionally, other types of recommendations can be used if the panel is not able to make a standard recommendation, such as:

1) **Only in research:** Recommendation for using interventions "only in research" could be appropriate if the current available evidence is clearly insufficient to support a decision and further research would clearly reduce uncertainty about the effects of the intervention or anticipate costs.
2) **No recommendation:** In rare cases where a panel remains reluctant due to very serious uncertainty regarding the effect estimates or other factors influencing the recommendation (e.g., closely balanced trade-offs, unknown or highly variable values and preferences, or resources), then a "no recommendation" could be appropriate.

Good practice statement

Good practice statements are substandard statements but might be appropriate when "a large body of indirect evidence that is difficult to summarize indicates that the desirable consequences of the intervention far outweigh its undesirable consequences (i.e., confidence is high, but summarizing the evidence systematically would be a poor use of resources)." [2]

Here are two recommendations that could be considered "good practice statements":

- Health services should be made available, accessible, and acceptable to sex workers based on the principles of avoidance of stigma, non-discrimination, and the right to health.[3]
- Triage people with tuberculosis symptoms. These recommendations suggest that persons with a sufficiently high probability of having tuberculosis should be promptly separated from other patients and undergo the appropriate investigations. [2]

Evidence to Decision framework

The evidence to decision (EtD) framework is a standardized approach to help integrate the different determinants of direction and strength recommendation (certainty of the evidence, balance of benefits and harms, values and preferences, resource use, acceptability, equity, and feasibility) to guide recommendation development and inform health care providers, policy makers, and the public.

More specifically, the EtD framework helps the guideline panel move from evidence to recommendations by:

- Informing panel members about the pros and cons of each option considered,
- Ensuring that all the various factors determining a recommendation are addressed,
- Providing a concise summary of the best available research evidence to inform judgments about each criterion,

- Helping structure discussion and identifying reasons for disagreements,
- Making the panel's judgment explicit and the basis for recommendations transparent to guideline users.

The following table shows the general structure of the **EtD framework** with additional detailed questions and explanations to consider when making judgments and explaining the relationship between the criterion and the recommendation (modified from the GRADE handbook).[1]

Criteria		Judgments	Questions	Explanations	Research evidence	Additional considerations
Problem	**Is there a problem priority?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Are the consequences of the problem serious (i.e., severe or important in terms of the potential benefits or savings)? Is the problem urgent? Is it a recognised priority (e.g., based on a national health plan)? Are a large number of people affected by the problem?	The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.		
Benefits & harms of the options	**Are the desirable anticipated effects large?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	The larger the benefit, the more likely it is that an option should be recommended.		
	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	The greater the harm, the less likely it is that an option should be recommended.		
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Are the desirable effects large relative to the undesirable effects?	The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e., the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.		
	What is the overall certainty of this evidence?	○ No included studies ○ Very low ○ Low ○ Moderate ○ High	What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision?	The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).		
Values and preferences	**Is there important uncertainty about how much people value the main outcomes?**	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no	How much do those affected by the option value each of the outcomes in relation to the other outcomes (i.e., what is the relative importance of the outcomes)? Is there evidence to support those value judgments, or is there	The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative		

		important uncertainty of variability ○ No important uncertainty of variability ○ No known undesirable	evidence of variability in those values that is large enough to lead to different decisions?	importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called "utility values."		
Resource use	**Are the resources required small?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	How large an investment of resources would the option require or save?	The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.		
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Is the cost small relative to the net benefits (benefits minus harms)?	The greater the cost per unit of benefit, the less likely it is that an option should be a priority.		
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies	Would the option reduce or increase health inequities?	Policies or programs that reduce inequities are more likely to be a priority than ones that do not (or ones that increase inequities).		
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Are key stakeholders likely to find the option acceptable (given the relative importance they attach to the desirable and undesirable consequences of the option; the timing of the benefits, harms and costs; and their moral values)?	The less acceptable an option is to key stakeholders, the less likely it is that it should be recommended, or if it is recommended, the more likely it is that the recommendation should include an implementation strategy to address concerns about acceptability. Acceptability might reflect who benefits (or is harmed) and who pays (or saves); and when the benefits, adverse effects, and costs occur (and the discount rates of key stakeholders; e.g., politicians may have a high discount rate for anything that occurs beyond the next election). Unacceptability may be due to some stakeholders: Not accepting the distribution of the benefits, harms, and costs Not accepting costs or undesirable effects in the short term for desirable effects (benefits) in the future Attaching more value (relative importance) to the undesirable consequences than to the desirable consequences or costs of an option (because of how they might be affected personally or because of their perceptions of the relative importance of consequences for others) Morally disapproving (i.e., in relationship to ethical principles such		

				as autonomy, nonmaleficence, beneficence or justice)		
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Can the option be accomplished or brought about?	The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e., the more barriers there are that would be difficult to overcome).		

The EtD framework also includes the following **conclusions** that the panel members must reach, which may include draft conclusions (modified from the GRADE handbook).[1]

Term	Question	Explanation	Judgment
Overall judgment across all criteria	What is the overall balance between all the desirable and undesirable consequences?	An overall judgment whether the desirable consequences outweigh the undesirable consequences, or vice versa (based on all the research evidence and additional information considered in relation to all the criteria). Consequences include health and other benefits, adverse effects and other harms, resource use, and impacts on equity	
Type of recommendation	Based on the balance of the consequences in relation to all of the criteria in the framework, what is your recommendation?	A recommendation based on the balance of consequences and your judgments in relation to all of the criteria, for example: ● Not to implement the option ● To consider the option only in the context of rigorous research ● To consider the option only with specified monitoring and evaluation ● To consider the option only in specified contexts ● To implement the option	
Recommendation (text)	What is your recommendation in plain language?	A concise, clear, and actionable recommendation	
Justification	What is the justification for the recommendation, based on the criteria in the framework that drove the recommendation?	A concise summary of the reasoning underlying the recommendation	
Subgroup considerations	What, if any, subgroups were considered and what, if any, specific factors (based on the criteria in the framework) should be considered in relation to those subgroups when implementing the option?	A concise summary of the subgroups that were considered and any modifications of the recommendation in relation to any of those subgroups	
Implementation considerations	What should be considered when implementing the option, including strategies to address concerns about acceptability and feasibility?	Key considerations, including strategies to address concerns about acceptability and feasibility, when implementing the option	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option?	Any important indicators that should be monitored if the option is implemented	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Any research priorities	

