Eastern Association for the Surgery of Trauma

Advancing Science, Fostering Relationships, and Building Careers

How to Write an EAST Practice Management Guideline (PMG) Using GRADE

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Writing an EAST Practice Management Guideline (PMG): A Step-By-Step How-To-Guide

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Section 1 - Introduction

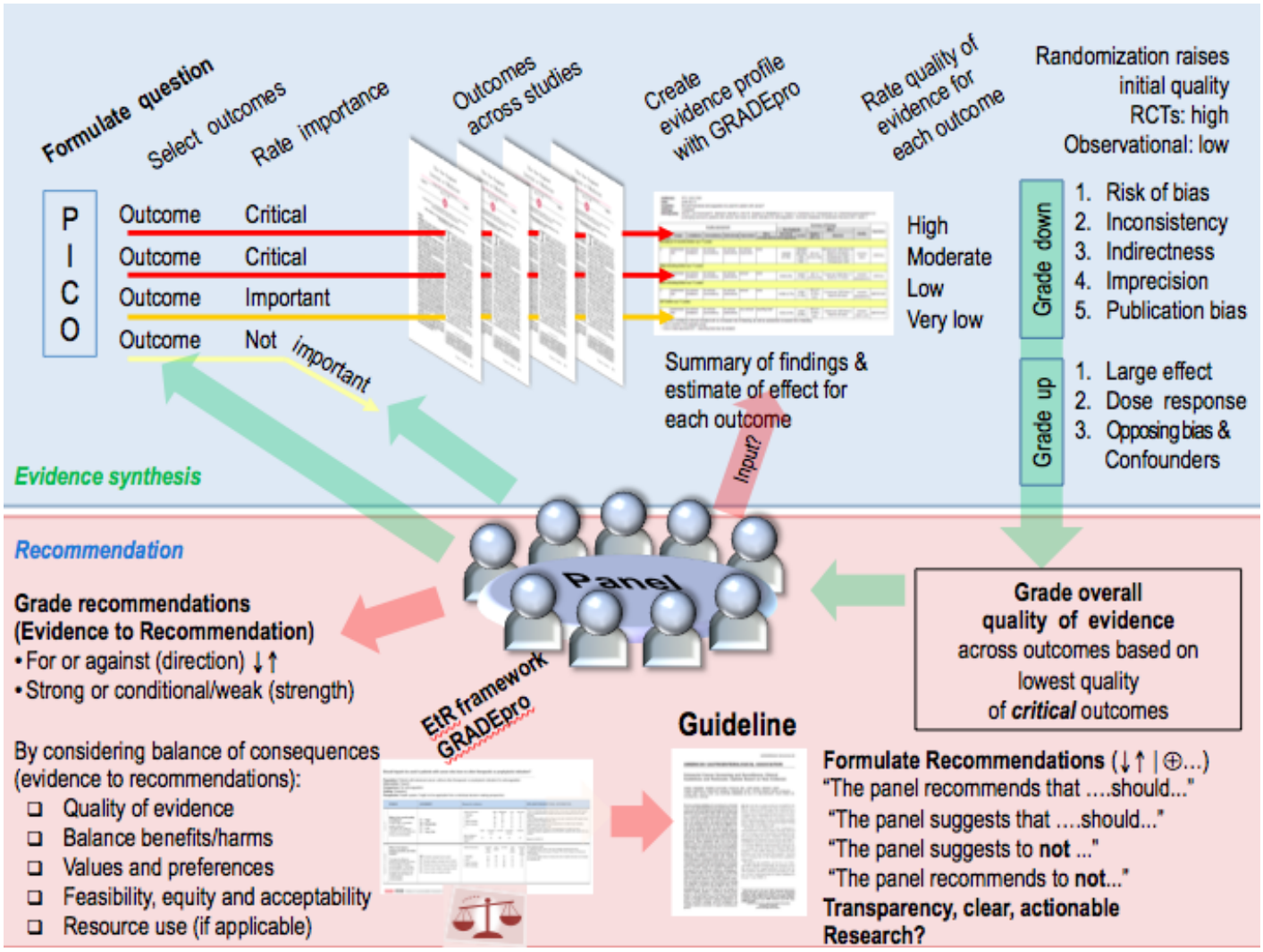
Over the past two decades, clinical guidelines have increased in number and importance for the evaluation and treatment of a wide spectrum of conditions. Today, many organizations including Eastern Association for the Surgery of Trauma (EAST), American College of Surgeons (ACS), Society of Critical Care Management (SCCM), American College of Emergency Physicians (ACEP), and the American College of Chest Physicians (ACCP) all issue guidelines that impact care of trauma, acute care surgery, and critical care patients. Although, historically, all strive to base their recommendations upon evidence based literature when available, until 2004 no universally accepted framework existed for creating practice management guidelines (PMGs). A working group, known as the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) group (http://www.gradeworkinggroup.org/) proposed a new single system for PMG development. In 2008, the group published their first comprehensive guide to utilizing GRADE methodology. [1] Since that time, over 90 organizations have now adopted the GRADE approach, including EAST in 2012. [2, 3]

GRADE provides a framework for both rating the quality of scientific evidence available and the application of this evidence to PMG development. One of the goals of GRADE is to move away from PMGs that rely heavily on expert opinion or biased interpretation of available evidence and towards a single system based upon transparent, systematic literature assessment. [4] Although many organizations have endorsed the use of GRADE, implementation into actual PMG development has been variable. This guide provided by EAST is intended to help members understand the GRADE approach, provide easy to follow steps in using GRADE, and highlight tips for successful PMG development based upon GRADE.

In brief, the recommended steps for developing an evidence-based EAST guideline using the GRADE approach are as follows: first, to define a topic of high clinical relevance; second, to assemble a multidisciplinary and well-balanced team of experts in the relevant clinical topic. While all of the team members do not need to have GRADE experience, someone with substantial expertise in applying GRADE, preferably a GRADE methodologist, should be included in the working group. The team subsequently should be educated on GRADE methodology and more explicit research questions developed. These questions are framed using the PICO (P-patient, I-intervention, C-comparators, O-outcome[s]) criteria. A systematic review and meta-analysis of relevant literature is then performed for each specific PICO question. The evidence is then rated using dimensions defined by GRADE: risk of bias, inconsistency, imprecision, indirectness, publication bias, large effect or dose effect of the intervention, and plausible residual confounding. [5] The resulting judgments are summarized in a table format (as evidence profiles or summary of findings tables) providing an overall quality of evidence rating for each outcome as well as across outcomes. Recommendations are then formulated as strong or weak/conditional for or against a management strategy considering not only the quality of evidence but also the balance of benefit to harm, patients' values and preferences as well as resource utilization. This process is

summarized in Figure 1, and more specific instructions are provided in the remainder of this document for each of the steps in creating a PMG utilizing GRADE methodology.

Figure 1. The EAST Practice Management Guideline Development Process (*Used with Permission from the GRADE working group)*



Section 2: Deciding on a PMG Topic

Overall Approach

- Choosing an appropriate topic for a Practice Management Guideline is the most important first step in the process
- For EAST, these topics may include and are categorized as trauma, emergency general surgery, surgical critical care, injury prevention
    - An EAST PMG Section Taskforce Leader oversees PMGs in each of these categories
- Strong topics ensure relevance and usefulness for patients, while weak topics add little to the medical literature

Potential Topics

- Guidelines can be developed for a variety of topics[6]:
    - Medical conditions (traumatic aortic injury; splenic lacerations)
    - Procedures (diagnostic peritoneal lavage, chest tube placement)
    - Signs or symptoms (Peritonitis after penetrating abdominal trauma)

Guideline Development Priorities

- Guideline topics should be of 1) high priority and they must also be 2) feasible.
- The Institute of Medicine has identified the following priority-setting criteria for guideline development:
    - Disease burden – extent of morbidity and mortality imposed by a condition
    - Controversy – degree of controversy or uncertainty about a particular topic
    - Cost – economic cost associated with a particular condition
    - New evidence – new data exists with the potential to change prior conclusions
    - Potential impact – potential to improve decision-making for the patient or the provider
    - Public or provider interest – stakeholders want an assessment to inform decision-making
    - Variations in care – reduction in variations in prevention, diagnosis, or treatment

Feasible Topics

- Topics should have
    - A sufficient base of published evidence
        - Ideally randomized controlled trials (RCTs), however, other types of studies can still be used to create trustworthy guidelines and lack of RCTs should not deter the team from moving forward
    - One or more systematic reviews or meta-analyses already published; in the absence of a high quality systematic reviews, it will be necessary to conduct one (which can be a major undertaking)
    - Relatively clear definitions of the condition or procedure under consideration[7]

- Consider soliciting potential topics from the members of the PMG section or other EAST sections (ex. Injury Control and Violence Prevention Section, Acute Care Surgery Section). These topics can then be presented to these sections for ranking and prioritization.

Section 3: Building Your Guideline Development Team

Overall Approach

- Each Guideline Development Team requires specific multidisciplinary team members who are capable of fitting certain roles
- Topic content experts are necessary, but not sufficient, for effective guideline development
- A well-chosen team will result in evenly distributed work while a poorly-chosen one will result in the Chair shouldering the burden of guideline development
- Potential financial and intellectual conflicts of interest will be considered when a chair is selected.
    - For example, if a person has published extensively in the stated topic, it may be more appropriate to select a Chair that does not have a potential intellectual conflict of interest.
- Conflicts of interest for potential team members should be considered prior to formally invited members to participate.

