Making the GRADE: The Art and Science of Creating High Quality Practice Management Guidelines

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2020 Annual EAST Meeting
Short Course #1
January 15, 2020

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Disclosures

Nothing to disclose

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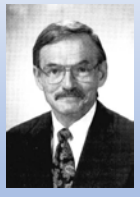
EAST PMGs

- EAST was an early leader in evidence based medicine for trauma
- In 1994, EAST president Michael Rhodes gave his presidential address
  - Entitled "Practice Management Guidelines for Trauma Care"
  - Created the EAST Practice Management Guidelines Committee



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Currently on website

https://www.east.org/

- EGS – Total 7 (GRADE 6)
- Injury Prevention – Total 12 (GRADE 8)
- Surgical Critical Care – Total 29 (GRADE 6)
- Trauma – Total 41 (GRADE 15)

- TOTAL – 89 (GRADE 35)

- Archived 35

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Currently under development

- Total of 33
  - EGS – 8
  - Injury prevention – 2
  - Surgical critical care – 4
  - Trauma – 19

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EAST 2019 meeting

- Emergency General Surgery
  - Gallbladder Disease in Pregnancy
  - Lower GI Bleeding
- Surgical Critical Care
  - Pleural Effusion
  - Tracheal Intubation
- Trauma
  - Adult Renal Trauma
  - Open Abdomen after Damage Control Laparotomy
  - Hemothorax
  - Thromboelastography
  - Traumatic Rhabdomyolysis

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Published 2019 (n=8)

- Antimotility agents for the treatment of non-infectious diarrhea in critically ill patients
- Promotility agents for the treatment of ileus in adult surgical patients
- Impact of the Affordable Care Act on Trauma and Emergency General Surgery
- Management of acute appendicitis in adults
- Pediatric blunt renal trauma
- Evidence-based review of trauma center care and routine palliative care processes for geriatric trauma patients
- Management of penetrating intra-peritoneal colon injuries
- Management of blunt force bladder injuries

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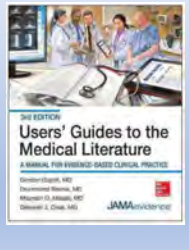
Educational materials

- EAST Guide on How to Write a Practice Management Guideline (white paper)
- The EAST Approach to guideline development using the GRADE methodology
- GRADE YouTube videos
- Attendance at US GRADE Network courses
- GRADE Working Group website
- Internal Education at annual EAST meeting (started January 2019)



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Traumacasts (How to?)

- The PMG committee has made a series of 9 videos
  - Education using the GRADE methodology
  - On YouTube https://www.youtube.com/watch?v=DKULStD1Aac&list=PLb_qu6L1kwWrP8Eu8dC7NXeFCh0kAxJdp&index=2

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Program

- Introductions & Welcome – John J. Como, MD, MPH & Shailvi Gupta, MD, MPH
- Steps Toward Generating a High-Quality PMG using GRADE – George Kasotakis, MD, MPH & Srinivas Reddy, MD
- Generating PICOs – Julius Cheng, MD, MPH & Nimitt Patel, MD
- Systematic Literature Search & Abstracts – Hiba Abdel Aziz, MD & Krista Haines, DO
- Manuscript Review & Data Extraction – John Lunde, DNP, ARNP, TNS & Brian Williams, MD

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Program (continued)

- RevMan & Introduction to Meta-Analysis – Nikolay Bugaev, MD & Lisa Kodadek, MD
- Using GRADEpro Software – Jin Ra, MD & Nicole Fox, MD, MPH
- Creating Recommendations – Rishi Rattan, MD & Kaushik Mukherjee, MD, MSCI
- Small Group Demonstrations of RevMan and GRADEpro Software

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Committee Chairs

- Nikolay Bugaev
- Rishi Rattan
- Brian WIlliams

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Introductions/Welcome

- Moderator
  - George Kasotakis - Duke University

- Vice Chair
  - Nicole Fox - Cooper Medical School of Rowan University

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EAST GRADE Course 2020
Steps Toward Generating a Quality PMG

George Kasotakis, MD MPH FACS FCCM
Srinivas Reddy, MD FACS

www.east.org @EAST_Trauma

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Disclosure

- No financial / commercial conflicts

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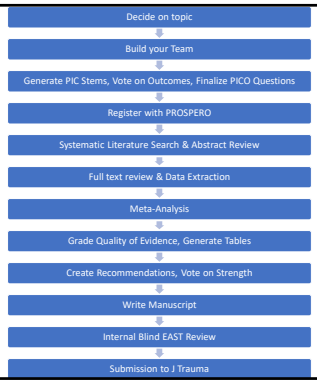

12 Steps to a GRADE PMG

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1. DECIDE ON PMG TOPIC

- Aim to work on a project you are enthusiastic about
- Ensure no other societies already have similar Guidelines already in place
- Ensure literature is available to address the proposed topic
- Duration: 2-3 weeks

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2. BUILD YOUR (or join a) TEAM

- Use your EAST Network to connect peers interested on the topic
- Consult with Guideline Committee Leadership to access volunteers
- All participants need to be EAST members* (approx. 6-10)
- Ensure balanced opinions on topic
- Duration: 2-3 weeks

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3. FORMULATE PICO QUESTIONS

- Select & carefully word your 2-4 PIC components
- Select various possible outcomes of interest
  - Can vary by PICO
- Rate Outcomes (1-9 Scale), include critical ones
- Finalize PICO Questions
  - Keep <3-4 PICOs, <3-4 Outcomes in each
- Duration: 4-6 weeks

P – Population
I – Intervention
C – Comparison
O - Outcome

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4. REGISTER WITH PROSPERO

- Register Project with PROSPERO (http://www.crd.york.ac.uk/PROSPERO) before the literature search
- Ensures you will not change the question(s) after the analysis
- Visit at end of project to summarize/disseminate results
- Duration: 20 min

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5. SYSTEMATIC LITERATURE SEARCH & ABSTRACT REVIEW

- Use a librarian and perform an exhaustive literature search (>2-3 search engines – PubMed, Cochrane, Embase, Web of Science, etc), compile list of *abstracts*
- Two reviewers look at each, determine whether it should be kept in analysis
  - Must include similar P
  - Both I & C
  - Provide information on O
- Use Excel, or Covidence, to keep track of work.
- Duration: 3-4 weeks

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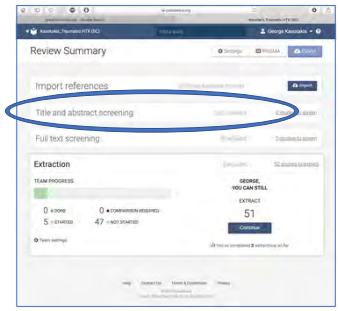
Example: Covidence



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Example: Abstract Screening

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6. FULL TEXT REVIEW & DATA EXTRACTION

- Repeat the same process on *full manuscripts.*
- Two reviewers look at each, determine whether it should be kept in analysis for same reasons, extract data regarding:
  - Primary Author – Publication year
  - Study Design
  - Reason for Exclusion, if any
  - Means, SDs for Intervention, Comparator continuous outcomes
  - 2x2 tables for Intervention, Comparator binary outcomes
- Use Excel, or Covidence to keep track of work.
- Duration: 3-5 weeks

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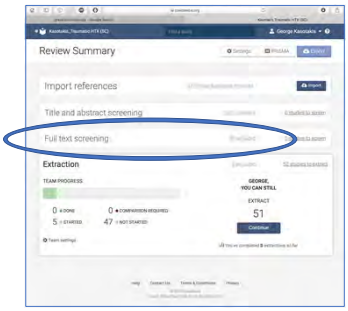
Example: Covidence



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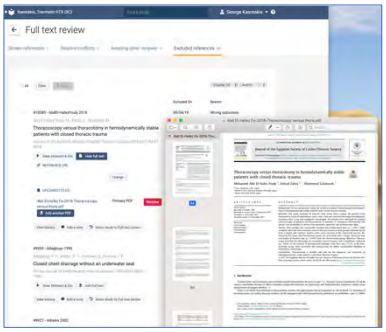
Example:
Full Text Review



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Example:
Data Extraction

Table 1

study	design	earlydead	earlyalive	latedead	latealive
Husman, 1993	Retrospective	2	18	5	18
Joseph, 2018	Retrospective review	5	15	43	24
Rostas, 2016	Retrospective	20	5	30	2
Costa, 1985	Retrospective review	12	2	30	5

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7. META-ANALYSIS

- Best performed by biostatistician.
  - (EAST can help if none available at your institution)
- Provides an evidence-based answer to your PICO question
- Common software packages:
  - RevMan
  - Stata
- Duration: 2 weeks

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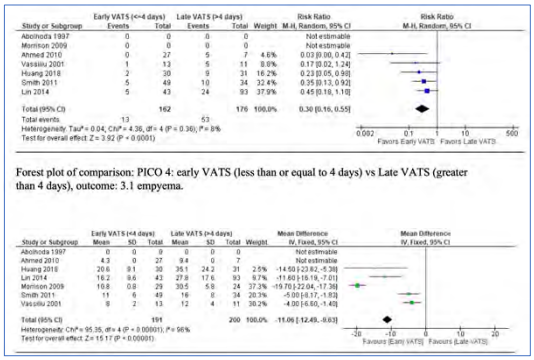
Example: Meta-Analysis



Forest plot of comparison: PICO 4: early VATS (less than or equal to 4 days) vs Late VATS (greater than 4 days), outcome: 3.1 empyema.

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8. GRADE QUALITY OF EVIDENCE, CREATE GRADE PRO TABLES

- GradePRO to accomplish
- Details discussed in upcoming presentation
- Provides evidence-based answer on strength of recommendation
- Duration: 2-3 weeks

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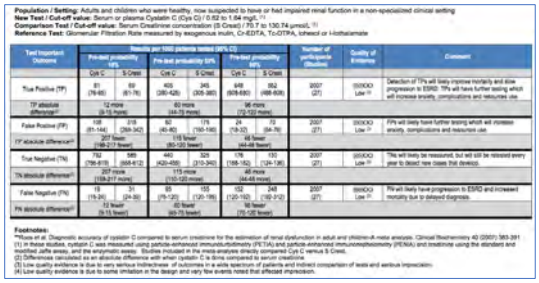
Example: GradePRO



Population / Setting: Adults and children who were healthy, now suspected to have or had impaired renal function in a non-specialized clinical setting
New Test / Cut-off value: Serum or plasma Cystatin C (Cys C) / 0.62 to 1.64 mg/L [1]
Comparison Test / Cut-off value: Serum Creatinine concentration (S-Creat) / 70.7 to 130.74 µmol/L [1]
Reference Test: Glomerular Filtration Rate measured by exogenous inulin, Cr-EDTA, Tc-DTPA, iohexol or I-iothalamate

Test Important Outcome	Results per 100 patients tested (95% CI)						Number of participants (Studies)	Quality of Evidence	Comment
	Pre-test probability 10%		Pre-test probability 50%		Pre-test probability 90%				
	Cys C	S-Creat	Cys C	S-Creat	Cys C	S-Creat			
True Positive (TP)	81 (76-85)	69 (61-76)	405 (380-426)	345 (305-380)	649 (608-683)	552 (488-608)	3007 (27)	⊕⊕⊕O Low [3]	Detection of TPs will likely improve mortality and slow progression to ESRD. TPs will have further testing which will increase anxiety, complications and resources use
TP absolute difference[2]	12 more (9-15 more)		60 more (44-75 more)		96 more (72-122 more)				
False Positive (FP)	108 (81-144)	216 (268-342)	92 (40-80)	175 (150-190)	24 (10-32)	72 (64-76)	2007 (27)	⊕⊕⊕O Low [3]	FPs will likely have further testing which will increase anxiety, complications and resources use
FP absolute difference[2]	207 fewer (189-217 fewer)		115 fewer (80-135 fewer)		48 fewer (44-48 fewer)				
True Negative (TN)	792 (756-819)	684 (658-612)	440 (420-456)	325 (310-340)	176 (168-182)	130 (124-136)	2007 (27)	⊕⊕⊕O Low [3]	TNs will likely be reassured, but will still be retested every year to detect new cases that develop.
TN absolute difference[2]	207 more (189-217 more)		115 more (110-120 more)		46 more (44-48 more)				
False Negative (FN)	19 (16-24)	31 (24-38)	95 (75-120)	155 (120-188)	152 (120-192)	248 (192-312)	2007 (27)	⊕⊕⊕O Low [3]	FN will likely have progression to ESRD and increased mortality due to delayed diagnosis.
FN absolute difference[2]	12 fewer (9-15 fewer)		60 fewer (45-75 fewer)		96 fewer (72-120 fewer)				

Footnotes:
**Ross et al. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adult and children-A meta analysis. Clinical Biochemistry 40 (2007) 383-391
(1) In these studies, cystatin C was measured using particle-enhanced immunoturbidimetry (PETIA) and particle-enhanced immunonephelometry (PENIA); and creatinine using the standard and modified Jaffe assay, and the enzymatic assay. Studies included in the meta-analyses directly compared Cys C versus S-Creat.
(2) Differences calculated as an absolute difference with when cystatin C is 50ms compared to serum creatinine
(3) Low quality evidence is due to very serious indirectness of outcomes in a wide spectrum of patients and indirect comparison of tests and serious imprecision
(4) Low quality evidence is due to some limitation in the design and very few events noted that affected imprecision.

