Recent GRADE Innovations

Gordon Guyatt
McMaster University

Plan

- Why bother listening to this talk
- How to judge certainty of evidence – precision
- How to interpret patient-reported outcomes
- Moving from evidence to recommendations
- Network meta-analysis
- Rapid recommendations evidence ecosystem

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>100 organizations have adopted GRADE

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Journal of Clinical Epidemiology ■ (2017) ■

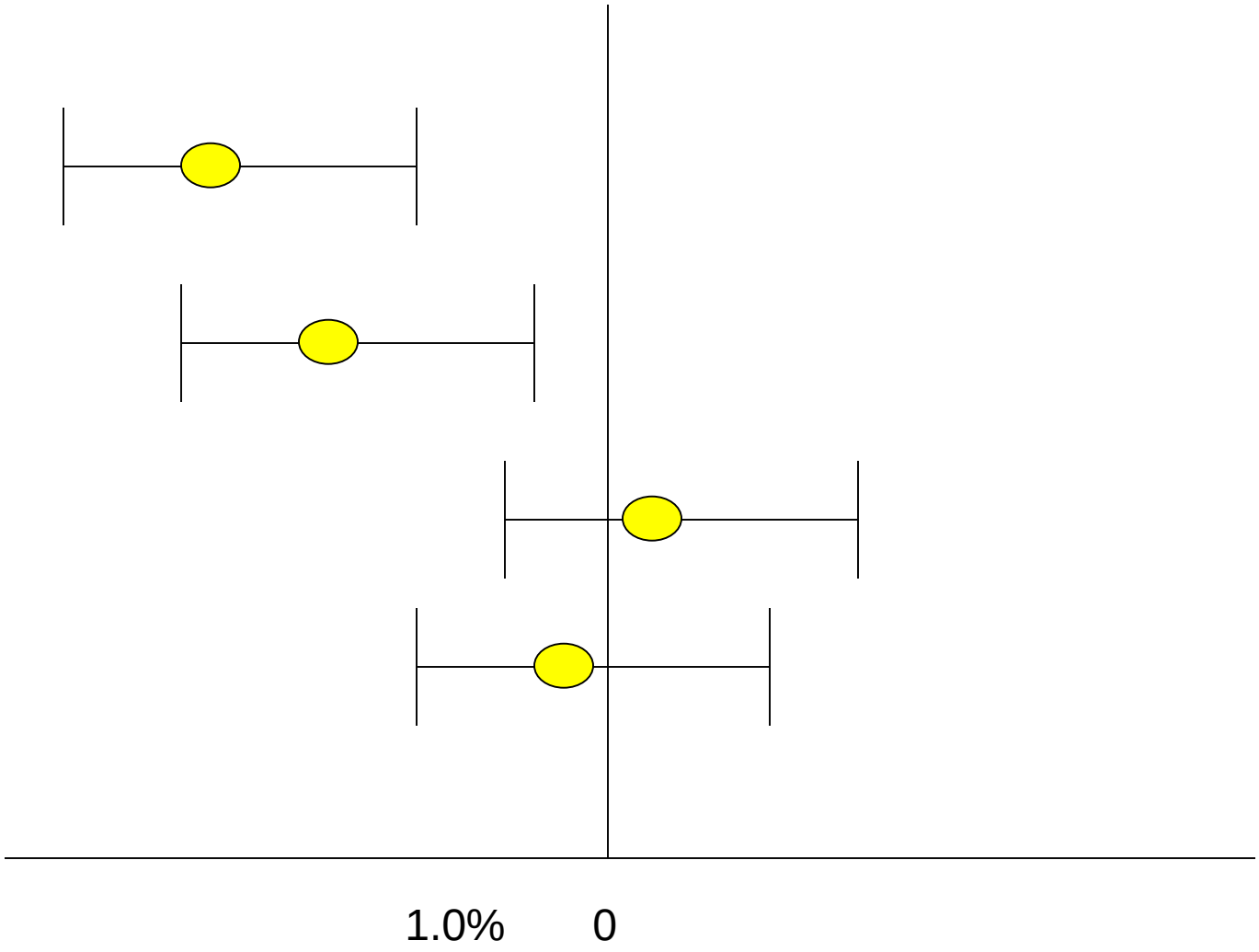
Journal of Clinical Epidemiology

ORIGINAL ARTICLE

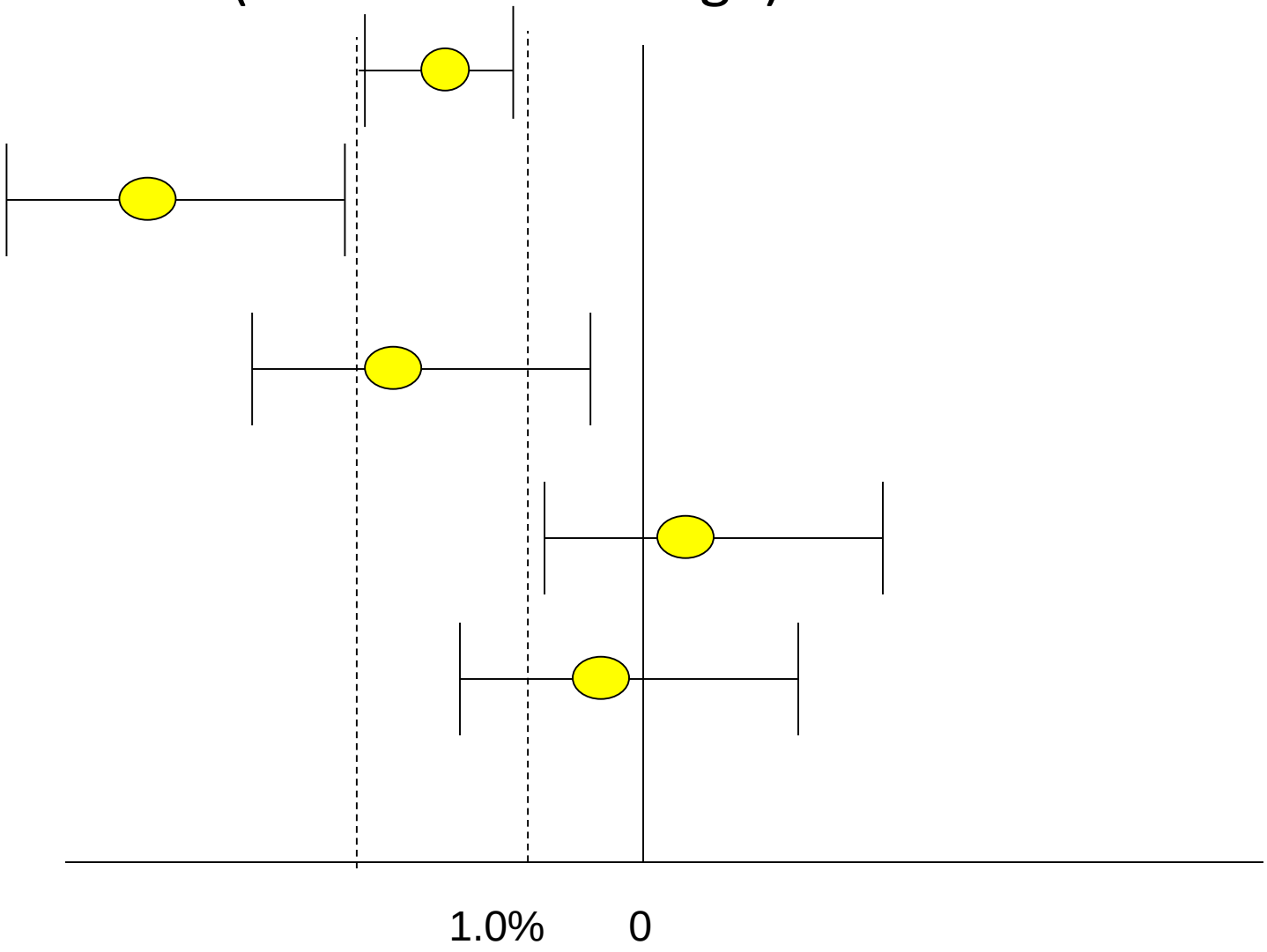
The GRADE Working Group clarifies the construct of certainty of evidence

