Fleischner Society Procedure
Publication Development and Oversight

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Fleischner Publication Types

The Fleischner Society has a rich history of published works previously designated as “Fleischner White Papers”. The following articulates a redefinition that collectively renames these as “Fleischner Documents” and subdivides them into distinct categories. [**Table 1** underscores the principal differences between these types of documents.] Past publications have fallen principally within the category of what are now described as “Position Papers”. The current system introduces formalized elements that support expected standards for these documents. Standard operating procedure (SOP) for Fleischner Society document production is in Appendix 1.

Fleischner Position Papers: Position Papers present Fleischner Society positions on a variety of topics, without making recommendations and without being formalized consensus statements. Examples include documents expressing positions on public policy, research, or technical information (e.g., how to perform a test or procedure). Position papers currently represent the majority of Fleischner Publications.

Examples of Position Papers include:

- Imaging of Pulmonary Hypertension in Adults: A Position Paper from the Fleischner Society
- Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

Fleischner Consensus Statements: Consensus Statements have methodologic rigor but do not formally grade the quality/certainty of the supporting evidence. Consensus Statements are developed and qualified through a modified Delphi process with transparency regarding the source of evidence and its limitations. Details are provided in the subsequent section titled, "Consensus Statements".

Examples of Consensus Statements include:

- The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society.
  Note: Required expediency for publication resulted in an abbreviated consensus process. The newness of the disease process limited structured review.
- Optimal approach to performing and reporting computed tomography angiography for suspected acute pulmonary embolism. A clinical consensus statement of the ESC Working Group on Pulmonary Circulation & Right Ventricular Function, the Fleischner Society, the Association for Acute CardioVascular Care (ACVC) and the European Association of Cardiovascular Imaging (EACVI) of the ESC, endorsed by European Respiratory Society (ERS), Asian Society of Thoracic Radiology (ASTR), European Society of Thoracic Imaging (in press-full details pending)

Fleischner Clinical Practice Guidelines (CPGs): Clinical Practice Guidelines include any document that makes evidence-based recommendations on patient care. Clinical Practice Guidelines make diagnostic and treatment recommendations that assist physicians, other healthcare practitioners, and patients to make decisions about the appropriate course of action in specific clinical situations. These documents are evidence-based, employ methodological rigor, and can include expert opinion-based recommendations absent higher-level evidence. Recommendations are made by the committee for specific pre-determined clinically relevant questions that are supported by a systematic review of the literature.

Clinical Practice Guidelines are resource intensive and typically undertaken by larger societies such as ACCP, ATS, ERS. At present, Fleischner Society participation in CPGs will often be in collaboration with other societies that adhere to detailed methodology requirements.

- Examples of Clinical Practice Guidelines include:
- Antithrombotic Therapy for VTE Disease Second Update of the CHEST Guideline and Expert Panel Report
- Screening for Lung Cancer CHEST Guideline and Expert Panel Report
  Note: this report contains both graded and ungraded recommendations.

Joint Statements and Fleischner Society Endorsed Documents: These documents are led by other societies and thus adhere to the document categories and corresponding methodology used by these other societies. Follow the SOP described in Appendix 1.

Table 1: Comparison of Fleischner Society Document Categories

Note: pragmatic evidence reviews do not necessarily require searching of multiple databases, formal assessment of certainty of evidence, or duplicate abstraction of data from individual studies; pragmatic reviews make use of existing systematic reviews when available

Document Type	**Purpose**	**Key Questions**	**Evidence Review**	**Quality/Certainty of Evidence**	**Grading of Recommendations**	**Formal consensus process**
Position paper	Positions on research, policy or technical issues; development of classification systems or definitions	Clearly articulated	Literature search	Quality assessment is optional	Suggestions related to patient care are not explicitly stated	Optional
Consensus statement	Suggestions for patient care (prevention, diagnosis or treatment) when direct evidence is sparse	PICO format	Pragmatic evidence review	Quality assessment is optional; otherwise, all suggestions assumed to be based on low certainty evidence	All suggestions related to patient care are assumed to be weak/conditional	Required (typically modified Delphi)
Clinical practice guideline	Evidence-based recommendations for patient care (prevention, diagnosis or treatment)	PICO format	Systematic evidence review	Mandatory use of GRADE process to determine certainty of evidence	Mandatory use of GRADE process to determine strength of recommendations related to patient care	Required (typically modified Delphi)

Publication Development Process

Overview

Publication development proceeds in three phases described below Figure 2, which summarizes the entire publication development workflow.