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9. CREATE RECOMMENDATIONS, VOTE ON STRENGTH

- Discuss findings of Meta-Analysis, Quality of Evidence. Formulate a Recommendation based on these.
- Vote on Strength of Recommendation:
  - **STRONG**: Intervention should be the new standard of care
  - **CONDITIONAL**: Intervention should be considered in the majority of cases
- Need >70% of votes for a strong recommendation!

- Duration: 2-3 weeks

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10. DRAFT MANUSCRIPT

- **Introduction**: Magnitude of the problem, current practices, data available, unknown factors, purpose of the project.
- **Methods**: Describe the PICO Formulation process, the literature search, data review and extraction, analysis.
- For each PICO, include:
  - **Qualitative Synthesis**: Discuss differences across analyzed manuscripts, how these may affect your recommendation. Comment on notable observations, specific subpopulations that may benefit more or less from the proposed intervention.
  - **Quantitative Synthesis**: Review / Discuss the Meta-Analysis results, present the GRADE Pro table findings.
- **Conclusion**: Summarize recommendation, reiterate potential exceptions.
- Duration: 3-4 weeks

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11. SUBMIT FOR INTERNAL BLIND REVIEW

- Submit to EAST Guidelines Committee leadership for blind review

- Duration: 1-2 weeks

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12. SUBMIT TO J. TRAUMA

- Submit to JoT (or other journal)
- Sign up to help with other PMGs!
- Duration: 1 afternoon

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Questions?

Want to Volunteer?

Email: George.Kasotakis@duke.edu or jcomo@metrohealth.org

Twitter: @gkasot or @johnjcomo

www.east.org @EAST_Trauma

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EAST GRADE Course 2020
PICO Question Formulation

Nimitt Patel MD and Julius Cheng MD MPH

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Disclosures

Content of this presentation is partly adapted from gradepro.org and/or lecture material presented at previous GRADE Pro course(s)

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Topic and Framing the Question

- Guideline recommendations should answer a focused and sensible health care question that leads to an action
- "PICO" framework is an accepted methodology for framing health care questions
- Contains four components:

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P I C O

- **P – Population** (the patient/population to which the recommendations would apply)
- **I – Intervention** (the intervention under investigation – therapeutic, diagnostic)
- **C – Comparator** (alternative intervention, control group intervention)
- **O – Outcome** (outcome or outcomes of interest)

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Framing the Question: Population

- Population:
  - age race, gender
- Condition:
  - disease, including explicit diagnostic criteria
- Setting:
  - community, hospital, outpatient

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Framing the Question: Intervention

(e.g. "experimental group")

- Components of a complex intervention
- Timing of exposures, route of administration
- Dose, duration of exposure or therapy

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Framing the Question: Comparison

(e.g. "control group")

- No intervention
- Standard therapy
- Placebo
- Active secondary comparator

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Framing the Question: Outcomes

- Mortality
- Morbidity
- Patient reported outcomes, functional outcomes
- Individual or community level outcomes

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PICO Question Generation

- Grade Guideline Development Tool allows for selection of two different formats for questions about management:
  - Should [intervention] vs. [comparison] be used for [health problem]?
  - Should [intervention] vs. [comparison] be used in [population]?
- And formats for questions about diagnosis:
  - Should [intervention] vs [comparison] be used to diagnose [target condition] in [health problem and/or population]?

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Example

- 52 year old male with a colon cancer and a remote history of DVT after trauma asks if he should be on heparin to decrease his risk of developing a clot. What is your PICO?

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Example

- 52 year old male with a colon cancer and a remote history of DVT after trauma asks if he should be on heparin to decrease his risk of developing a clot. What is your PICO?

- P – adult outpatient with cancer
- I – prophylactic heparin
- C – no heparin
- O – morbidity, VTE, major bleeding, quality of life

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Lumping vs Splitting

In forming a question, the decision on what to study can vary in scope:

"Lumping:"
- broad question with range of interventions

"Splitting:"
- narrow question with narrow range of interventions

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Lumping vs Splitting

- Advantages of Lumping:
  - Informative when large range of options
  - Useful for policymakers
  - Mitigates double efforts
  - Potential larger literature pool for data
- Advantages of Splitting:
  - Focus on particular intervention question not answered previously
  - Condenses literature pool for analysis

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Lumping vs Splitting

- Disadvantages of Lumping/Splitting:
  - May be invalid (minimizing different groups)
  - Time consuming and complex
  - Interpretation may be difficult
  - Can be too specific with too many questions and lack of supporting data if "over split"

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Refining the Question

- Avoid *post hoc* change of question
  - Do NOT make the question fit the data
- May need to refine question as new studies are identified
  - May need to consider repeating literature search if this is the case

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Outcomes Selection – Initial Evaluation

Choosing outcomes to be studied:

- Be Comprehensive – "brainstorming" all outcomes
- Expand outside the literature
- Safety considerations (often under-reported)
- Patient-important: need input from patient/clinicians/public
  - Desirable or undesirable from *patient* point of view

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Prioritizing Outcomes - Focus

- Distilling down the range of outcomes under study
- Selection of outcomes for evaluation:
  - "Critical" / "Important" / "Less Important"
  - Process should be driven by *importance over evidence*
- Study team "votes" on which outcomes to focus on

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Prioritizing Outcomes - Focus

- Avoid undue influence – team ratings should respond to team leader individually
- Rating outcomes - (1-9 scale):
  - 1-3 not important
  - 4-6 important, but not critical for making a decision
  - 7-9 critical for making a decision
- Typically, critical outcomes considered in the final recommendation
- IMPORTANT: You are NOT ranking the outcomes you are rating them!!!!!!!!

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Questions?

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Systematic Literature Review and Abstract Screening

Krista Haines DO & Hiba Abdelaziz MD

Disclosures

- We have nothing to disclose

How do you start (#1)?

1. Do quick, informal PubMed search to identify pertinent articles, to ensure data are available for your project.
2. Check PROSPERO, Cochrane, Other Physician Professional Societies for similar reviews on this topic.

Add a librarian to your team

- Most standards—including the Cochrane handbook and the IoM standards for systematic reviews—recommend working with a librarian

Rethlefsen ML, Farrell AM, Osterhaus Trzasko LC, Brigham TJ. **Librarian coauthors correlated with higher quality reported search strategies in general internal medicine systematic reviews**. Journal of Clinical Epidemiology (2015), doi: 10.1016/j.jclinepi.2014.11.025.

"LIS co-authored SRs had higher quality search strategies than other SRs, leading to a more comprehensive, true systematic review."

Rethlefsen ML, Murad MH, Livingston EH. **Engaging medical librarians to improve the quality of review articles.** JAMA (2014), Sep 10;312(10):999-1000. doi: 10.1001/jama.2014.9263

"[Medical Librarian] neutrality and expertise can help minimize bias in the review process, leading to more robust and unbiased review articles."

4

How do you start, #2?

1. Use your institution's librarian for the formal literature search.
2. Will use the full PICOs (including Outcomes) to generate search strategies across various search engines

Complex process, utilize available advanced skills to ensure quality of final recommendation.

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Anatomy of a Good Literature Search

- Identify all the studies (and relevant data from the studies) that may pertain to the research question.
  - Be as broad as possible at this stage – may exclude later
- Develop a thorough/reproducible search strategy for at least 3 databases; document every step.
- Seek additional papers indirectly (papers from other meta-analyses?)

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Databases beyond PubMed

- EMBASE
- Cochrane Central Register of Controlled Trials
- Cumulative Index of Nursing and Allied Health Literature (CINAHL)
- Embase
- Web of Science
- Scopus
- ERIC
- Web of Science
- Scopus
- …and more!

SEARCH AT LEAST 3!!!

7

Establish inclusion/exclusion criteria

Determine Inclusion & Exclusion criteria a priori (before the literature search is conducted)

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Common Inclusion Criteria

1. Studies that include patient population similar to the PICO population
   1. Eg adult patients with penetrating colon injury
2. **Must** include groups with **BOTH** interventions being compared in each PICO Question
   Eg managed with primary repair vs. resection & anastomosis.
3. Primary Prospective or Retrospective studies
   1. Overwhelming majority retrospective chart reviews/database analyses in trauma

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Common Exclusion Criteria

1. Case Reports
   1. Eg papers with 1-2 patients
2. Expert Opinions, Commentaries
   Eg papers stating opinion with no hard science.
3. Reviews, Meta-analyses
   Although may help identify additional primary articles
4. Animal Studies
   Eg. Basic science articles
5. Non-English Articles

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SEARCH

'In patients with of hip osteoarthritis and femoroacetabular impingement, should orthobiologics be administered vs. routine care?'

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Search

Topic: Is there a benefit to administration of various orthobiologics in the treatment of hip osteoarthritis and femoroacetabular impingement?
Date: 01/12/16

PubMed, Embase, Web of Science

Database: PubMed

Set #		Results
1	orthobiologics[tiab] OR orthobiologic[tiab] OR "Ortho-Biologics"[tiab] OR "Ortho-Biologic"[tiab] OR "Platelet-Rich Plasma"[Mesh] OR "Platelet-Rich Plasma"[tiab] OR "Stem Cells"[Mesh] OR "Stem Cells"[tiab] OR "Stem Cell"[tiab] OR "growth factors"[tiab] OR "growth factor"[tiab] OR "Autologous conditioned serum"[tiab] OR ACS[tiab] OR "Autologous blood injection"[tiab] OR ABI[tiab] OR "thrombocyte rich plasma"[tiab] OR TRP[tiab]	640734
2	("Hip Pain"[tiab] OR "femoroacetabular impingement"[tiab] OR "extra articular impingement"[tiab] OR "extraarticular impingement"[tiab] OR "psoas impingement"[tiab] OR ischiofemoral impingement[tiab] OR ischio femoral impingement[tiab] OR "subspine impingement"[tiab] OR anterior inferior iliac spine impingement[tiab] OR "AIIS impingement"[tiab] OR "trochanteric impingement"[tiab] OR pelvic impingement[tiab] OR "buttock pain"[tiab] OR piriformis[tiab] OR trochanter[tiab] OR "ischial tuberosity"[tiab] OR "hip impingement"[tiab] OR tenosynovitis[tiab] OR "tendon entrapment"[tiab] OR Acetabulum impingement[tiab] OR FAI[tiab] OR "femoroacetabular impingement"[MeSH Terms] OR "Femoroacetabular impingement"[tiab] OR "hip preservation" OR "osteoarthritis, hip"[MeSH Terms] OR ((hip[tiab] OR "hip"[mesh]) AND (osteoarthritis[tiab] OR arthritis[tiab]))	29851
3	#1 AND #2	318
4	#3 NOT (Editorial[pryp] OR Letter[pryp] OR Case Reports[pryp] OR Comment[pryp]) AND English[lang]	292

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Use of Online Literature Review Software

E.g. Covidence (www.covidence.org) – EAST may help facilitate access

There is special software to help you screen through the THOUSANDS of results retrieved by your search!

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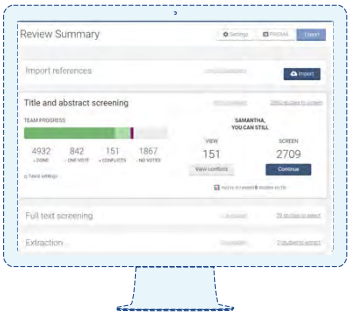
Covidence homepage

- Tracks overall progress at each step
- Tracks Reviews
- Tracks Conflicts
- Abstracts: 4000 articles = 8000 items to be screened



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Covidence screening page

- Easily screen with Yes, No, Maybe just by looking at title, abstract
- Keep Inc/Exc criteria in mind
- Highly efficient, 200/hr
- Can be done on phone

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Resolve Conflicts

1. Studies that have different answers from the two reviewers, must be adjudicated by 3rd (usually PMG leader)
2. <u>Err on the side of inclusion.</u>
   Can always exclude later.
3. Automatically create your PRISMA flow chart at the end of literature review

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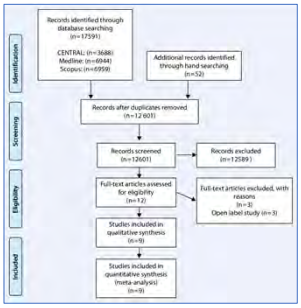
PRISMA Flowchart



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EAST GRADE course 2020 Manuscript Review & Data Extraction

Brian H. Williams, MD, FACS
John R. Lunde, DNP, AGACNP-BC, TCRN, FCCM

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Full Text Review and Data Extraction

Step 1: Retrieval

- Download all full manuscripts for 'included' abstracts
- Put in online folder for all team members to access, Or upload to online lit review software (eg Covidence)

Step 2: Repeat review process for full manuscripts

- Process similar to abstract review - Reviewers need to match
- Increase efficiency by combining with data abstraction
- Allow 3-4 weeks. **Keep everyone on track!!**

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PRISMA

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Reviewers	First Author	Year of Pub	Title	Patient population	Study Design	Include	Reason for Exclusion
				1. Surgery 2. Trauma 3. SICU 4. Medicine 5. Peds	1. PRCT 2. Retrosp 3. Observ.	1: Yes, 0: No	1: No Int/Comp groups 2: Not primary study 3: Case report 4. Animal study 5. Not in English 6. Other
AG, DC							
AG, GK							
GK, DC							

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Intervention Sample Size	Intervention– Continuous Outcome 1 mean	Intervention– Continuous Outcome 1 SD	Comparison Sample Size	Comparison– Continuous Outcome 1 mean	Comparison– Continuous Outcome 1 SD	p-value

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Example

Title: Preperitoneal Packing for Pelvic Fracture Hemorrhage

PICO 1:

In blunt trauma patients who are unstable due to their pelvic fractures (pelvic binder is on), should initial preperitoneal packing vs. initial angiography be performed to decrease transfusion requirements and mortality?