Wording of recommendations

Recommendations should always be clear for the understanding and interpretation and answer the initial clinical question. The different elements of the PICO format should be stated: **patients or population** for whom the recommendation is intended and a recommended **intervention** as specific and detailed as needed. Unless it is obvious, the **comparator** should be specified.
For **strong recommendations**, the appropriate wording is "**we recommend**..." or "**clinicians should**..." For **weak recommendations**, the appropriate wording is "**we suggest**..." or "**clinicians might**..."

Supplementary resources on developing recommendations

For more information on how to go from evidence to recommendations, see the GRADE handbook[1], the JCE GRADE series[4] and free online training modules available at cebgrade.mcmaster.ca.

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14. Manuscript Format

IDSA CPGs should follow the format listed below. Of note, **the guideline will not exceed 50 double-spaced pages (excluding tables and references)**.

Title Page

If the document is a **new** CPG, the title should take the following form: "Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 20YX Guideline on Treatment of X in Y."

For example, "Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2017 Guideline on Diagnosis and Treatment of Furunculosis in Outpatients."

If the document is an **update** to a previously published CPG, the title should take the following form: "Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 20YZ Update on Treatment of X in Y."

For example, "Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2017 Update on Diagnosis and Treatment of Furunculosis in Outpatients."

The short title (for the running foot) will take the following form:

"IDSA X Guideline"

For example, "IDSA Furunculosis Guideline"

The title must be followed by superscript (1) that will lead the reader to a footnote on page one that states IDSA's disclaimer:

"It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of a patient's individual circumstances. While IDSA makes every effort to present accurate and reliable information, the information provided in these guidelines is "as is" without any warranty of accuracy, reliability, or otherwise, either express or implied. Neither IDSA nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented."

Abstract

The abstract should succinctly define the topic and scope of the guideline, the patient populations to which the guideline will apply and the target audience (end-users).

For example:

"This guideline is intended for use by healthcare professionals who care for outpatients with recurrent furunculosis, including specialists in infectious diseases, general practitioners, dermatologists, and any clinicians and healthcare providers caring for these patients. This document does not provide detailed recommendations on infection prevention and control aspects related to recurrent furunculosis. The panel's recommendations for the diagnosis and treatment of recurrent furunculosis are based upon evidence derived from topic-specific systematic literature reviews."

Executive Summary

The Executive Summary is the only part of the guideline published in print and will include a very brief introduction followed by a listing of the recommendations within the guideline. When the guideline is an updated version of a previously published guideline, the introduction can include an outline of the major differences between the two versions prior to the presentation of the recommendations.

The following paragraph should be included within the brief introduction, just prior to the listing of recommendations:

> "Summarized below are the recommendations with comments related to the clinical practice guideline for X. A detailed description of background, methods, evidence summary and rationale that support each recommendation, and research needs can be found online in the full text."

Section titles of the CPG should be clearly identified, followed by the clinical question, the related recommendations, and comments/remarks/values and preferences, if applicable.

SECTION TITLE

I. State the clinical question

Recommendation(s)

1. State the recommendation answering the clinical question using the pre-specified format (i.e., PICO format: stating the population/intervention and comparator). Standard wording: either "we suggest" or "we recommend" according to the SoR (*strength of recommendation, quality of evidence*).

   Comments (optional, maximum 1 or 2 sentences):

   If needed, succinctly state critical information for decision-making and implementation of the recommendations. The full explanation should be presented in the "Rationale for recommendation." The comments section can include: definition of a term (e.g., high-risk of exposure means XYZ), complementary information (e.g., antibiotic therapy for a standard duration of XYZ), values and preferences (e.g., this recommendation places a high value in achieving XYZ benefits and/or avoiding XYZ harms), contextualization (specific circumstances where the implementation of the recommendation could vary), or other pertinent considerations (e.g., explanation for making a discordant recommendation).

For example:

"**TREATMENT OF RECURRENT FURUNCULOSIS**

I. What therapy should be used for decolonization in patients with recurrent furunculosis?

Recommendations

1. In patients with recurrent furunculosis despite hygiene measures, we suggest decolonizing with mupirocin and chlorhexidine (*weak recommendation, low quality-evidence*).
2. In patients with recurrent furunculosis, we suggest not using oral antimicrobial therapy over topical therapy for decolonization (*weak recommendation, moderate quality-evidence*).

   Values and preferences: These recommendations place a high value on avoiding adverse drug effects, *C. difficile* infections, antibiotic resistance, and increased costs related to oral antibiotics."

Introduction (maximum 2-3 paragraphs)

This section outlines the rationale for the development of this CPG such as a description of the burden of the condition, importance of the healthcare intervention to clinicians and patients, perceived or documented variability in practice, uncertainty or controversy concerning appropriate management or use, resources and associated costs, and need for this guideline to facilitate decision-making in clinical practice and improve patient outcomes.

Scope and purpose

The purpose and scope of the guideline should include the topics under review and the target population as well as the targeted audience.

> For example, "The purpose of this guideline is to provide evidence-based guidance on the most effective diagnosis and management of recurrent furunculosis in adult patients. While many concepts addressed in these guidelines might be applicable to pediatric patients, the recommendations are not intended for such patients. The target audience for these guidelines includes general physicians, pediatricians, infectious diseases specialists, dermatologists, and any clinicians and healthcare providers caring for this condition."