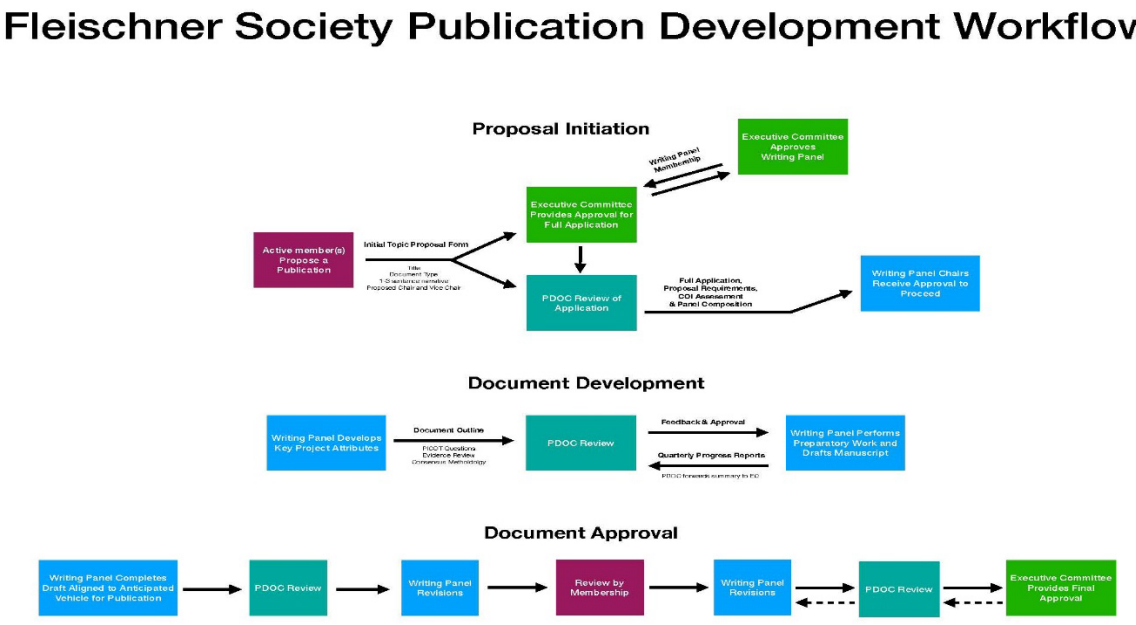

Figure 2: Publication development workflow

<u>Document Development timeline</u>

Proposal initiation to response/comments from EC and PDOC- 2 months

Document development- 12 months

If delayed beyond 24-months, ongoing document development is contingent on detailed PDOC project update and approval

Document submission to PDOC through final EC approval- 3 months

Proposal Initiation

1. A publication proposal submission will consist of a statement of proposed title, document type, proposed writing committee chair and vice-chair and a narrative describing either a new

topic for publication development or an update to an existing publication. The narrative should include a statement of purpose that establishes how the publication would uniquely contribute to the literature and to medical practice, the impact, the reach (FS is international) and whether collaboration is required. Submission will be to the PDOC chair and the EC via a staff liaison. The submitter may also submit a list of proposed writing panel members noting those who may have already engaged in ideation for the publication. A detailed description of writing panel membership and roles is included in Appendix 2.