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Example

Injury, Int. J. Care Injured 47 (2016) 395–401

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Retroperitoneal packing or angioembolization for haemorrhage control of pelvic fractures—Quasi-randomized clinical trial of 56 haemodynamically unstable patients with Injury Severity Score ≥33

Qinghu Li [a], Jinlei Dong [a], Yongliang Yang [a], Guodong Wang [a], Yonghui Wang [a], Ping Liu [b], Yohan Robinson [c,*], Dongsheng Zhou [a,*]

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Example

Mean values were presented with standard deviation. Differences in baseline values were tested with one-way analysis of variance (ANOVA).

Results were compared for both treatment groups with univariate ANOVA and adjusted for treatment group, sex, cause of injury and type of pelvic fracture entered as factors, and age, ISS, and preoperative PRBC units as covariates.

Logistic regression analysis of covariates for primary outcome parameter mortality and secondary outcome parameter complications was performed, and odds ratio (OR) presented with 95% confidence intervals.

To identify predictive values of baseline variables for outcome a multivariate analysis of variance (MANOVA) of primary and secondary endpoints (mortality, complications, time from admission to angiography/surgery, procedure/surgical time, days on ICU, postoperative PRBC units administered, and secondary procedures) was performed with treatment group, sex, cause of injury and type of pelvic fracture as factors, and age, ISS, and preoperative PRBC units as covariates. A p-value < 0.05 was considered as statistically significant.

Results

Patients' demographics

Between February 2003 and February 2013 56 patients were included in the study. Of these 27 patients were randomized to the ANGIO group and 29 to the PACK group. The inclusion flow chart is displayed in Figure 1. The baseline data are shown in Table 1 for both groups. No baseline differences between ANGIO and PACK groups were noted for age, sex, injury mechanism, or pelvic fracture type. The ISS in the ANGIO group was lower than in the PACK group (43 ± 7 vs 48 ± 6; $p = 0.005$) (Fig. 2).

Outcome variables

Time

The mean time from admission to angiography for the ANGIO group was 102 ± 27 min (range 76–214) versus a median time from admission to the operating theatre of 77 ± 19 min (range 43–125) for the PACK group ($p < 0.001$). In the PACK group, 5 patients underwent additional exploratory laparotomy of which 2 required repairs of visceral injuries. The surgical time was counted for the retroperitoneal packing alone. The intervention in the ANGIO group took with 84 ± 11 min (range 62–105) longer than the 60 ± 14 min (range 41–92) in the PACK group, if the time for repairing visceral injuries was excluded ($p = 0.006$) (Table 2).

Blood transfusion

The ANGIO group received 10.9 ± 1.8 units (range 6–14) PRBC units before angiography completion, and 6.4 ± 1.7 units (range 4–10) in the first 24 h after angiography. The PACK group required 11.2 ± 2.3 units (range 7–16) before completion of pelvic packing and the concurrent operative procedures, and 5.2 ± 1.8 units (range 3–10)

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# ID	1st Author/year	Reviewer 1	Reviewer 2	type of the study	population	# of patients total	# patients Packing
3856		KM	RR	EXCLUDE FROM			
3857		KM	RR	pRCT (quasi)	Adult	56	29
3858		KM	RR	Retrospective cohort	Adult	7 (1 died on	3
3859		KM	RR	Retrospective cohort	Adult	24	11
3891		KM	RR	EXCLUDE ENTIRELY			
3896		KM	RR	EXCLUDE ENTIRELY			

Packing # blood transfusions	Packing mortality	Packing % complications, type of complications	# paients Angiography (PICO 1)	Angiography (PICO 1) # blood transfusions	Angiography (PICO 1) mortality	Angiography 1) complications, complication
5±2	4/29 = 13.8%	3/29 = 10% infection	27	6±2	5/27 = 19%	1/27 = 4% infectio
NR	1/5 = 20%	NR	1	NR	0/1 = 0%	NR
9.0±8.0	4/11 = 36.3%	NR	13	5.0±4.4	9/13 = 69.2%	NR

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Example

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Example

in the first 24 h after leaving the operating theatre. In the first 24 h after the surgery the amount of PRBC units transfused was similar in the ANGIO group and in the PACK group ($p = 0.124$).

Efficacy of bleeding control and secondary procedures

In the PACK group the gauzes used for packing were removed in 26 patients after 2 days, while 3 patients required extended packing up to 5 days because of continuing haemorrhage. A secondary procedure was performed to control persistent bleeding for several patients in both groups. Nine patients in the ANGIO group underwent secondary pelvic packing for persistent bleeding, while 6 patients in the PACK group required pelvic angiography after pelvic packing for ongoing hypotension following packing ($p = 0.353$). In the ANGIO group, the days on the ICU were 4.9 ± 1.8 (range 2–8), and 4.3 ± 2.3 (range 1–9) in the PACK group ($p = 0.214$).

Mortality

Five patients died in the ANGIO group, one from renal failure after 16 days, two from MOF after 9 days and 14 days after surgery, and two from massive bleeding 32 h after embolisation. The mortality of the ANGIO group was 18.5% ($n = 5$). Four patients died in the PACK group, the case died from severe traumatic brain injury after 2 days, two from MOF 9 and 12 days after surgery, and one with an open pelvic fracture after 16 days because of sepsis. No patient in the PACK group died of massive bleeding. The mortality in the PACK group was 13.8% ($n = 4$). Mortality rates did not differ between the ANGIO and PACK group ($p = 0.449$). The logistic regression analysis did not find any effect of covariates on mortality (Table 3).

Complications

In the ANGIO group, only one case of superficial infection was seen after 9 days, which recovered after two weeks of intravenous antibiotic therapy. The infection rate was therefore 3.7% ($n = 1$). In the PACK group, three patients, including 2 open pelvic fractures, were treated for deep postoperative infection, which occurred after 7–9 days. One patient died after 16 days and the other two recovered by surgical intervention including surgical debridement, lavage, drainage, and the use of intravenous antibiotics. The rate of infection in the PACK group was 10.3% ($n = 3$) and insignificantly greater than in the ANGIO group ($p = 0.491$). Other complications included MOF (2 patients in ANGIO group and 2 in PACK group) ($p = 0.120$), renal failure (one patient in ANGIO group) ($p = 0.561$), and DVT (one patient in ANGIO group and one in PACK group) ($p = 0.508$). No other complications such as necrosis of gluteal muscle or ischemic necrosis of bladder were found in the two groups. The postoperative complication rate was not different in both groups ($p = 0.731$). In the logistic regression analysis lower ISS ($p = 0.07$) and C-type pelvic fracture type ($p = 0.09$) had a trend towards more complications (Table 3).

Prediction of outcome with baseline values

The multivariate analysis revealed that treatment group was the most predictive factor for the dependent outcome variables

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Risk of bias assessment

Critical in determining validity
One of several assessments of quality of evidence
Cochrane tool recommended:

riskofbias.info

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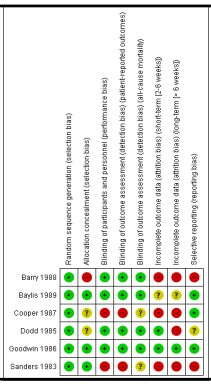
Figure 8.6.a: Example of a 'Risk of bias' table for a single study (fictional)

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk.	Quote: "patients were randomly allocated." Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).
Allocation concealment (selection bias)	High risk.	Quote: "...using a table of random numbers." Comment: Probably not done.
Blinding of participants and personnel (performance bias)	Low risk.	Quote: "double blind, double dummy"; "High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution)." Comment: Probably done.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk.	Quote: "double blind". Comment: Probably done.
Blinding of outcome assessment (detection bias) (Mortality)	Low risk.	Obtained from medical records; review authors do not believe this will introduce bias.
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	High risk.	4 weeks: 17/110 missing from intervention group (9 due to 'lack of efficacy'); 7/113 missing from control group (2 due to 'lack of efficacy').
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	High risk.	12 weeks: 31/110 missing from intervention group; 18/113 missing from control group. Reasons differ across groups.
Selective reporting (reporting bias)	High risk.	Three rating scales for cognition listed in Methods, but only one (with statistically significant results) is reported.



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Questions??

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RevMan5

Nikolay Bugaev
Tufts Medical Center
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General information

- Free
- Download at Cochrane website
- Indicate the academic use
- Register
- Select your operating system

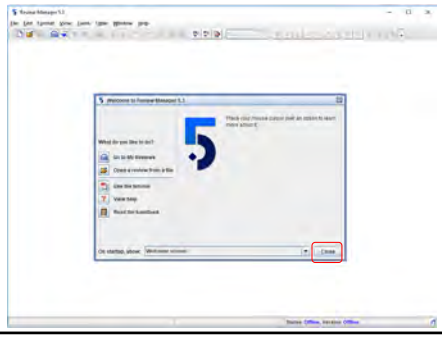
2

LEARNING OBJECTIVES

1. Open new review
2. Insert included studies
3. Add comparison
4. Add outcome
5. Enter data
6. Create figure
7. Delete study/comparison/outcome/figure

3

Open new review 1.1



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Open new review 1.2

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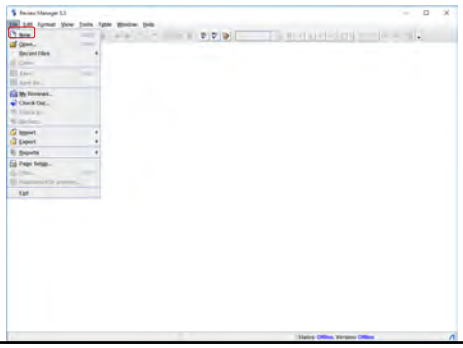
Open new review 1.3



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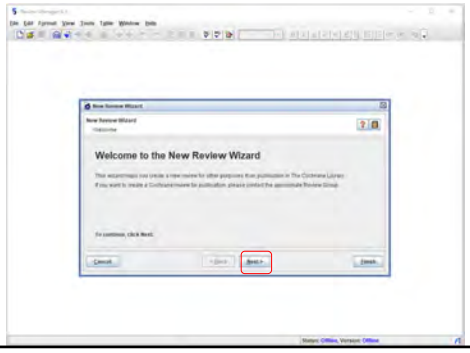

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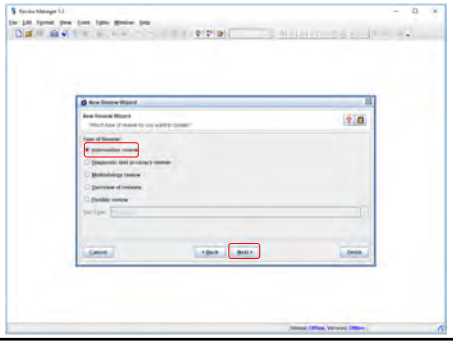

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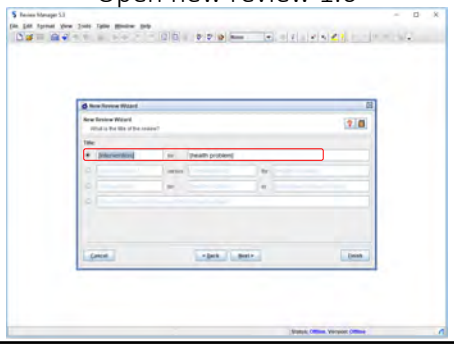

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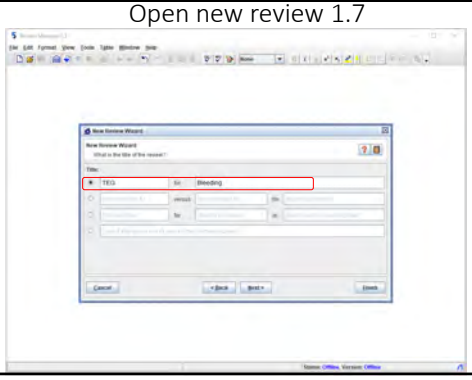

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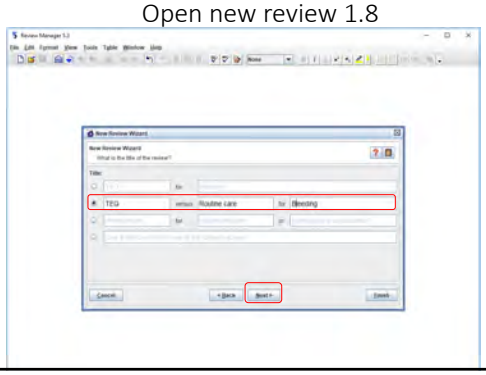