Monica Hultcrantz[a,b,*], David Rind[c,d], Elie A. Akl[e,f], Shaun Treweek[g], Reem A. Mustafa[e,h], Alfonso Iorio[e,i], Brian S. Alper[j,k], Joerg J. Meerpohl[l,m], M Hassan Murad[n], Mohammed T. Ansari[o], Srinivasa Vittal Katikireddi[p], Pernilla Östlund[a,q], Sofia Tranæus[a,q,r], Robin Christensen[s], Gerald Gartlehner[t,u], Jan Brozek[e,i], Ariel Izcovich[v], Holger Schünemann[e,i], Gordon Guyatt[e,i]

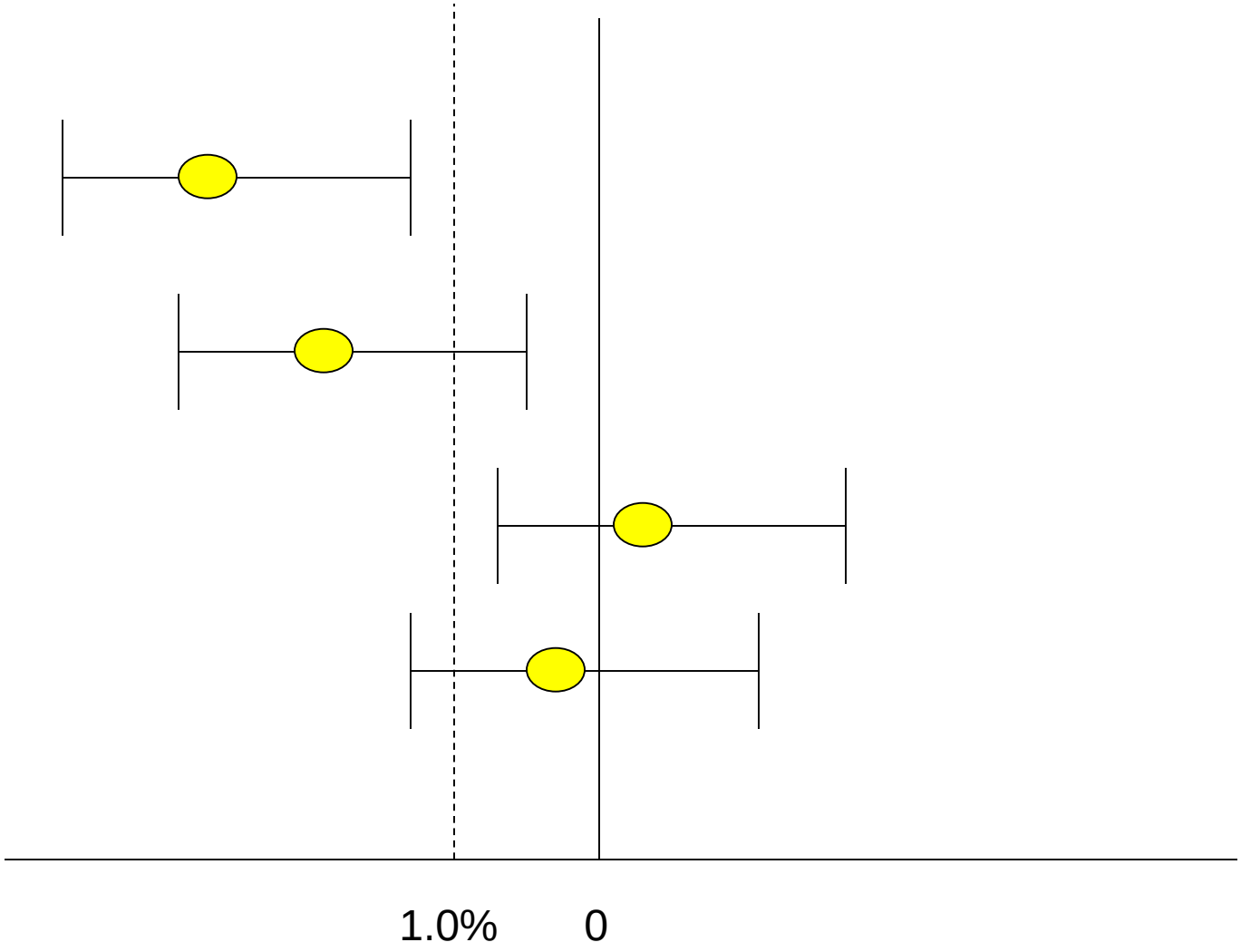
Certainty that the RR is not 1



Certainty that the treatment has a small (or medium or large) effect



Certainty that evidence supports a recommendation



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Interpreting patient-reported outcomes