Methodology

The methodology section describes the process underlying each of the following subsections: guideline panel composition, disclosure and management of potential COIs, clinical questions and evidence review, and development of clinical recommendations.

Clinical practice guidelines

> "Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.[1]"

Guideline Panel Composition

> "The IDSA elected X co-chairs to lead the guideline panel. A total of Y subject-matter experts comprised the full panel, which included specialists in infectious diseases, XYZ. X other societies, XYZ, provided representatives with expertise in XYZ. Both academic and community practitioners were included. Guideline methodologists, XYZ, oversaw all methodological aspects of the guidelines. XYZ worked as the librarians in charge of all issues related to the systematic identification of scientific evidence and literature for all PICO (Patient/Population[P]; Intervention/Indicator[I]; Comparator/Control[C]; Outcome[O]) questions. XYZ were in charge all administrative and logistic issues related to the guideline panel. XYZ were in charge all conflicts of interest (COI) issues."

Disclosure and Management of Potential Conflicts of Interest

> "All prospective panelists were required to disclose any actual, potential, or perceived COIs prior to inclusion in the panel. The disclosures were used to categorize the panelists as cleared for full participation, allowed to participate with recusal from certain aspects of guideline development, or disqualified from participation. The co-chairs remained free of any financial COI during the entire guideline development process, meaning avoidance of any relationship with pharmaceutical or device companies that had products in development or

being marketed for pneumonia. Furthermore, all panelists were precluded from participating in any marketing-related activities (i.e., lectures or advisory boards directly funded by a pharmaceutical or device company with interests related to the guideline subject(s). Panelists were required to disclose to the IDSA and the chairs any new activities that had the potential to be viewed as a COI prior to engaging in the activity. The SPGC Chair and Executive Committee of the IDSA BOD (listed relevant groups as appropriate to the specific guideline) determined if specific activities were allowed under the societies' COI rules. Assignments of panelists to specific PICO questions were made as to minimize any COI concerns. At the beginning of each meeting, whether face-to-face or by teleconference, panelists were required to disclose any new potential COI or prior relevant COI to the subject matter to be discussed."

Scope definition (optional)

If applicable, the process used to determine the scope and topic prioritization of the guideline should be summarized in this section (e.g., IDSA members survey, review of other organizations recent guidelines to avoid redundancy, panel review of last guideline to evaluate potential recommendations change, and/or panelists voting on topics prioritization).

Clinical Questions and Evidence Review

"An initial list of relevant clinical questions for these guidelines was created by the co-chairs and then submitted to the whole panel for review and discussion. After the committee prioritized the proposed questions via an anonymous online survey, the final set of clinical questions was approved by the entire committee. All outcomes of interest were identified *a priori,* and the guideline committee explicitly rated their relative importance for decision making. Each clinical question was assigned to a pair of panelists.

X expert health sciences librarians designed literature searches to address every clinical question. Searches were limited to studies performed in X population, those published in English, and those published after 20XX. The following electronic databases were searched: Pubmed/Medline, EMBASE and Cochrane Database for Systematic Reviews. The initial literature searches were performed on YY/20XX and then updated on YY/20XX. Studies published up to YY/20XX were included if pertinent to these guidelines. To supplement the electronic searches, panelists have the option of contacting experts and manually searching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles. The titles and abstracts of all identified citations were screened and all potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria.

The results of the literature searches were thoroughly reviewed by the panelists followed by selection and evaluation of the relevant articles. Once the articles were selected, the panelists in conjunction with the co-chairs and the methodologists team decided if a qualitative and/or a quantitative analysis was appropriate. Panelists were not required to update their recently performed meta-analyses, done in collaboration with methods experts, with results of the last search unless there was likelihood that doing so would result in a change to the strength or direction of a recommendation.

Evidence summaries for each question were prepared by the panel members using the GRADE approach for rating the confidence in the evidence[2] (Figure 1). The summaries of evidence were discussed and reviewed by all committee members and edited as appropriate. The values and preferences for a specific outcome could have a higher or lower value placed on it for different PICO questions; this variation happened because the value was always

evaluated in the context of all other outcomes relevant to each PICO question. Once the analyses were completed, the panelists presented their data and findings to the whole panel for deliberation and drafting of recommendations. Literature search strategies, evidence tables, evidence profiles, and additional data, including meta-analysis results, can be found in supplementary materials."

Development of Clinical Recommendations

"All recommendations were labeled as either 'strong' or 'weak' (conditional) according to the GRADE approach. The words 'we recommend' indicate strong recommendations and 'we suggest' indicate weak recommendations. Figure 1 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policy makers. Although there is arguably ongoing need for research on virtually all of the topics considered in this guideline, 'Research Needs' were noted for recommendations in which the need was believed by the panelists to be particularly relevant. High-quality evidence was lacking for several recommendations. Strong recommendations were sometimes made in the setting of lower-quality evidence when the panelists believed that most individuals would desire the recommended course of action, and that most well-informed clinicians would agree, despite the low-quality evidence. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group.[3]

The entire panel met X number of times. All members of the panel participated in the preparation of the guideline and approved the final recommendations. Feedback was obtained from external peer reviewers. The XYZ associations reviewed and endorsed the guideline. The IDSA Standards and Practice Guidelines Committee and the IDSA Board of Directors reviewed and approved the guideline prior to dissemination."

Revision Dates

"At least every two years, the SPGC will determine the need for revisions to the guideline based on an examination of current literature and the likelihood that any new data will have an impact on the recommendations. If necessary, the entire expert panel will be reconvened to discuss potential changes. Any revision to the guideline will be submitted for review and approval to the IDSA SPGC and Board of Directors."