2. The EC and PDOC will simultaneously consider the proposal and if meritorious, will request the preparation and submission of a full proposal to the PDOC consisting of:
    a. a draft outline of the proposed text and other accompanying materials,
    b. a list of proposed writing committee members, noting those who may have already engaged in ideation for the publication, and
    c. COI Disclosures for the proposed Chair and Vice-Chair of the writing panel.
3. The PDOC will vet the proposal and request refinements as needed.
4. In the interest of enhancing the perspective and dissemination of Fleischner Publications, at the time of empanelment of the writing panel, the EC may consider inviting an allied society to participate on the writing committee with consideration that the allied society might publish an executive summary of the Fleischner Publication.
5. Proposed panelists are required to submit their COI disclosure within two weeks of an invitation to participate on a writing panel. Disclosures will be assessed by the COI Committee. The COI Committee will make any needed recommendations for revision of the writing panel to the PDOC and EC prior to final approval. The EC will establish a final list of writing panelists and communicate that back to the PDOC.
6. Each candidate receiving a management plan or disapproval will receive a call from the COI Committee before a formal decision letter is sent.
7. The PDOC will confirm the final approval of the proposal and writing panel membership and will establish a timeline for document development with the writing panel chair, typically 12 months.

Document Development

(This process is skipped for the Joint Statements)

1. A document outline will be submitted to the PDOC within two months of proposal approval. The outline will include:
    a. Clinical questions (and their PICOT elements) will be drafted by the writing panel and

provided to the PDOC for review and approval.

b. Evidence review plan

c. When applicable, a consensus or recommendation determination plan

2. Once approved by the PDOC, then the writing committee commences evidence review, decision making, and manuscript drafting.

3. Writing panel chairs will provide progress updates on a quarterly basis. Once the document outline is approved, then document development is expected to be completed within 6-12 months.

Document Review and Approval

1. Upon manuscript completion by the writing committee, the manuscript will be submitted to the PDOC to initiate review. The chair of the PDOC will assign two PDOC members to review the document with particular attention to the document's compliance with the core elements and structure described previously in this document. If necessary, the PDOC chair can invite an ad hoc PDOC reviewer. The reviews should provide instructions to direct subsequent manuscript editing. The PDOC chair will share these reviews with the writing committee and provide guidance on required and recommended edits.

2. Upon completion of the edits by the writing committee an annotated copy of the manuscript indicating the edits together with a narrative description of edits made or rebuttals to requested edits will be submitted to the PDOC chair. The chair may review the edits directly or choose to share them with the two primary reviewers to assess their adequacy. Additional edits may be requested by the PDOC for the writing committee to address.

3. Once the manuscript is acceptable to the PDOC, then the chair of the PDOC will submit the manuscript to Executive Committee for distribution to all active members and senior members of the society for a 30-day review period. During this time, members will submit their comments to the PDOC who will collate and organize the reviews.

4. Upon conclusion of the member review period, the PDOC chair will aggregate and submit reviews to the writing committee for further edits. Upon completion of the revisions, the writing committee will submit a newly annotated copy of the manuscript indicating the edits together with a narrative description of edits made or rebuttals to requested edits to the PDOC chair for review.

5. Once satisfactorily revised to accommodate input from societal members, a clean version of the revised manuscript will be submitted to the Executive Committee for final approval. In instances where additional edits are requested by the executive committee, the PDOC chair will serve as liaison between the EC and the writing committee until revisions are completed and the manuscript attains final approval by the executive committee.

6. In collaboration with the Executive Committee, the writing committee may reach out to other societies to see if they would be interested in endorsing the statement or guideline. The writing committee may also consider developing an executive summary to be made available to societies that endorse the work. In these instances, they may want to either publish the executive summary in their journal or provide a link on their website for their members to access the executive summary. This may occur at any stage of the process according to the differing requirements of external societies.
7. The writing committee chair will provide journal(s) recommendations for publication to the EC. Following approval of a submission strategy by the EC, the writing committee chair will proceed with submission to the chosen journal.