- Treatment 1.6 cm. less pain on 10 cm. VAS
- Important or not?
- Compendium of all anchor based MIDs known humankind
  - A. Corrasco, T. Devji
  - Include credibility of MIDs

Measurement of Health Status

Ascertaining the Minimal Clinically Important Difference

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Controlled Clinical Trials 10:407–415 (1989)

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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

Insufficient, need to consider:

Feasibility

Acceptability

Equity

-Treatment / Diagnosis/Screening

- Individual / population

- Coverage decisions

- Health system and public health

Evidence to Decision Frameworks

RESEARCH METHODS AND REPORTING

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction

Pablo Alonso-Coello,[1,2] Holger J Schünemann,[2,3] Jenny Moberg,[4] Romina Brignardello-Petersen,[2,5] Elie A Akl,[2,6] Marina Davoli,[7] Shaun Treweek,[8] Reem A Mustafa,[2,9] Gabriel Rada,[10,11,12] Sarah Rosenbaum,[4] Angela Morelli,[4] Gordon H Guyatt,[2,3] Andrew D Oxman[4] the GRADE Working Group

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Introduction

Healthcare decision making is complex. Decision-making processes and the factors (criteria) that decision makers should consider vary for different types of decisions, including clinical recommendations, coverage decisions, and health system or public health recommendations or decisions.[1-4] However, some criteria are relevant for all of these decisions, including the anticipated effects of the options being considered, the certainty of the evidence for those effects (also referred to as quality of evidence or confidence in effect estimates), and the costs and feasi-

If guidelines are not developed systematically and transparently, clinicians are not able to decide whether to rely on them or to explore disagreements when faced with conflicting recommendations.[12]

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group has previously developed and refined a system to assess the certainty of evidence of effects and strength of recommendations.[13-15] More than 100 organisations globally, including the World Health Organization, the Cochrane Collaboration, and the National Institute for

Evidence to Decision Frameworks

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines

Pablo Alonso-Coello,[1,2] Andrew D Oxman,[3] Jenny Moberg,[3] Romina Brignardello-Petersen,[2,4] Elie A Akl,[2,5] Marina Davoli,[6] Shaun Treweek,[7] Reem A Mustafa,[2,8] Per O Vandvik,[3] Joerg Meerpohl,[9] Gordon H Guyatt,[2,10] Holger J Schünemann,[2,10] the GRADE Working Group

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Introduction

Clinicians regularly face situations with two or more alternative actions. Each alternative often has different advantages and disadvantages, including differences in effectiveness, adverse effects, costs and other factors (criteria). To make these choices, clinicians rely on recommendations from clinical practice guidelines,[1] other recommendations (such as from colleagues or experts) or implicit rules for decision making, such as based on their personal experience or what others do. To ensure trustworthiness, clinical practice guidelines are made rationale for different types of decisions.[5] In this second article, we describe the use of EtD frameworks for clinical recommendations and how they can help clinicians and patients who use those recommendations.

We will use the scenario in box 1 to illustrate the use of EtD frameworks for clinical recommendations.[6-8] The question posed for the panel in this scenario was: "Should patients with atrial fibrillation and a moderate to high risk of stroke who are currently taking warfarin switch to dabigatran?" The panel specified the question details, including the population, intervention, com-

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ORIGINAL ARTICLE

GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health

Holger J. Schünemann[a,b,c,*], Reem Mustafa[a,c,d], Jan Brozek[a,b,c], Nancy Santesso[a,c], Pablo Alonso-Coello[a,c,e], Gordon Guyatt[a,b,c], Rob Scholten[f], Miranda Langendam[c,g], Mariska M. Leeflang[g], Elie A. Akl[a,c,h], Jasvinder A. Singh[c,i], Joerg Meerpohl[c,j], Monica Hultcrantz[k], Patrick Bossuyt[g], Andrew D. Oxman[l], GRADE Working Group