Pre-Team Selection Phase

- EAST Practice Management Guidelines Section to review proposals submitted from the EAST Guidelines Underdevelopment web page (https://www.east.org/education/practice-management-guidelines/guidelines-under-development/proposal).
    - When submitting for review, submit the names of your core team
- EAST PMG Section assigns project Chairs and topics
- Chairs develop “informal question” and core team members (Chair, EAST Senior, EAST PMG Section liaison, GRADE methodologist)

Team Selection Phase

- Create a final team using assistance of the PMG Section, an electronic call for volunteers via EAST or those that volunteered at the EAST Annual Assembly
    - Content, GRADE methodology, systematic review methodology experts are highly suggested and can be provided by the PMG section.
        - Content Experts:
            - It is suggested that at least 50% of the team composition should be EAST membership, which should easily cover Trauma Surgery, Acute Care Surgery, Surgical Critical Care
            - Consider relevant surgical specialties: Orthopedics, Neurosurgery, Vascular, Thoracic, Ophthalmology, Ear-Nose Throat, Surgical Oncology, Cardiac, Colorectal, Hepatopancreaticobiliary, Transplant, Minimally Invasive/Laparoscopy, Oral-Maxillofacial, Plastics
            - Consider relevant medical specialties: Emergency Medicine, Anesthesiology, Neurology, Cardiology, Gastroenterology, Transplant Medicine, Infectious Disease, Primary Care, Hepatology, Endocrine, Rheumatology, Nephrology, Geriatrics, Palliative Care, Podiatry, Psychiatry, Physiatry-

Rehabilitation, Diagnostic Radiology, Interventional Radiology
        - Consider Allied Health Professionals: Nursing, Physical Therapy, Occupational Therapy, Speech-Language Pathology, Neuropsychology, Social Work
        - Consider Patient-Centered Advocates: family members, survivors, outreach personnel, non-profit leadership
    - Systematic review methodology expert:
        - This expert should have either formally performed a Cochrane-level systematic review before, have relevant training, planning to take a Cochrane type course, possess relationships with strong medical librarians, and/or expert mentors who can guide this process
        - Should be intimately involved in data extraction sheet creation (example in Appendix), protocol creation, registration of protocol, and group data capture
        - This expert should be capable of performing a meta-analysis
        - If no systematic reviews exist in the topic area, having an expert in searching for relevant articles is important for a successful literature search.
        - Often, a dedicated medical librarian or informationist can fulfill some of these roles[8]
    - GRADE methodologist:
        - This expert should have undergone formal GRADE training and ideally been part of a prior EAST PMG constructed
    - Chair: BE AWARE OF HOW YOU WORK, communicate, and motivate others
        - Avoid the "Ringlemann Effect" (group effectiveness is inversely proportional to group size)
            - "Often, a small team of snipers can accomplish far more than a full-scale ground invasion."

- Read information about Systematic Reviews (http://www.cochrane.org/training/cochrane-handbook)
    - The team should recognize the Systematic Review is much more transparent, replicable, and protocolized, as compared to expert consensus
    - Review recent EAST guidelines that used the GRADE methodology (see Section 18) [9-13]
- Read Information about GRADE (see Section 5 - Educating Your Team Regarding GRADE Methodology)
    - The team's GRADE expert should also be able to distill the GRADE essentials for the group
    - They should possess and be able to operate GRADEPro or GDT software for manuscript level table construction of final team recommendations

- Submit final team roster to EAST PMG Task Force Leader, with each member completing COI forms (See Section 4 – Obtaining Conflict of Interest Information)

Section 4: Dealing with Conflicts of Interest

Overall Approach

- Issues with conflict of interest continue to undermine PMG's created by specialty societies[14]
- Oftentimes, authors on writing committees are seen as experts in the field due to previous publications though bias may exists, either consciously or unconsciously, as to the literature reviewed, included, and with the final provided recommendations
- Writing groups may want to consider a leader without multiple publications in that particular subject to mitigate potential conflict of interests
- There is a critical need for PMG creators to address conflict of interest at the beginning of the development process through a standardized and transparent approach.
- All writing group members will declare all potential conflicts of interest prior to beginning work on the guideline
- The EAST PMG Section will use the *Journal of Trauma and Acute Care Surgery's* COI forms, and the writing group leader will obtain these completed forms prior to beginning the project. These forms can be obtained at: http://www.editorialmanager.com/jt/default.aspx
- These forms will be reviewed by both the writing group leader, the EAST PMG Section Taskforce Leader (for that topic), and the EAST PMG Section Chair. All will maintain copies of these forms during the PMG creation process.
- Obtaining this information early in the process prevents delays and allows for management of any relevant conflicts early. These same forms can be utilized when the PMG is submitted to the *Journal of Trauma and Acute Care Surgery*

Section 5: Educating Your Team Regarding GRADE Methodology

Overall Approach

- The GRADE system is not simply a grading or rating scheme
- The GRADE approach involves a comprehensive, organized, and structured process for evaluating research evidence and developing guideline recommendations[5]
- Three resources to educate the writing team about the GRADE approach for the development of PMGs are:
    - The article entitled "The Eastern Association of the Surgery of Trauma approach to practice management guideline development using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology" by Andrew Kerwin MD et al.[3]
    - The GRADE Working Group Website, publications section
        - http://www.gradeworkinggroup.org/publications/index.htm)
    - In person workshops on the GRADE system. Some EAST members have found the courses taught by the New York Academy of Medicine and the GRADE Working Group to be extremely helpful especially for PMG Section members and writing group Chairs
        - http://www.nyam.org/fellows-members/ebhc/
        - http://www.gradeworkinggroup.org/news.htm#workshops
        - http://gradeconf.org
- The EAST PMG Section will with work with individual writing groups to identify EAST members as well as national experts to aid with methodology issues
- We highly recommend that the GRADE expert participate with the writing group beginning at the start of the development process
- Although the GRADE methodology utilizes multiple sequential steps, the general process can be divided into three main components:
    1. Establishment of process
    2. Synthesis of evidence
    3. Development of recommendations

1. Establishment of process

- Determine the healthcare problem and the clinical questions
- Create the workgroup panel of content and methodology experts
- Agree on team leadership and group functional processes
- Assess and declare any conflict of interest

2. Synthesis of evidence

- Formulate and define the questions (PICO questions)
    - Populations (P)
    - Interventions (I)
    - Comparators (C)
    - Outcomes (O)
- Consider all outcomes that the population may experience
- Rate importance of each outcome

    - Critical
    - Important
    - Less important
- Systematic review and summary of evidence
- Rate quality of evidence for each outcome
    - Initial quality of evidence
        - High
        - Moderate
        - Low
        - Very low
- Create evidence profiles and summary of findings for each question
- Downgrade quality of evidence (as appropriate as per GRADE guidance)
    - Risk of bias
    - Inconsistency
    - Indirectness
    - Imprecision
    - Publication bias
- Upgrade quality of evidence (as appropriate as per GRADE guidance)
    - Large effect
    - Dose-response
    - Plausible residual confounding

3. Development of recommendations

- Consider balance of consequences
    - Benefits versus harms and burden
    - Values and preferences
    - Resource implications
    - Equity, feasibility, and acceptability
- Direction of recommendation
    - For
    - Against
    - Can't give a recommendation
- Strength of recommendation
    - Strong
    - Weak/Conditional
- Wording of recommendation
    - "We recommend…"
    - "We conditionally recommend…"
    - "We conditionally recommend against…"
    - "We recommend against…"
    - "We have no recommendation…"
- Justify and explain recommendations
- Remark on patients' values and preferences, implementation and feasibility

Section 6: Developing PICO questions

Overall Approach

Once a guideline topic has been decided upon, the guideline developers must begin by framing the questions. Although informal questions are helpful initially to draft the scope of the guideline, subsequent steps involves careful development of very focused, rather than broad or open ended, questions.

The PICO format

- The specific questions are best designed using the PICO format:
    - P Patient
    - I Intervention
    - C Comparators
    - O Outcome(s)

Examples

- Poor examples of PICO questions:
    - "How do I manage a blunt splenic injury?"
    - "Is angioembolization useful in the management of blunt splenic injury?"
- Well-written examples of PICO questions:
    - "In patients with blunt splenic trauma (P), should angioembolization (I) be performed compared to no angioembolization (C) to improve splenic preservation (O) in patients treated with non-operative management?"
    - "In adult patients with *Clostridium difficile* associated disease (P) does early surgery (I) compared to late surgery as defined by vasopressor use (C) decrease mortality (O)?"
    - "In adult patients with an open or closed femur fracture (P) does early (within 24 hours of injury) open reduction and internal fixation (I) compared to delayed (beyond 24 hours following injury) open reduction and internal fixation (C) decrease the incidence of VTE (O)?"
        - Since the PICO questions are meant to be specific and outcome-centric this above question could be rewritten for each outcome (i.e. mortality, pneumonia, amputation, infection, non-union/malunion) related to the timing of open reduction and internal fixation.

Section 7: Deciding on Outcomes in GRADE

Overall Approach

- Within the GRADE system, it is important to consider and include all possible outcomes, especially those that are directly important to patients.
- Once these are determined, they should be evaluated to decide which ones should influence the decision-making process. [15]

Generating a list of potential outcomes

- First, educate the group on the outcomes scale and scoring system (see example, Figure 1)[16]
    - GRADE uses a 9-point scale (9 [critically important] to 1 [less important])
        - 7-9: critical for making a decision and should definitely be included in the final Evidence Profile and defines the overall quality of evidence across outcomes for each PICO
        - 4-6: important but not critical for making a decision (inclusion in the Evidence Profile may depend on how many other important outcomes are determined; those outcomes are also included when deciding on balance between benefits and harms and burden)
        - 1-3: less important and not included in the GRADE Evidence Profile
    - This is NOT a rank order (i.e. most important to least important). More than one outcome can have the same importance rating (i.e. two outcomes can each score 8).
- Start broadly and include all relevant outcomes at first.
- Potential outcomes can come from published studies, but you should also consider others that might be important to the decision makers or patients.

Figure 1. Classification of important outcomes of embolization of blunt splenic injuries[17]

Outcome Type	Value	Outcome
Critical Outcomes	9	Mortality
	8	Splenic salvage
	7	Need for further transfusions
Important Outcomes	6	Arterial access complications
	5	Contrast induced nephropathy
	4	Contrast allergy
Limited Importance Outcomes	3	Resource utilization
	2	Need for narcotics
	1	

Evaluating and Choosing Outcomes

- Once the outcomes have been classified, they should be voted upon by all members of the writing team (Figure 2)
    - First, each group member gives an individual importance rating for each outcome
    - Second, review discrepancies between group members and clarify intent of the ratings
        - You may need to discuss outcomes that have widely varying votes in order to come to a consensus score, rather than using the numerical mean/median score
- Come to a group consensus on ratings for relative importance for each outcome
- Choose up to 7 outcomes that are most important for decision making and will be included in the evidence profile
- Please be sure to communicate to your writing team members the importance of these outcome ratings that may also have profound implications for the overall quality of evidence rating

Figure 2. Rating Outcomes[13]

PMG Member	Hospital Survival	Neurologically Intact Survival	Bloodborne Pathogen Exposure	Costs
1	7	9	6	4
2	9	8	7	3
3	8	9	7	3
4	8	9	7	3
5	9	8	6	5
6	9	7	5	3
7	9	9	5	5
8	9	9	6	3
9	9	7	4	1
10	9	9	6	2
Mean	8.6	8.4	5.9	3.2
SD	0.8	0.8	1	1.2
Median	**9**	**9**	**6**	**3**
Min	7	7	4	1
Max	10	9	7	5
	Critical	**Critical**	**Important**	**Limited**

Section 8: Systematic Review

Overall Approach

- Modeled from the Cochrane systematic review format – rigorous and protocolized
    - Guideline panels base their recommendations on systematic reviews based on the quality of the studies reviewed and magnitude of effect reported
    - GRADE methodology is used to rate overall quality of evidence for each outcome of the entire body of published articles.