Appendix 1: Standard Operating Procedure for Fleischner Society document production

EC: Executive Committee
PDOC: Publication Development and Oversight Committee
SMS: Scientific Meeting Subcommittee
MOU: Memorandum of Understanding

	Official Fleischner Society Documents		**Fleischner Society Endorsed Documents**
Type of documents	Guidelines, Consensus Statements, Position Papers, and Projects		Guideline, statement, review, perspective, others
Major budget	Fleischner Society		Conducting societies/committees
Name of the document	"Fleischner Society" should be in the name of the document		"Fleischner Society endorsed/endorsement" should be acknowledged
Conducting society/committee	Fleischner Society	Fleischner Society and other societies/committees	Other societies/committees
Budget	Fleischner Society	Fleischner Society and other societies/committees	Other societies/committees. Independent from Fleischner Society. Processing fee of EC, PDOC, and for the use of the name of "Fleischner Society" might be paid to the Fleischner Society from other societies/committees if necessary.
Authorship/member of the project	Corresponding and first author should be Fleischner Society member. The first and senior authors should be active Fleischner Society members. When a project initiated and led to completion by an active member who subsequently takes senior status, that	Corresponding and first author should be the member of the leading society or committee. Authors should comprise a reasonable balance between the societies or committees	Corresponding and first author should be the member of the leading society or committee. Appropriate number of authors (reasonable balance of authors between the societies of committees) should be Fleischner Society member (active or senior).

	person to remain first or senior author.		
COI	Yes by Fleischner Society	Yes by conducting society/committee	Yes by conducting society/committee
Systematic review	Yes by Fleischner Society	Yes by Fleischner Society or other society/ committee	Yes By the rule of the conducting societies/committees
Internal peer review	Yes. Reviewed by PDOC and EC. In case of worldwide emergency review by all members could be waived.	Yes. Reviewed by Fleischner Society (PDOC and EC) and other societies/committees. In case of worldwide emergency review by all members could be waived.	Yes By the rule of the conducting societies/committees.
Approval of the project	Review by PDOC with recommendation and final approval by EC		Review by PDOC with recommendation and final approval by EC

- For the Joint Statement, the Memorandum of Understanding should be signed by all co-sponsoring societies.

Appendix 2: Writing Panel Composition and Roles

The writing panel chair will propose writing panel membership to the PDOC, which will provide guidance to the chair to assure a suitability of size, expertise, and diversity to accomplish the tasks specific to the proposed document. Final approval of the writing committee will be by the Executive Committee upon recommendation of the PDOC. Writing panels typically should have 1-2 members per PICO question with a minimum of 6-8 panel members.

Membership on a Writing Panel will be limited primarily to active and senior members of the Fleischner Society. Members-elect may participate upon approval of the EC. Non-members with critical expertise or representing key stakeholder groups may be included on the writing panel with approval of the EC. If patients or patient representatives are considered important to a document's preparation, then the scope of patient involvement will be defined by the writing panel chair and the DOC prior to patient recruitment.

Writing Panel Chair(s)

The Writing Panel Chair will be responsible for the following items. Depending upon the scope and structure of the document proposal, a writing panel co-chair may be designated who will share these responsibilities in a pre-determined manner.

- Coordinate the activities of the writing panel and serve as principal liaison with the PDOC.
- When working with a co-chair, coordinate and collaboratively designate the distribution of roles and responsibilities amongst the panel chairs.
- Prepare a timeline for document development and establish deadlines for the completion of intermediate and final stages. The timeline and subsequent revisions, if needed, will be approved by the PDOC.
- Recruit a suitably diverse writing panel, including content experts, diverse professional disciplines, geography, gender, and seniority. When there is a gap in Fleischner Society expertise, EC and PDOC can approve an outside expert to be included in the writing committee.
- Chair conference calls and face to face meetings of the Writing Panel.
- When appropriate and working with a methodologist, assure that procedures for key question development, systematic review, Delphi ratings, document development and review comply with societal guidelines
- Submit initial proposal, develop timeline, and provide annual progress reports
- Identify a medical librarian to facilitate the systematic review

Methodologist

The methodologist will be a member of the Fleischner Society, however it may be necessary to retain the efforts of an external methodologist when society members are unable to fulfill this role.

