

Appendix 6 (as supplied by the authors): Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in a meta-analysis of randomized controlled trials

Quick Instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a *single proposed effect modification at a time*; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is *not* part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s):

If available, protocol reference(s):

State a single outcome and, if applicable, time-point of interest (e.g. mortality at 1 year follow-up):

State a single effect measure of interest (e.g. relative or absolute risk difference):

State a single potential effect modifier of interest (e.g. age or comorbidity):

Was the potential effect modifier measured before randomization? yes, continue no, stop here and refer to manual for further instructions

Credibility Assessment

1: Is the analysis of effect modification based on comparison within rather than between trials?

<input type="checkbox"/> Completely between	<input type="checkbox"/> Mostly between or unclear	<input type="checkbox"/> Mostly within	<input type="checkbox"/> Completely within
<i>Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.</i>	<i>Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information</i>	<i>Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information</i>	<i>All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g. meta-analysis of interactions</i>

Comment:

2: For within-trial comparisons, is the effect modification similar from trial to trial? Not applicable: no or one within-RCT comparison

<input type="checkbox"/> Definitely not similar	<input type="checkbox"/> Probably not similar or unclear	<input type="checkbox"/> Mostly similar	<input type="checkbox"/> Definitely similar
<i>Effect modification reported for two or more trials and clearly different directions</i>	<i>Effect modification not reported for individual trials or too imprecise to tell</i>	<i>Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude</i>	<i>Effect modification reported for two or more trials, similar in direction, only some differences in magnitude</i>

Comment:

3: For between-trial comparisons, is the number of trials large? Not applicable: no between RCT comparison

<input type="checkbox"/> Very small	<input type="checkbox"/> Rather small or unclear	<input type="checkbox"/> Rather large	<input type="checkbox"/> Large
<i>1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression</i>	<i>3-4 in smallest subgroup; 6-10 in continuous meta-regression</i>	<i>5-9 in smallest subgroup; 11 to 15 in continuous meta-regression</i>	<i>10 or more in smallest subgroup; more than 15 in continuous meta-regression</i>

Comment:

4: Was the direction of effect modification correctly hypothesized a priori?

<input type="checkbox"/> Definitely no	<input type="checkbox"/> Probably no or unclear	<input type="checkbox"/> Probably yes	<input type="checkbox"/> Definitely yes
<i>Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible</i>	<i>Vague hypothesis or hypothesized direction unclear</i>	<i>No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification</i>	<i>Prior protocol available and includes correct specification of direction of effect modification, e.g. based on a biologic rationale</i>

Comment:

5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

<input type="checkbox"/> Chance a very likely explanation	<input type="checkbox"/> Chance a likely explanation or unclear	<input type="checkbox"/> Chance may not explain	<input type="checkbox"/> Chance an unlikely explanation
<i>Interaction or meta-regression p-value >0.05</i>	<i>Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable</i>	<i>Interaction or meta-regression p-value ≤0.01 and >0.005</i>	<i>Interaction or meta-regression p-value ≤0.005</i>

Comment:

6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

<input type="checkbox"/> Definitely no	<input type="checkbox"/> Probably no or unclear	<input type="checkbox"/> Probably yes	<input type="checkbox"/> Definitely yes
<i>Explicitly exploratory analysis or large number of effect modifiers tested (e.g. greater than 10) and multiplicity not considered in analysis</i>	<i>No mention of number or 4-10 effect modifiers tested and number not considered in analysis</i>	<i>No protocol available but unequivocal statement of 3 or fewer effect modifiers tested</i>	<i>Protocol available and 3 or fewer effect modifiers tested or number considered in analysis</i>

Comment:

7: Did the authors use a random effects model?

<input type="checkbox"/> Definitely no	<input type="checkbox"/> Probably no or unclear	<input type="checkbox"/> Probably yes	<input type="checkbox"/> Definitely yes
<i>Fixed (or common) effect or fixed effects model explicitly stated</i>	<i>Probably fixed effect(s) model</i>	<i>Probably random (or mixed) effects</i>	<i>Random (or mixed) effects explicitly stated</i>

Comment:

8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? not applicable: not continuous

<input type="checkbox"/> Definitely no	<input type="checkbox"/> Probably no or unclear	<input type="checkbox"/> Probably yes	<input type="checkbox"/> Definitely yes
<i>Analysis based on exploratory cut point(s), e.g. picking cut point associated with highest interaction p-value</i>	<i>Analysis based on cut point(s) of unclear origin</i>	<i>Analysis based on pre-specified cut point(s), e.g. suggested by prior RCT</i>	<i>Analysis based on the full continuum, e.g. assuming a linear or logarithmic relationship</i>

Comment:

9 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 3.9) not applicable

yes, probably decrease yes, probably increase

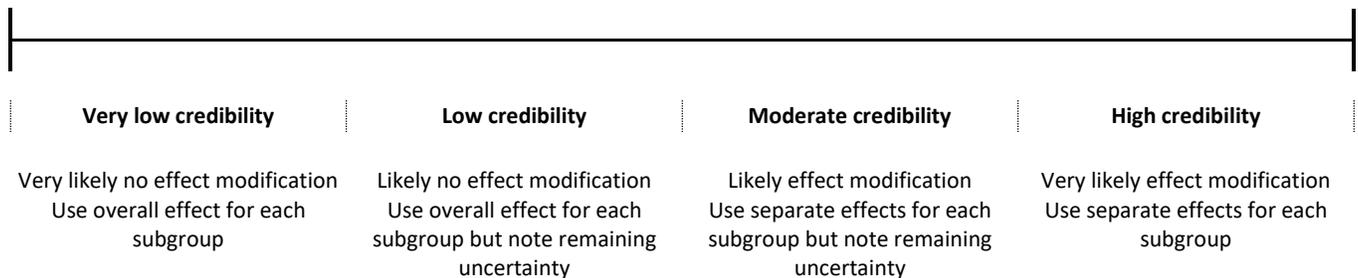
Comment:

10: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably decrease credibility or unclear → very low
- Two or more responses definitely decrease credibility → maximum usually low even if all other responses satisfy credibility criteria
- One response definitely decreases credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably decrease credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably decrease credibility → high very likely

Place a mark on the continuous line (e.g. hit "x" in electronic version)



Comment: