Systematic reviews: From evidence to recommendation

Session 3 – July 2, 2014

Bringing in the patient/client: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) process

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Objectives:

Discuss, within the context of systematic reviews

- what is considered evidence and why
- how evidence is qualified and synthesized
- how evidence is turned into recommendations for clinicians and other practitioners

Topics:

1. Overview of the process and tools of systematic reviewing, with a focus on assessment and synthesis of evidence, and the idea of a research design-based pyramid of evidence underlying conclusions and recommendations
2. How the American Academy of Neurology and others have brought in research design details and quality of research implementation in grading evidence, and have gone beyond intervention research
3. The GRADE approach, with its emphasis on the values and preferences of patients/clients, and flexibility in grading evidence: fit with disability and rehabilitation research
4. A discussion of future developments in methods of qualifying and synthesizing evidence that might benefit disability/rehabilitation practice

Questions?

June 18 session topics:

- Oxford CEBM hierarchies, covering about all questions an EBP practitioner might ask
- AAN hierarchies, also covering various questions, with stronger focus on creating (rather than using) a systematic review

Today's topic - GRADE: more sophistication, more complication

- "Grading of Recommendations Assessment, Development and Evaluation"
- Developed since about 2000 by an international group of EBP (mostly EBM) specialists
- Published in *Allergy* (3 papers, 2009-11: introductory), *BMJ* (6 papers, 2008: focused on user perspective), and an ongoing series in the *J Clin Epidemiol* (2011-; to date, 15 out of a planned 20 papers: directed to producers) (see references on SEDL's KTDRR website)
- Ideas being widely copied (with/without modifications) by other guideline developers (AAN, Oxford CEBM, NICE, WHO, etc.)
- Many publications using GRADE (hard to find if abbreviation is used in abstract: 'GRADE' abbreviation: 113,295 hits; full name: 84 hits)

GRADE used in disability and rehabilitation

(easily found ones only)

- Horticultural therapy for schizophrenia. *Cochrane Database Syst Rev*. 2014
- Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. *Cochrane Database Syst Rev*. 2013
- Non pharmacological interventions for spasticity in multiple sclerosis. *Cochrane Database Syst Rev*. 2013
- A systematic review of effectiveness of complementary and adjunct therapies and interventions involving equines. *Health Psychol*. 2013
- Kinematics of the cervical adjacent segments after disc arthroplasty compared with anterior discectomy and fusion: a systematic review and meta-analysis. *Spine (Phila Pa 1976)*. 2012
- KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009

Four major characteristics of GRADE

- GRADE is for creating systematic reviews and for creating guidelines, with separate steps for each: (1) do a systematic review (or use one or more existing systematic reviews); (2) create the guideline
- GRADE is outcome-focused: evidence is reviewed and summarized separately for each (important) outcome (positive and negative) of an intervention or a diagnostic process; then cross-outcome evidence is used to make a recommendation, taking importance of each in mind
- GRADE offers little in the way of standard algorithms that need to be followed; it focuses instead on reviewers/guideline developers making explicit their values, assumptions, judgments, etc. that go into qualifying the evidence and creating the end product, and documenting these: transparency is a central element
- GRADE deals with Tx and Dx only – not Px, etc.

GRADE's fit into the guideline development process: 1

1. Prioritize problem
2. Establish review team and/or guideline panel
3. Define questions to be addressed
4. Find and critically appraise systematic reviews(s)

   and/or

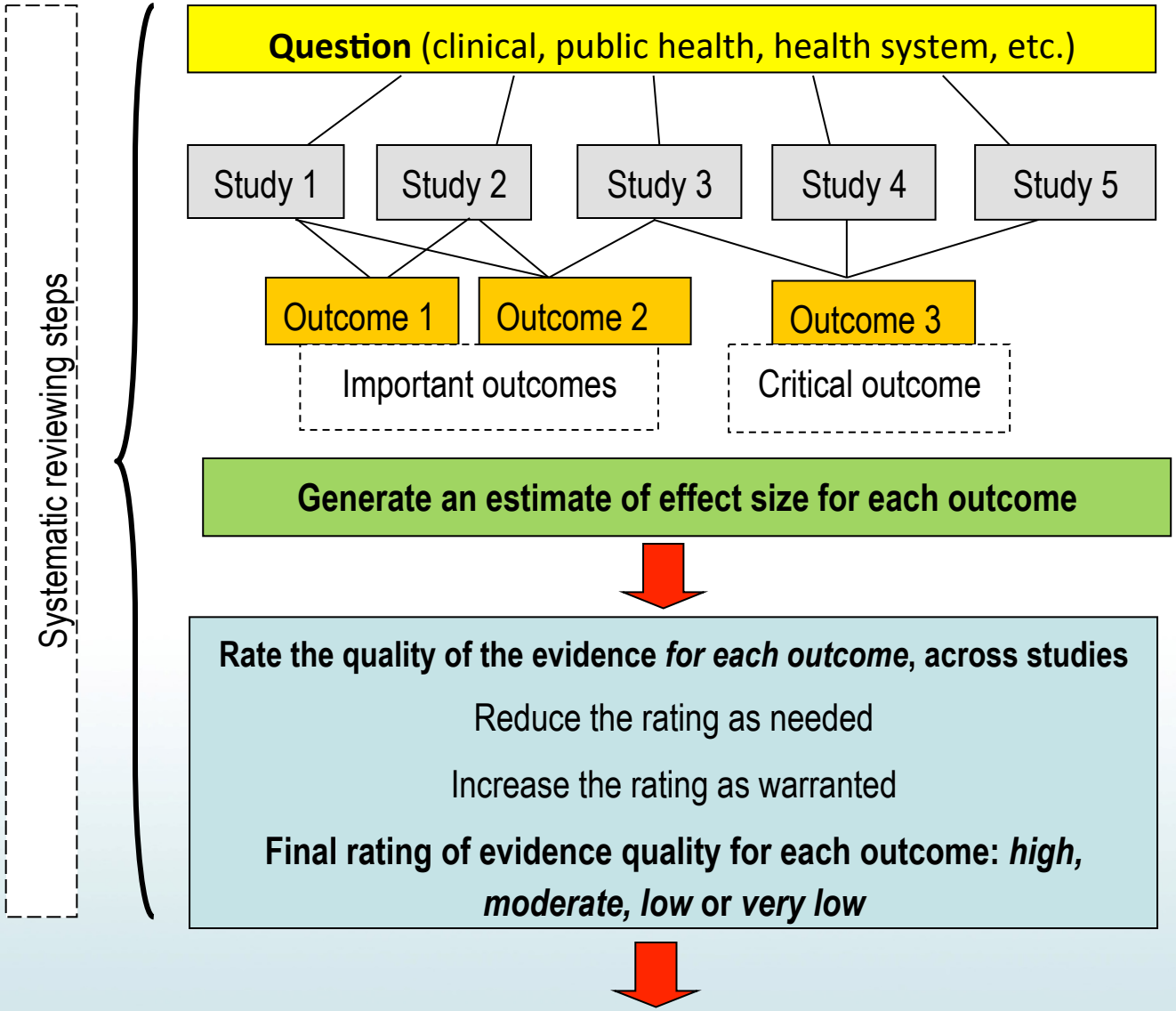
   prepare protocol(s) for systematic review(s) and prepare systematic review(s): searches, selection of studies, data collection and analysis
5. (Re)assess the relative importance of outcomes
6. Prepare an evidence profile, including (1) an assessment of the quality of evidence for each outcome and (2) a summary of the findings