Also, when possible a co-methodologist may be designated to assist the primary methodologist.

The methodologist will have the following responsibilities:

- Serve as a consultant to the chair(s) and medical librarian for the design and execution of the systematic review
- Support the chair(s) and medical librarian in development of evidence tables
- Facilitate application of GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to establish the quality of evidence and the strength of the recommendations

Medical Librarian

- Perform the initial phases of the systematic review, including literature search and preliminary evidence selection under direction of Chair and Methodologist
- Draft evidence tables

Criteria for Authorship

The preparation of Fleischner Publications is an intensive process and requires the active engagement of all writing committee members. Consequently, conditions for authorship will include substantive participation in question writing, systematic evidence review, ratings of evidence, and manuscript drafting as determined by the Writing Panel Chair and approved by the PDOC.

External Support

The retention of a medical librarian is expected for Fleischner documents and may require funding. EC has allocated funding for a medical librarian to support the necessary systematic evidence review for Fleischner Documents.

Appendix 3: Detailed Process Guidelines

As indicated in Table 1, the preparation of Fleischner Documents will follow a consistent prescription including the development of **key questions** using PICO elements and **systematic review** of the evidence base. CPGs and Consensus Statements also require the formulation of recommendations using **Modified Delphi** methods. Finally, CPGs require structured **grading of the recommendations**. Details regarding these four elements follow:

Key Questions

The first step in the development process of all Fleischner Documents is to determine the key clinical questions to address. Key clinical questions are aligned with the priorities listed in **Table 2** and refined into PICOTS elements, defining the appropriate patient populations (P), interventions (I), comparators (C), patient-important outcomes (O), timeframe (T) and setting (S)[1]. There should be fewer than ten questions and preferably 6-8 questions in total per guideline or statement.

For a thorough discussion of the PICOTS framework and examples of key questions, please refer to the references listed in the footnote below.

[1] Rubin G. D. (2021). CT Diagnosis of COVID-19: A View through the PICOTS Lens. *Radiology*, *301*(1), E375–E377. https://doi.org/10.1148/radiol.2021211454

Matchar, D. B. (2012). Introduction to the Methods Guide for Medical Test Reviews. In S. M. Chang & D. B. Matchar (Eds.), *Methods Guide for Medical Test Reviews* (Review ed.). AHRQ Rockville (MD): Agency for Healthcare Research and Quality (US). Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22834022&retmode=ref&cmd=prlinks

Criteria for Selection and Prioritization of Key Clinical Questions and Recommendations for Development or Updating
Relevance of a clinical question to the practice of medicine
Available interventions (eg, new drugs or devices) or diagnostic techniques
Evidence on the existing benefits and harms of interventions
Outcomes considered important
Metrics are attributable to the outcomes
Enhancements or modifications to current practice
Resources available for health care
Strategic importance to the Fleischner Society

Table 2: The criteria in this table are used to select and prioritize topics for development or revisions. These topics may be new key clinical questions submitted for consideration for de novo development or existing previously published recommendations that have been proposed for updating. These same criteria are useful for both guidelines and consensus statements. (Adapted from CHEST 2014; 146(1):182-192)

Systematic Review (Bibliographic Documentation)

Fleischner Documents will be based on comprehensive and systematic reviews of the published medical literature in accordance with the highest standards. A systematic evidence review will include four activities – literature search, study selection, quality assessment and evidence pooling, when required based on the type of document proposed (Table 1). Each are discussed below and are adapted from CHEST 2014; 146(1):182-192.

