Conflict of interest/experience

- GRADE developer and advocate
  - professional life over 10 years
- author two handbook chapters
  - 11 presenting results and SoF tables
  - 12 interpreting results and drawing conclusion
- experience with multiple guideline groups
  - most intense ACCP antithrombotic therapy
  - all clinical
  - recently, all using GRADE

GRADE Uptake

Agencia sanitaria regionale, Bologna, Italia
Agency for Health Care Research and Quality (AHRQ)
Allergic Rhinitis and Group - Independent Expert Panel
American College of Cardiology Foundation
American College of Chest Physicians
American College of Emergency Physicians
American College of Physicians
American Endocrine Society
American Society of Gastrointestinal Endoscopy
American society of Interventional Pain Physicians
American Thoracic Society (ATS)
BMJ Clinical Evidence
British Medical Journal
Canadian Agency for Drugs and Technology in Health
Cochrane Collaboration
EBM Guidelines Finland
Emergency Medical Services for Children National Resource Center
European Association for the Study of the Liver
European Respiratory Society
European Society of Thoracic Surgeons
Evidence-based Nursing Sudtirol, Alta Adiga, Italy
German Agency for Quality in Medicine
Infectious Disease Society of America
Japanese Society of Oral and Maxillofacial Radiology
Joslin Diabetes Center
Journal of Infection in Developing Countries
Kidney Disease International Guidelines Organization
National and Gulf Centre for Evidence-based Medicine
National Institute for Clinical Excellence (NICE)
National Kidney Foundation
Norwegian Knowledge Centre for the Health Services
Ontario MOH Medical Advisory Secretariat
Polish Institute for EBM
Scottish Intercollegiate Guideline Network (SIGN)
Society of Critical Care Medicine
Society of Pediatric Endocrinology
Society of Vascular Surgery
Spanish Society of Family Practice (SEMFYC)
Stop TB Diagnostic Working Group
Surviving sepsis campaign
Swedish Council on Technology Assessment in Health Care
Swedish National Board of Health and Welfare
University of Pennsylvania Health System for EB Practice
UpToDate
World Health Organization (WHO)

Guideline concerns

- reviews we need aren't available
- choice between multiple agents
  - bigger and bigger issue for guidelines
- what can Cochrane do
  - more "network meta-analyses"
  (mixed treatment comparisons, multiple treatment meta-analysis)
- requires special statistical expertise

What are the needs of guideline developers?

Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

To trade-off guideline developers need ALL important outcomes

- think like a guideline developer

Chapter 5 Handbook: "Cochrane reviews should include all outcomes that are likely to be meaningful to clinicians, patients (consumers), the general public, administrators and policy makers. Outcomes considered to be meaningful, and therefore addressed in a review, will not necessarily have been reported in individual studies."

- quality of life in cancer studies

Mortality High vs low PEEP in ALI and ARDS

Population	No. of participants (trials) †	Higher PEEP	Lower PEEP	Adjusted Relative Risk (95% CI; *P*-value) ‡	Adjusted Absolute Risk Difference (95% CI)	Quality
Patients with ARDS	1892 (3)	324/951 (34.1%)	368/941 (39.1%)	0.90 (0.81 to 1.00; 0.049)	-3.9% (-7.4% to -0.04%)	High
Patients without ARDS	404 (3)	50/184 (27.2%)	41/220 (18.6%)	1.37 (0.98 to 1.92; 0.065)	6.9% (-0.4% to 17.1%)	Moderate (imprecision)

		Quality Assessment					***Summary of Findings***			
							Quality	**Relative Risk (95% CI) p-value**	**Illustrative risks**	
Outcome	**No. of patients (studies)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			**Example control rate**	**Associated risk with PVL**
Hospital mortality	1,664 (9)	Inability to blind. 2 trials stopped early with few events and large effects; were also confounded by 'open lung' strategies.	p = 0.07 I^2 = 45.6% Varied populations, interventions. Not robust in sensitivity analyses	Direct	Precise	Undetected	Moderate (due to inconsistency)	0.82 (0.68 – 0.99) p = 0.04	40%	32.8% (27.2 – 39.6)
Barotrauma	1,497 (7)	Inability to blind.	p = 0.24 I^2 = 25.3% Varied populations, interventions	Direct	Imprecise	Undetected	Moderate (due to imprecision)	0.90 (0.66 – 1.24) p = 0.53	NS	NS
Paralysis	1,202 (5)	Inability to blind.	p = 0.004 I^2 = 59% Varied populations, interventions, measurements	Direct	Precise	Undetected	Moderate (due to inconsistency)	1.37 (1.04 – 1.82) p = 0.03	30%	41.1% (31.2 – 54.6)
Dialysis	173 (2)	Inability to blind.	p = 0.26 I^2 = 22.8% Varied populations, interventions	Direct	Imprecise	Undetected	Moderate (due to imprecision)	1.76 (0.79 – 3.90) p = 0.16	NS	NS