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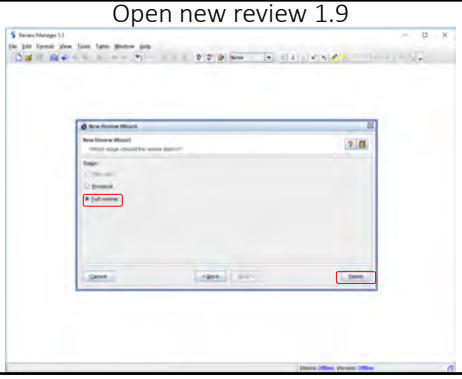

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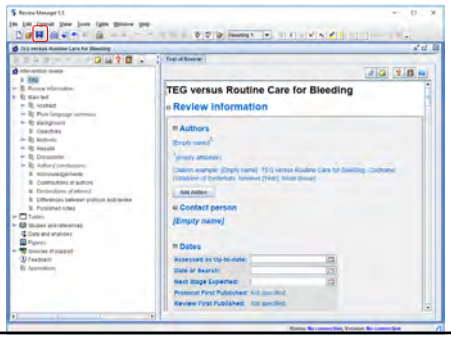

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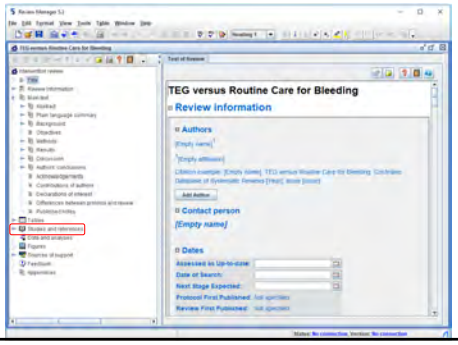
Insert included studies 2.1



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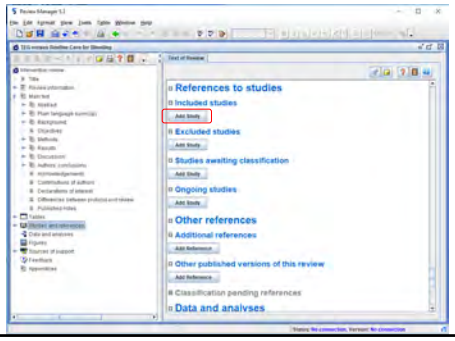

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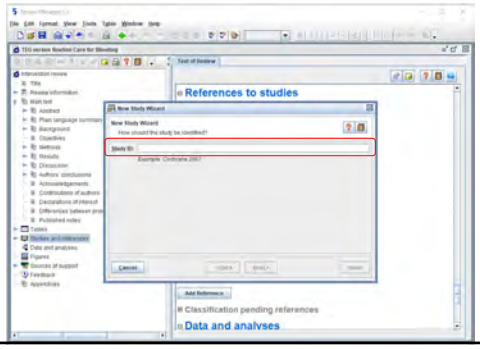

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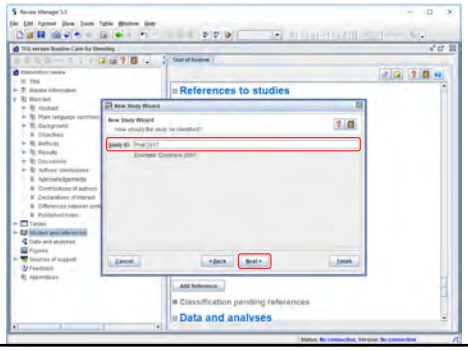

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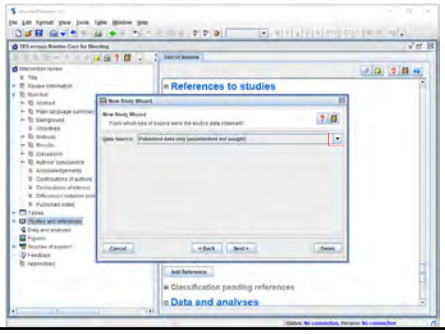

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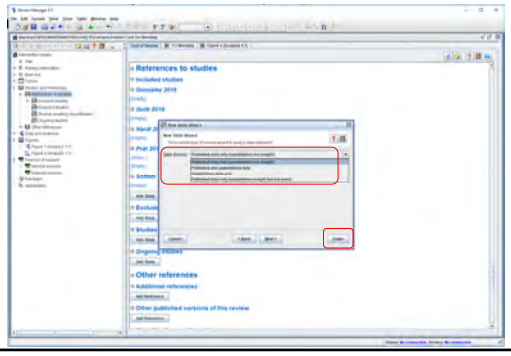

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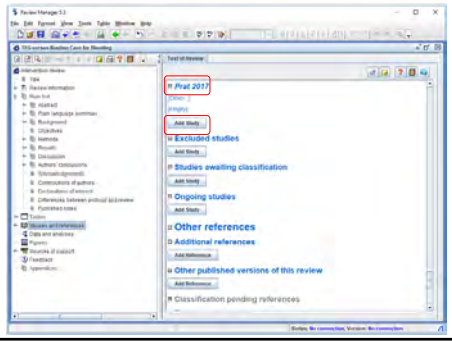

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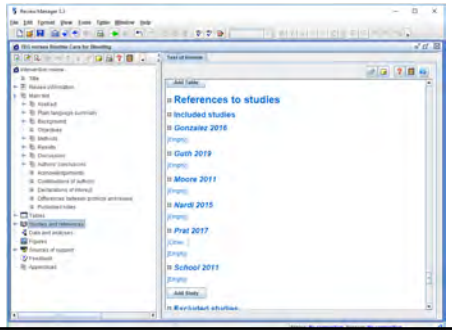
Add comparison 3.1



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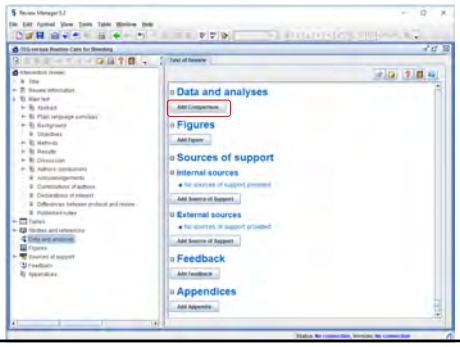

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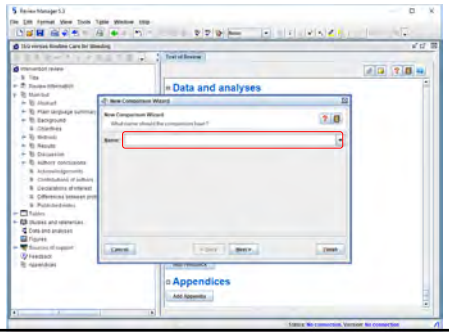

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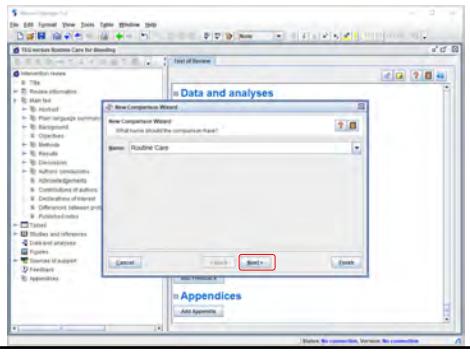

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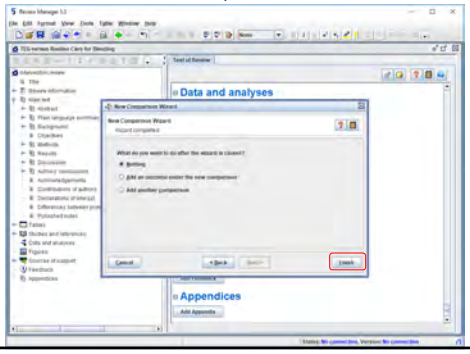

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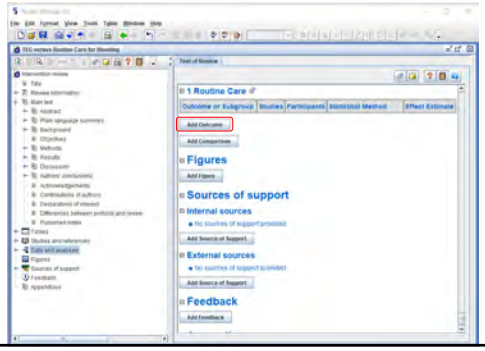

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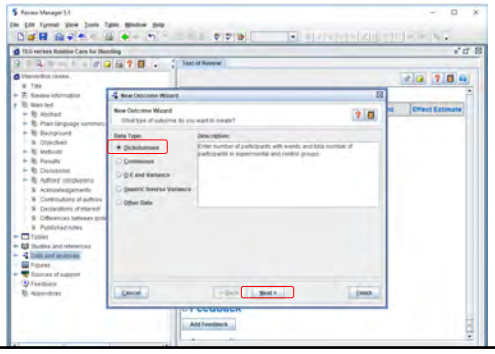

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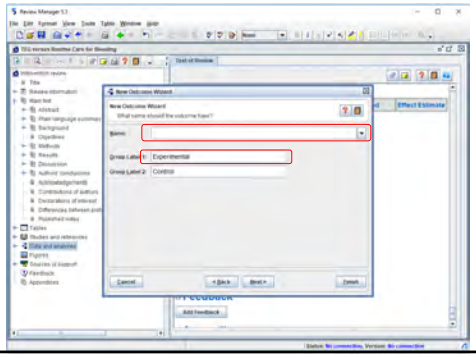

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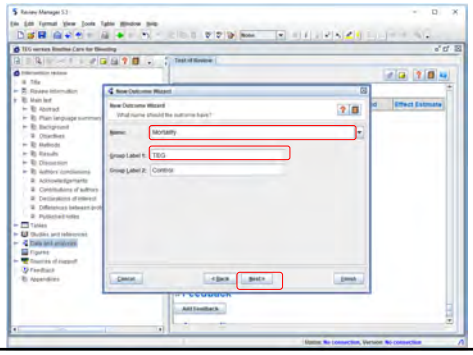

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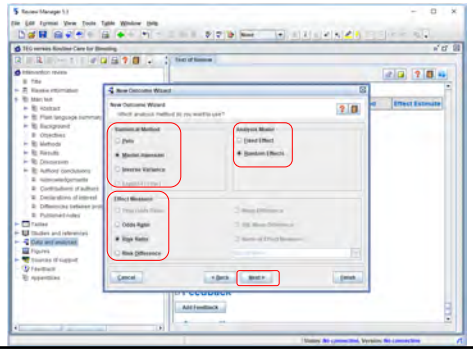


30

Statistical Method

- **Mantel – Haenszel** – weight given to each study depends upon which effect measure is used (OR, RR, RD), better statistical properties than inverse variance when there are few events
  - Generally the default fixed effect method of meta-analysis
- **Inverse Variance** – weight given to each study is chosen to be the inverse of the variance of the effect estimate (one over the square of its standard error)
  - Larger studies with smaller standard errors are given more weight than smaller studies with larger standard errors
- **Peto** – similar to inverse variance but weight given by sum of 'O-E' statistics where O is observed events and E is expected events in the experimental intervention group of each study

31

Analysis Models for Meta-Analysis

- **Fixed Effect** – assumes all studies are estimating the same (fixed) treatment effect
  - When there is no heterogeneity among included studies, fixed effect and random effects will give identical results
- **Random Effects** – allows for differences in treatment effect from study to study
  - In the presence of heterogeneity among included studies, random effects weights the studies more equally than fixed effect and corresponding claims of statistical significance will be more conservative

32

Effect Measure

- **Odds Ratio** = odds of event in experimental group/odds of event in control group
- **Risk Ratio** = risk of event in experimental group/risk of event in control group
- **Risk Difference** = risk of event in experimental group – risk of event in control group

33

Effect Measure

Results of a clinical trial displayed as 2x2 table:

	Event (Success)	No Event (Fail)	Total
Experimental Intervention	S_E	F_E	N_E
Control Intervention	S_C	F_C	N_C

- **Odds Ratio** = $\frac{S_E/F_E}{S_C/F_C} = \frac{S_E F_C}{F_E S_C}$
- **Risk Ratio** = $\frac{S_E/N_E}{S_C/N_C}$
- **Risk Difference** = $\frac{S_E}{N_E} - \frac{S_C}{N_C}$

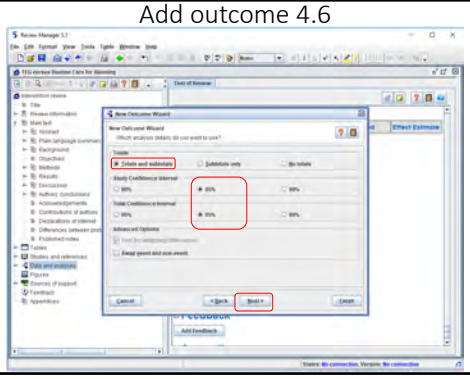
34

Effect Measure

- **Peto Odds Ratio** – only used to pool odds ratios
  - Uses inverse variance approach
  - Utilizes an approximate method of estimating the log odds ratio
  - Works well when intervention effects are small, events are not common, and studies have similar number of experimental and control participants
  - May introduce bias if applied inappropriately
  - Not recommended for default approach to meta-analysis