GRADE's fit into the guideline development process: 2

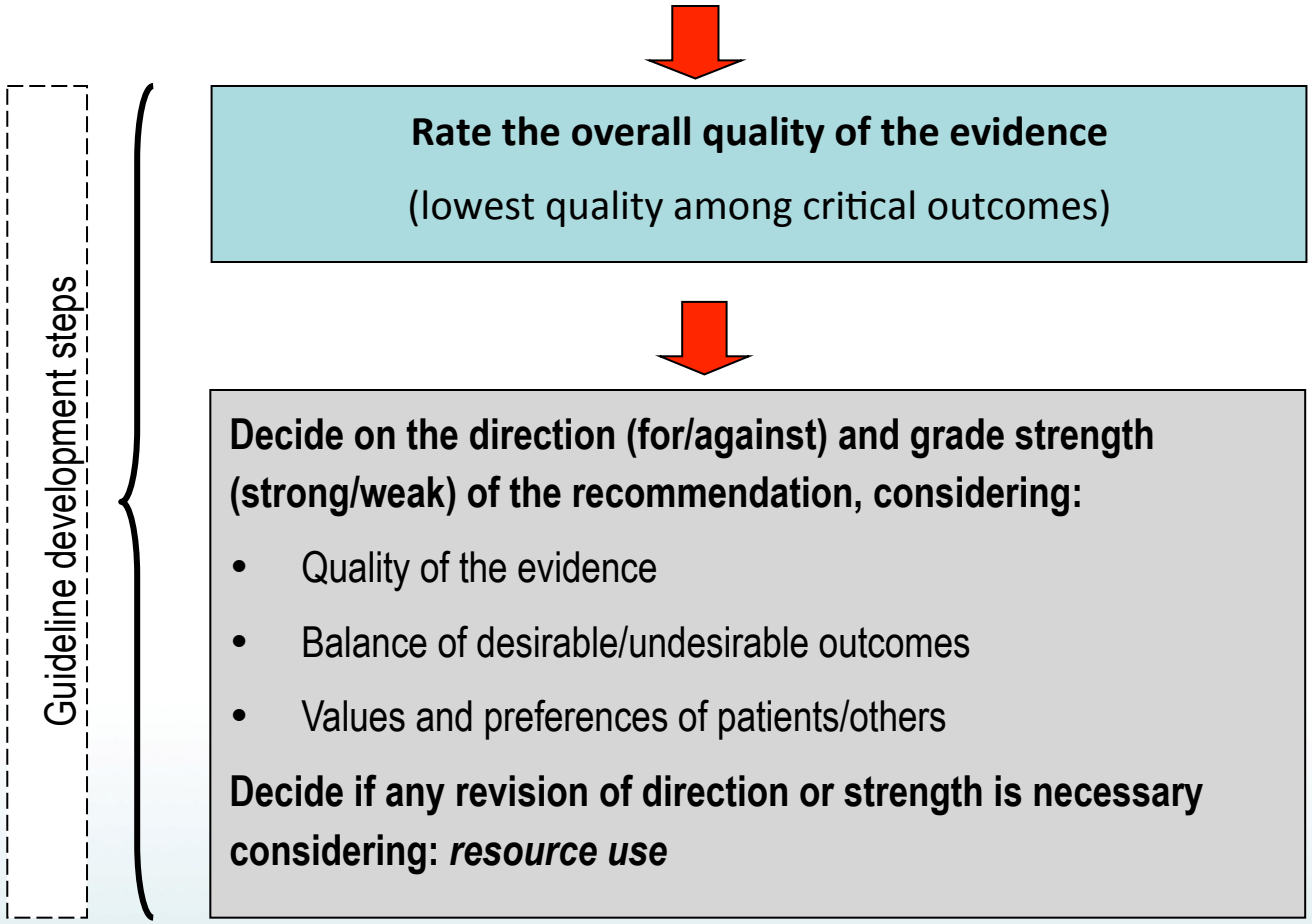
7. If developing guidelines: Assess the overall quality of evidence and decide on the direction and strength of the recommendation(s)
8. Draft the systematic review or guideline
9. Consult with stakeholders and/or external peer reviewers
10. Disseminate the review or guideline
11. Update review or guideline when needed
12. Adapt guideline, if needed
13. Prioritize recommendations for implementation
14. Implement or support implementation of the guideline
15. Evaluate the impact of the guideline and implementation strategies
16. Update the systematic review and guideline

Questions?

Schematic view of GRADE's process for developing recommendations (1)



Schematic view of GRADE's process for developing recommendations (2)



Step 3. Define the questions to be addressed

- PICO(T)(S) recommended
  - **P**opulation
  - **I**ntervention (incl. diagnostic intervention)
  - **C**omparator
  - **O**utcomes
    - Positive, negative, costs, other burden
    - Rated on a 1-9 scale of importance
      - 1-3: unimportant
      - 4-6: important
      - 7-9: critical
  - **T**ime point / time frame
  - **S**etting: resource-rich vs resource-poor countries

Step 3. Rate the importance of the outcomes

- Ideally based on (systematic reviews of) patient ratings of relative importance of various outcomes
- Second best, ratings put together ad-hoc by patient groups
- Third best, proxy ratings by panel members

- 7-9: critical
- 4-6: important
- 1-3: of limited importance

Importance of outcomes and their evolution

- Step 3: Preliminary classification before the evidence is reviewed, to guide evidence searching
- Step 5: Reassessment of relative importance after the evidence has been reviewed, to make sure outcomes not considered in step 3 but found in literature review are given their proper weight (e.g. rare but serious adverse effects)
- Step 7: In making a recommendation and deciding on its strength, take the (revised) importance into account in judging the balance between desirable and undesirable effects of an intervention

Step 4. Find and critically appraise systematic reviews(s) and/or prepare protocol(s) for systematic review(s) and create systematic review(s): searches, selection of studies, data collection and analysis

- Given the need to extract outcomes and classify quality of evidence based on information that is not likely to be in the available systematic reviews, GRADE panel may need to redo existing reviews
- Evidence needs to be rated *separately for each outcome*, as the quality of evidence may differ by outcome

Study design	Quality of evidence	Rate evidence quality lower if:	Rate evidence quality higher if:
RCT →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Effect size +1 Large +2 Very large Dose response +1 Evidence of a gradient Plausible confounding +1 All would reduce a demonstrated effect OR +1 All would suggest a spurious effect when actual results show no effect
	Moderate		
Observa-tional study →	Low		
	Very low		

From "GRADE Guidelines: 1. Introduction-GRADE Evidence Profiles and Summary of Findings Tables" by G. Guyatt, A. D. Oxman, E. A. Akl, R. Kunz, G. Vist, J. Brozek, J., . . . H. J. Schunemann, 2011, Journal of Clinical Epidemiology 64(4), 383-394. Copyright © 2011 by Elsevier Inc. All rights reserved. SEDL used with fee-based permission from Copyright Clearance Center's Rightslinks service.