Before You Start

- Identify an information specialist who is trained in systematic reviews
    - Most university-affiliated libraries have people (often termed "medical librarian" or "informationist") with this expertise[8]
    - Additional information in Section 2, Chapter 6 in Cochrane Handbook – Free, online (http://handbook.cochrane.org/)
- Develop a plan (protocol) to document search strategy and sources, and how the review will be conducted
    - Time/date
    - Database of origin
    - Background and Methods
- Software you will need:
    - A reference manager:
        - **EndNote** (not free [your academic institution may provide you with a significant discount on the purchase])
            - http://endnote.com/
        - **RefWorks** (free)
            - https://www.refworks.com/
            - Available through your academic institution with on-line 'how to's" or in person with your medical library personal
    - Review Manager
        - **RevMan** (Cochrane) - Free, online.
            - Data cannot be shared by users unless working on an actual Cochrane review
            - http://tech.cochrane.org/revman
        - **GRADEpro/GDT** - Free, online
            - http://www.guidelinedevelopment.org

Sources for Literature Review

- Database
    - Major: Pubmed, EMBASE, Cochrane (Central Register of Controlled Trials [CENTRAL] http://www.thecochranelibrary.com), LILACS.
    - Subject-specific: PsychINFO; BiblioMap (Centre database of health promotion research)-free on the internet; Database of Promoting Health Effectiveness Reviews (DoPHER) – free on the internet;

    - Citation: Web of Science (scientific.thomson.com/products/wos/), Scopus (info.scopus.com/overview/what/)
- Hand-searching of journals
- Bibliography/References
- Table of contents in journals
- Meeting proceedings/Abstracts ("Gray literature")

Conducting the Search

- Searches should be broad initially to allow for full capture of potential articles
- Controlled Vocabulary (i.e. MeSH in PubMed)
    - Use a variety of search terms
    - Alternative spellings/plurals
    - Related terms and synonyms
- Keywords
    - Truncate if possible
    - MeSH terms in PubMed – Medical Subject Headings
    - Start with broader terms, narrower are automatically included
- Use PICO question as a guide
    - (**P**opulation OR Synonym OR . . .) AND (**I**ntervention OR Synonym OR . . .) AND (**C**omparator OR Synonym OR . . .) AND (**O**utcome)
    - Keep simple at first, use initial search to explore MeSH
    - Be careful to use Boolean operators correctly
- Filter by study type
- Try to include languages other than English – should be able to find a translator for most things

Documenting the Search

- Timing
    - Year of publication
    - Date accessed
- Search strategy for each database
- Sources other than database
- Your final search strategy and findings will be presented as a PRISMA flow diagram within your manuscript (see Figure 1)

Using the Search

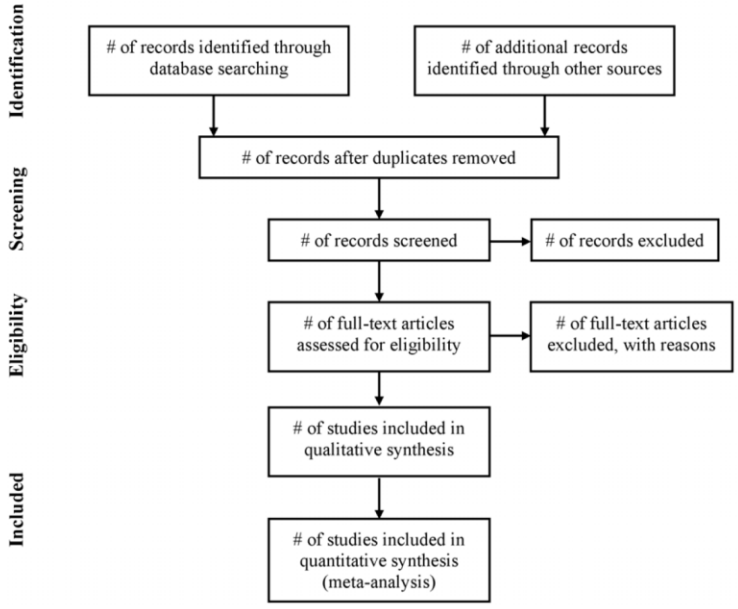
- Enter each publication into a reference manager
- De-duplication – filter out publications that appear in more than one database
- Title and Abstract Review – Two independent reviewers to determine paper inclusion: yes, possibly include (maybe), or do not include (no)
    - All "Yes" and "Maybe" by either person should be pulled for full-text review
- Full-text review for suitability based on PICO-based inclusion/exclusion criteria
    - Include (yes), possibly include (maybe), or do not include (no)
    - All "Yes" included; "Maybe" requires resolution by consensus of the 2 reviewers
- Would like at least 20-50 articles for full-text review, 15-30 for systematic review

- Perform data extraction *(*see Section 9 - Data Extraction*)*
- Decision for articles to include for qualitative synthesis and quantitative synthesis.

<u>Parts of the Systematic Review</u>

- Background/Intro
- Methods
- Results
    - QUALitative Synthesis/Analysis
        - Overview of the results of the studies
        - Includes all outcomes evaluated
        - Summary of outcomes that are not discretely measureable
        - ALWAYS included: a systematic review *may also* include a quantitative synthesis (meta-analysis), but it always includes a qualitative synthesis
    - QUANTitative Synthesis/Meta-analysis *(*see Section 10 - Performing a Meta-Analysis*)*
        - Need a CRITICAL and MEASURABLE outcome
        - Decide measure of association: varies, but in general use RR for high-prevalence outcomes (>20%)
        - Plug data from extraction tables into RevMan to create Forest Plots
        - For event rates, keep in mind that RevMan records “event” as the worse outcome when generating the forest plots
        - GRADE Profile (see Section 12 - Grading the Quality of Evidence)
        - Recommendations and Conclusion (See Section 13 - Creating Recommendations)

Figure 1. Example of PRISMA flow diagram to describe literature search strategy[18]



Section 9: Data Extraction

Overall Approach

- Protocolized with data extraction forms using PRISMA guidelines
- READ http://www.prisma-statement.org - Always Keep in mind the 27-item PRISMA checklist while developing your protocol, all the way to manuscript submission (JOT-ACS requires it)
- Resist the urge to create your own data collection sheet
- Resist the urge to find articles independent of the formalized search
- Resist the urge to extract data independently

Data Extraction

- Create Your Protocol and Register at http://www.crd.york.ac.uk/PROSPERO/
    - Stage of review at time of this submission: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO
        - Title
        - Authors with Affiliations
        - Review Question (PICO)
        - Search Databases to be Used
        - URL to search strategy
        - Types of study to be included
        - Condition or domain being studied
        - Participants/ population
        - Intervention(s), exposure(s)
        - Comparator(s)/ control
        - Outcome(s) primary and secondary
        - Data extraction, (selection and coding)
        - Risk of bias (quality) assessment
        - Strategy for data synthesis
        - Analysis of subgroups or subsets
        - Dissemination plans
        - Contact details for further information
        - Organizational affiliation of the review
        - Funding sources/sponsors
        - Conflicts of interest
- What is a Systematic Review? What is a Meta-Analysis? What is a Protocol?
    - http://www.thecochranelibrary.com/view/0/AboutCochraneSystematicReviews.html
    - http://www.cochrane.org/handbook
- Locate your data extraction sheet for the final papers included
    - See Appendix (Section 17)
        - Example from the Centers for Disease Control (CDC)
        - Worksheet for risk of bias assessment for systematic reviews (from GRADE)

- Worksheet for risk of bias assessments for observational trials (from GRADE)
- Worksheet for risk of bias assessments for RCTs (from GRADE)

Section 10: Performing a Meta-Analysis

Overall Approach

- Be sure to include a methodology expert who can guide the team through the meta-analysis process.
- A meta-analysis is a statistical technique for combining data from multiple independent, sufficiently comparable studies to assess outcomes related to a specific intervention.
- Not all systematic reviews will yield a meta-analysis since often, the studies are not amenable to combining if they are too heterogeneous
- However, every meta-analysis should always follow a rigorous systematic review
- Studies must be sufficiently similar regarding populations, interventions, comparisons, outcomes, and timing (PICOT) to be pooled for meta-analysis

Common tools for performing meta-analyses

- Rev-Man http://tech.cochrane.org/revman/download
- Stata http://www.stata.com/
- Meta-analyst (open source) http://www.cebm.brown.edu/open_meta

Data Entry

- Data are entered in a spreadsheet-like format. See below.