Literature Search

The medical librarian and methodologist in collaboration with the writing committee chair and panelists, will develop search strategies for all PICO questions. Inclusion and exclusion criteria for selecting the evidence base will be established based upon the PICOTS questions. In some situations, a single search may apply to multiple questions. Searches will be run in various databases such as, but not limited to: MEDLINE via PubMed, the Cochrane Library, CINAHL, EMBASE, and any topic-specific database. For CPGs, searches should also be conducted in the Guidelines International Network (GIN) Library and National Guidelines Clearinghouse (NGC) to identify any existing guidelines.

Study Selection (Evidence Screening)

The medical librarian and methodologist will work with the writing panel to determine which studies to include through two rounds of screening as described below:

1. Title and Abstract Review - Content experts will sequentially review the titles and abstracts of all of the search results. At least 2 panelists are assigned to review all of the titles and abstracts. Recommendations for inclusion should be made independently in parallel and then compared. Any disagreement regarding which studies to include should be resolved through discussion or by a third reviewer.
2. Full-Text Review – The full-text article of all studies that passed round 1 review will be retrieved by the medical librarian and reviewed by at least 2 panelists for their inclusion,

typically with data extracted for each eligible publication by one author and data accuracy verified by a second author. Recommendations for inclusion should be made independently in parallel and then compared. Any disagreement regarding which studies to include should be resolved through discussion or by a third reviewer.

Decisions regarding the exclusion and inclusion of studies should be documented and presented in a PRISMA diagram in the final publication.

Quality Assessment

The methodologist will assess the quality of all studies that pass full-text review. All eligible articles will be assessed using standardized tools available through the Cochrane Community and possible to-be-developed Fleischner-specific assessment tools.

Data Abstraction and Pooling of Evidence

Individual study data will be extracted into structured evidence tables by the methodologist with the help of the medical librarian. A standard evidence table template is provided at the end of this section.

An evidence table development tool may be used to create evidence profiles and summary of findings tables that collectively summarize the quality of the body of evidence for each outcome, using five key categories: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

The outcome of the assessment of these five categories leads to a final rating of the quality of evidence (High, Moderate, Low, or Very Low quality of evidence), which will be reflected in the recommendation (see section Grading the Recommendations).

Formulating Recommendations (for Clinical Guidelines only)

Fleischner Society CPGs adhere to the methodology of the partnering organization if such a partner exists for a given project, or to the IOM if not working with a partner organization.

Recommendations must be specific and actionable, including as much detail as the evidence allows. The grade of the recommendation includes 2 domains: (1) type of recommendation (strong or weak) and (2) quality of the evidence as determined from the evidence profile.

Once evidence profiles are completed, the writing panel, under the guidance of the methodologist, will work through GRADE's Evidence to Decision (EtD) Framework (**Appendix 4**). The EtD tool may be used as a structured framework that asks the writing panel a series of questions based on set criteria to determine whether to recommend for or against an intervention.

The result of this discussion will be a formal recommendation drafted by the methodologist. The following general format should be used when formulating a recommendation, with the grading applied at the end.

- Begin with the appropriate patient population, inclusive of any limiting factors.

- Propose the recommended service, test, therapy, procedure, etc., using “we recommend” for strong recommendations and “we suggest” for weak recommendations or consensus-based statements
- Make specific, unambiguous, and actionable statements that contain as much detail as the evidence permits about the administration of the intervention.
- List the grade with level of evidence in parentheses at the end of the statement.
- Exclude references from the formal recommendations.

When possible, patient values and preferences should be reflected in either the recommendations or the associated remarks. These remarks and other caveats appear below the recommendation and grading but are considered integral to the recommendation. Patient preferences are especially pertinent in weaker recommendations when wide variability in patient choice is anticipated.