A more expansive listing of designs (Brozek et al. 2009)

(Unable to clear copyright in time for presentation. You may down-load the original article for free and view the content in Table 3.)

Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, Phillips B, Lelgemann M, Lethaby A, Bousquet J, Guyatt GH, Schünemann HJ; GRADE Working Group. (2009). Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy, 64*(5):669-77.

http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2009.01973.x/full

See Table 3:
http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2009.01973.x/full#t3

Current GRADE descriptions of the levels of evidence

Rank	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Rating down: study limitations resulting in increased risk of bias: 'small d' issues in RCTs

- Lack of allocation concealment
- Lack of blinding (patients, clinicians, outcome assessors)
- Incomplete accounting of patients and outcome events
  - Attrition
  - Failure to use intent-to-treat analysis
- Selective outcome reporting bias ('publication bias in situ')
- Other limitations
  - Stopping early for benefit
  - Use of unvalidated outcome measures (e.g. PROs !!!)
  - Carryover effects in a cross-over RCT
  - Recruitment bias in cluster-randomized trials

Rating down: study limitations resulting in increased risk of bias: 'small d' issues in observational studies

- Failure to develop and apply appropriate eligibility criteria, e.g.
  - Under- and overmatching in case-control studies
  - Exposed and unexposed cases in cohort studies selected from different populations
- Flawed measurement of both exposure and outcome, e.g.
  - Differences in measurement of exposure (e.g. recall bias)
  - Differential surveillance of the exposed and unexposed in cohorts
- Failure to adequately control confounding, e.g.
  - Failure to accurately measure all prognostic factors
  - Failure to match for/statistically adjust for prognostic factors
- Incomplete follow-up

Rating down: Imprecision

- Defined as: the confidence interval around the estimated effect size is unacceptably wide
- There is no definition of / cut-off for 'too wide'
- Seriousness of the problem depends on the balance of benefits and costs (side effects, burdens) of a treatment
  - If there are serious downsides to a treatment, there is a great need to know what exactly the effect size is, within a very narrow confidence interval
  - If a treatment is cheap and has no or very minor side effects, we do not worry about a wide confidence interval (even if it may include 0?)

Rating down: Imprecision

- GRADE suggests taking into account:
  - Patient value and preference judgments: importance of outcomes
  - Adverse effects
  - Burden on patient
  - Resource use
  - Sample size (individual and pooled studies) and event rate (number of events per 1,000 clients)

  in setting criteria for 'too wide' and in deciding whether to rate down the evidence, one or even two levels

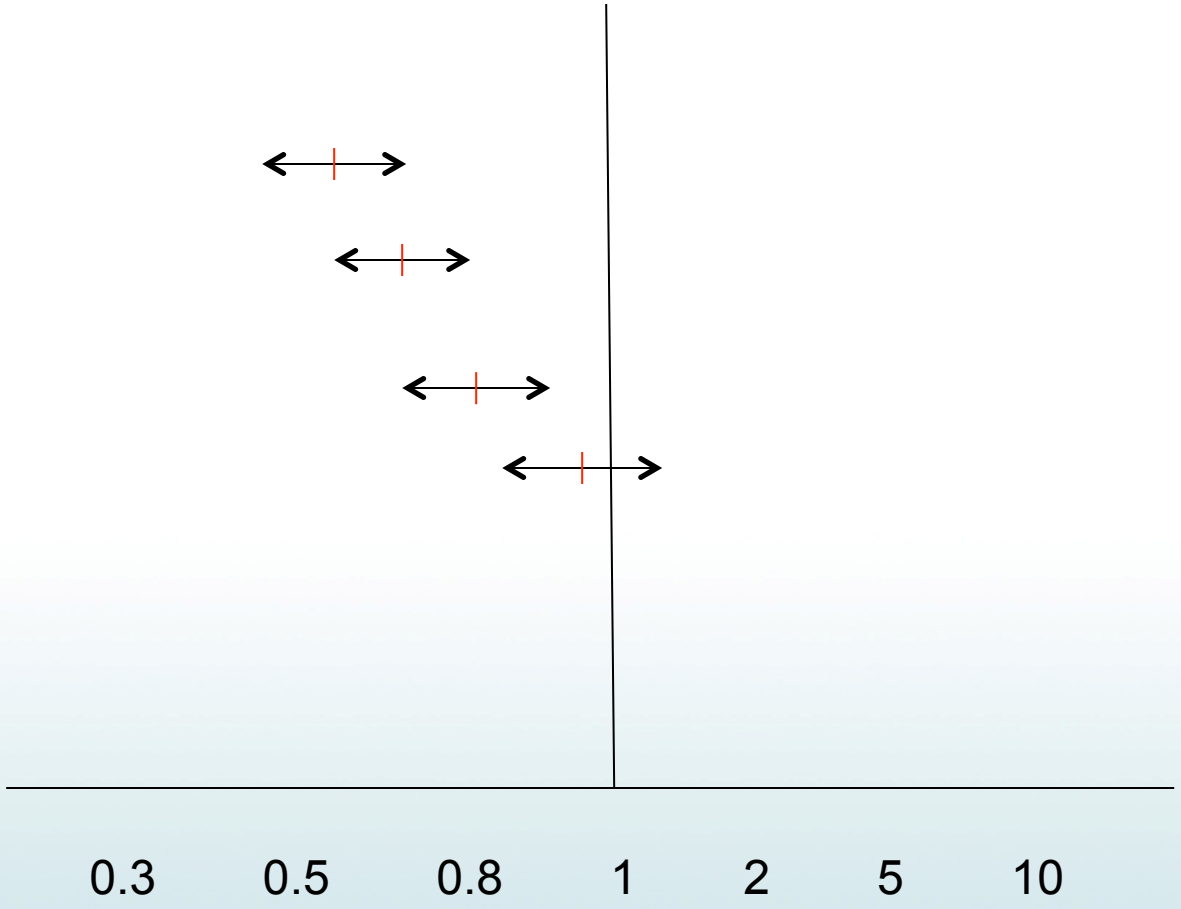
Rating down: inconsistency in magnitude of results (effect sizes) of studies

- In GRADE discussed as relevant to intervention studies using dichotomous outcomes only, not for Dx studies and not for treatment studies using continuous outcome measures
- Focus is on relative risk (risk ratio, hazard ratio, odds ratio) – relative risk often is stable from study to study even if absolute risk reduction varies based on population characteristics and other issues
- Relative risk may vary based on the following:
  - Population
  - Intervention (dose, cointerventions, comparator)
  - Outcomes (e.g. duration of follow-up)
  - Study methods (e.g. low-risk vs high-risk RCT)