Author	Year	Intervention	Treated Events	Treated Subjects	Control Events	Control Subjects	N
Miller	2000	HCTZ vs nothing	0	100	35	65	165
Smith	2005	HCTZ vs. nothing	15	1150	106	1670	2820
Jones	2007	Furosemide vs. nothing	1	1673	160	1371	3044
Ryan	2009	HCTZ vs. Furosemide	0	500	0	600	1100
…	…	…	…	…	…	…	…

Common outcomes reporting

- Meta-analysis compare outcomes of two groups generally as an odds ratio (OR) or relative risk (RR) [19]
- Less frequently, risk difference and hazard ratio are reported.
- Consequently, we will focus on OR and RR.
- Odds ratio (OR) – The odds that an outcome will occur given exposure to an intervention[20]
    - OR = $(I_1/C_1)/(I_2/C_2)$. See below

	Outcome 1 (Bad)	Outcome 2 (Good)	Total
Intervention 1	I_1	I_2	NI
Control/Intervention 2	C_1	C_2	NC
Total	N_1	N_2	N

- Interpretation:
    - OR=1 – Intervention does not affect the odds of outcome 1
    - OR>1 – Intervention 1 associated with higher odds of outcome 1
    - OR<1 – Intervention 1 associated with lower odds of outcome 1
- Relative risk (RR) – The probability that an outcome will occur given exposure to an intervention
    - RR = $(I_1/N_1)/(C_1/NC)$
        - RR=1 – Intervention does not affect the risk of outcome 1
        - RR>1 – Intervention 1 associated with higher risk of outcome 1
        - RR<1 – Intervention 1 associated with lower risk of outcome 1

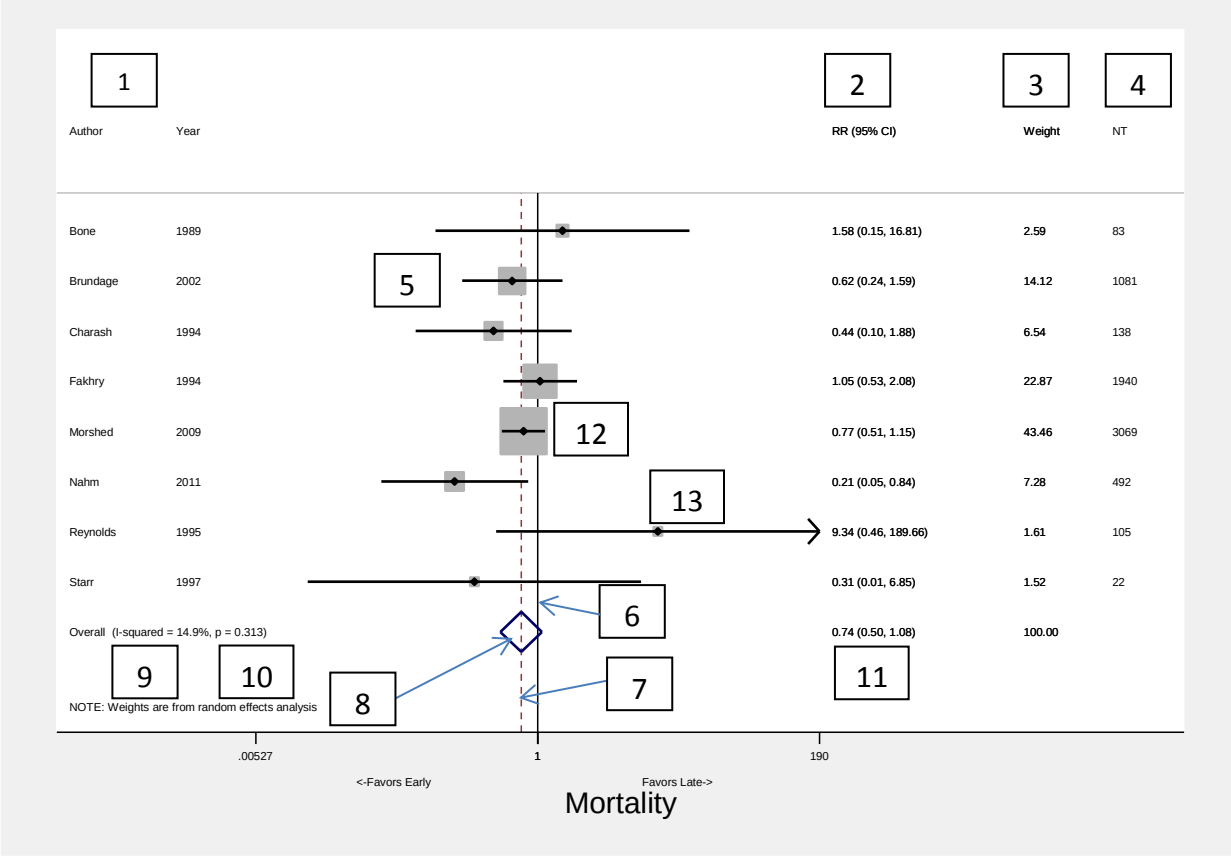
Analysis: Effects models

- Random effects models consider both within-study and between-study variability and assumes that studies included in the meta-analysis are a random sample from all possible studies. The DerSimonian Laird random effects model is most frequently used and is generally the preferred model for meta-analysis.[19]
- Fixed effects models consider only within-study variability which assumes that studies use identical methods, patients, and measurements.

Considerations for meta-analysis results (see Figure 1)

- Magnitude of effect – The farther from the null line, the greater the magnitude of effect of an intervention. The overall effect estimate may be skewed by studies with outlying point estimates.
- Confidence Interval – A confidence interval that crosses 1, visually indicated by the null line, indicates no statistically significant difference
- Weighting – Meta-analyses are weighted by the sample size of each included study, so a large study will provide greater weight to the overall estimate than smaller studies. The overall effect estimate may be skewed by studies with atypical sample sizes.
- Heterogeneity (I^2) – A measure of inconsistency across included studies ranging from 0-100% where lower numbers indicate less heterogeneity (i.e. more consistent)
- Sensitivity Analyses – A sensitivity analysis selectively removes studies that may artificially influence the results. Examples of studies that may be removed for sensitivity analysis include incomparable interventions (e.g. a study of diuretics that includes HCTZ and furosemide when all other studies include only HCTZ), different demographic characteristics of patients, poor quality studies, temporality (i.e. studies published years ago may not be applicable to current practice).
- Subgroup analyses – Stratified analysis of studies exploring the same outcome of interest. Subgroup analyses may be done by patient demographics (e.g. sex, race), interventions (e.g. HCTZ only, HCTZ or furosemide, furosemide only), or timing (e.g. surgery within 6 hours, surgery within 12 hours, etc). Subgroup analyses to be performed should be defined beforehand in the protocol and be limited in numbers to avoid spurious findings.

Figure 1. Sample meta-analysis results



1 – Individual study identifiers
2 – Point estimate and confidence interval for each included study
3 – Percent weight of each study based on sample size
4 – Total sample size of each study
5 – Point estimate (black dot), 95% confidence interval (black line), and weight (grey box) for each study
6 – Null line indicating no statistically significant difference
7 – Point estimate for the overall pooled effect
8 – Confidence interval for the overall pooled effect
9 – Measure of heterogeneity (I^2)
10 – P-value for the overall pooled effect
11 – Point estimate and confidence interval for the overall pooled effect
12 – Study with a large sample size
13 – Outlying point estimate

Section 11: Tools to Assist with Meta-analysis & Presenting Findings: RevMan and GradeproGDT

Overall Approach

- Review Manager (RevMan) is the Cochrane Collaboration's software for preparing and maintaining Cochrane reviews; and it will be a useful tool when writing a guideline
    - Available at http://ims.cochrane.org/revman
- GRADEproGDT is available to assist review authors in the preparation of 'Evidence Profile' tables. Its use is limited to personal computers
    - Available at http://www.guidelinedevelopment.org

RevMan

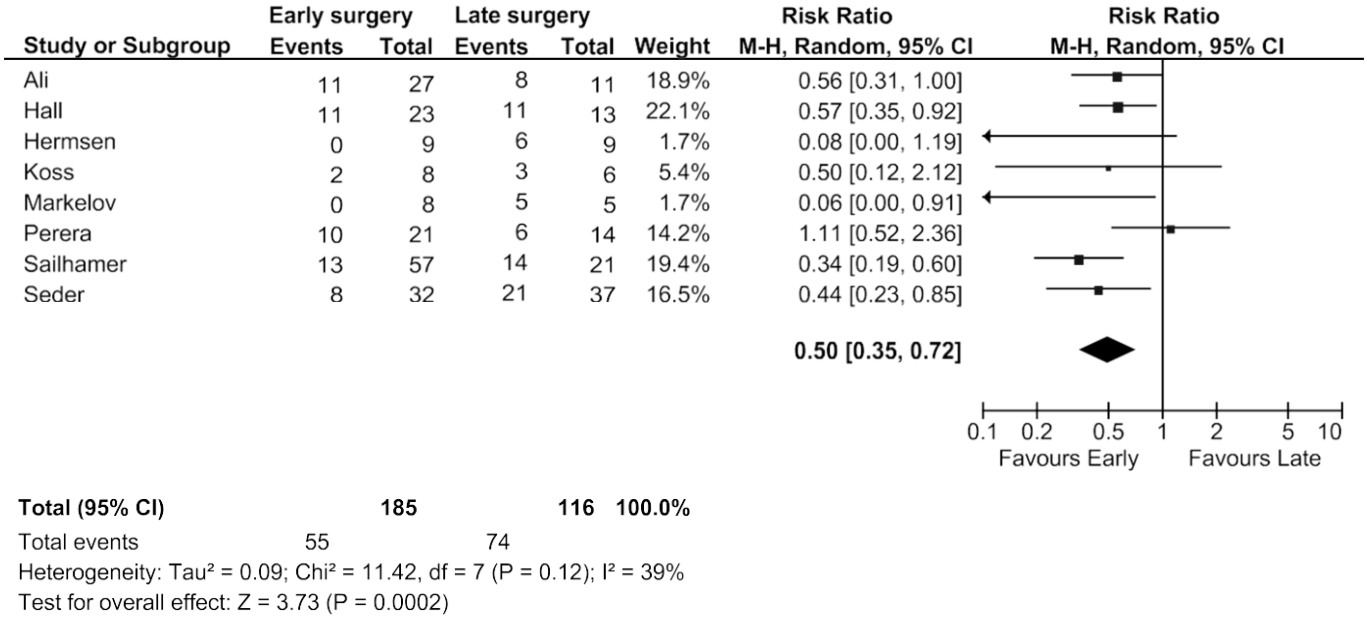
- RevMan facilitates preparation of protocols and full reviews, including text, characteristics of studies, comparison tables, and study data
- It can perform meta-analysis of the data entered and present the results graphically as a forest plot (Figure 1)
- RevMan will allow the user to:
    - Add studies
    - Add outcome
    - Data entry
    - Conduct meta-analysis
    - Add new comparison
    - Introduce subgroups
    - Generate plots and graphs

Interpretation of RevMan output

- Forest plots
    - Standardized format of forest plots
    - Displays effect estimates and confidence intervals for both individual studies and meta-analyses
    - Each study is represented by a block at the point estimate of intervention effect with a horizontal line extending either side of the block
        - Area of the block indicates the weight assigned to that study in the meta-analysis
        - Horizontal line depicts the confidence interval (which usually is a 95% confidence interval)
    - The area of the block and the confidence interval convey similar information, but both make different contributions to the graphic
    - Confidence interval - depicts the range of intervention effects compatible with the study's result and indicates whether each was individually statistically significant
    - Size of the block draws the eye towards the studies with larger weight
        - Usually those with narrow confidence intervals contribute more to the pooled results