Background information (optional, maximum of 2-3 paragraphs)

This section can be used to clarify the following considerations:

1) **Definitions**: Any important definitions that would help clarify the recommendations should be specified in this section to ensure clarity.
2) **Scope and topic prioritization**: Any critical issues that will not be addressed within the guideline such as: a) clinical questions that were not prioritized since there is no controversy, no uncertainty, or no variation in current practice (i.e., the state-of-the-art course of action is known and generally applied in practice); b) clinical questions that appeared in the previous version of the guideline which will not be updated since no new data has emerged since the last version of the recommendation and thus are not likely to change.
3) **Background questions**: Any critical questions that needed to be addressed for the development of the recommendations, for the decision-making process and for the optimization of their implementation in specific clinical circumstances. This background information can include risk factors (e.g., risk factors for antibiotic resistance in X infection),

baseline risks (e.g., epidemiology of X according to geographical distribution), prognostic factors (e.g., expected difference in outcomes according to immune status).

Recommendations

SECTION TITLE

II. State the clinical question

Recommendation(s)

1. State the recommendation (*strength of recommendation, quality of evidence*)
   Comments (if needed)

Evidence Summary

This section should minimally provide a summary of the supporting evidence either by presenting the results of a relevant, high-quality and recent systematic review or of a newly conducted systematic review (meta-analysis or narrative synthesis) as well as the certainty (quality) of the presented evidence. Pertinent data in support of the recommendation should be presented in tabular form wherever possible. Subsequent topically organized subsections can be used to review specific recommendation resulting from the same clinical question.

Rationale for recommendation

This section should minimally provide a summary of all determinants that were considered in the development of the recommendation such as quality (certainty) of evidence, balance between benefits, harms and burdens, patients' values and preferences, resources and cost, applicability, feasibility, and equity, as applicable.

When multiple recommendations are answering one clinical question, the following structure is advised for clarity:

SECTION TITLE

III. State the clinical question

Recommendations

1. State the first related recommendation (*strength of recommendation, quality of evidence*)
   Comments (if needed)
2. State the second related recommendation (*strength of recommendation, quality of evidence*)
   Comments (if needed)

Evidence Summary

Addressing both recommendations.

Rationale for recommendation

Addressing both recommendations.

Research needs (optional, maximum 1-2 paragraphs)

Throughout the development of a CPG, the panel will identify important clinical questions as well as gaps in the literature. Thus, CPGs should comment on studies in progress that may help answer the clinical question more definitively and suggest areas for further study. Although there is arguably ongoing need for research on virtually all of the topics considered in a specific guideline, research gaps identified by the panel should be identified. Research Needs considered to be particularly acute should be mentioned in this section to help advance future clinical care and treatment. Principles to be considered when proposing and prioritizing research topics include clinical consequences or burden of disease, feasibility, economic consequences, broadness of applicability, and degree of

uncertainty.

Notes

"Acknowledgements. The expert panel expresses its gratitude for thoughtful reviews of an earlier version by…".

"***Disclaimer.*** It is important to realize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); should not be considered inclusive of all proper treatments methods of care, or as a statement of the standard of care; do not mandate any particular course of medical care; and are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Whether and the extent to which to follow guidelines is voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented."

"**Financial support.** The guideline was financially supported by the Infectious Diseases Society of America whereby IDSA provided financial support for the administrative structure enabling guideline development. All panelists have participated on a voluntary basis and none received any financial compensation for their participation."

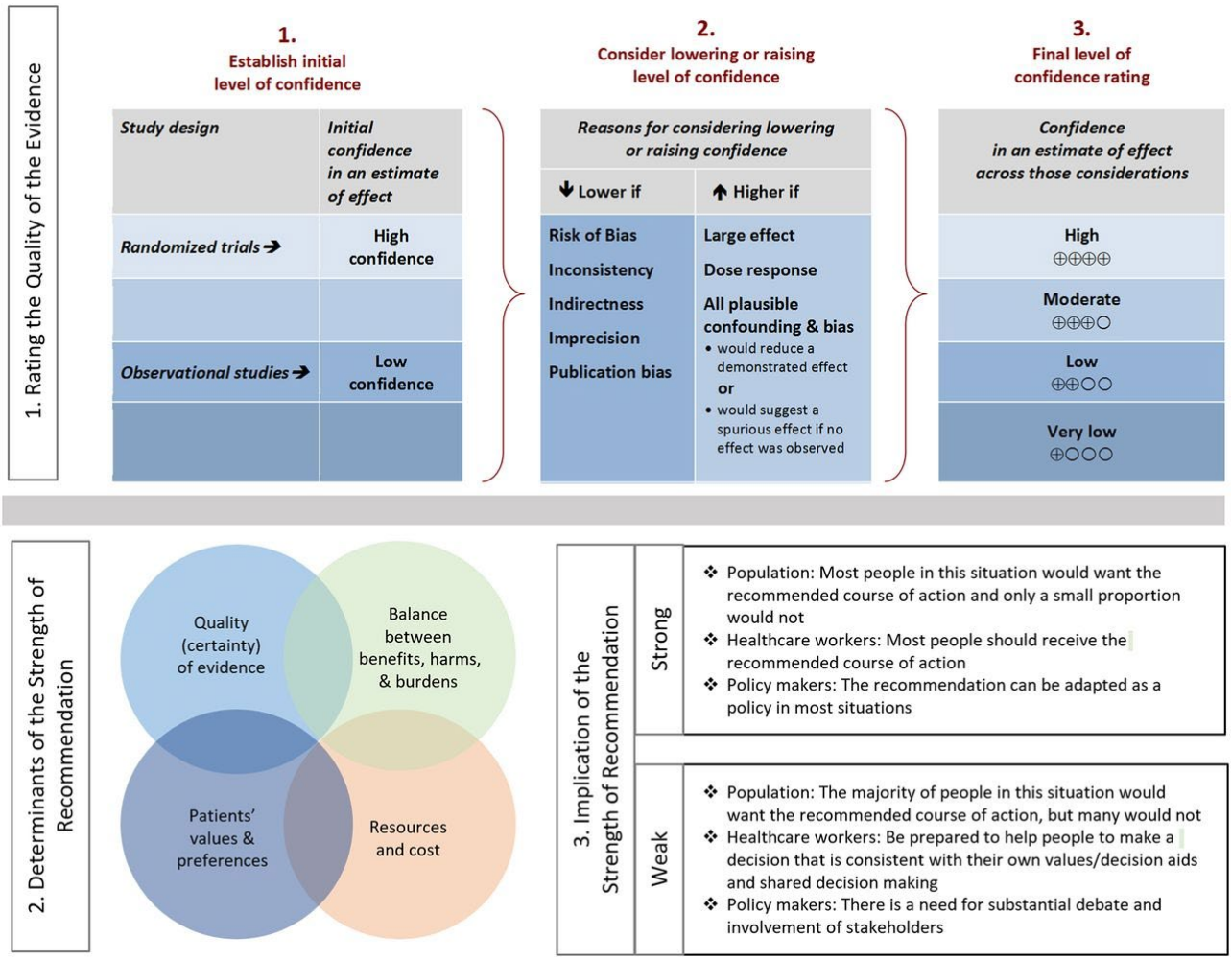
"*Potential Conflicts of Interest.* The following list is a reflection of what has been reported to the IDSA. In order to provide thorough transparency, DSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the SPGC Chair, the SPGC liaison to the development panel and the BOD liaison to the SPGC and, if necessary, the Executive Committee of the BOD. This assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. A.B.C. has received research grants from DEF and GHI, J.K.L. has received honoraria from MNO and served as a participant on research contracts for consultant for PQR, and S.T.U. served as a consultant for VWX and received a patent from the University of YZ. All others, no conflicts."