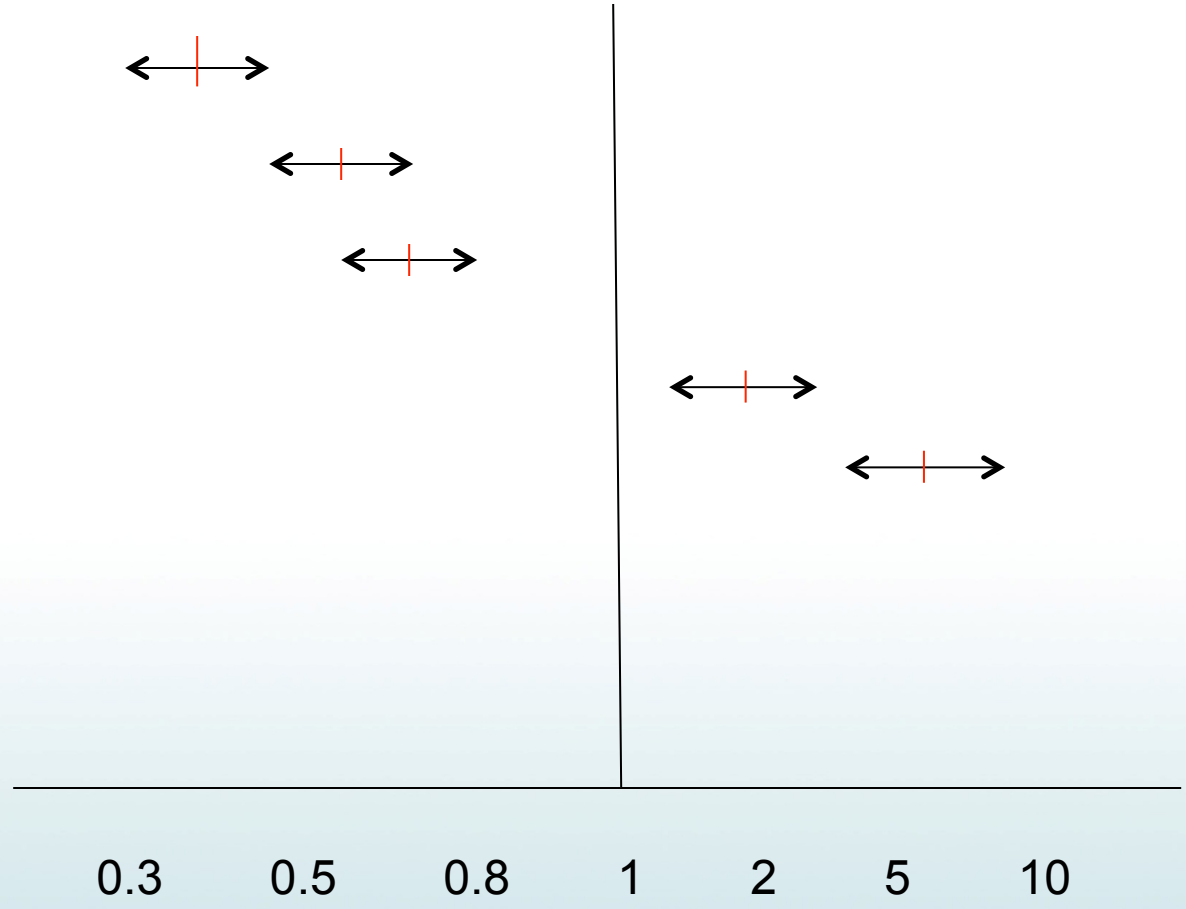
Rating down: inconsistency in magnitude of results (effect sizes) of studies

- Effect-size differences due to population, intervention, outcome:
  - should be expected
  - can be formally tested based on a-priori hypotheses
  - may result in different recommendations for different subgroups, outcomes, interventions
- When these factors do not explain inconsistency, reviewers should consider rating down evidence when:
  - Point estimates vary widely across studies
  - Confidence intervals show minimal or no overlap
  - Statistical test for heterogeneity shows a low p value
  - I^2 (a measure of heterogeneity not taking sampling into account) is large
  - Inconsistency reduces confidence in results in relation to a particular decision