35

Add outcome 4.6



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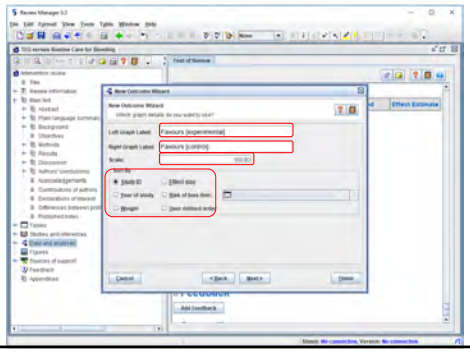

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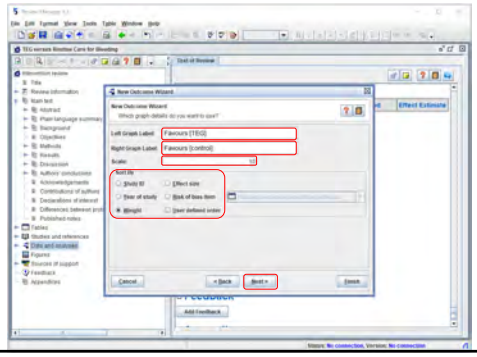

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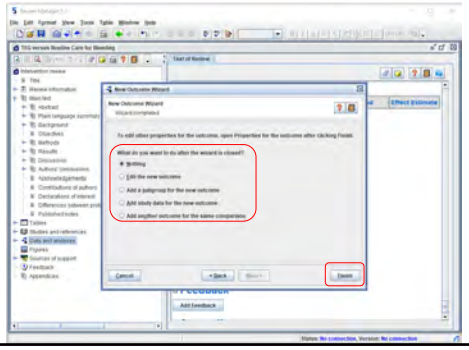

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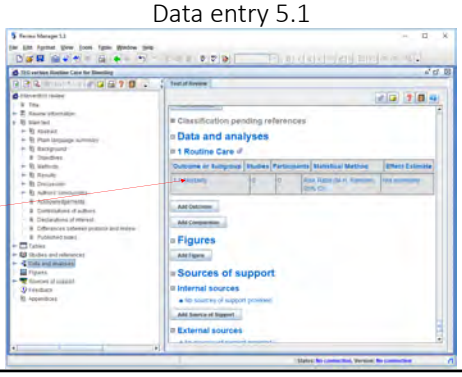

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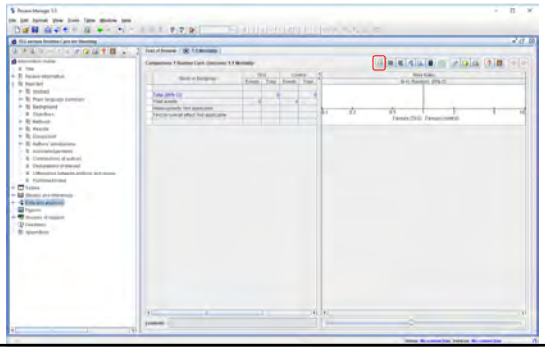

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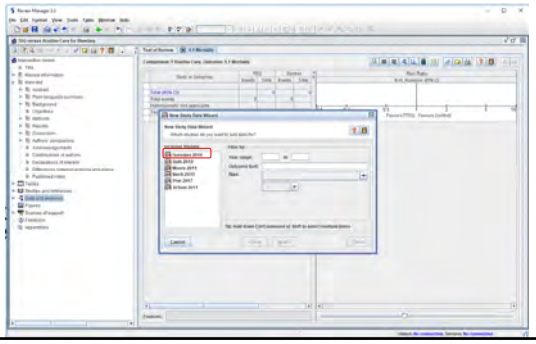

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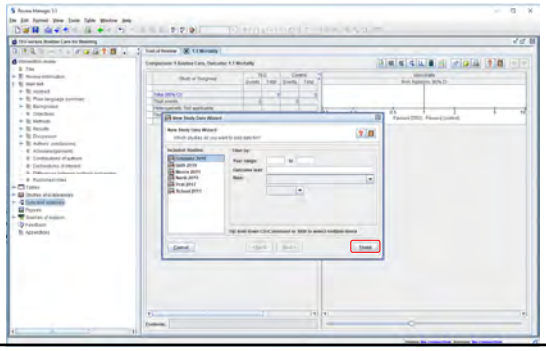

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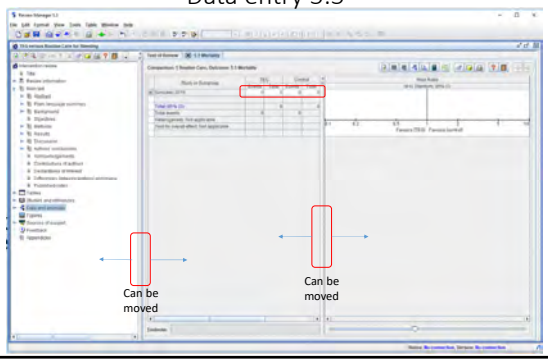

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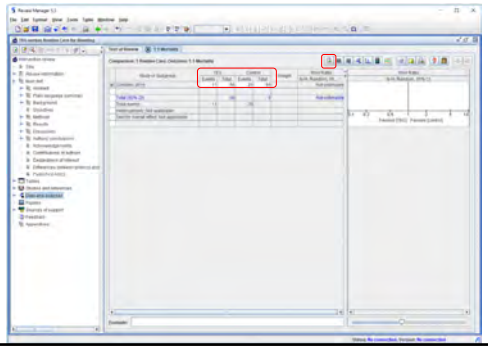

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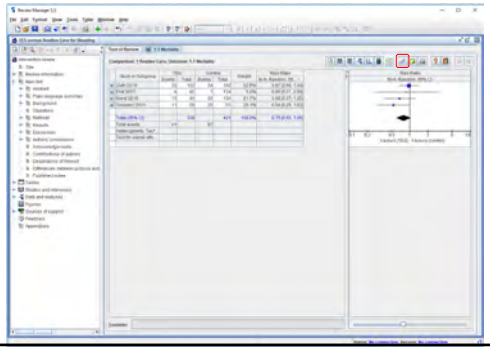

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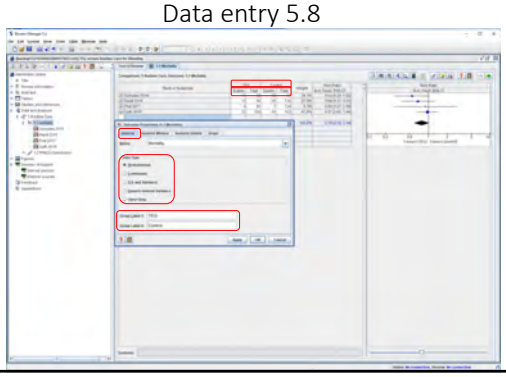

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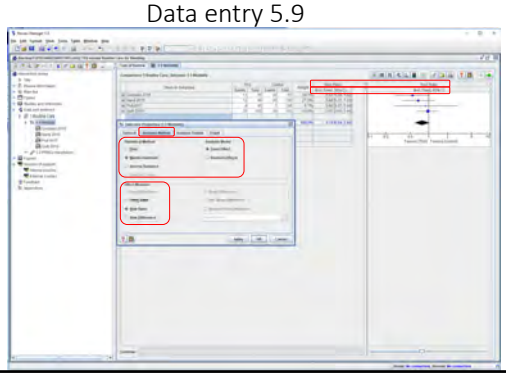

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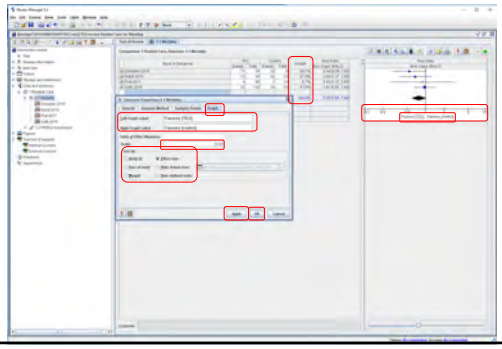

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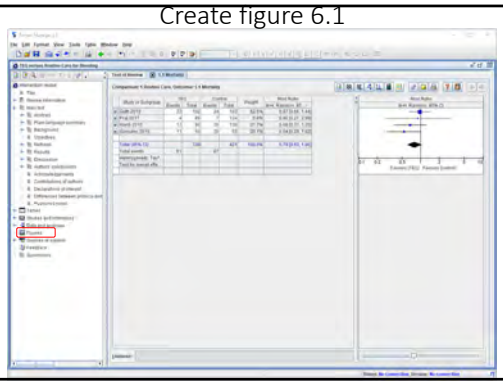

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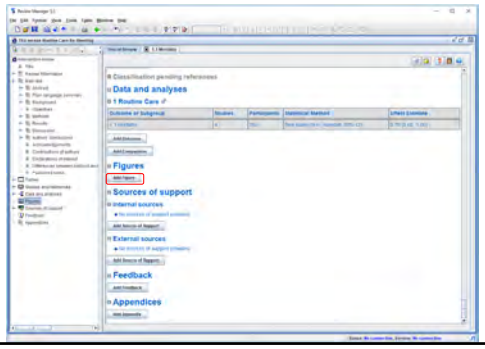

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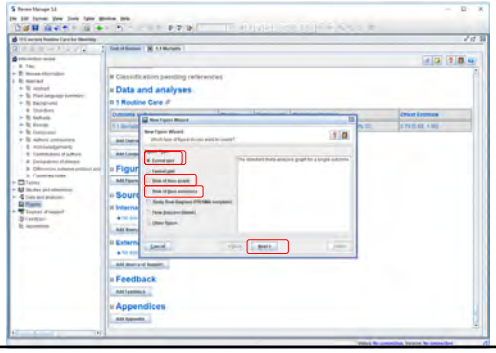

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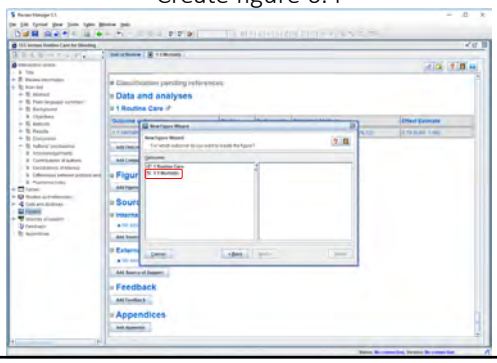

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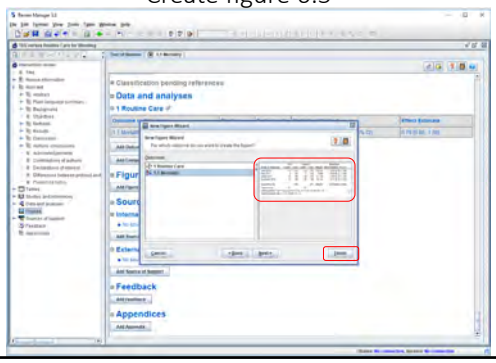

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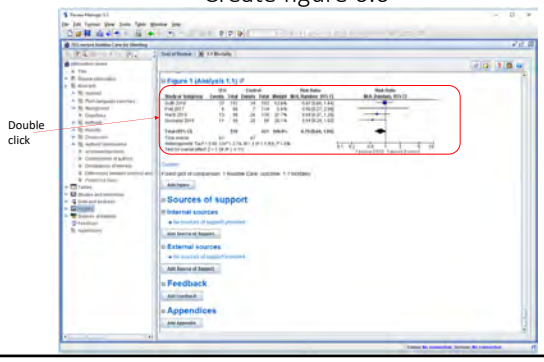

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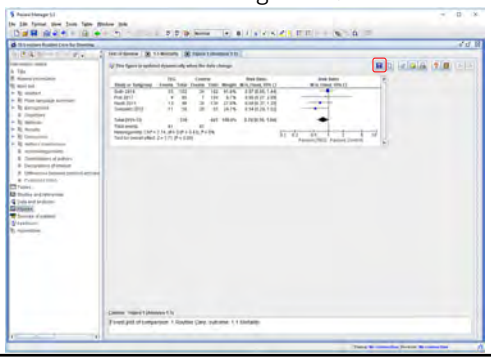

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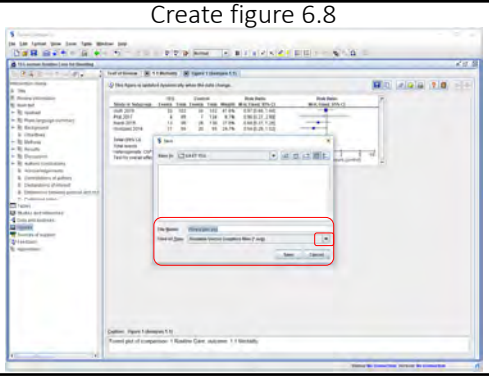