guidelines in any way must contact IDSA for approval in accordance with the terms and conditions of third-party use, in particular any use of the guidelines in any software product."

Tables, Figures and other Artworks

The total number of tables, figures and other artwork should generally not exceed **10**. The first figure should outline the IDSA grading system for ranking recommendations in clinical guidelines. Remaining tables and figures should serve as easy references for clinicians making diagnoses and treatment decisions. Any tables, figures, or other artwork that are adapted from other sources must have permission to use/adapt/reprint the information from the originator before the guideline is submitted for publication. Exception is when a table, figure, etc. is published in an IDSA journal (*CID*/*JID*). Tables, figures and other artwork should follow the same general format that is outlined on the *CID* website: http://www.journals.uchicago.edu/page/cid/msprep-tables.html and http://www.journals.uchicago.edu/page/cid/msprep-art.html

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network) [4]



References

1. Clinical Practice Guidelines We Can Trust. In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds.: The National Academies Press, 2011:15.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336:924-6.
3. Guyatt GH, Schunemann HJ, Djulbegovic B, Akl EA. Guideline panels should not GRADE good practice statements. J Clin Epidemiol 2015; 68(5): 597-600.
4. U.S. GRADE Network. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology, 2015. url: http://www.gradeworkinggroup.org/.

15. Review Process for Guideline Approval and Endorsement

The IOM standards regarding the development of CPGs require peer reviewing, which should involve all relevant stakeholders (e.g., scientific and clinical experts, organizations, patients, and the public) to ensure for accuracy, validity, practicality, clarity, comprehensiveness, organization, and usefulness of the recommendations.

IDSA employs two types of multistep review process:

1) Review process for approval
    a) Applies to guidelines developed by IDSA as the sole engaged organization or by IDSA in partnership with other organizations.
    b) Requires **external** and **internal reviews**, by IDSA alone or by IDSA and partner organizations.
    c) IDSA recently reviewed this process to optimize the turnaround time while ensuring its high-quality process.
2) Review process for endorsement
    a) Applies to guidelines entirely developed by other organizations in presence of an official IDSA representative from their onset.
    b) Requires that the other organizations proceed to their own external and internal review process, while IDSA will **internally review** for potential endorsement.

Reviewers' comments should be kept confidential and a record should be kept of the rationale for modifying or not modifying the guideline in response to each comment.

Review process for guideline approval

This review process should be followed for both new guidelines and updates. The expected timeframe for the entire review process for guideline approval is approximately 3 months. This timeframe should be strictly followed if IDSA is the sole engaged organization, but IDSA recognizes that this process could be prolonged when partnering with other organizations.

As recommendations are finalized, the panel writes the manuscript. Simultaneously, chairs propose at least 3 external peer reviewers and IDSA headquarters contact them in advance to assess future availability and COI.

Panel finalizes the manuscript. Panel SPGC liaison reviews extensively and approves the manuscript for external/internal review. IDSA headquarters produce and disseminate a timeline/calendar with expected deadlines for all concerned participants.