Inconsistency that is immaterial to the decision to recommend the treatment



Inconsistency that should lead to a decision to rate down the evidence



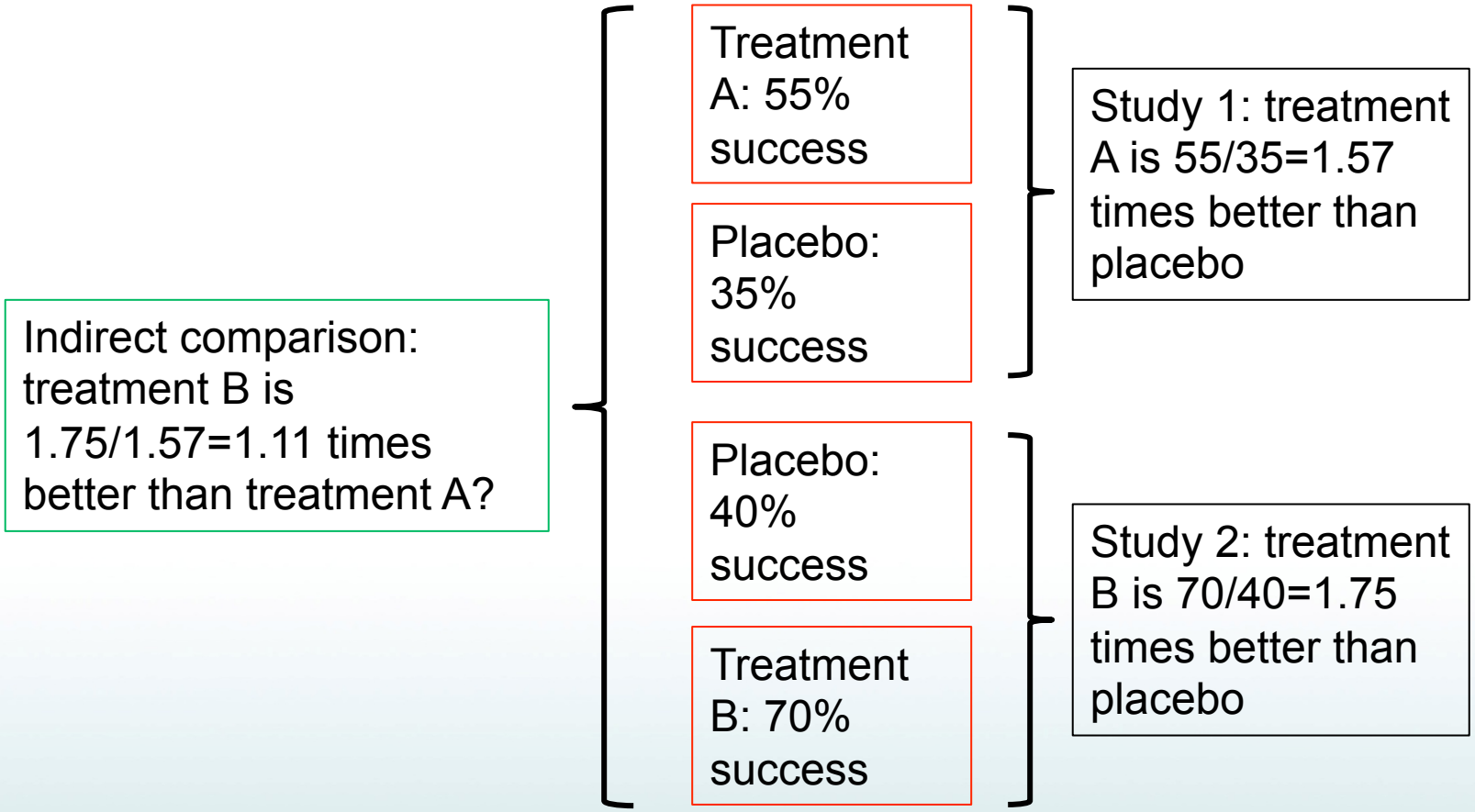
Rating down: indirectness of evidence

- When the studies providing evidence match the clinical question [PICO(T)(S)], evidence is considered direct
- When there is no 100% match, the evidence is 'indirect', and reviewers should consider rating down the evidence
- Rating down should also be considered if two treatments of interest are not compared directly in the studies available, but through a third intervention, most likely a placebo (AKA network meta-analysis)

Three types of indirectness

indirectness	example
population	Cognitive rehabilitation was studied in patients with stroke, not in the group of interest, patients with TBI
intervention	High-intensity exercise as part of cardiac rehabilitation is the intervention of interest, but most existing studies have investigated low-intensity exercise
outcome	Existing intervention studies have addressed increasing the ability of persons with SCI to perform various office tasks (ICF Activities), but none has studied actual return to work in an office setting (ICF Participation)

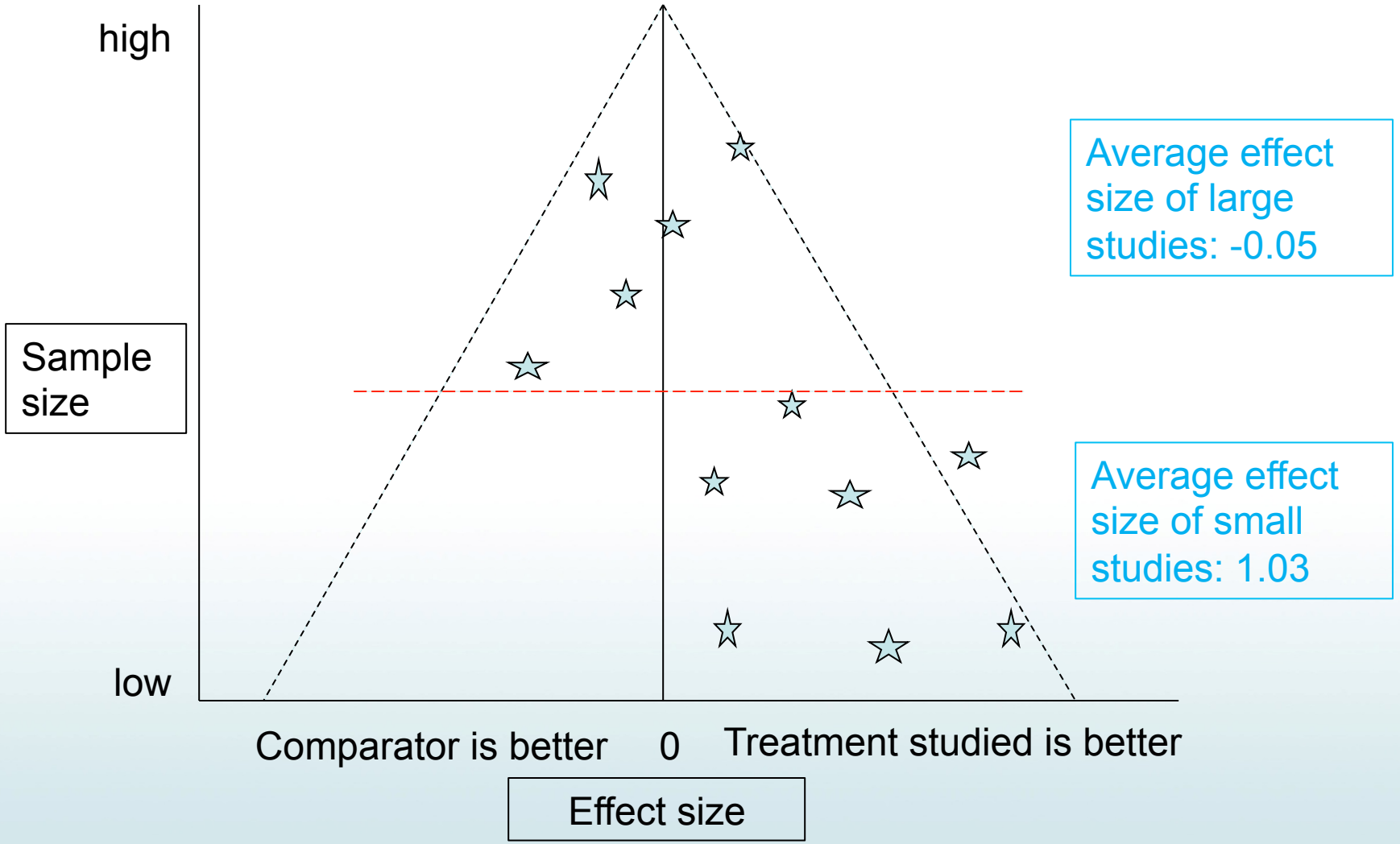
And the fourth type of indirectness



Rating down: publication bias

- Non-publication of 'negative' studies because of lack of interest by (1) author; (2) peer reviewer; (3) editor
- Non-publication of negative studies by big pharma
- Late publication because of 'bouncing' of the manuscript toward low-quality journals (time-lag bias)
- Only 'positive' studies are published, unless well-done large negative studies with sufficient power manage to 'break through'
- Consequence: effect sizes in systematic reviews are artificially inflated toward the treatments studied

Rating down: publication bias funnel plot



Rating down: publication bias

- Detection of publication bias:
  - Funnel plot (not very reliable – uses eye-balling)
  - Fill and trim tests
  - Tests based on the statistical significance reported
  - Meta-analysis for each of successive years of publication (detection of time-lag bias)
- Counteracting publication bias: dig up unpublished studies (much easier with the increasing registration of studies, on e.g. clinicaltrials.gov)
- More feasible action: if one (preferable more) 'detectors' suggest publication bias, rate down evidence
- GRADE suggests going down one level only

Rating up the evidence

- Three primary reasons for rating up the quality of the evidence
  - Large effect size
  - Dose-response gradient
  - All plausible confounders/biases increase our confidence in the estimated effect
- Likely occurring infrequently
- Mostly in cases of observational studies (including otherwise very low quality evidence, such as before-after studies and time series studies)

Rating up: large effect size

- Clinical interventions that practitioners have confidence in, and that indeed have a large effect size
  - Modeling suggests that with relative risk (RR) > 2 or RR < 0.5 confounding is 'not likely' to be an explanation, and quality rating can be improved by 1 level
  - With RR > 5 or RR < 0.2, this becomes 'very unlikely' and a 2 level quality rating increase may be justified
- Often onset of change is almost immediate, and improvement curve is steep
- Knowledge that without in intervention there would be deterioration or at best no improvement adds to our confidence
- Often there is indirect evidence to support our believing in a large treatment effect