- RevMan provides a flexible framework for producing forest plots. Forest plots **should** be produced for most guidelines and selected as figures to appear as an integrated part of the published guideline

Figure 1. Example of Forest Plot[9]



Additional RevMan Resources:

- A full user guide as well as tutorials is available at http://tech.cochrane.org/sites/tech.cochrane.org/files/uploads/documents/revman/RevMan_5.2_User_Guide.pdf
- A video walking the user thru a step by step process is available at : https://www.youtube.com/watch?v=axSkcRnr_cY

GRADEproGDT

- GRADEproGDT is the updated version of GRADEpro and is used in conjunction with RevMan to produce 'Evidence Profile' tables. See Figure 2
- GRADEproGDT program retrieves data from RevMan.
- The program leads the user through the process of a GRADE assessment, and produces a table that can be readily imported into RevMan as a 'Evidence Profile' table.
- ***Key point***: Once the 'Evidence Profile' table is generated it cannot be modified in RevMan. If mistakes are made the user will have to start over to produce another table

- Tips for generating the table:
    - The title of each 'Evidence Profile' table should specify the clinical question, framed in terms of the population under study.
        - Make it clear exactly what comparison of interventions is being made
    - The first rows of each 'Evidence Profile' table should provide the following 'header' information:
        - Patients or population
            - This further clarifies the population (and possibly the sub-populations) of interest
            - Ideally the magnitude of risk of the most crucial adverse outcome at which treatment is directed is also included

Figure 2. Sample Evidence Profile Table[9]

Question: Should Total vs Partial or No Resection- Ultimate Procedure be used for C. difficile Colitis?

Bibliography: . [Intervention A] versus [intervention B] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Partial or No Resection- Ultimate Procedure	With Total		Risk with Partial or No Resection- Ultimate Procedure	Risk difference with Total (95% CI)
Reduction in mortality (CRITICAL OUTCOME)											
554 (17 studies)	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	serious[2]	undetected	⊕◯◯◯ **VERY LOW**[1,2,3,4] due to imprecision	37/81 (45.7%)	201/473 (42.5%)	**RR 0.86** (0.56 to 1.31)	**457 per 1000**	**64 fewer per 1000** (from 201 fewer to 142 more)

[1] Minor clinical and methodologic heterogeneity, not directly related to outcome

[2] Confidence intervals wide and have potential for favorability in either direction

[3] Greater than 10% reduction in mortality

[4] Potential confounding by delay in TAC

Section 12: Grading the Quality of Evidence

Overall Approach

- In the context of GRADE guideline development, the quality of evidence specifically refers to the evaluators' confidence that the reviewed effect estimates are adequate to support a particular decision or recommendation

Categorizing Evidence Quality

- In order to provide consistent categorization of evidence quality, GRADE uses four specific categories: High, Moderate, Low, and Very Low.
- Their definitions are as follows:
    - High
        - Very confident that the true effect lies close to that of the estimate of the effect
    - Moderate
        - 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)
    - Low
        - Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect)
    - Very low
        - Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)

Process of Rating Quality of Evidence

- The process of rating the quality of evidence begins at study design – either randomized trials or observational studies – and then proceeds either upwards or downwards. The figure below summarizes the stepwise process whereby a category of quality is reached (Figure 1).
- The exact definitions for each of these criteria are beyond this "How To" guide, and can be found in the references. [21-25] However, it is important to note that consistency in their use is essential in order to allow for appropriate adherence to GRADE standards. Some examples of how to note that evidence was upgraded or downgraded follow:

  "The evidence for this outcome was upgraded for a strong association, and the overall quality of evidence was moderate."[11]

  "However, the evidence was downgraded for imprecision, and the overall quality was very low."[11]

  "For one of our critical outcome measures, we rated up the quality of evidence from low quality to moderate quality for magnitude of effect, given the consistently high negative predictive value (100%) of a normal C-spine CT result for the finding of an unstable C-spine injury" [12]

Figure 1. Rating Evidence Higher or Lower based on Modifying Factors[26]

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomized trials	High ⇒	Risk of Bias • −1 Serious • −2 Very serious Inconsistency • −1 Serious • −2 Very serious Indirectness • −1 Serious • −2 Very serious Imprecision • −1 Serious • −2 Very serious Publication bias • −1 Likely • −2 Very likely	Large effect • +1 Large • +2 Very large Dose response • +1 Evidence of a gradient All plausible residual confounding • +1 Would reduce a demonstrated effect • +1 Would suggest a spurious effect if no effect was observed	High (four plus: ⊕⊕⊕⊕) Moderate (three plus: ⊕⊕⊕O) Low (two plus: ⊕⊕OO) Very low (one plus: ⊕OOO)
Observational studies	Low ⇒			

Section 13: Creating Recommendations

Overall Approach

- Definition – the *strength of a recommendation* "reflects the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects."
- Implications of recommendations have clinical as well as medico-legal effects (Figure 1).

Figure 1. Sample Consequences of Interventions

Effect of Intervention on:	**Desirable Effect**	**Undesirable Consequence**
Morbidity & Mortality	Reduction	Increase
Quality of Life	Improved	Deleterious impact
Burden of Treatment	Reduction	Greater
Use of Resources	Reduced	Increased

Making a recommendation

- ***Key point:*** determining the strength of a recommendation is distinct from rating the quality of the evidence in aggregate
- The primary rating determinants:
    - The overall quality of the evidence across outcomes
    - The balance between benefits and harms and burdens
    - Patients' values and preferences
    - Resource considerations

GRADE offers only two levels of action strength

- Strong recommendation
    - Used when the desirable effects of adherence to a recommendation clearly outweigh the undesirable effects, or clearly do not
    - We recommend using the phrase "we recommend" or "we recommend against"
- Weak (conditional) recommendation
    - Used when the tradeoffs are less certain – either because of low-quality evidence or because the available evidence suggests that the desirable and undesirable effects are closely balanced; or patients' values and preferences vary widely or are uncertain; or the resource use involved may not be worth in relation to the benefit achieved.
    - We recommend using the phrase "we conditionally recommend" when a weak recommendation is warranted

Factors that affect the strength of a recommendation

- Balance between desirable and undesirable effects
- Quality of the evidence

- Uncertainty or variability in values and preferences
- Uncertainty about whether the intervention represents a wise use of resources (cost)

Implications of Recommendations[27]

- The implications of a strong recommendation are:
    - For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered
    - For clinicians—most patients should receive the recommended course of action
    - For policy makers—the recommendation can be adopted as a policy in most situations.
- The implications of a weak recommendation are:
    - For patients—most people in your situation would want the recommended course of action, but many would not
    - For clinicians— although most patients will want the intervention, you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences
    - For policy makers—policy making will require substantial debate and involvement of many stakeholders[27]

Evidence Profile

- Once the choice of strength of recommendation is made, the rationale for the choice should be explained in what is known as an ‘evidence to decision table’.

Key Action Statements

- Recommendations should be *key action statements* (Figure 2).
- An ideal key action statement describes WHO *may, should, or must* do WHAT to WHOM under WHAT CIRCUMSTANCES and HOW and WHY.
- Key action statements are prescriptions of a specific behavior of a provider.
- They should be unambiguous and precise, not vague or nonspecific
- They should not be statements of fact
- In general, less frequent variation in action is expected for a strong recommendation than for a weak recommendation.

Figure 2. Sample Action Statements[9]

Question	Recommendation
PICO#1	In adult patients with Clostridium Difficile Associated Disease (CDAD), we strongly recommend that patients undergo early surgery, prior to the development of shock and need for vasopressors. **Strong recommendation** (very low quality of evidence, very large magnitude of effect)
PICO#2	In adult patients with Clostridium Difficile Associated Disease (CDAD) undergoing surgery, we conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery) when the diagnosis of Clostridium Difficile colitis is known. **Conditional recommendation** (very low quality of evidence).

Tips on Making Recommendations

- If the recommendation is strong, the writer should consider the use of the verb "should" or "recommend."
- If the recommendation is weak, "may" or "conditionally recommend" should be considered.

Displaying Recommendations

- GRADE offers preferred symbolic representations and a preferred number/letter representation for quality of evidence and grades of recommendation (see Figure 3):

Figure 3. Symbolic Representations of Recommendation Quality[9]

Quality of evidence	
High quality	⊕⊕⊕⊕ or A
Moderate quality	⊕⊕⊕◯ or B
Low quality	⊕⊕◯◯ or C
Very low quality	⊕◯◯◯ or D
Strength of recommendation	
Strong recommendation for using an intervention	↑ ↑ or 1
Weak recommendation for using an intervention	↑ ? or 2
Weak recommendation against using an intervention	↓ ? or 2
Strong recommendation against using an intervention	↓ ↓ or 1

EAST will use the following format for **STRONG** recommendations:
"We recommend..."
"We recommend against ..."

EAST will use the following format for **WEAK** recommendations:
"We conditionally recommend..."
"We conditionally recommend against…"

Section 14: Gaining Consensus on Recommendations

Background:

1. Guideline panels have grown to be large and diverse.
2. This may result in difficulty in decision making.
3. Achieving consensus may be difficult or not possible.

Example from the Surviving Sepsis Campaign:

> Difficulties achieving consensus highlighted the need for a formal approach to the resolution of disagreement
>
> a. A recommendation for or against an intervention, versus some alternative, required that at least 50% of participants to be in favor, with no more than 20% favoring the alternative
>   i. The options could be judged to be equal
> b. For a recommendation to be considered strong, instead of weak, at least 70% of the group members had to vote for it as a strong recommendation

GRADE grid (below) – provides a useful and efficient way to examine the range of opinions and permits polling within the group.

In general, voting should be anonymous.

Example taken from Surviving Sepsis Campaign – GRADE grid for various topics:

For a given topic, members may vote for one if the following, and votes are entered into the GRADE grid below:

- Desirable consequences of an intervention clearly outweigh undesirable (GRADE score 1)
- Desirable consequences of an intervention probably outweigh undesirable (GRADE score 2)
- Tradeoffs equally balanced or uncertain (GRADE score 0)
- Undesirable consequences of an intervention probably outweigh desirable (GRADE score 2)
- Undesirable consequences of an intervention clearly outweigh desirable (GRADE score 1)

GRADE grid for recording panellists' views in development of guidelines (including examples of propositions from the Surviving Sepsis Campaign and number of panellists who voted for each option)

	GRADE score				
	1	2	0	2	1
Balance between desirable and undesirable consequences of intervention	Desirable clearly outweigh undesirable	Desirable probably outweigh undesirable	Trade-offs equally balanced or uncertain	Undesirable probably outweigh desirable	Undesirable clearly outweigh desirable
Recommendation	Strong: "definitely do it"	Weak: "probably do it"*	No specific recommendation	Weak: "probably don't do it"	Strong: "definitely don't do it"
For each proposition below, please mark with an "X" the cell that best corresponds to your assessment of the available evidence, in terms of benefits versus disadvantages					
Use of (as opposed to no use of):					
Low dose steroids in patients with septic shock responsive to fluids and vasopressors	0	5	4	8	4
Low dose steroids in patients with septic shock poorly responsive to fluids and vasopressors	5	16	0	0	0
SDD in ventilated patient (local and systemic)	0	9	4	8	1
rhAPC in patients with septic shock and high risk of death	6	15	1	0	0

SDD=selective digestive decontamination, rhAPC= recombinant human activated protein C.

*Participants were provided with guidance on factors to be taken into account in formulating a recommendation (box 1) and the implications of strong versus weak recommendations (box 2).

Votes are then tallied.

If at least 50% of participants to be in favor, with no more than 20% favoring the alternative – a recommendation for or against an intervention, versus some alternative, can be made.

The options can be judged to be equal.

For a recommendation to be considered strong, instead of weak, at least 70% of the group members need to have voted for it as a strong recommendation.

Reference:

Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* 2008; 337: 327-330.

Section 15: Manuscript Format for EAST Practice Management Guidelines

Overall Approach

In an effort to streamline the review process and eventual use by the public, the Section has created a manuscript format. The Section looks to *the Journal of Trauma and Acute Care Surgery* (JOT-ACS) as its primary publication platform. Before writing, it is highly suggested that the writing group review the instructions for authors provided by the journal:

http://www.editorialmanager.com/jt/default.aspx

Of special note, the JOT-ACS conflict of interest form should be completed prior to the formulation of PICO questions (see Section 4- Obtaining Conflict of Interest Information). Issues that arise will need to be discussed with the Task Force Leader as well as the Chair of the PMG Section. These same conflicts of interest can be used during the submission process unless new issues are identified during the period of PMG generation

JOT-ACS will limit manuscripts to **5000 words**. Furthermore, the structured **abstract is limited to 300 words** and a **total of 8 figures and tables (to include a final "Summary of Recommendations" figure)** can be included for the print edition. Other figures and tables will need to be noted as for the electronic version within the manuscript. The working group should carefully select the final tables and figures to be included. As in the past, forest plots for quantitative syntheses (if possible) and evidence tables are provided for each Topic/PICO question. A figure summarizing the final recommendations, "Summary of Recommendations", is mandatory and should be placed in a box (Figure 3).

Suggested Manuscript Format

TITLE: *Individual Writing Group Title*: A practice management guideline from the Eastern Association for the Surgery of Trauma

ABSTRACT

- Structured
- 300 words
- Key terms

INTRODUCTION

OBJECTIVES

- Explain the main objective or highlight the major issue within the topic
- List the PICO questions by number

INDENTIFICATION OF REFERENCES

- Who did the search (if you had a professional librarian say so), how performed (what medical subject headings [MeSH terms] were used on what search platforms [Pubmed, Embase, etc]), dates of papers included (month and year), inclusion and exclusion criteria. Want to describe so that it is a repeatable process
- *A priori* description of how papers are to be included or excluded.

OUTCOME MEASURE TYPES

- How were the PICO "O's" decided for each question, how ranked or voted upon by writing members? Which were deemed "critical"

DATA EXTRACTION AND METHODOLOGY

- Describe the methods of extracting data as a whole or by each PICO question if different methods were used
- Detailed description of the number of papers included and excluded
    - Include a PRISMA diagram of papers included and excluded. This is your first figure.
- Brief description of statistical methods used if a meta-analysis was performed.

RESULTS FOR "TOPIC (PICO 1)"

- The titles for the individual section should describe the PICO being examined
    - Ex) "Management of Pancreatic Injuries with Duct Disruption (PICO 3)"

Qualitative Synthesis

- A focus should be to summarize key/seminal articles in the literature or those that have the largest influence on the quantitative synthesis (forest plot generation) or recommendation

Quantitative Synthesis (if possible)

- Meta-analysis with risk ratio and I^2 generation
- Should include forest plot creation (RevMan), description and <u>insertion as a figure</u> (see Figure 1)

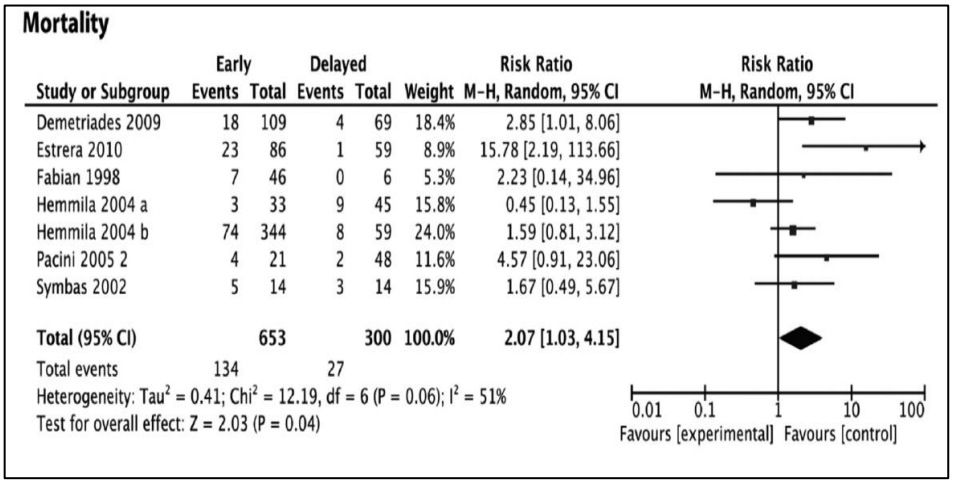


Figure 1 – Sample Quantitative Synthesis[11]

Grading the Evidence

- A brief explanation of the risk of bias, inconsistency, indirectness, imprecision, or publication bias found for each outcome and how they changed the overall quality (a "why" of the quality assessment section of the Evidence Profile Table)
- Explain the overall, final quality of the literature used
- Create evidence profile and include table (via Gradepro from RevMan import of data (Figure 2)

Figure 2 – Sample Evidence Profile Table[11]

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Open repair	**With Endovascular repair**		**Risk with Open repair**	**Risk difference with Endovascular repair** (95% CI)
Mortality (CRITICAL OUTCOME)											
2588 (37 studies) 30 days	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	undetected	⊕⊕⊖⊖ **LOW**[1]	326/1753 (18.6%)	66/835 (7.9%)	**RR 0.54** (0.41 to 0.7)	**Study population**	
										186 per 1000	**86 fewer per 1000** (from 56 fewer to 110 fewer)
										Moderate	
										167 per 1000	**77 fewer per 1000** (from 50 fewer to 99 fewer)
Stroke (CRITICAL OUTCOME)											
1789 (12 studies) 30 days	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	undetected	⊕⊕⊖⊖ **LOW**[1]	15/1301 (1.2%)	12/488 (2.5%)	**RR 1.5** (0.67 to 3.34)	**Study population**	
										12 per 1000	**6 more per 1000** (from 4 fewer to 27 more)
										Moderate	
										7 per 1000	**3 more per 1000** (from 2 fewer to 16 more)
Paralysis/Spinal cord ischemia (CRITICAL OUTCOME)											
2061 (21 studies) 30 days	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2] due to large effect	46/1468 (3.1%)	3/593 (0.51%)	**RR 0.35** (0.17 to 0.7)	**Study population**	
										31 per 1000	**20 fewer per 1000** (from 9 fewer to 26 fewer)
										Moderate	
										59 per 1000	**38 fewer per 1000** (from 18 fewer to 49 fewer)

[1] some studies with few patients and overall few events

Recommendations

- Summarizes the quality of literature in comparison to the side effects, literature variability, values and preferences of patients
- Bold the recommendation statement
- EAST will use the following format for **STRONG** recommendations:
  - "We recommend..."
  - "We recommend against..."
- EAST will use the following format for **WEAK** recommendations:
  - "We conditionally recommend..."
  - "We conditionally recommend against…"

RESULTS FOR "TOPIC (PICO 2)" etc. for each PICO/topic

Qualitative Synthesis

Quantitative Synthesis
Grading the Evidence
Recommendation

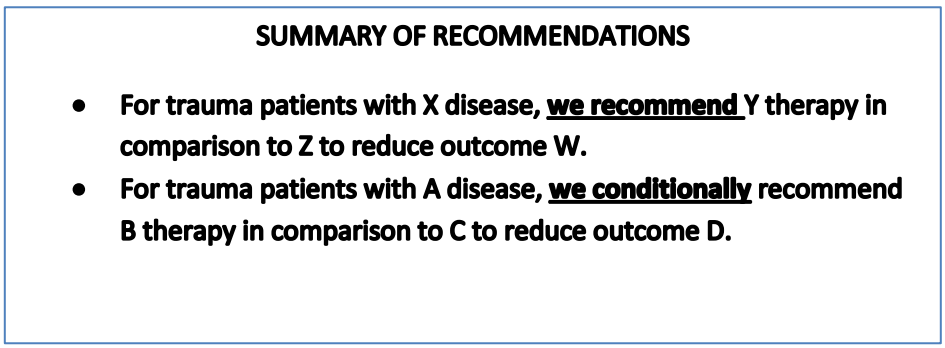
USING THESE GUIDELINES IN CLINICAL PRACTICE

- Clarify a practical approach to using the presented information. How would you implement these recommendations at your institution?

CONCLUSION

- Brief highlight of the findings and recommendations
- A final figure with bullet points of the recommendations is mandatory (Figure 3)

Figure 3. Summary of Recommendations



Section 16 – *The Journal of Trauma and Acute Care Surgery* Submission Process

Overall Approach

The EAST PMG Section has cultivated a special relationship with the JOT-ACS. For successful publication in this journal, the following steps for submission have been suggested:

1. A final (fully vetted and approved by all members of the writing group) manuscript will be provided by the first author to the Task Force Leader and Chair of the PMG Section.

2. The Chair and Task Force Leader will review with 2 other blinded reviewers from the Section (not associated with its development).

3. Blinded reviews will be provided back to the primary author for revision by the entire author group.

4. When a final product is completed and approved by the entire author group, resubmission to the Task Force Leader and Chair will occur.

5. The resubmission will be reviewed by the Task Force Leader, Chair, and the 2 blinded reviewers. If approved, the final manuscript will be circulated in a secure fashion to the members of the PMG Section for final comment.

6. After approval of the PMG Section, submission can occur by the primary author to JOT-ACS.

7. The primary author will need to alert the Chair and Task Force Leader that the submission/upload occurred. The Chair will then contact the Editors of JOT-ACS to alert them of the submission.

8. The JOT-ACS review process will follow those outlined within the instructions for authors (http://www.editorialmanager.com/jt/default.aspx).

9. The primary author will continue to update the Chair and Task Force Leader during the JOT-ACS review process.

10. Upon acceptance, the EAST PMG web page will be updated.

11. Upon publication, the EAST PMG web page will be updated with the PDF link. The manuscript will also be contained within the “Collections” section on the JOT-ACS web page. The application for inclusion within the National Guidelines Clearinghouse will begin at this point (see Section 16).

Section 17 – Submitting to the National Guideline Clearinghouse (NGC)

The Practice Management Guidelines Section of EAST now requires that all PMGs be submitted to the National Guidelines Clearinghouse (NGC). NGC has specific inclusion criteria for the clinical practice guidelines to be eligible for publication on their website. The NGC utilizes the 2011 definition of a clinical practice guideline developed by the Institute of Medicine which defines a guideline as "a statement 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." PMGs that are developed adhering to this EAST manual should be eligible for inclusion in the NGC. Below are the specific steps and inclusion criteria for the NGC.

NGC Inclusion Criteria:

- Guidelines must contain systematically developed statements "including recommendations intended to optimize patient care"
- Statements must assist "…practitioners and patients to make decisions about appropriate health care for specific conditions."
- Guidelines must be based on systematic reviews
- Guidelines must contain all of the following supporting documents:
    - An explicit statement that the guideline is based on a systematic review
    - A description of the search strategy (list the databases used, search terms used, time period included in the literature search, date literature search performed)
    - Study selection details (number of studies identified, number of included studies, inclusion and exclusion criteria)
    - Detailed description of evidence tables
    - Summary of evidence synthesis that relates the evidence to the recommendations
- An assessment of the benefits and harms of recommended care and alternative care is required in either the guideline or the supporting documents
- Full text guideline available in English upon public request.

Section 17 – Appendix

Sample Data Extraction Form from the Centers for Disease Control
(http://www.cdc.gov/vaccines/acip/recs/GRADE/downloads/handbook.pdf)

Author, Year:
Name of reviewer: Date completed:

I. Methods
Study design:
Number randomized or enrolled (total and per group):
Number analyzed (total and per group):
Losses to follow up (for each outcome):

II. Participants
Setting:
Country:
Age:
Gender (% female):
Race/ethnicity:
Inclusion criteria:
Exclusion criteria:
Equivalence of baseline characteristics:

III. Interventions
Intervention group:
Comparison group:

IV. Outcomes

V. Notes
Type of study (published/unpublished):
Funding source:
Study period:
Reported subgroup analyses:

Form 2a. Assessment of risk of bias for randomized controlled trials[a]

Author, Year:

Name of reviewer: Date completed:

Criteria	Description	Yes /No/ Unclear	Quote from study
Adequate allocation sequence generation	The investigators describe a random component in the sequence generation process (e.g. computer random number generator). Problem if "pseudo" or "quasi" randomization with allocation by day of week, birth date, chart number, etc.		
Adequate allocation sequence concealment	Those enrolling patients cannot foresee the group to which the next enrolled patient will be allocated (e.g. central allocation, sequentially numbered sealed envelopes)		
Adequate blinding of participants and personnel	Study participants and personnel are not aware of the arm to which patients are allocated		
Adequate blinding of outcome assessors	Outcome assessors are not aware of the arm to which patients are allocated (assess separately for each outcome; outcomes may be grouped as subjective and objective)		
Incomplete outcome data addressed	Loss to follow-up; adherence to the intention to treat principle when indicated[b] (assess separately for each outcome; outcomes may be grouped as short-term and long-term)		
Free of selective outcome reporting	Study reports all pre-specified or expected outcomes. Problem if reporting of some outcomes and not others on the basis of the results		
Free of other biases	For example: extreme baseline imbalance; differential diagnostic activity		

[a]See Cochrane handbook, Chapters 8 and 16 (http://www.cochrane-handbook.org/).
[b]Intention-to-treat analyses may not be appropriate for adverse events or non-inferiority studies (ref: Cochrane handbook, Chapter 16, Section 16.2.1).
For observational studies, see http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
For controlled before-after and interrupted time series, see www.epoc.cochrane.org/epoc-author-resources.

Form 2b. Assessment of risk of bias for cluster-randomized trials[a]

Author, Year:

Name of reviewer: Date completed:

Criteria	Description	Yes /No/ Unclear	Quote from study
Recruitment bias	Individuals are recruited to the trial after the clusters have been randomized; knowledge of whether each cluster is an intervention or control cluster could affect the types of participants recruited. Strategies to minimize the possibility of selection bias include inclusion of all individuals within a cluster or recruitment of individuals by a person masked to the cluster allocation.[b]		
Baseline imbalance	Baseline imbalance between the randomized groups, in terms of either the clusters or the individuals. Statistical adjustment for baseline characteristics can help reduce concern about the effects of baseline imbalance.		
Loss of clusters	Loss of clusters from a trial may lead to bias. In addition, missing outcomes for individuals within clusters may lead to a risk of bias. For example, differential adherence and follow-up can occur for whole clusters or individuals in a cluster.		
Incorrect analysis	The clustering effect is not taken into account in the analysis. Such analyses produce erroneously narrower standard errors that will result in too much weight in a meta-analysis if they remain uncorrected.		
Comparability with individually randomized trials	In a meta-analysis including both cluster and individually randomized trials, or including cluster-randomized trials with different types of clusters, possible differences between the intervention effects being estimated [because of herd effect] need to be considered. If intervention effect is still demonstrated in individually randomized trials, a confident conclusion about the presence of an effect can be drawn. Herd effects may be different for different types of cluster.		
Other biases			

[a]See Cochrane handbook, Chapter 16.3 (http://www.cochrane-handbook.org/).

[b]Campbell MK et al. CONSORT Statement: extension to cluster randomised trials. BMJ 2004;328:702-8.

Form 3a. Data abstraction for dichotomous outcomes

Author, Year:
Name of reviewer:
Date completed:

Outcome (as stated in study)				
	Intervention group		Comparison group	
Time at follow-up	n (Number with outcome)	N (Total number in group)	n (Number with outcome)	N (Total number in group)
Notes:				

Outcome (as stated in study)				
	Intervention group		Comparison group	
Time at follow-up	n (Number with outcome)	N (Total number in group)	n (Number with outcome)	N (Total number in group)
Notes:				

Outcome (as stated in study)				
	Intervention group		Comparison group	
Time at follow-up	n (Number with outcome)	N (Total number in group)	n (Number with outcome)	N (Total number in group)
Notes:				

Form 3b. Data abstraction for continuous outcomes

Author, Year:
Name of reviewer:
Date completed:

Outcome (as stated in study)						
Time at follow-up	Intervention group			Comparison group		
	n	Mean (95% CI)	SD[a]	n	Mean (95% CI)	SD[a]
Notes:						

Outcome (as stated in study)						
Time at follow-up	Intervention group			Comparison group		
	n	Mean (95% CI)	SD[a]	n	Mean (95% CI)	SD[a]
Notes:						

Outcome (as stated in study)						
Time at follow-up	Intervention group			Comparison group		
	n	Mean (95% CI)	SD[a]	n	Mean (95% CI)	SD[a]
Notes:						

[a]Standard deviation (SD) = Standard error * square root of total participants in group (n). If SD is not reported, it can be computed from 95% CI (see Cochrane handbook, Chapter 7, Section 7.7.3).

Form 4. Determining evidence type

Name of reviewer:
Date completed:

Criteria	Assessment (circle one for each criterion)	Reasons for assessment	Evidence type[a] (Circle one per outcome)
OUTCOME:			
Risk of bias	No serious (-1) very serious (-2)		1
Inconsistency	No serious (-1) very serious (-2)		2
Indirectness	No serious (-1) very serious (-2)		3
Imprecision	No serious (-1) very serious (-2)		4
Publication bias	Unlikely likely (-1) very likely (-2)		
Strength of association	No Large (+1) Very large (+2)		
Dose response relation	No Yes (+1)		
Opposing plausible residual confounding or bias	No Yes (+1)		

[a]Evidence type:

1= Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.
2= RCTs with important limitations, or exceptionally strong evidence from observational studies.
3= Observational studies, or RCTs with notable limitations.
4= Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

WORKSHEET FOR RISK OF BIAS ASSESSMENT for SYSTEMATIC REVIEWS

PICO QUESTION #	
Author's Last Name	
Year	
Journal	
Vol, Issue, Pages	
REVIEWER	

AMSTAR ASSESSMENT OF BIAS TOOL FOR SYSTEMATIC REVIEWS

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

YES	
NO	
Can't Answer	
Not Applicable	

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

YES	
NO	
Can't Answer	
Not Applicable	

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

YES	
NO	
Can't Answer	
Not Applicable	

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

YES	
NO	
Can't Answer	
Not Applicable	

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

YES	
NO	
Can't Answer	
Not Applicable	

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

YES	
NO	
Can't Answer	
Not Applicable	

Note: Acceptable if not in table format as long as they are described as above.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

YES	
NO	
Can't Answer	
Not Applicable	

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

YES	
NO	
Can't Answer	
Not Applicable	

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

YES	
NO	
Can't Answer	
Not Applicable	

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

YES	
NO	
Can't Answer	
Not Applicable	

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

YES	
NO	
Can't Answer	
Not Applicable	

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

POOLED TREATMENT EFFECTS

Critical Outcome 1: Analgesia (as assessed with VAS or other validated scale):

Mean pain score in CONTROL	Mean pain score in EXPERIMENTAL
Method for assessing pain (e.g. VAS, etc.)	

Critical Outcome 2: Mortality (30-day or in-hospital mortality—specify)

Deaths in Control Group	Deaths in Experimental Group
How was mortality assessed? (e.g., 30-day mortality, in-hospital mortality, etc.)	