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ADMINISTRATION
TASKS
TEAM
SCOPE
DOCUMENT SECTIONS
PROGNOSIS
COMPARISONS
EVIDENCE TABLE
RECOMMENDATIONS
PRESENTATIONS
DISSEMINATION

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

- (•) Large
- ( ) Moderate
- ( ) Small
- ( ) Trivial
- ( ) Varies
- ( ) Don't know

Detailed judgements

2: ITT) (deaths reported)	1 per 100	**11 per 100** (1 to 90) [10]			
Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)	**Study population**		not estimable	(1 RCT) [14]	⨁⨁◯◯ LOW [4,5,15]
	0 per 100	**NaN per 100** (NaN to NaN)			
Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)	**Study population**		**RR 1.37** (1.10 to 1.77) [17]	132 (1 RCT) [1,16]	⨁⨁◯◯ LOW [4,5,15]
	58 per 100 [1]	**79 per 100** (63 to 100) [1]			
Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) 20 (assessed with: Microbiological endpoints)	**Study population**		**RR 0.39** (0.11 to 1.40) [22]	37 (1 RCT) [18,20,21]	⨁◯◯◯ VERY LOW [5,15,19]
	52 per 100 [21]	**20 per 100** (6 to 73) [20]			
	Low				
	0 per 100	**0 per 100** (0 to 0)			
	Moderate				
	0 per 100	**0 per 100** (0 to 0)			

Consensus on this criterion.

What is the overall certainty of the evidence of effects?

- (•) Very low
- ( ) Low
- ( ) Moderate
- ( ) High
- ( ) No included studies

Detailed judgements

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)	CRITICAL	⨁⨁◯◯ LOW
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1	CRITICAL	⨁◯◯◯

All critical outcomes measured There were concerns about imprecision (due to small sample size and few events), and indirectness (due to (1) background MDR-TB treatment not being consistent with currently recommended regimens and (2) to the use of a surrogate outcome, i.e. culture conversion).

There were also concerns on the risk of bias (due to the inappropriate exclusion of 19

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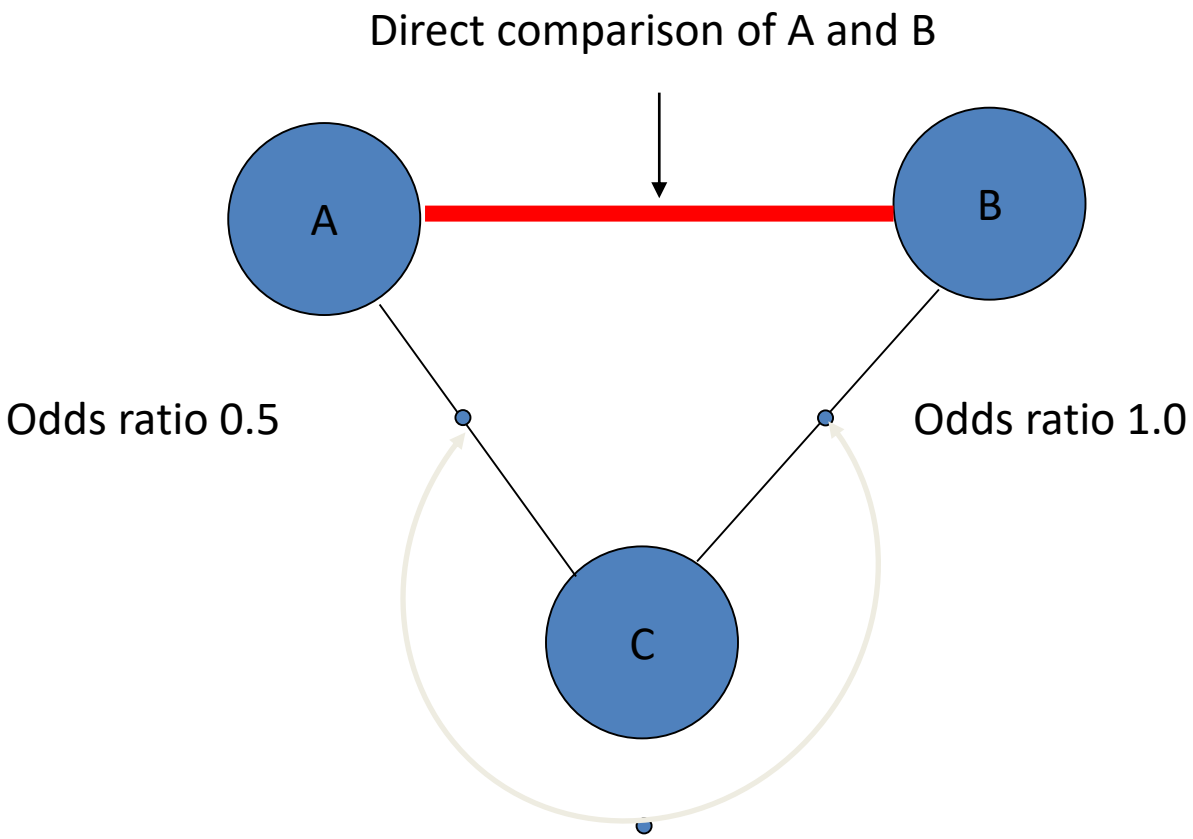
Rationale for Network Meta-Analyses