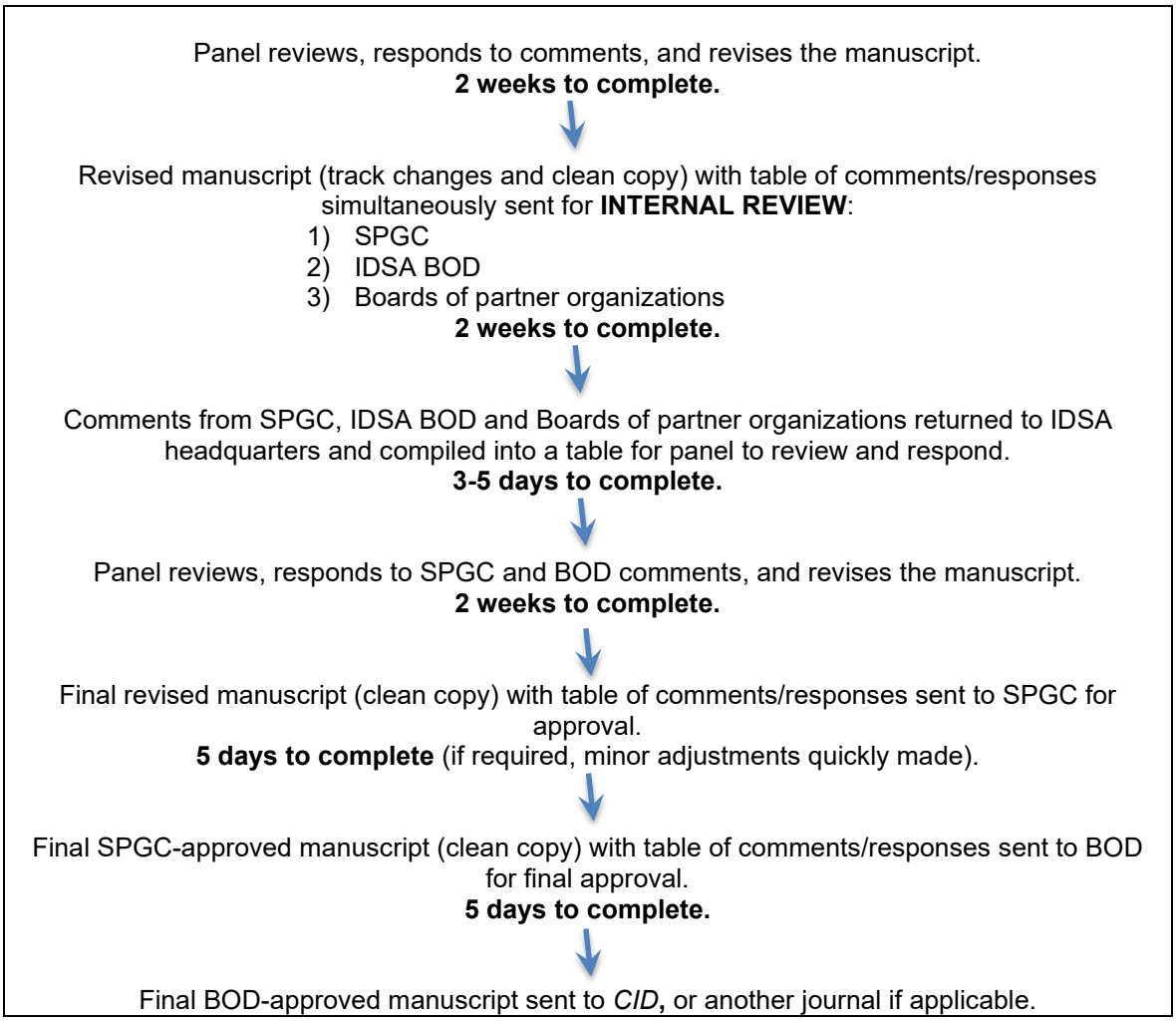
Manuscript simultaneously released for **EXTERNAL REVIEW** by:

1) Previously selected COI-cleared IDSA external peer reviewers (≥ 3)
2) Reviewers selected by partner organizations, if applicable
3) Stakeholders (potential endorsing organizations, patient representative, and/or general public), if applicable

2 weeks to complete.

Comments from all reviewers/stakeholders returned to IDSA headquarters and compiled into a table for panel to review and respond.

1 week to complete.



External review

IDSA external peer review

The chairs of the guideline under review should propose between three to six external peer reviewers, which should include:

1) National or international experts on the CPG topic, representatives from the clinical practice setting, and/or pediatric representative, when warranted
2) IDSA members (at least two of proposed external reviewers)

The final list of external reviews will be selected by SPGC chair according to IDSA COI clearance of proposed reviewers. Of note, other external reviewers can be selected by the SPGC chair independently from the list provided by the CPG chairs.

Stakeholders review

1) Endorsing organizations

   If applicable, potentially endorsing organizations (either involved from inception or engaged later during the process) will have the opportunity to provide input with their level of endorsement:

   - Full endorsement of the guideline as written
   - Full endorsement of the guideline with comments for consideration
   - Conditional endorsement of the guideline pending response to comments

- No endorsement of the guideline

If the review is returned to IDSA within the proposed timeframe, comments will be considered, and the organization will be acknowledged within the manuscript prior to publication. If the review is returned to IDSA later than the proposed time frame, the organization will only be acknowledged on the IDSA website.

2) Patients' representatives

   If applicable, patients' representatives who were involved in the development of the guideline will have the opportunity to provide input.

3) General public

   If applicable, a draft of the guideline will be made available to the general public for comments. A call will be issued for public review and the draft and public comments will be posted on the IDSA website. In general, a two-week time frame for public review will be allowed.

Internal review

SPGC review

The SPGC Chair will designate two primary reviewers among the Committee to review and comment on the guideline, but the entire Committee will have the opportunity to provide input, if desired. Primary reviewers should consider the following questions when reviewing the guideline:

- Are all recommendations consistent within the stated purpose and scope of the guideline?
- Are clinically important and feasible recommendations made?
- Are evidence tables and summary of evidence text provided adequately to support recommendations?
- Are rationales of recommendations provided adequately to explain the SoR?
- Are all recommendations adequately graded?
- Are areas of uncertainty and exceptions clearly identified?
- Are recommendations and key clinical points displayed in a table when possible?
- Are all recommendations referenced appropriately?
- Are the recommendations consistent with other IDSA documents?

Furthermore, to assess the comprehensiveness, completeness and transparency of reporting in the guideline, the SPGC reviewers should use the **AGREE Reporting checklist** (Appraisal of Guidelines for REsearch & Evaluation) (See http://www.agreetrust.org/resource-centre/agree-reporting-checklist/ for more information).

IDSA Board of Directors

The Board liaison to the SPGC will designate two primary reviewers among the BOD to review and comment on the guideline, but the entire BOD will have the opportunity to provide input, if desired.

Review process for endorsement

Policy for organizations seeking IDSA endorsement

IDSA acknowledges that many organizations produce quality guidelines that are relevant and appropriate to the mission and interests of IDSA and its membership. IDSA is committed to systematically evaluating these guidelines and disseminating them to its membership. IDSA encourages other organizations to inform them of their intent to request endorsement as early in the process of developing the guideline as possible.