Pressure limited ventilation in ALI and ARDS

Thrombolysis vs heparin for pulmonary embolus

Quality Assessment						Summary of Findings			
						Quality	Relative Effect Relative (95% CI) or WMD	Illustrative comparative risks	
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias			Thrombolysis	No Thrombolysis
Mortality	Possible ↓[1]	Possibly inconsistent [2]	No problem	Imprecise[3]	Undetected	Moderate or low	0.70 (0.37 -1.30)	4.3%	5.9%
Outcome									
Recurrent PE	Possible ↓1	Possibly inconsistent2	No problem	Imprecise3	Undetected	Moderate or low	0.67 (0.33 – 1.37)	2.7%	4.3%
Outcome									
Major bleeding	Possible ↓1	OK	No problem	Imprecise3	Undetected	Moderate or low	1.42 (0.81 – 2.46)	9.1%	6.1%
Outcome									
Minor Bleeding	Possible ↓1	OK	OK	Precise	Undetected	High or moderate	2.63 (1.53 – 4.54)	22.7%	10%

[1] Most trials unconcealed, unblinded, no report of loss to follow-up
[2] We aren't sure whether to believe the sub-group analysis of hemodynamically compromised versus no hemodynamically compromised PE
[3] Confidence interval includes important benefit and important harm
[4] Minor bleeding not reported for sub-groups

Thrombolysis vs heparin for pulmonary embolus

Quality Assessment						Summary of Findings			
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Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias			Thrombolysis	No Thrombolysis
Mortality	Possible ↓[1]	Possibly inconsistent [2]	No problem	Imprecise[3]	Undetected	Moderate or low	0.70 (0.37 -1.30)	4.3%	5.9%
Outcome									
Recurrent PE	Possible ↓[1]	Possibly inconsistent [2]	No problem	Imprecise[3]	Undetected	Moderate or low	0.67 (0.33 – 1.37)	2.7%	4.3%
Outcome – observational study – rate up for large effect 1 or 2									
Major bleeding	Ok	Ok	No problem	Ok	Undetected	Moderate or high	2.5	21.7%	8.8%
Outcome									
Minor Bleeding	Possible ↓[1]	Uncertain[4]	Possible ↓	Precise	Undetected	High or moderate	2.63 (1.53 – 4.54)	22.7%	10%

[1] Most trials unconcealed, unblinded, no report of loss to follow-up
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Thrombolysis vs heparin for pulmonary embolus

Quality Assessment						Summary of Findings			
						Quality	Relative Effect Relative (95% CI) or WMD	Illustrative comparative risks	
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias			Thrombolysis	No Thrombolysis
Mortality (angio)	Possible ↓[1]	No problem	Indirect	No problem	Undetected	Moderate or low	0.47	6.0%	12.7%
Outcome									
Recurrent PE (angio)	Possible ↓[1]	No problem	Indirect	No problem	Undetected	Moderate or low	0.61	4.3%	7.1%
Outcome – observational study – rate up for large effect 1 or 2									
Major bleeding	Ok	Ok	No problem	Ok	Undetected	Moderate or high	2.5	21.7%	8%
Outcome									
Minor Bleeding	Possible ↓[1]	Uncertain[4]	Possible ↓	Precise	Undetected	High or moderate	2.63 (1.53 – 4.54)	22.7%	10%

[1] Most trials unconcealed, unblinded, no report of loss to follow-up
[2] We aren't sure whether to believe the sub-group analysis of hemodynamically compromised versus no hemodynamically compromised PE
[3] Confidence interval includes important benefit and important harm
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Conclusions

- get comfortable with GRADE
  - great benefit of uniformity
- consider multiple treatment meta-analysis
- specify all patient important outcomes
  - not just those in the RCTs
- look for evidence relevant to all outcomes
  - may mean reviewing observational studies, RCTs in other populations
- produce comprehensive, well-annotated evidence profiles