- Many disease areas many alternatives exist
- Clinicians/patients need to know relative merits
- Simultaneous comparison multiple treatments
  - Consider direct and indirect evidence
- Network meta-analysis

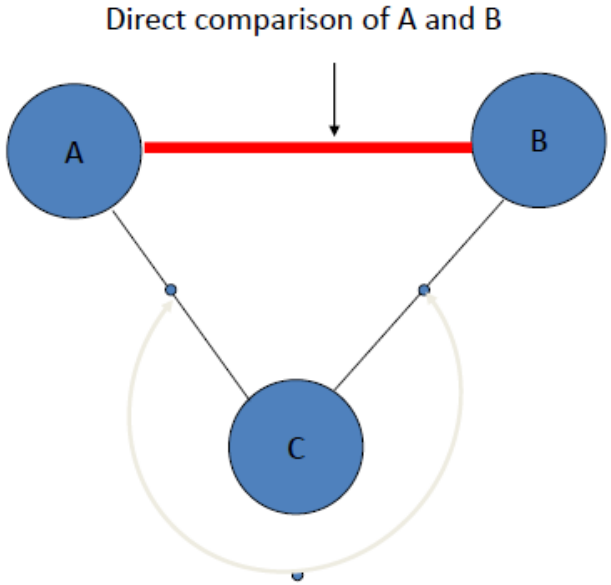

Direct comparison of A and B
A
B
C
Odds ratio 0.5
Odds ratio 1.0

RESEARCH METHODS & REPORTING

A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis

Network meta-analysis (NMA), combining direct and indirect comparisons, is increasingly being used to examine the comparative effectiveness of medical interventions. Minimal guidance exists on how to rate the quality of evidence supporting treatment effect estimates obtained from NMA. We present a four-step approach to rate the quality of evidence in each of the direct, indirect, and NMA estimates based on methods developed by the GRADE working group. Using an example of a published NMA, we show that the quality of evidence supporting NMA estimates varies from high to very low across comparisons, and that quality ratings given to a whole network are uninformative and likely to mislead.

Milo A Puhan[1], Holger J Schünemann[2], Mohammad Hassan Murad[3], Tianjing Li[4], Romina Brignardello-Petersen[5], Jasvinder A Singh[6], Alfons G Kessels[7], Gordon H Guyatt[2], for the GRADE Working Group



High certainty evidence and direct evidence contributes as much as indirect evidence

Rate the direct estimate

- Risk of bias
- Inconsistency
- Indirectness
- Publication bias

Not sufficient evidence; moderate, low, or very low certainty

Rate the indirect estimate

- Lowest of the ratings of the two direct comparisons forming the most dominant first-order loop
- Intransitivity