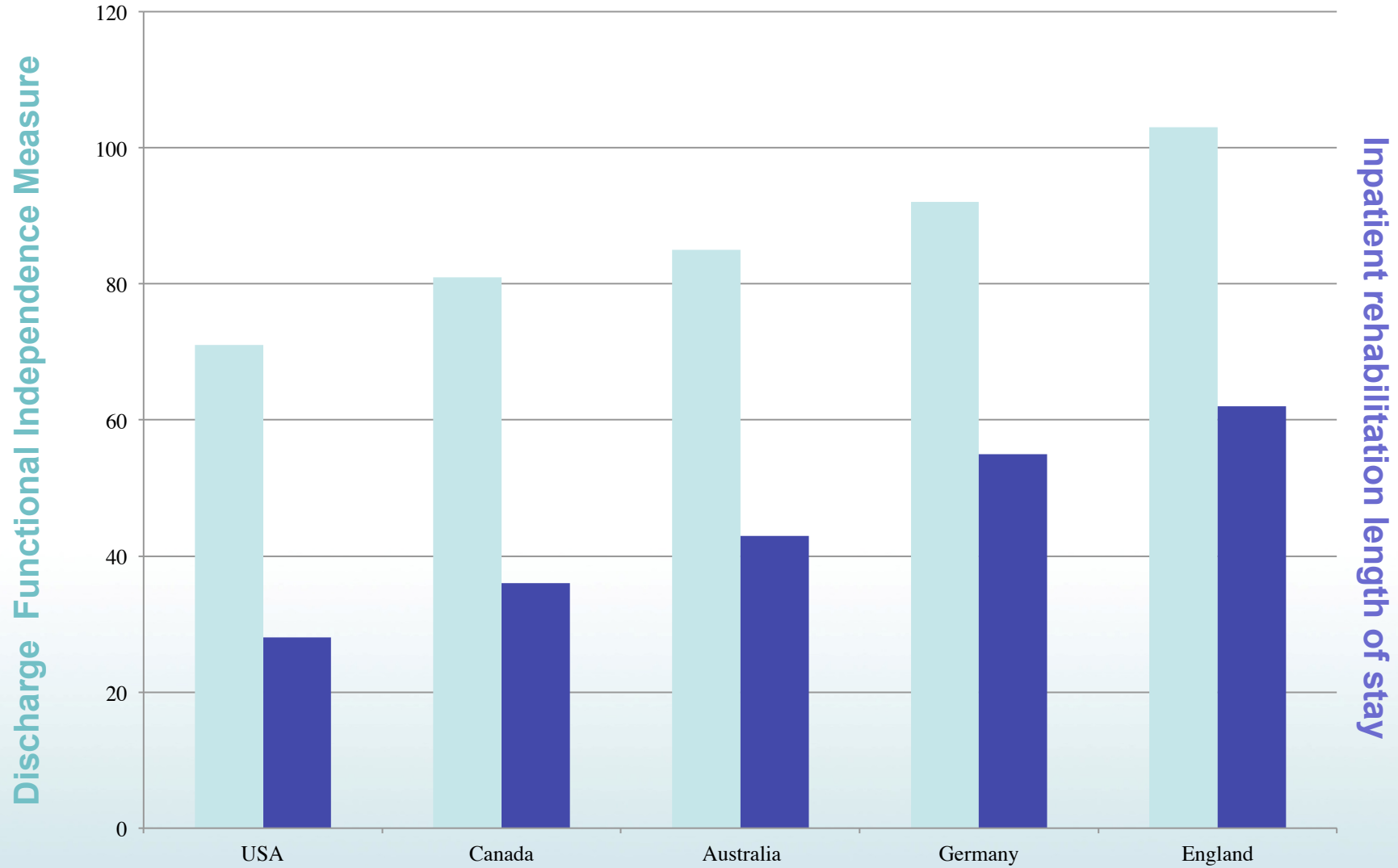
Rating up: large effect size examples

- Instant improvement of mobility in patients with new onset SCI provided with a wheelchair
- <1% of 500 patients with SCI developing, over a year's time, a pressure ulcer with a new model seat cushion, vs known incidence of >10% with various existing models
- Deteriorating mobility in women with arthritic knees, instantly reversed by knee replacement

