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Subgroup Analysis in Guideline Development Criteria for more context-sensitive recommendations

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Declaration of Conflict of interest

“To the best of my knowledge, I declare that I, and any of my co-authors have no actual or potential conflict of interest in relation to this presentation.”

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Membership:

- Expertise cell, Working group Development of Primary Care Guidelines (WOREL), Belgium
- Academic Centre of General Medicine, Catholic university of Louvain, Belgium

Why subgroup analysis matters ?

Opportunities

- understanding variability in treatment effect across populations, conditions, or settings
- addressing concerns due to expected heterogeneity and indirectness
- 🎯 Tailoring context-specific recommendations¹ and individualize patient care²

Challenges

- clinical relevance
- credibility

Avoiding over-interpretation and bias

Existing tools:

-  SUN12² (RCTs) and ICEMAN³ (RCTs and MA)

¹Booth A, Moore G, Flemming K, Garside R, Rollins N, Tunçalp Ö, Noyes J. Taking account of context in systematic reviews and guidelines considering a complexity perspective. BMJ Glob Health. 2019 Jan 25;4(Suppl 1):e000840. doi: 10.1136/bmjgh-2018-000840. PMID: 30775011; PMCID: PMC6350703.

²Sun X, Briel M, Busse J W, You J J, Akl E A, Mejza F et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review BMJ 2012; 344 :e1553 doi:10.1136/bmj.e1553

SUN12 vs. ICEMAN

Domain	SUN 12 ² (RCT)	ICEMAN ³ (RCT and MA)
Design	- Subgroup is a baseline characteristic - A priori hypothesis ≤5 hypotheses tested	- A priori hypothesis - Limited or adjusted number of tests
Analysis	- Significant interaction test - Independent interaction effect	- Significant statistical interaction - Avoid arbitrary cut points (for continuous variables) - Sufficient study count (Sufficient number of studies) - Replicated across RCTs (consistency across trials)
Context	- Pre-specified direction - Consistent with prior studies - Supported by indirect evidence - Consistency across outcomes	- Pre-specified direction - Supported by prior evidence

²Sun X, Briel M, Busse J W, You J J, Akl E A, Mejza F et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review BMJ 2012; 344 :e1553 doi:10.1136/bmj.e1553

³Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, Gagnier J, Borenstein M, van der Heijden GJMG, Dahabreh IJ, Sun X, Sauerbrei W, Walsh M, Ioannidis JPA, Thabane L, Guyatt GH. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ. 2020 Aug 10;192(32):E901-E906. doi: 10.1503/cmaj.200077. PMID: 32778601; PMCID: PMC7829020.

Case example – WOREL

Guideline Acute sore throat

Design	Intervention	Outcome	Heterogeneity (I ²)	Effect Size (RR, 95% CI)
5 RCTs including 851 patients	Oral and IM corticosteroids	Complete resolution of pain at 24 hours	67% Substantial	2.4 (1.29-4.47) Sample size sufficient
Pre-specified sub-group analysis  4 RCTs (774 patients)	Oral corticosteroids		51% Moderate	1.88 (1.13, 3.14) Sample size sufficient
Pre-specified sub-group analysis  2 RCTs (191 patients)	IM corticosteroids		33% Low	4.59 (1.62-13.03) Sample size insufficient/imprecision 
The test for interaction : p-value of 0.13 → differences likely due to chance 				

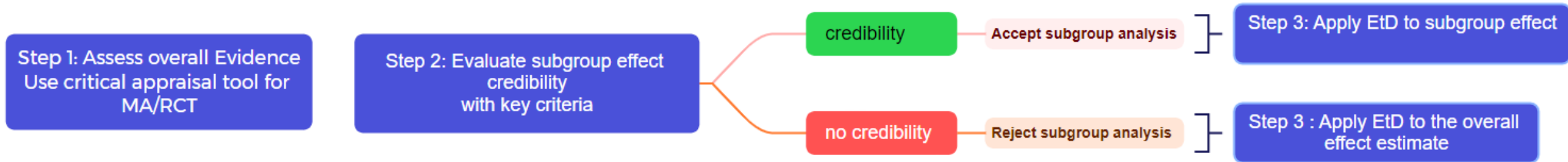
de Cassan, S., Thompson, M. J., Perera, R., Glasziou, P. P., Del Mar, C. B., Heneghan, C. J., & Hayward, G. (2020). Corticosteroids as standalone or add-on treatment for sore throat. Cochrane Database Syst Rev, 5(5), Cd008268.
 doi:10.1002/14651858.CD008268.pub3 . Critical appraisal : high quality (++)

Key Criteria for Subgroup Analysis

- ✓ A priori hypothesis (pre-specified in protocol)
- ✓ Correct direction
- ✓ Statistically significant interaction
- ✓ Sufficient number of studies (for meta-analysis)

Balance between in-depth statistical analysis and pragmatism

Logic flow for guidelines development



Take-home messages

- Be cautious with subgroup analysis
- Use key criteria for credibility
- Reflect decisions transparently in Evidence-to-Decision (EtD) framework



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Thank you for your attention!
Questions?