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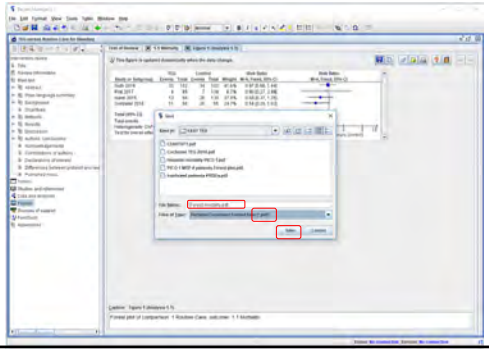

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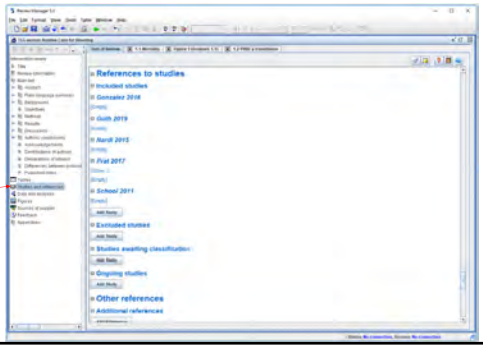
Double click



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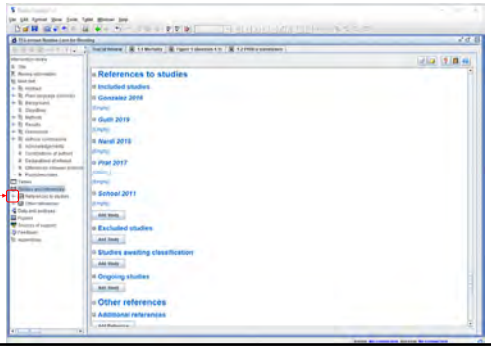

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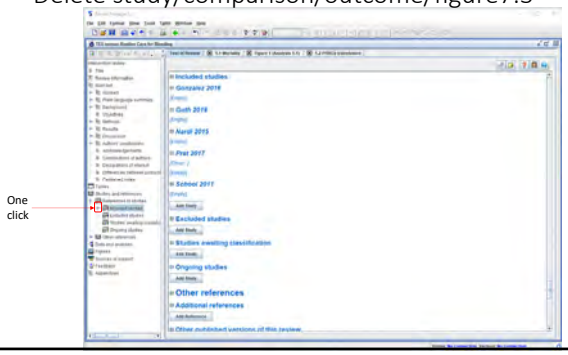

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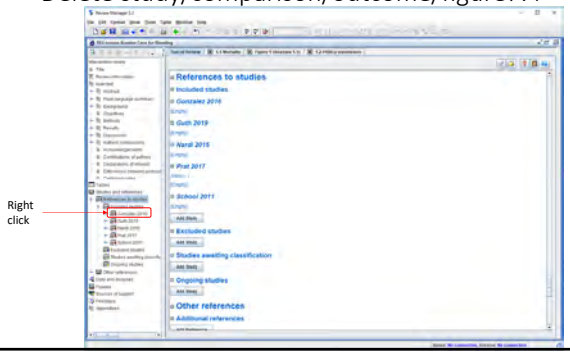

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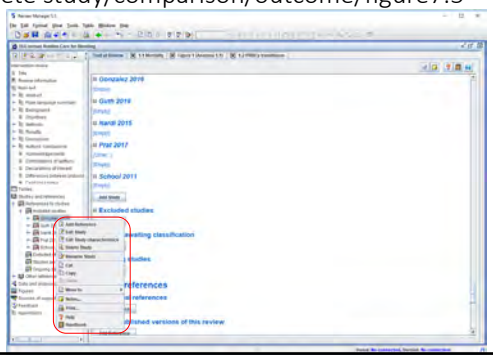

63

Thank you!

EAST GRADE Course 2020
Using GRADEpro Software

Jin Ra MD, FACS
Nicole Fox MD, MPH, FACS, CPE

1

GRADEpro GDT main functions

- Support professional individuals and groups in creating complete healthcare guideline development from team composition and management, subject inception, generation of recommendations, authoring the final recommendations and the dissemination of the guidelines.

2

Getting Started

- Using the Chrome browser, open the website for GRADEpro GDT
  - https://gradepro.org/
- Click on "log in/sign up"
- Create a new account and click the box to agree to the "Terms of Service" and the "Privacy Policy"
  - If you already have an account, just log in.
- After you have logged in, you will see the GRADEpro GDT dashboard

3

GRADEpro Handbook

https://gdt.gradepro.org/app/handbook/handbook.html

- Free online guide that describes the GRADE process
- Divided into chapters that correspond to the steps of applying GRADE approach.
- There are hyperlinks for certain terms and concepts to access definitions and specific sections elaborating on those concepts
- It is intended to accompany the GRADEpro software

Create a New Project

- Click either a "New Project" in the right upper corner or "Import Project"
- A box will open up to name the project and the type
  - For the "Type" we will choose "Full Guideline"
- The next screen shows a panel on the left with several options to choose from:
  - Creating tasks
  - Create team members, conflicts of interest forms
  - The scope of the project
  - Adding references, prognosis, comparisons, etc

Settings

- You can choose the standard GRADE template or modify the base template to fit your needs.
- Different templates are also available

Tasks

- Click “Tasks” to add/delete tasks to the calendar
- Click “Checklist” to review the steps necessary to create your guideline.
- It provides pointers and ways you can organize your group and keep track of your guideline development.
- There are also references if needed for your review in each information box.

Team

- You can add team members in this section
- Under “conflicts of interest” you can send forms, reminders as well as what type of form to be sent to members

Scope

- Under the “General” tab it is basically a proposal page you can fill in
  - Title
  - Purpose
  - Perspective
  - Target population
  - Setting
  - Key co-existing conditions
  - Types of interventions
  - Key stakeholders and users
  - Key resources
  - Existing documents

Scope- cont'd

- "Questions" tab
  - You can add a management, diagnostic, or free form a PICO question and send it to the group.
- "Outcomes" tab
  - You can add an outcome and send to the group

References

- You can add all of your resources either manually or imported

Prognosis

- You can add a prognostic question here

Comparisons

- You can add a management or diagnostic question or you can import questions. Then hit "Save".
- Once you add a question, click on the box:
  - The next screen will be your "Evidence Table"
  - You will "Add Outcome" you are going to study.
  - Next fill in the "certainty assessment" section
  - Then fill in the "summary of findings" section

Comparisons-cont'd

- "Recommendations" tab: Judgement, Research Evidence and additional consideration can be entered
  1. Problem
  2. Desirable effect
  3. Undesirable Effects
  4. Certainty of Evidence
  5. Values
  6. Balance of Effects
  7. Resources Required
  8. Certainty of evidence of required resources
  9. Cost effectiveness
  10. Equity
  11. Acceptability
  12. Feasibility

After all areas are filled in, below you will be able to seethe "Summary of Judgments"

Then you can determine the "Type of Recommendation"

Comparisons-cont'd

- "Conclusions"
  - Here you can add the following
    - Recommendation
    - Justification
    - Subgroup considerations
    - Implementation considerations
    - Monitoring and evaluation
    - Research priorities
- "Presentation" tab
  - You can select who the presentation is for which will change the format of the information displayed and the recommendation.

Multiple Comparisons

- Enables users to compare multiple interventions between each other within a single recommendation framework.
- Can compare date from 3-8 PICO questions.

Panel Voice

- Here you can choose a questions and you will go to "Evidence to Decision" table to edit it or see voting results.
- Under "responses" you will be able to see the number of responses and if you click on the number you can see who has not voted yet and be able to send them a reminder.
- The "status" section will show which " Evidence to Decision" table part in each question is ongoing or closed.
- "Actions" will display which action you can perform:
  - Send, resend, close current part, send next part, and finish question
- "Feedback status" is where you can see the matrix of responses for each question that you sent to the panel members and send reminders

Document Sections

- Here you can create, modify and export the complete guideline document.
  - Abstract
  - Executive Summary
  - Table of Contents
  - Introduction
  - Scope and Purpose
  - Methods
  - How to Use These Guidelines
  - General Issues Necessary for Correct Interpretation and Implementation of Recommendations
  - Key Questions
  - Recommendations
  - Plans for Updating Guidelines
  - Updating or Adapting Recommendations Locally
  - Conclusions
  - References
  - Appendices

Dissemination

- Create Decision Aids
- Publish Table to Online Database
- Transform Guideline to Mobile App

Eastern Association for the Surgery of Trauma
east

EAST GRADE course 2020
Creating Recommendations

Kaushik Mukherjee MD MSCI FACS
Rishi Rattan MD FACS

www.east.org @EAST_Trauma

1

Context

- Clinical and medicolegal implications
- Reflects authors' confidence of net desirable effect of intervention
- Separate from rating quality of evidence
- More than just synthesizing evidence

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2

The Gold Standard Paper on this Topic

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: going from evidence to recommendations

The GRADE system classifies recommendations made in guidelines as either strong or weak. This article explores the meaning of these descriptions and their implications for patients, clinicians, and policy makers.

Guyatt GH[1], Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group BMJ. 2008 May 10;336(7652):1049-51.
doi: 10.1136/bmj.39493.646875.AE.

3

More than just synthesizing evidence

- Scientific evidence (quality, valuation of outcomes)
  - You can have a recommendation based on low-quality evidence or vice versa
- Risk-benefit ratio
  - If the benefits are small but the risks high, recommendation unlikely
- Values/wishes of those affected by intervention
  - Particularly relevant for palliative care, pain management, cancer, etc
- Feasibility (acceptability, cost, resources, etc)
  - May be difficult to recommend a highly expensive or resource-intensive treatment

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4

Strength

- Recommendation (we recommend/recommend against) aka "strong recommendation"
  - Desirable clearly outweigh the undesirable effects, or clearly do not
- Conditional Recommendation (we conditionally recommend/recommend against) aka "weak recommendation"
  - Tradeoffs less certain (low-quality, effects balanced, feasibility uncertain)
- No Recommendation
  - Generally cases where evidence is so minimal or poor that the collective data do not support a conclusion
  - Individual providers should discuss the risks/benefits with their patients and make a decision using their best judgment

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5

Recommendation

- For patients: most would want the recommended course of action
- For clinicians: new standard of care, most should receive intervention
- For policy makers: can be adopted as a policy in most situations
- Potential medicolegal implications…

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Conditional Recommendation

- For patients: most would want, but many would not
- For clinicians: employed in majority of cases with discussion
- For policy makers: substantial debate, stakeholder involvement

No Recommendation

- For patients: some may want, some may not
- For clinicians: may be employed based on provider judgment and discussion with the patient
- For policymakers: Wait for more evidence

Tips on Making Recommendations

- Goal for consensus, otherwise anonymous voting
  - Need 50% approval, no more than 20% favoring alternative
  - Strong recommendations need 70% approval
  - GRADE grid, other EAST-approved methods when consensus elusive
- Be transparent about all steps in manuscript
- Convert PICO question into statement

Questions

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EAST GRADE course 2020
Drafting the Manuscript

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Overall approach

- Review recent guidelines from task force for format
- *J Trauma Acute Care Surg* requirements (primary journal)
  - *JACS, Annals of Surgery, JAMA Surgery, Surgery* are all potential secondary journals
  - Don't get discouraged—it's just like publishing anything else (takes patience)
- Divide and conquer sections, limiting authors for accountability
  - Keep track of who's doing what

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Introduction

- Standard introduction (problem, known/unknown, bridging gap)
- Objectives
- PICO questions (include formulation, outcomes valuation)

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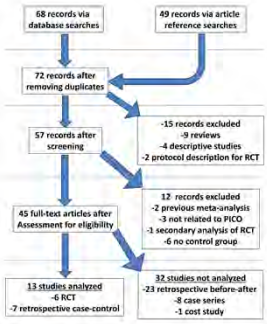
Methods

- Detailed literature search strategy, screening process (PRISMA chart)
- Inclusion/exclusion criteria
- Data extraction, grading methodology (including conflict adjudication)
- Statistical analyses, software used



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Results

- Qualitative synthesis (systematic review)
- Quantitative synthesis (meta-analysis), if possible
- Evidence Profile Table
- Summary of Findings Table
- Grey literature narrative review?