Eligibility criteria for IDSA endorsement

Guidelines submitted for endorsement by IDSA will first be evaluated for eligibility. Eligibility for endorsement does not guarantee that the request for endorsement will be accepted.
The following eligibility criteria will be applied:

1) A formal request needs to be made to the IDSA SPGC.
2) IDSA is represented (by at least one official representative) from the onset of the development process and the IDSA SPGC and BOD are afforded the opportunity to review and comment on the guideline before finalization.
3) Guidelines are relevant and appropriate to the mission and interests of IDSA and its membership and not duplicative of existing IDSA guidelines.
4) Proposed guidelines for endorsement were developed according to IDSA standards regarding COI regulations, methodological aspects and format of the guideline.
5) The proposed guideline development process is free of any inappropriate support or influence from industry.

Endorsement Process

Once accepted, requests for endorsement will be sent for further evaluation:

- SPGC review
    - The SPGC Chair will designate two primary reviewers among the Committee to review and comment on the guideline, but the entire Committee will have the opportunity to provide input, if desired.
    - Reviewers will provide comments and recommend to the BOD on their level of endorsement:
        - Full endorsement of the guideline as written
        - Full endorsement of the guideline with comments for consideration
        - Conditional endorsement of the guideline pending response to comments
        - No endorsement of the guideline
- BOD review
    - The Board liaison to the SPGC will designate two primary reviewers among the BOD to review and comment the guideline, but the entire BOD will have the opportunity to provide input, if desired.
    - Reviewers will provide comments and decide on their final level of endorsement.
    - The BOD will communicate the final set of comments and decision on the level of endorsement to the concerned organization.

References

1. Clinical Practice Guidelines We Can Trust. In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds.: The National Academies Press, 2011:15.
2. Brouwers MC, Kerkvliet K, Spithoff K; AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ 2016;352:i1152.
3. AGREE website (http://www.agreetrust.org/agree-ii/).

16. Updating and Retiring Guidelines

Maintaining CPG content with the emerging literature and best practices in the field of infectious diseases is challenging. It requires continuous commitment to monitor and review the guideline in the requested time frame, to ultimately either validate its content, request an update, or retire the guideline.

Monitoring literature and guideline revision

To evaluate the continued validity of the guideline, co-chairs are responsible for:

1) Monitoring literature regularly after guideline publication to identify new and potentially relevant evidence that might influence current recommendations
2) Monitoring changes in current practice that might warrant a change to the guideline

IDSA guidelines should be reviewed at least once **every two years**. In some cases, evidence on a specific topic may evolve quickly and may warrant more frequent revisions than the proposed time frame.

Criteria for update request

In cases where new and potentially relevant evidence has been identified, the co-chairs need to assess whether this new evidence warrants a modification of current recommendations. Situations in which an evidence-based guideline necessitates updating include changes in available interventions, in evidence on benefits or harms of available interventions, in new population targeted, in the values placed on important outcomes, in the resources available in healthcare, or if the evidence results in practice changes.[1]

Additionally, the co-chairs should also evaluate the need for new recommendations on areas not previously addressed within the context of the current guideline; this may be necessary, for example, when data becomes available on novel therapeutics or emerging diseases.

Guideline updates or additions should focus on **substantive changes to current recommendations** rather than those that have minor clinical impact.

Update request process

Every two years, IDSA Staff will contact the co-chair(s) to complete an evaluation form to either:

1) Confirm that the guideline is “Revised and Valid on Month, Date, Year.” This information will appear on the IDSA website.
2) Request for an update with supplementary information such as type of update, rationale, and references for the supporting evidence.

If the need for an update arises prior to the two years contact period, the co-chairs should inform IDSA staff so that further discussion and plans can be made for the initiation of an update.

Typically, five to seven years after publication, guidelines will automatically be considered for a full or section update.

Types of updates available

IDSA provides different options for guidelines updates in addition to full updates. The choice of updates is based on the extent of revision and/or addition needed and the desired strategy for updating.[2]

Types of updates	Extent of revision and/or addition needed	Desired strategy for updating	Examples	Number of PICOs
Full update	More than one section need updating: 1) Many clinical questions/ recommendations need to be updated 2) New clinical questions/ recommendations need to be added 3) Many clinical questions need to be removed	To fragment the topic in smaller guidelines with narrower scope (to reduce turnaround time)	Guideline on meningitis was fragmented in 2 guidelines: nosocomial meningitis/ventriculitis and community-acquired meningitis	Maximum: 20
Section update	Only one section needs updating: 1) Many clinical questions/ recommendations need to be updated 2) New clinical questions/ recommendations need to be added 3) Many clinical questions need to be removed	Either: 1) Update each section as needed 2) Fragment each guideline in sections and update each section sequentially: diagnosis, treatment, prevention, and/or infection control	ATS/IDSA are developing sequential guidelines on tuberculosis: diagnosis of TB, treatment of active tuberculosis (drug-susceptible and drug-resistant), and treatment of latent tuberculosis (prevention)	For diagnostic, infection control or prophylaxis/ prevention sections: Maximum: 5 For treatment section: Maximum: 10
Exceptional update	One or very few clinical questions/recommendations need updating: 1) Clinical question/ recommendation needs to be updated 2) Clinical question/ recommendation needs to be added	Usually, this exceptional update will be developed in situation where new evidence emerges or errors in a guideline after its publication, and where no full or section update is planned or needed. This type of update can only be applied if the guideline was published with the last 5-7 years.	New evidence on the use of monoclonal antibodies emerged following the publication on the guideline on *Clostridium difficile*-associated diarrhea	Maximum: 1 or 2
No update	After revision, there is: 1) No new evidence that would modify recommendations 2) No evidence from clinical practice that any recommendations need to be modified	Usually, the decision to consider a guideline "reviewed and valid" can only be made if published within the last 5-7 years. After this period of time, a full or section update needs to be considered.		
Retiring guideline	After revision, most of sections and/or recommendations are considered invalid or obsolete	Topic not prioritized by membership and SPGC		

Updates prioritization

Despite the desire or need for an update, the SPGC will make the final decision to prioritize topics or types of updates. All types of updates (including exceptional updates) will need approval by the SPGC prior to starting revision.