Critical Outcome 3: Postoperative pulmonary complications (PPCs)

PPCs in Control Group	PPCs in Experimental Group
Types of PPCs reported (i.e. pneumonia, etc.)	

Critical Outcome 4: Pulmonary function tests (PFTs)

Values in Control Group	Values in Experimental Group
PFTs reported (i.e., VC, FEV1, FVC, etc.)	

Critical Outcome 5: Requirement for mechanical ventilation

Number intubated in Control Group	Number intubated in Experimental Group

Important Outcome 1: Hospital length of stay

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

Important Outcome 2: Ventilator days

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

WORKSHEET FOR RISK OF BIAS ASSESSMENT and OUTCOMES: OBSERVATIONAL TRIALS

PICO QUESTION #	
Author's Last Name	
Year	
Journal	
Vol, Issue, Pages	
REVIEWER	

DOWNS AND BLACK ASSESSMENT OF BIAS TOOL

REPORTING BIAS

1. **Is the hypothesis/aim/objective of the study clearly described?** There must be a clear statement of the objective, i.e. to measure the effectiveness of x in population y with respect to z, even if x, y, and z are not clearly described.

Yes	**1**	
No	**0**	

2. **Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are mentioned in the Results section, the question should be answered no. In case-control studies the case definition should be considered the outcome.

Yes	**1**	
No	**0**	

3. **Are the characteristics of the patients included in the study clearly described in the Introduction or Methods Section?** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case definition and the source for controls should be given.

Yes	**1**	
No	**0**	

4. **Are the interventions of interest clearly described in the Introduction or Methods section?** Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	**1**	

No	**0**	☐

5. **Are the distributions of principal confounders in each group of subjects to be compared clearly described?** A list of principal confounders should be provided (see checklist below). Definition of *confounder*: A confounder causes the disease or outcome, is associated with the exposure or intervention, but is not affected by the exposure.

Yes	**2**	☐
Partially	**1**	☐
No	**0**	☐

POTENTIAL CONFOUNDERS:
[If necessary, continue with comments on last page]

6. **Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. This question does not cover statistical tests (see below).

Yes	**1**	☐
No	**0**	☐

7. **Does the study provide estimates of the random variability in the data for the main outcomes?** In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data, the standard error, standard deviation, or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	**1**	☐
No	**0**	☐

8. **Have all important adverse events that may be a consequence of the intervention been reported?** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. A list of possible adverse events should be provided.

Yes	**1**	
No	**0**	

9. **Have the characteristics of patients lost to follow-up been described?** This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no when a study does not report the number of patients lost to follow up.

Yes	**1**	
No	**0**	

10. **Have 95 percent CIs and/or actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.0001?**

Yes	**1**	
No	**0**	

EXTERNAL VALIDITY

11. **Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

12. **Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

13. **Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?** For the study to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

INTERNAL VALIDITY

14. **Was an attempt made to blind study subjects to the intervention they have received?** For studies where the patients would have no way of knowing which intervention they received, this should be answered yes (i.e. if patients were likely unconscious, this would apply).

Yes	**1**	
No	**0**	
Unable to determine	**0**	

15. **Was an attempt made to blind those measuring the main outcomes of the intervention?**

Yes	**1**	
No	**0**	
Unable to determine	**0**	

16. **If any of the results of the study were based on "data dredging," was this made clear?** Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

17. **In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?** If different lengths of follow-up were adjusted for by, for example, survival analysis, the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	**1**	

No	**0**	☐
Unable to determine	**0**	☐

18. **Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data.** For example, non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	**1**	☐
No	**0**	☐
Unable to determine	**0**	☐

19. **Was compliance with the interventions reliable?** Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no.

Yes	**1**	☐
No	**0**	☐
Unable to determine	**0**	☐

20. **Were the main outcome measures used accurate (valid and reliable)?** For studies where the outcomes measured are clearly described, the question should be answered yes.

Yes	**1**	☐
No	**0**	☐
Unable to determine	**0**	☐

INTERNAL VALIDITY-CONFOUNDING/SELECTION BIAS

21. **Were the patients in different intervention groups recruited from the same population?** For examples, patients for all comparison groups should be selected from the same hospital. When there is no information concerning the source of patients included in the study, answer unable to determine.

Yes	**1**	☐
No	**0**	☐
Unable to determine	**0**	☐

22. **Were study subjects in different intervention groups recruited over the same period of time?** For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

23. **Were the subjects randomized to intervention groups?** Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example, alternate allocation would score no because it is predictable.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

24. **Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?** All non-randomized studies should be answered no.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

25. **Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?** Answer no if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders in the different treatment groups was not described, or the distribution of known confounders different between the treatment groups but was not taken into account in the analysis. In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered as no.

Yes	**1**	
No	**0**	
Unable to determine	**0**	

26. **Were losses to patients to follow-up taken into account?** If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the

proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	**1**	☐
No	**0**	☐
Unable to determine	**0**	☐

TREATMENT EFFECTS

Critical Outcome 1: Analgesia (as assessed with VAS or other validated scale):

Mean pain score in CONTROL	**Mean pain score in EXPERIMENTAL**
Method for assessing pain (e.g. VAS, etc.)	

Critical Outcome 2: Mortality (30-day or in-hospital mortality—specify)

Deaths in Control Group	**Deaths in Experimental Group**
How was mortality assessed? (e.g., 30-day mortality, in-hospital mortality, etc.)	

Critical Outcome 3: Postoperative pulmonary complications (PPCs)

PPCs in Control Group	**PPCs in Experimental Group**
Types of PPCs reported (i.e. pneumonia, etc.)	

Critical Outcome 4: Pulmonary function tests (PFTs)

Values in Control Group	Values in Experimental Group
PFTs reported (i.e., VC, FEV1, FVC, etc.)	

Critical Outcome 5: Requirement for mechanical ventilation

Number intubated in Control Group	Number intubated in Experimental Group

Important Outcome 1: Hospital length of stay

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

Important Outcome 2: Ventilator days

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

WORKSHEET FOR RISK OF BIAS ASSESSMENT and OUTCOMES: RCT

PICO QUESTION #	
Author's Last Name	
Year	
Journal	
Vol, Issue, Pages	
REVIEWER	

1. JADAD SCORE (not recommended by the GRADE Working Group):

Item	Point	Comment
Randomization		
Blinding		
Patients accounted for		
TOTAL		

2. COCHRANE RISK OF BIAS TOOL:

SEQUENCE GENERATION

YES/NO/UNCLEAR	Comment

ALLOCATION CONCEALMENT

YES/NO/UNCLEAR	Comment

BLINDING (of participants, personnel, and outcome assessors)

YES/NO/UNCLEAR	Comment

INCOMPLETE OUTCOME DATA

YES/NO/UNCLEAR	Comment

SELECTIVE OUTCOME REPORTING

YES/NO/UNCLEAR	Comment

OTHER SOURCES OF BIAS

YES/NO/UNCLEAR	Comment

<u>OUTCOMES</u>

Critical Outcome 1: Analgesia (as assessed with VAS or other validated scale):

Mean pain score in CONTROL	Mean pain score in EXPERIMENTAL
Method for assessing pain (e.g. VAS, etc.)	

Critical Outcome 2: Mortality (30-day or in-hospital mortality—specify)

Deaths in Control Group	Deaths in Experimental Group
How was mortality assessed? (e.g., 30-day mortality, in-hospital mortality, etc.)	

Critical Outcome 3: Postoperative pulmonary complications (PPCs)

PPCs in Control Group	PPCs in Experimental Group
Types of PPCs reported (i.e. pneumonia, etc.)	

Critical Outcome 4: Pulmonary function tests (PFTs)

Values in Control Group	Values in Experimental Group
PFTs reported (i.e., VC, FEV1, FVC, etc.)	

Critical Outcome 5: Requirement for mechanical ventilation

Number intubated in Control Group	Number intubated in Experimental Group

Important Outcome 1: Hospital length of stay

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

Important Outcome 2: Ventilator days

Days, Control Group	Days, Experimental Group
Duration of follow-up? (e.g., 1 vs. 3 months, etc.)	

JADAD SCORING GUIDANCE:

Item	Maximum points	Description	Examples
Randomization	2	1 point if randomization is mentioned	"The patients were randomly assigned into two groups"
		1 additional point if the method of randomization is appropriate	The randomization was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes
		Deduct 1 point if the method of randomization is inappropriate (minimum 0)	The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week
Blinding	2	1 point if blinding is mentioned	"The trial was conducted in a double-blind fashion"
		1 additional point if the method of blinding is appropriate	Use of identical tablets or injectables, identical vials Use of tablets with similar looks but different taste
		Deduct 1 point if the method of blinding is inappropriate (minimum 0)	Incomplete masking
An account of all patients	1	The fate of all patients in the trial is known. If there are no data the reason is stated	"There were 40 patients randomized but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol"

The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: ▪ Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: ▪ Sequence generated by odd or even date of birth; ▪ Sequence generated by some rule based on date (or day) of admission; ▪ Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: ▪ Allocation by judgement of the clinician; ▪ Allocation by preference of the participant; ▪ Allocation based on the results of a laboratory test or a series of tests; ▪ Allocation by availability of the intervention.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: ▪ Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); ▪ Sequentially numbered drug containers of identical appearance; ▪ Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: ▪ Using an open random allocation schedule (e.g. a list of random numbers); ▪ Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); ▪ Alternation or rotation; ▪ Date of birth; ▪ Case record number; ▪ Any other explicitly unconcealed procedure.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; ▪ Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; ▪ Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; ▪ Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient information to permit judgement of 'Yes' or 'No'; ▪ The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any one of the following: ▪ No missing outcome data; ▪ Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); ▪ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; ▪ Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; ▪ For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; ▪ For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ▪ 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; ▪ Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: ▪ Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); ▪ The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	Any of the following: ▪ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; ▪ The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'NO' (i.e. high risk of bias).	Any one of the following: ▪ Not all of the study's pre-specified primary outcomes have been reported; ▪ One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; ▪ One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); ▪ One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; ▪ The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgement of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgement of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: ▪ Had a potential source of bias related to the specific study design used; or ▪ Stopped early due to some data-dependent process (including a formal-stopping rule); or ▪ Had extreme baseline imbalance; or ▪ Has been claimed to have been fraudulent; or ▪ Had some other problem.
Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: ▪ Insufficient information to assess whether an important risk of bias exists; or ▪ Insufficient rationale or evidence that an identified problem will introduce bias.

Section 19- Bibliography and Links to Published EAST GRADE PMGs

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