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Evidence Profile Table

Appendix 2. Evidence Profile Table

	Study Design	Risk of Bias**	Certainty Assessment Inconsistency	Indirectness	Imprecision	Other Considerations	Certainty	Importance
Critical Outcomes	RCT RCCS	Serious Serious	Not serious Serious	None None	None None	None None	Low Low	Critical Critical
Critical Functional Outcomes	RCT	Serious	Not serious	None	None	None	Low	Critical
Important Outcomes	RCT RCCS	Serious Serious	Not serious Serious	None None	None None	None None	Low	Important Important

*RCT = Randomized Controlled Trial, RCCS = Retrospective Case-Control Study
**Risk of bias was felt to be due to lack of allocation concealment and lack of blinding

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Summary of Findings Table

Table 2. Summary of Findings and Factors Affecting the Recommendation

Outcome	Anticipated Absolute Effect (95% CI)		Relative Effect (95% CI)	Participants (Studies)
	Risk with Standard Care	Risk with Orthogeriatric Care		
Critical Outcomes				
Hospital Mortality (RCT)	43/1000	37/1000 (14, 94)	OR 0.84 (0.31, 2.28)	1043 (4)
Hospital Mortality (RCCS)	63/1000	49/1000 (43, 57)	**OR 0.78 (0.67, 0.90)**	13591 (5)
1-Year Mortality (RCT)	247/1000	194/1000 (137, 274)	OR 0.77 (0.50, 1.19)	490 (2)
1-Year Mortality (RCCS)	164/1000	143/1000 (135, 171)	OR 0.84 (0.68, 1.04)	3434 (2)
Discharge to Home (RCT)	288/1000	360/1000 (203, 553)	OR 1.39 (0.63, 3.06)	803 (3)
Critical Functional Outcomes				
Mobility at 6 Months (SPPB, RCT)	Ref	**0.78 (0.28, 1.29)**		567 (2)
Mobility at 12 Months (SPPB, RCT)	Ref	0.53 (-0.05, 1.1)		477 (2)
Cognitive Status at 4 Months (MMSE, RCT)	Ref	1.07 (-0.05, 2.15)		569 (2)
Cognitive Status at 12 Months (MMSE, RCT)	Ref	**1.57 (0.4, 2.73)**		477 (2)
Functional Status at 4 Months (NEADL, RCT)	Ref	**5.86 (2.61, 9.1)**		574 (2)
Functional Status at 12 Months (NEADL, RCT)	Ref	**1.11 (0.36, 1.85)**		493 (2)
Functional Status at 4 Months (BADL, RCT)	Ref	**1.01 (0.28, 1.73)**		575 (2)
Functional Status at 12 Months (BADL, RCT)	Ref	**4.02 (0.57, 7.47)**		493 (2)
Important Outcomes				
Length of Stay (days, RCT)	Ref	-1.02 (-4.44, 2.41)		3663 (6)
Length of Stay (days, RCCS)	Ref	1.87 (-3.14, 7.07)		13591 (5)
Hospital Medical Complications (RCT)	333/1000	444/1000 (314, 586)	OR 0.70 (0.40, 1.24)	548 (2)
Hospital-acquired Pressure Ulcers (RCT)	106/1000	42/1000	**OR 0.30 (0.15, 0.60)**	548 (2)

Criteria	Summary of Judgments
Significant Problem	Yes
Desirable Effects	Moderate
Undesirable Effects	Small
Certainty of Evidence	Low
Values	Probably no important uncertainty or variability
Balance of Effects	Probably favors the Intervention
Acceptability	Probably yes
Feasibility	Probably yes
Final Recommendation	Conditional Recommendation

*RCT = Randomized Controlled Trial, RCCS = Retrospective Case-Control Study, SPPB = Short Physical Performance Battery, MMSE = Mini-Mental Status Exam, NEADL = Nottingham Extended

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Recommendations

- Incorporates evidence and aforementioned considerations
- Methodology transparency, especially if no consensus
- Figure that integrates recommendations into practice

We *conditionally recommend* that for elderly adults with hip fracture, orthogeriatric treatment be performed as opposed to standard treatment.

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Conclusion

- Standard discussion section summary
- "Using these guidelines in clinical practice" section
- "Summary of recommendations" table

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Questions

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12 Steps to EAST Practice Management Guideline (PMG) Development

Eastern Association for the Surgery of Trauma

Advancing Science, Fostering Relationships, and Building Careers

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January 2019

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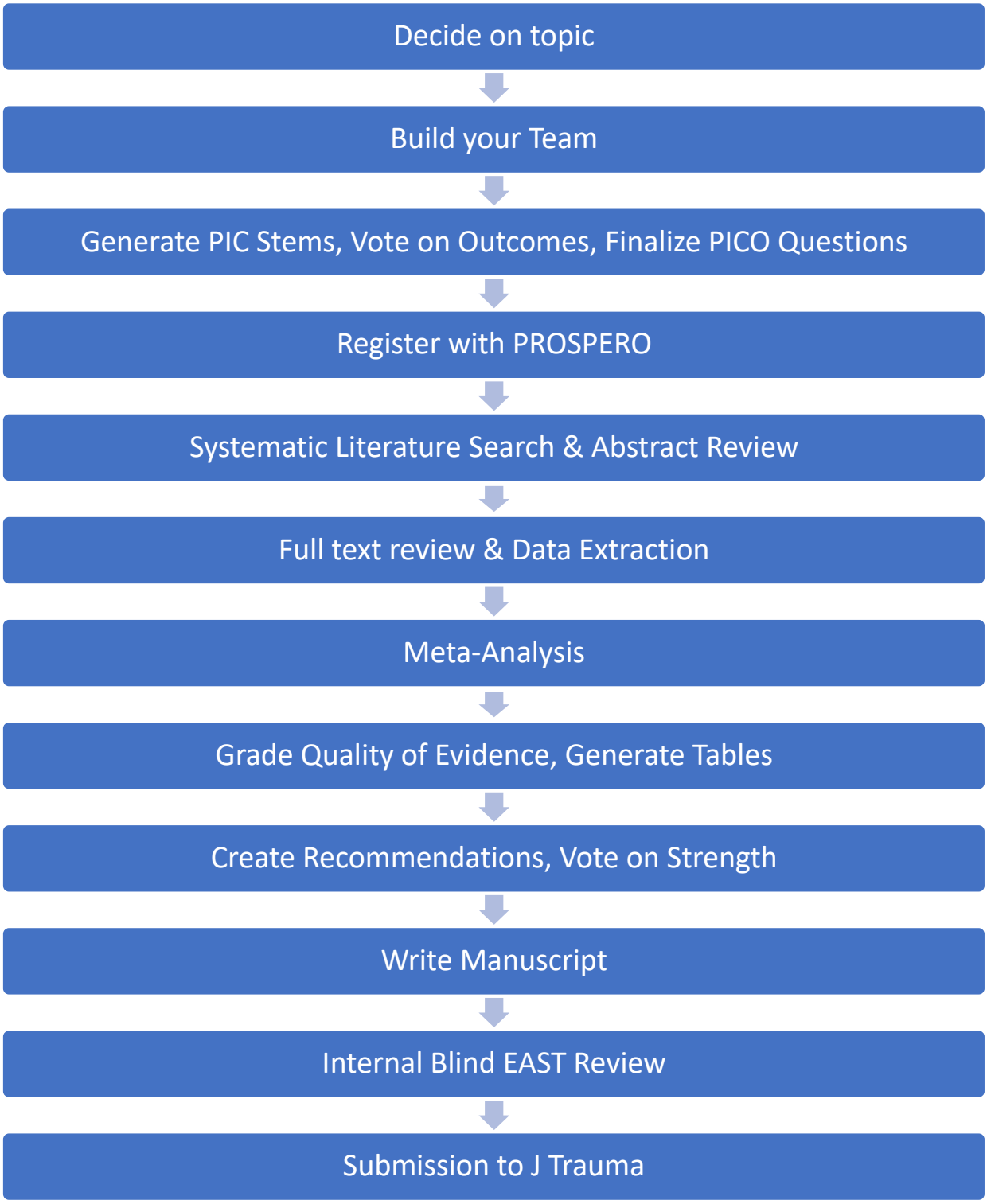
12 Steps to EAST PMG Development



1. DECIDE ON PRACTICE MANAGEMENT GUIDELINE (PMG) TOPIC

- Decide to create a Guideline on something you are enthusiastic about and feel you can contribute something more.

- Ensure that no other societies have already a Guideline in place for the exact same topic (look at Western Trauma, AAST, other non-surgical societies that may be relevant to the topic, etc).

- Do a quick literature search to ensure there is enough data available on the topic. The importance of this step, cannot be overstated! It can save a lot of time and effort later on, if discussions are had and progress is made on a topic with little or no available literature.

- **Duration: 2-3 weeks**

2. BUILD YOUR TEAM

- Use your EAST network to gather peers who share your excitement about the topic you want to look into, and sign them up yourself!

- As a list of volunteers interested in participating in PMG development exists, feel free to ask the Guideline Committee leadership to connect you with potential candidates.

- Visit https://www.east.org/education/practice-management-guidelines/guidelines-under-development/proposal and provide details of your PMG proposal. If/when approved, it will be available on the EAST website for more volunteers to sign up!

- While topic experts are desirable in the team, ensure that opinions held by team members among the team are well-balanced, and there are no conflicts of interest.

- All team members need to be EAST members! An exception can be made when expertise may be available outside the trauma community (e.g. you are looking at rhabdomyolysis and feel a nephrologist would be able to add significant expertise).

- Ensure all group members are aware that they are expected to contribute equally to the workload.

- Set up a conference call among group members (Christine Eme - ceme@east.org - can help you with this) to start getting to know each other, exchange contact information, inquire about each other's practice patterns on the topic of interest, and start identifying potential questions that could/should be addressed on the PMG.

- In general, it is a good idea to keep notes of what is discussed in each conference call, and share afterwards with everyone on the team, including those that were unable to participate. Helps bring everyone up to speed!

- **Duration: 2-3 weeks**

3. FORMULATE PICO STEMS, VOTE ON OUTCOMES, FINALIZE PICO QUESTIONS

- Once you have decided on specific topics/questions to be addressed, start framing them in the **PICO** format: Decide on a specific patient population (**P**) (e.g. patients with high grade blunt splenic injury), and pick two methods that can be used to address the problem at hand, the Intervention (**I**) and the Comparator (**C**). (e.g. angioembolization vs splenectomy). '**O**' refers to the outcomes, which are discussed below.

- These are best and most efficiently decided via email. Ensure you include everyone in the group!

- Whenever you ask for feedback on something like this, set a deadline to respond by (around a week), or you will consider that non-responding group members are ok with the proposed questions/outcomes/results/etc. If you are not receiving feedback / responses from a few members repeatedly, contact them individually to ensure they are still interested in the project.

- Aim to address not topics that are very obvious and have been the standard of care for decades (e.g. In patients with gunshot wounds to the abdomen presenting with hemodynamic instability and peritonitis, should immediate operative intervention vs observation be considered), but areas where management is still reasonably controversial and variable (e.g. In patients with persistent neck pain after blunt trauma and negative CT imaging, should MRI imaging be obtained vs prolonged c-spine immobilization), or topics where new technology or methodology has recently become available (e.g. In patients with hemorrhagic shock after penetrating trauma, should thromboelastography be used to guide resuscitation vs low-ratio component therapy be undertaken)

- Remember that <u>each outcome</u> requires its own literature search, abstract & manuscript review, data extraction and analysis, so choose wisely the number of questions / outcomes you want to address. 2-3 PICO Questions with 1-3 outcomes each is a good number for a PMG.

- With the PIC stems available, it is time to decide on the Outcomes (O). Come up with a broad list of potential outcomes for each PICO, both specific to the studied topic, plus some broad commonly measured outcomes (e.g. mortality, ICU LOS, hospital LOS, duration of mechanical ventilation, etc). Share with the group and ask if they have any others they would like to add in one or more PICOs. <u>*Best done via email, not conference call*</u>.

- The outcomes are specific to and tailored to each PICO, and different PICO questions covering the same topic may cover different outcomes.

- When the final list of potential outcomes for each PIC stem is available, send again to the group, and ask *everyone* to rate each outcome on a scale from 1-9, with 9 being very important, and 1 of very little importance. Stress that each rating should be specific for the PICO question asked: e.g. although survival is obviously the most important outcome, it should not be rated as the most important when the goal is ventilator weaning.

- Stress that each member has to respond to you privately (so they do not influence one another). Set a small internal deadline, as discussed earlier! Send individual emails to those who have not responded by then, asking for a response. You need a rating for each outcome for each PICO from every member of your group!

- Calculate the means of the ratings for each outcome for each question - there can only be up to 7 per PICO question. Even that is too many usually, as each outcome requires its own analysis. You may have to typically limit to just the critical ones (those with a rounded mean of 7-9), and perhaps the important ones (those with a rounded mean of 4-6). The outcomes of limited importance (rounded means of <4) are typically not studied.

- Keep track of the list of outcomes and their ratings for each PICO question, as this process is commonly included in the manuscript!

- **Duration: 4-6 weeks**

4. REGISTER YOUR GUIDELINE WITH PROSPERO

- Register your project to PROSPERO (http://www.crd.york.ac.uk/PROSPERO) – ideally before the literature search, and definitely before data extraction!!! Takes less than 20 minutes! You describe the project in a few words, and state what questions you will be addressing. The purpose of this topic is so that questions do not change after the results of the review.

- Remember to visit again at the end of the project, and state your findings / recommendations.

- **Duration: 30 minutes**

5. SYSTEMATIC LITERATURE SEARCH & ABSTRACT REVIEW

- **Use your institution's librarian** for your literature search – they are typically far more comfortable running complex searches (each search engine uses different methodology). **Search at least 3 different search engines** (PubMed, Cochrane, Embase, Web of Science, etc). Try to use broad search terminology, especially if you are aiming to do just one literature search for all PICOs combined (have librarian use Boolean terms). Keep track of the exact terms / methodology used, as most journals will ask for it (usually as an e-supplement) at the time of manuscript submission.