Rate the network estimate

- Rating of direct estimate OR
- Rating of estimate that contributes the most OR
- Higher between direct and indirect rating
- Incoherence
- Imprecision

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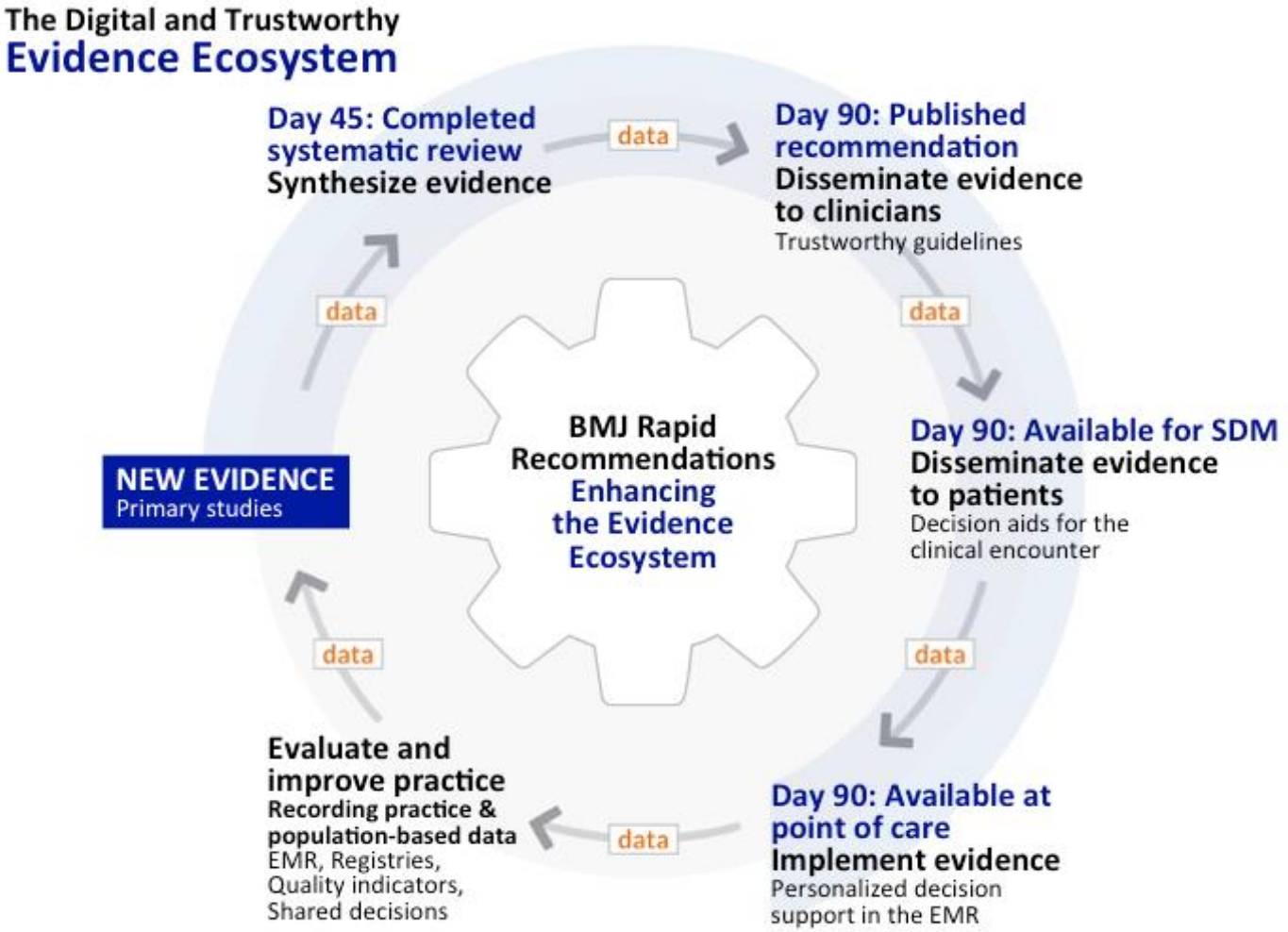
Trustworthy, Efficient, Timely Evidence Ecosystem in Action



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