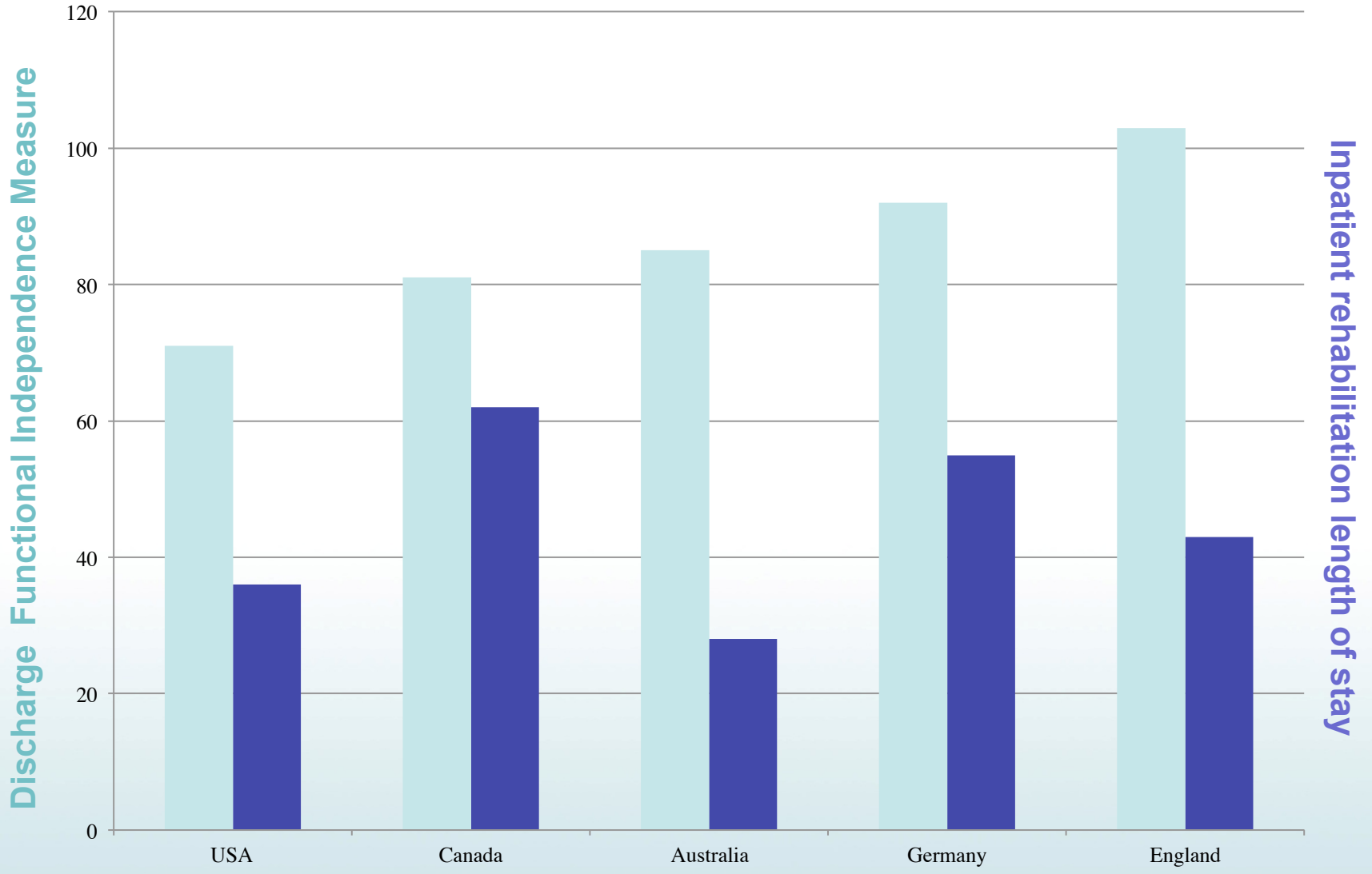
Rating up: dose response

- If a (steep) dose-response gradient is found within studies or between studies, we are more likely to belief that the effect of the intervention is not a result of chance, or of poor study design and implementation

Dose-response relationship



Does longer length of stay result in improved functional status?

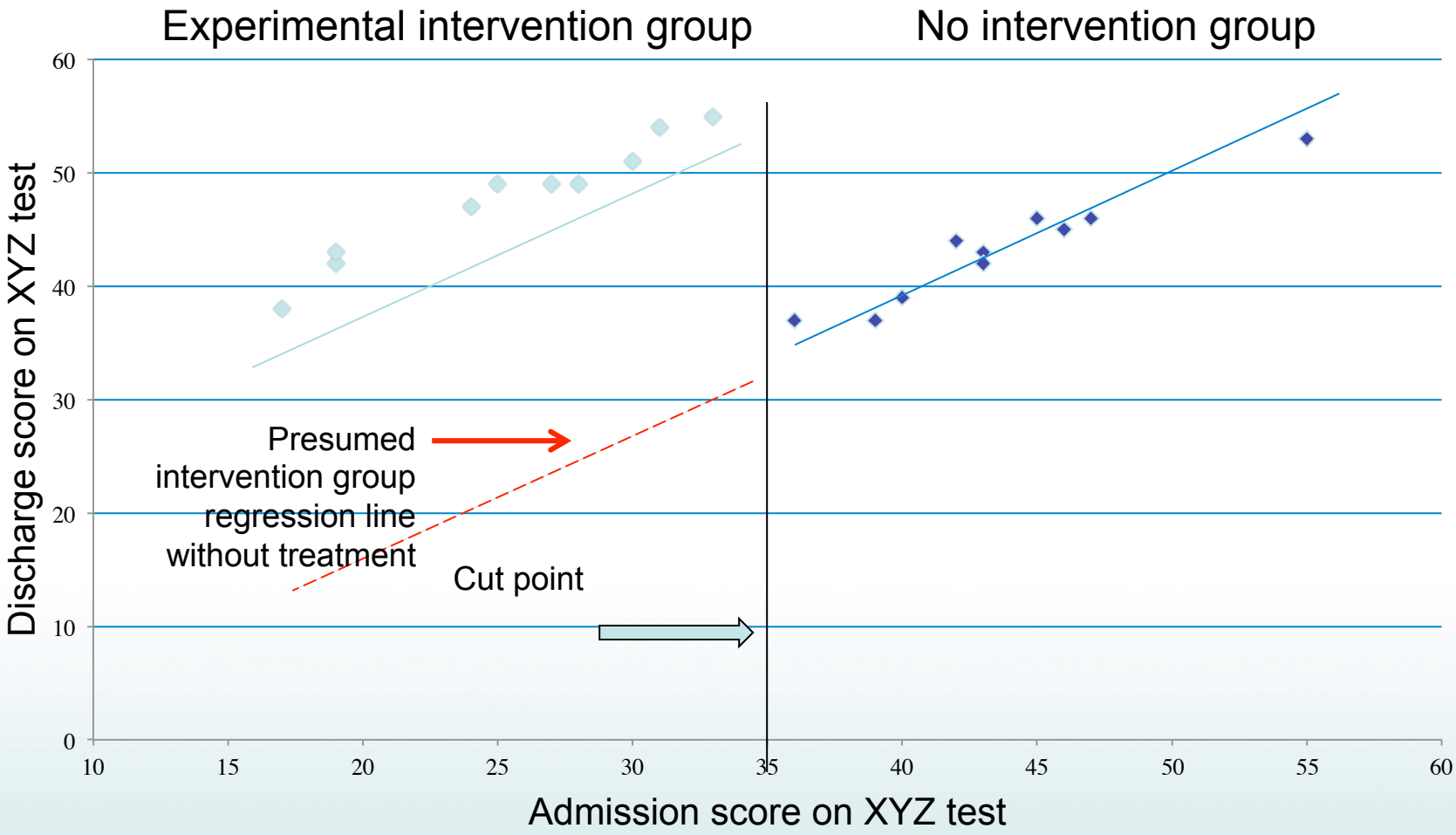


Rating up: confounders

- Because in observational research there is no randomization that will equally distribute all confounders (factors with an impact on the outcome) between the two groups that are being compared (at least when N is > 200 per group: law of large numbers), these need to be taken into account statistically, e.g. by means of
  - ANCOVA
  - Propensity scores
- Only factors that were actually measured, and measured well, can be statistically controlled for
- What remains is 'residual confounding' or 'residual biases'

Rating up: confounders

- In unusual circumstances, ALL plausible confounders unaccounted for in the adjusted analysis would result in an UNDERestimate of the treatment effect (rather than an overestimate, the usual problem), e.g.
  - Only the sicker, less able patients only get the treatment, yet they have better outcomes than the untreated patients with more ability at baseline
  - (*Regression discontinuity design*)


Experimental intervention group
No intervention group
Discharge score on XYZ test
Admission score on XYZ test
Presumed intervention group regression line without treatment
Cut point
0
10
20
30
40
50
60
10
15
20
25
30
35
40
45
50
55
60

Step 5. (Re)assess the relative importance of outcomes (guideline developers only)

- The careful review of studies may suggest outcomes of the intervention that were not considered initially, but are important if not critical
- Especially (rare) adverse events with catastrophic consequences – e.g. permanent disability

Step 6. Prepare an evidence profile, including (1) an assessment of the quality of evidence for each outcome and (2) a summary of the findings

- Evidence profiles (EPs)
  - Include explicit judgment of each factor that determines the quality of evidence for each outcome (limitations, inconsistency, indirectness, imprecision & large effect size, dose-response, plausible confounding)
  - Include data – e.g. N of patients in pooled group(s), pooled relative and absolute risk, etc.
  - Are prepared for review authors, and for anyone who questions a quality assessment