Annually, the SPGC will review all requests for updates and will use the following criteria to help prioritize the next year plan for guideline development:

- Relevance to current clinical practice by IDSA membership (based on the most recent survey)
- Redundancy with other society/organization recently published guidelines on the same topic
- Other considerations specific to ID such as public health issues, outbreaks, or emerging diseases
- Year of publication of the last iteration of the guideline
- Need for a significant update and the type of update needed (full, section or exceptional)
- Need to reassess the scope of the guideline

Once the decision has been made to update a guideline, the guideline panel will be convened (including at least two new members). The methodology to develop any type of update should follow the different steps and procedures explained throughout this Handbook, from panel selection to publication. All updates will be published in the appropriate journal or living website, including exceptional updates since even a solitary recommendation needs to be comprehensively assessed and presented in a readily accessible format to the membership.

If the SPGC decision was not to update a guideline even though recommended by the co-chairs, the co-chairs will have the opportunity to discuss other strategies, such as considering different type of updates or retiring the guideline.

"Rapid" updates

All types of updates can be "rapid", but a shorter turnaround time will be possible if any of the following criteria are present:

- Fragmentation of the initial guideline topic (narrower scope or section updates)
- Restricted number of PICO questions (i.e., exceptional updates are more likely to have a short turnaround time)
- Updating already existing PICOs enabling the same methodology to be used (search strategy, EP tables and EtD framework).
- Living systematic reviews being conducted during the interim timeframe
- Experienced panel members in the current methodology
- Availability of resources (program staff, methods staff) and dedication of co-chairs and panel members

Retiring guideline

Annually, the SPGC will review all guidelines that are potentially invalid and will use the following criteria to propose retirement:

- Relevance to current clinical practice of the IDSA membership (based on the most recent survey)

- Redundancy with other society/organization recently published guidelines on the same topic
- Year of publication of the last iteration of the guideline (5-7 years after publication, guideline retirement should be considered)
- Need for a significant update due to practice changes, but lack of literature supporting revision

Once the decision has been made to retire a guideline, the guideline will be removed from the IDSA website and a link will refer the readership to the journal website or to Pubmed for retrieval of the retired guideline for the inquiring reader. Despite the retirement of a guideline, the co-chairs can always resubmit a new topic proposal per current guidance in the Handbook for the consideration of the SPGC.

References

1. Clinical Practice Guidelines We Can Trust. In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds.: The National Academies Press, 2011:15.
2. NICE. The guidelines manual. 2012. Chapter 14: Updating published clinical guidelines and correction errors. url: https://www.nice.org.uk/process/pmg6/chapter/updating-published-clinical-guidelines-and-correcting-errors

17. Dissemination and Related Policies

Pre-publication and publication process

Once approved by the IDSA BOD, the CPG will be submitted for publication in *Clinical Infectious Diseases* (*CID*) with the understanding that publication is ultimately the decision of the Editor. As of 2010, full text of IDSA Guidelines will appear in electronic format only, with an executive summary in print. Guidelines must continue to adhere to a strict page limit (see chapter on "Manuscript format" of this Handbook).

Panel members are required to observe a strict policy of confidentiality of guideline documents, draft and final, pending guideline publication and are required to keep content of panel deliberations confidential.

Guideline derivatives

Panel Chair(s) will be asked to assist in the review of potential derivative products. The Chair(s) are expected to carefully review these products to ensure that the content is consistent with the published guideline. The purpose of these products is to more widely disseminate, in a practical and user-friendly form, the recommendations contained in the guideline.

Ideally, these companion products will be developed as the first full draft of the guideline document is assembled and circulated for review, aiming for joint approval and release. Examples of guideline derivatives include:

- Pocketcards (print and digital versions)
- National Guideline Clearinghouse Summary
- Slide Sets
- Podcast
- Other future derivatives

Author permission to use guideline content

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Related policies

Guideline policy internal and external usage

IDSA CPGs serve as an integral part of the organization's communication regarding evidence-based research used in the realm of infectious diseases. Many times, IDSA members and the public request to discuss and/or use the guideline at various conferences and continuing medical education

(CME) activities. As a result, IDSA has developed standard policies for use of these guidelines. It is important to remember that all guidelines are confidential and embargoed until time of publication.

Policy at IDSA meetings

IDWeek, the annual IDSA conference, serves as the perfect opportunity for invited IDSA guideline panel chairs to present new or revised CPGs to the IDSA membership during the "New Clinical Practice Guidelines Symposium." During these presentations, specific recommendations should not be considered final nor should they be reproduced or disseminated in any form by unauthorized individuals or groups until fully vetted, approved, and published by IDSA (and its collaborators, if applicable).

Policy for outside IDSA meetings and industry-sponsored symposia

IDSA CPGs that are **in development** (i.e., they have not been reviewed and approved by IDSA or its collaborators) **WILL NOT** be presented at any meeting outside of the SPGC-sponsored symposium at **ID**Week without the approval of IDSA Staff and the SPGC Chair. Recommendations and specific text are not permitted for dissemination nor should they be discussed in detail at these sessions.

Policy for continuing medical education activities

IDSA CPGs that are **in development** (i.e., they have not been reviewed and approved by IDSA or its collaborators) **WILL NOT** be used by any entity to develop any continuing educational activity, tools, or products. **Published** IDSA CPGs may be discussed and/or disseminated provided that:

- IDSA Headquarters reviews and approves the CME activity content before finalized and disseminated
- Proper acknowledgement of IDSA is given and the published article is referenced appropriately.