- Gather all abstracts in an Excel sheet, and remove the duplicates. Then **assign each abstract to two group members for review**. They have to decide whether it should be included or not, and if excluded why. (see example Sheet below)

- Instead of manually keeping track of abstract reviews, the process may be automated via literature managing software, such as:
    - **Covidence** (covidence.org) (requires subscription)
    - **Rayyan** (rayyan.qcri.org/welcome) (free), and
    - **Colandr** (https://www.colandrapp.com/signin) (free)

  Help guides are available for all three:
    - http://support.covidence.org/help_center
    - https://libraryguides.mcgill.ca/rayyan/gettingstarted
    - https://www.colandrcommunity.com/training.html

  These web-based tools facilitate collaboration, storing, accessing and reviewing available data

- For abstracts to be included in the next step (full manuscript review), they need to include a patient population similar to the one you are studying, and must include groups with the two interventions being compared in your PICO. Case reports, commentaries, reviews, and animal studies are excluded. Although meta-analyses are also excluded, they can be useful to help identify literature that should be included in your PMG. Depending on availability of translation services at your institution, you may limit your search to the English language, or not.

- The reason for exclusion for each abstract has to be recorded. Common reasons include: 1. Study does not include intervention & comparator groups, 2. Not a primary study (e.g. commentary, meta-analysis, review), 3. Case report, 4. Animal study, 5. Not in English, 6. Other. If more than one reasons exist for an abstract, select the higher one on the list.

- Allow 2-3 weeks for abstract review (depending on number of abstracts assigned per reviewer).

- The group leader has to now combine the data from group members in a single master sheet, and adjudicate any differences. Alternatively, any of the automated literature review web-based solutions may help with record keeping. Please keep track of the above, as it will be needed for the PRISMA Study Flow sheet.

- **Duration 3-4 weeks**

Reviewers	First Author	Year of Pub	Title	PMID	Abstract	Include	Reason for Exclusion
						1: Yes, 0: No	1: No Int/Comp groups 2: Not primary study 3: Case report 4. Animal study 5. Not in English 6. Other
AG, DC							
AG, GK							
GK, DC							

6. FULL TEXT REVIEW & DATA EXTRACTION

- Find and download the full manuscripts of all 'to be included abstracts' from your institution's library. Place them all on an online folder, and share with the group. If you don't have access to all manuscripts, ask if any other members can find them and also place them in the online folder (The online literature review solutions may also help with this task).

- Repeat the review process with the full manuscripts (whether they should be included). To be more efficient, you can combine this step with data extraction. Each manuscript should again be evaluated by two members of the group. The data extracted from the two reviewers need to match. If not, adjudicate. (see sample data extraction Sheet below)

- Allow 3-4 weeks for this task, depending on number of manuscripts & available reviewers. Make sure everyone stays on track! Communicate closely with members that may be falling behind and motivate them politely as needed!

Reviewers	First Author-Year	Patient population	Study Design	Include	Reason for Exclusion
		1. Surgery 2. Trauma 3. SICU 4. Medicine 5. Peds	1. PRCT 2. Retrosp 3. Observ.	1: Yes, 0: No	1: No Int/Comp groups 2: Not primary study 3: Case report 4. Animal study 5. Not in English 6. Other
AG, DC					
AG, GK					
GK, DC					

(continued)

Intervention – sample size	Intervention – Continuous Outcome 1 Mean	Intervention – Continuous Outcome 1 SD	Comparison – sample size	Comparison – Continuous Outcome 1 Mean	Comparison – Continuous Outcome 1 SD	p-value

(continued)

Intervention – sample size	Intervention – number with Outcome 1	Intervention – number without Outcome 1	Comparison – sample size	Comparison – number with Outcome 1	Comparison – number without Outcome 1	p-value

- **Duration: 3-5 weeks**

7. META-ANALYSIS

- Time for the meta-analysis! If you don't have access to a statistician with the skill, EAST can help!
- Two of the most commonly used software packages for meta-analyses include:
    - **RevMan** (https://community.cochrane.org/help/tools-and-software/revman-5) (free for academic use)
    - **Stata** (https://www.stata.com)

- **Duration: 2 weeks**

8. GRADE QUALITY OF EVIDENCE, GENERATE TABLES ON GradePRO

- Once you have the results of the **meta-analysis**, including your **Forest plots**, and have a **Study Characteristics table** (summarizing the patient population, intervention and control, and outcomes of the analyzed studies), generate a separate table for each Outcome on GRADEpro (https://gradepro.org) . Then, select the type of outcome (**dichotomous**, **continuous**, **time-to-event**, **narrative** depending on the type of measurement); and choose **pooled**.

- Fill out the **number of studies** analyzed and the **type of study design** (if there are more than one study type, eg both observational and randomized controlled trials (RCTs), you may separate them in two smaller tables, or take their pooled effect. Typically, in there will overwhelmingly be more observational trials than RCTs), and the number of patients in each Intervention and Control group. You don't need to enter any info in the **Control Risk** section. (If you do, select a low, moderate or high risk of the condition under study depending on its incidence in the general population – commonly quoted in most Background / Introduction manuscript sections.)

- Add the **number of patients** that developed the outcome of interest in each the **Intervention** and **Control** groups, as well as the **Effect Estimate**, as determined from your meta-analysis in the **Relative Effect** (for dichotomous outcomes - the **Absolute** Effect is automatically calculated) or **Absolute Effect** (for continuous outcomes) column. **Certainty** of evidence is automatically calculated. Ensure that the type of risk selected is the same as that calculated in the meta-analysis (Relative Risk vs. Odds Ratio vs. Hazard Ratio vs. Rate Ratio for binary outcomes, or mean difference vs. standardized mean difference vs. mean vs. median for continuous)!
    - Use **Mean Difference** (equivalent to Weighted Mean Difference) if all studies use the same measure for the continuous outcome (e.g. all studies use hours or days to measure time). Select **Standardized Mean Difference** if different investigators have used variable scales to measure the same outcome (e.g. 10-point pain scale vs. a 4-point pain scoring system)

- Finally, enter the rating of each outcome, as voted by the group (Step 3 of this guide) in the last column.

- **Now it's <u>time for a conference call</u>**, and *<u>it is very important for everyone to participate,</u>* so the quality of the evidence can be rated! (It is a good idea to have reviewed this section of the document before the conference call, and to have it available for reference).

- First, decide as a group whether the **Control Risk** (discussed earlier) is *low*, *moderate* or *high*, then enter that incidence, as discussed above.

- Then rate the quality of evidence, *as a group*, based on the quality of the reviewed studies (the results of the **meta-analysis/Forest plots**, and the **Study Characteristics table** will come in handy for this task!) *This is best done on a conference call, as a consensus needs to be reached!*

  To rate the quality of evidence in the ensuing columns, consider the following:

- **Risk of Bias:** When data are derived mostly from low quality studies.
  Downgrade quality for: lack of blinding/randomization (limited RCTs); most evidence from retrospective studies

- **Inconsistency:** Signifies that different studies show different results.
  Downgrade quality for: Outcomes from different studies all over the map; I2 >70%

- **Indirectness:** Patient populations, Interventions, Comparators and Outcomes in reviewed studies are not the exactly the same as the one tackled in the PICO Question.
  Downgrade quality for: When any of the above is dissimilar to the what the PICO question studies, and believe that these differences may affect the final outcome.

- **Imprecision**: Different studies show widely ranging results.
  Downgrade quality for: A small number of studies included (usually <3-5) per outcome; the pooled Confidence Intervals are wide; there is uncertainty about the magnitude of the effect.

- **Publication Bias:** When only studies with a positive result/association have been published.
  Downgrade quality for: Small number of studies (usually <3-5/outcome); asymmetry in Funnel plot; vast majority of studies published show a positive association.

- **Other Considerations:**
  Upgrade quality for:
  i. Large treatment effect (e.g. if there is a narrow Confidence Interval that is not crossing the no-effect vertical line of the Forest plot)
  ii. Dose-response gradient (outcome increases proportionally with intervention dose, e.g. higher risk of bleeding with higher INR, greater survival in sepsis with earlier administration of ABx and achievement of source control);
  iii. If there is plausible residual confounding that could strengthen support for the intervention (e.g. the intervention increases survival in sicker, more comorbid patients, and those comorbidities have not been accounted for in the analysis)

- **DOWNGRADE** quality of evidence, for (whenever you do, add an explanation for why you choose to do so, by clicking on the icon on the top right hand corner of Grade Pro):

- **Risk of bias** (in general, due to lack of randomized studies – the majority of trauma studies. For more granular guidance, the Cochrane Risk of Bias Assessment Tool – available at www.riskofbias.info – can be filled out. More specifically, it is lower when the following were not met in the majority of included studies:
    - Random sequence generation in treatment allocation (addresses selection bias)
    - Allocation concealment (addresses selection bias)
    - Blinding of participants (addresses performance bias)
    - Blinding of outcome assessment (addresses detection bias)
    - Incomplete outcome data (addresses attention bias)
    - Selective reporting (addresses reporting bias)
- **Inconsistency** (when Heterogeneity is high – in general if I^2>70%)
- **Indirectness** (patient populations, interventions, comparators, outcomes not the same across studies, and these differences may affect how the outcome is determined)
- **Imprecision** (Small number of patients, wide pooled Confidence Intervals, uncertainty about the true magnitude of effect)
- **Other Considerations**
    - **Publication bias** (small number of studies available, only publications available with a positive effect, asymmetry in Funnel's plot, Eggert's test results from Meta-analysis)

- **UPGRADE** quality of evidence for (under the Other Considerations column):
    - **Large effect** (pooled effect estimate far away from the no-effect vertical line on the Forest plot)
    - **Dose-response gradient** (outcome increases proportionally with intervention dose, eg higher risk of bleeding with higher INR; the earlier antibiotics are administered in sepsis, the greater the survival benefit, etc)
    - **Plausible residual confounding** (when it strengthens support for the treatment effect, eg when an intervention increases survival in sicker patients with more comorbidities)

- **Duration: 2-3 weeks**

9. CREATE RECOMMENDATIONS, VOTE ON STRENGTH

- You can discuss this step at the time of the Grading the Evidence conference call, or at a subsequent one. Review the meta-analysis results and Grade Pro summary tables, and create recommendations for each PICO question.

- Decide on the strength of the recommendation for each PICO: **Strong** (should be the new standard of care) vs **Conditional** (intervention should be employed in the majority of applicable cases). To decide on strength, consider:
    - The quality of the evidence
    - The Risk-to-benefit ratio of implementing the recommendation
    - Patients' values / wishes
    - Cost and resources needed to implement the recommendation
    - Acceptability among physicians and patients
    - Feasibility

- **Go with the lowest quality of evidence for the harmful critical outcomes, and if none, by the highest quality of evidence for the beneficial critical outcome.**
  The Quality of Evidence for the harmful critical outcomes trumps the Quality of Evidence for the beneficial critical outcomes. (Important outcomes can be ignored in making recommendations if the risk for harm is considerable)

- If no consensus is reached at the conference call, follow up with email votes. Include the results of the vote in the manuscript! ***This process is public and all group members need to be comfortable with the recommendation being made!***

- ***For a recommendation to be strong, at least 70% of the group has to approve a strong recommendation*.**

- Word your recommendations based on the format of the PICO questions (e.g. In adult penetrating trauma patients who present with hemodynamic instability and peritonitis, we recommend immediate operative intervention (versus observation) to improve survival, decrease complications, shorten length of stay and allow earlier return to work).

- **Duration: 2-3 weeks**

10. DRAFT MANUSCRIPT

- Time for manuscript writing!

- Start with an introduction that states the magnitude of the problem, the current practice, and data already available. Then state what is still unknown, the purpose of the project, and the questions to be addressed.

- Clearly state the Objectives of the project, describe the PICO formulation process, the literature search, and data extraction methodology. If you have been diligent with the previous steps, all the information should be readily available to you.

- For each PICO, include a **Qualitative Synthesis** and a **Quantitative Synthesis** section.

- In the **Qualitative Synthesis** section, discuss differences in patient populations recruited, methodology employed, and findings among the reviewed manuscripts. Critically discuss these differences, and how they may affect your final recommendation. Also comment on notable observations from the literature review, if practice patterns seem to have changed over time, if there are specific subpopulations that may benefit more or less from the studied intervention, other nuanced observations that may sway management one way or another.

- In the **Quantitative Synthesis**, review and discuss the results of the meta-analysis, and present the findings on the GRADE pro tables.

- Finally, include a **Conclusion** section, where you summarize the recommendations, and reiterate any exceptions where the recommendations may be particularly or not applicable.

- Include a table with the PICO questions and Recommendations, for those who will not read the full manuscript.

- **Duration: 3-4 weeks**

11. SUBMIT TO EAST FOR INTERNAL BLIND REVIEW

- Submit to the Guidelines Committee leadership for blinded review.
- Edit your manuscript based on reviewers' comments.

- **Duration: 1-2 weeks**

12. SUBMIT TO THE JOURNAL OF TRAUMA

- Good luck!
- Don't forget to sign up to help with other PMGs in development!

- **Duration: 1 afternoon**