GRADE evidence profile: antibiotics for children with acute otitis media

Quality assessment						Summary of findings					
						Number of patients			Absolute risk		
No of studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo	Antibiotics	Relative risk (95% CI)	Control risk[a]	Risk difference (95% CI)	Quality
Pain at 24h											
5 (RCT)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	241/605	223/624	RR 0.9 (0.78−1.04)	367/1,000	Not Significant	⊕⊕⊕⊕ High
Pain at 2–7 d											
10 (RCT)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	303/1,366	228/1,425	RR 0.72 (0.62−0.83)	257/1,000	72 fewer per 1,000 (44−98)	⊕⊕⊕⊕ High
Hearing, inferred from the surrogate outcome abnormal tympanometry—1 mo											
4 (RCT)	No serious limitations	No serious inconsistency	Serious indirectness (because of indirectness of outcome)	No serious imprecision	Undetected	168/460	153/467	RR 0.89 (0.75−1.07)	350/1,000	Not Significant	⊕⊕⊕○ Moderate
Hearing, inferred from the surrogate outcome abnormal tympanometry—3 mo											
3 (RCT)	No serious limitations	No serious inconsistency	Serious indirectness (because of indirectness of outcome)	No serious imprecision	Undetected	96/398	96/410	RR 0.97 (0.76−1.24)	234/1,000	Not Significant	⊕⊕⊕○ Moderate
Vomiting, diarrhea, or rash											
5 (RCT)	No serious limitations	Serious inconsistency (because of inconsistency in absolute effects)	No serious indirectness	No serious imprecision	Undetected	83/711	110/690	RR 1.38 (1.09−1.76)	113/1,000	43 more per 1,000 (10−86)	⊕⊕⊕○ Moderate

From Table 1. GRADE evidence profile: antibiotics for children with acute otitis media from "GRADE Guidelines: 1. Introduction-GRADE Evidence Profiles and Summary of Findings Tables" by G. Guyatt, A. D. Oxman, E. A. Akl, R. Kunz, G. Vist, J. Brozek, J., . . . H. J. Schunemann, 2011, *Journal of Clinical Epidemiology 64*(4), p. 387.

Step 6. Prepare an evidence profile, including (1) an assessment of the quality of evidence for each outcome and (2) a summary of the findings

- Summaries of findings (SoFs)
  - Includes assessment of the quality of the evidence, but not detailed judgments
  - Concise summary of key information
  - Prepared for a broader audience, including end users of the systematic review / guidelines

Summary of finding: antibiotics for acute otitis media in children

Antibiotics compared with placebo for acute otitis media in children

Patient or population: Children with acute otitis media
Setting: High- and middle-income countries
Intervention: Antibiotics
Comparison: Placebo

	Estimated risks (95% CI)					
	Control risk[a]	Intervention risk				
Outcomes	Placebo	Antibiotics	Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
Pain at 24h	367 per 1,000	330 per 1,000 (286–382)	RR 0.9 (0.78–1.04)	1229 (5)	⊕⊕⊕⊕ High	
Pain at 2–7 d	257 per 1,000	185 per 1,000 (159–213)	RR 0.72 (0.62–0.83)	2791 (10)	⊕⊕⊕⊕ High	
Hearing, inferred from the surrogate outcome abnormal tympanometry—1 mo	350 per 1,000	311 per 1,000 (262–375)	RR 0.89 (0.75–1.07)	927 (4)	⊕⊕⊕○ Moderate[b]	
Hearing, inferred from the surrogate outcome abnormal tympanometry—3 mo	234 per 1,000	227 per 1,000 (178–290)	RR 0.97 (0.76–1.24)	808 (3)	⊕⊕⊕○ Moderate[b]	
Vomiting, diarrhea, or rash	113 per 1,000	156 per 1,000 (123–199)	RR 1.38 (1.09–1.76)	1,401 (5)	⊕⊕⊕○ Moderate[c]	Ideally, evidence from nonotitis trials with similar ages and doses (not obtained) might improve the quality of the evidence.

From Table 2. Summary of finding: antibiotics for acute otitis media in children from "GRADE Guidelines: 1. Introduction-GRADE Evidence Profiles and Summary of Findings Tables" by G. Guyatt, A. D. Oxman, E. A. Akl, R. Kunz, G. Vist, J. Brozek, J., . . . H. J. Schunemann, 2011, *Journal of Clinical Epidemiology 64*(4), p. 388.

Step 7. If developing guidelines: Assess the overall quality of evidence and decide on the direction and strength of the recommendation(s)

- The level of evidence quality (high, moderate, low, very low) assigned to the *critical* outcome that has the *lowest* quality evidence is the level given to the intervention with respect to *all its outcomes*
- Recommendations are in favor of intervention or against
- GRADE uses two strengths of recommendations only: strong and weak= discretionary= conditional
- Direction and strength of recommendation are based on
  - Quality of the evidence
  - Balance of desirable vs undesirable outcomes
  - Values and preferences of patients
  - Resource use (cost) of the intervention

Questions?

Advantages of GRADE (compared to many/ all alternative evidence development approaches

1. Clear separation between quality of evidence and strength of recommendations *
2. Explicit and comprehensive criteria for downgrading or upgrading quality of evidence
3. Explicit consideration of the relative importance of various outcomes to patients
4. Explicit acknowledgement of values and preferences that are used/assumed when making recommendations
5. Transparent process of moving from evidence to recommendations

Advantages of GRADE (compared to many/ all alternatives

6. Explicit advice to make recommendations about the most appropriate course of action, even when very little evidence is available
7. Grading the strength only for recommendations about the diagnostic or therapeutic course of action, but not about prognosis or etiology
8. Clear and pragmatic interpretation of ‘strong’ and ‘weak’ recommendations
9. Balance between simplicity and methodological comprehensiveness

(Brozek et al., 2009, Guyatt et al., 2011)

Limitations of GRADE

1. GRADE does not deal with questions of risk or prognosis
2. Application of GRADE to 'motherhood' statements is problematic: why spend time on recommendations everyone agrees on ("rehabilitation is good"), what evidence would there be relevant to such issues
3. GRADE covers steps 3-7 out of 1-16 only
4. GRADE has not been developed well / not tested out on questions on diagnostic tests, public health, health systems.
5. GRADE does not offer guidance about designs other than (1) RCTs and (2) observational studies including a control group

Limitations of GRADE

6. GRADE does not eliminate disagreements between panelists – just makes transparent judgments about importance of outcomes, quality of evidence, strength of recommendations
7. GRADE approach in assessing risk of bias emphasizes simplicity and parsimony over completeness. Specifically, a scale to quantitatively measure 'methodological quality' is not used
8. Empirical evidence underlying rules for grading down/ grading up evidence absent or not strong

(Brozek et al., 2009, Guyatt et al., 2011)

Questions?

Wrapping Up

Thank you for participating!

We invite you to:

- Provide your input on today's session
- Share your ideas for future sessions
- Participate in the Community of Practice to continue the dialogue
- PLEASE CONTACT US:

joann.starks@sedl.org

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