Peer Review and Consensus Methods

Formal consensus methods are a key element of both clinical guidelines and consensus statements. Consensus methods aim to determine the extent to which experts agree. They seek to overcome some of the disadvantages normally found with decision-making in groups or committees, which are commonly dominated by one individual or by coalitions representing vested interests. In open committees, individuals are often not ready to retract long-held and publicly stated opinions, even when these have been proved to be false. *From BMJ 1995;311:376-80*

Voting on recommendations is to be conducted by the writing panel using modified Delphi methods. The chair is charged with ensuring that conflicted managed panelists refrain from participating in relevant sections of the deliberations.

Recommendations are presented with supporting evidence and voted upon in their entirety, including grades and associated remarks. Under extraordinary circumstances, if requested, specific grades may be discussed and voted upon separately from the recommendations.

The GRADE grid (**Table 3**) defines the level of agreement or disagreement with the proposed recommendations. All votes require 75% participation of those eligible to vote. Approval requires at least 70% of the votes combined for “strongly agree” or “agree.” Negative recommendations are similarly approved, with a negative connotation in the recommendation itself and not by votes in disagreement. Disagreement is defined as voting against the proposed recommendation as written.

1	2	3	4	5
Strong agreement: “definitely do it”	Weak agreement: “probably do it”	No specific recommendation	Weak disagreement: “probably don’t do it”	Strong disagreement: “definitely don’t do it”

Table 3 – *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) grid. The GRADE grid is used for voting on a proposed recommendation or suggestion and for achieving panel consensus. This five-point Likert scale allows panelists to express strong or weak support for or against the proposed clinical statement. To achieve consensus, at least 80% of the voters must vote either positively or negatively, which includes both strong and weak agreement combined (1 & 2 above) or strong and weak disagreement combined (4*

& 5 above), respectively.

Recommendations achieving only 67% to 79% agreement may be published with a section labeled "additional remarks," permitting those with minority opinions to address their concerns. Recommendations achieving <67% agreement are not published; however, the authors may state that these recommendations were controversial and further research might solidify consensus.

Grade for Guidelines

Grading of the Evidence

GRADE (Grading of Recommendations Assessment, Development and Evaluation) is a framework to rate the evidence. The system encompasses two dimensions: (1) balance of benefits to harms, risks, or burdens, including confidence in the estimate of effect, and (2) level of evidence for the body of research supporting the recommendation (Table below)

Strength of the Recommendation: Balance of Benefits to Harms'

Recommendations are strong when benefits clearly outweigh harms or vice versa. In the latter case, there could be a strong negative recommendation (eg, a strong recommendation not to follow a specific therapy). Strong recommendations (Grade 1) include the persuasive language "we recommend." However, when benefits and harms are closely balanced, and it is possible additional research might change either the direction or strength of a recommendation, it is considered weak, and statements read, "we suggest." When benefits clearly outweigh harms, most if not all patients would choose the intervention; the recommendation is clearly Grade 1. But when there is considerable variability in patients' preferences, tradeoffs between desirable and undesirable consequences are less clear, and recommendations are weaker (ie, Grade 2).

Quality of Evidence Underlying the Recommendation

The quality of the body of evidence underlying the recommendation is reflected in A, B, or C scores. Grading evidence is usually the purview of the methodologists, but content experts should contribute. The quality criteria include limitations in study designs, imprecision, indirectness (relative to the PICOTS elements), inconsistency or heterogeneity of results across studies, and risk of reporting or publication bias. In general, study designs such as RCTs start as high-quality evidence but are subject to downgrading based on these criteria. Observational studies start low but may be upgraded if they meet design standards and (1) there is a large magnitude of effect, (2) there is a statistically significant effect even with the presence of bias, or (3) there is a dose-response gradient.

Grade Ratings

The strength of the recommendations is organized and reported according to **Table 4**.

Grade of Recommendation	Strength of the Recommendation: Benefits vs Risks, Harms, and Burdens, Grade 1 or 2	State of the Scientific Evidence: Methodologic Strength of Supporting Evidence, Grade A, B, or C	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burden, or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burden, or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low or very low-quality evidence (1C)	Benefits clearly outweigh risk and burden, or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low or very low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

Table 4: The Fleischner grading system defines the grades based on two key dimensions: (1) the balance of benefits of the proposed action as compared with the possible harms or risks and (2) the methodologic quality of the supporting evidence. Both factors are represented in the overall grade, with the former represented by 1 or 2 and the latter by A, B, or C. The methodologic quality is initially based on the hierarchy of study design, but studies can be upgraded or downgraded based on specific criteria (eg, existence of methodologic flaws, directness, precision, consistency of results).

GRADE Summary of Findings Example

heparin compared to no heparin for patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation

Bibliography: Akl EA, Gunukula SK, van Doormaal FF, Barba M, Kuipers S, Middeldorp S, Yosuico VE D, Dickinson HO, Schünemann H. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No heparin	Risk difference with Heparin (95% CI)
Mortality	2531 (8 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to inconsistency	**RR 0.93** (0.85 to 1.02)	**Moderate**	
				649 per 1000	**45 fewer per 1000** (from 97 fewer to 13 more)
Symptomatic VTE	2264 (7 studies) 12 months	⊕⊕⊕⊕ **HIGH**[1]	**RR 0.55** (0.37 to 0.82)	**Moderate**	
				29 per 1000	**13 fewer per 1000** (from 5 fewer to 18 fewer)
Major bleeding	2843 (9 studies) 12 months	⊕⊕⊕⊖ **MODERATE**[1,4] due to imprecision	**RR 1.3** (0.59 to 2.88)	**Moderate**	
				7 per 1000	**2 more per 1000** (from 3 fewer to 13 more)
Minor bleeding	2345 (7 studies) 12 weeks	⊕⊕⊕⊖ **MODERATE**[1,4] due to imprecision	**RR 1.05** (0.75 to 1.46)	**Moderate**	
				27 per 1000	**1 more per 1000** (from 7 fewer to 12 more)
Health related quality of life the Uniscale and the Symptom Distress Scale (SDS); Better indicated by lower values	0 (1 study) 12 months	⊕⊕⊖⊖ **LOW**[6] due to risk of bias, imprecision	Not estimable[5]	See comment	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1] Vast majority of studies had allocation concealment, and used blinded outcome and adjudication. We did not downgrade although there was some concern about lack of blinding in some studies; the overall risk of bias was felt to be very low.
[2] There is moderate heterogeneity among studies included in the analysis of death at 12 months (I2=35%). The subgroup analysis for mortality at 12 months was statistically significant and suggested survival benefit in patients with SCLC but not in patients with advanced cancer. Overall we decided to downgrade by one level when considering these issues along with imprecision.
[3] CI interval includes effects suggesting benefit as well as no benefit.
[4] CI includes possibility of both harms or benefits., [5] The scores for the 2 scales were similar for the 2 study groups, both at baseline and at follow-up, [6] High risk of bias and only 138 patients enrolled.

Appendix 4: Sample Evidence Table

Characteristics of Included Studies

Study Name	Study Design	Participants Description	**Intervention Description** (Include Dose and Duration)	**Control Description** (Include Dose and Duration)	Outcomes Assessed	Funding and conflicts of interest

Statistical Data for a Categorical Outcome (one table per outcome)
Outcome:
Measurement:
F/u time:

Study Name	Intervention			Control		
	Number with event	Number randomized	Number of participants with missing data	Number with event	Number randomized	Number of participants with missing data

Statistical Data for a Continuous Outcome (one table per outcome)
Outcome:
Measurement:
F/u time:

Study Name	Intervention				Control			
	Mean	SD	Number Randomized	Number of participants with missing data	Mean	SD	Number Randomized	Number of participants with missing data

Harms, Patient Burden and Preferences and Cost data

Study Name	**Harms** (Adverse Events)	**Patient Burden and Preferences** (if reported)	**Cost-Effectiveness Data** (if reported)

Appendix 5: Evidence to Decision (EtD) Framework

	JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

	○ No known undesirable outcomes		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		