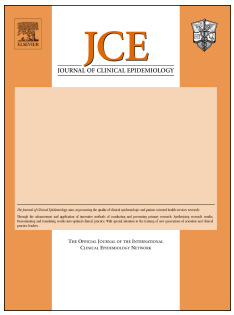

A decision algorithm for assessing indirectness in Core GRADE

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Letter to Editor:

In the recent *Core GRADE 5: Rating certainty of evidence—assessing indirectness* [1], published in The BMJ, and in the complementary Journal of Clinical Epidemiology article, *Core GRADE Unpacked: A Summary of Recent Innovations in Complementary GRADE Methodology* [2], we outlined the Core GRADE principles and explained how Core GRADE users can judge whether or not to rate down for indirectness when Population, Intervention, Comparator, or Outcome (PICO) elements diverge from the target PICO. Subsequent to these publications, we have reflected on the desirability of an algorithm to assist users in making this decision and decided such an algorithm would be helpful. *Figure 1* presents the algorithm as a logical, stepwise complement to the existing text.

The process begins by determining whether the evidence is direct or indirect. Although indirectness is rarely a concern in systematic reviews of direct evidence, it is frequently an issue in guidelines or HTAs in which the PICO in the relevant studies differs from the target PICO. Thus, when recognition of the limitations of direct evidence (low or very low certainty

for a particular outcome) prompts an explicit search for indirect evidence, serious concerns about indirectness are very likely to arise.

For Population-Intervention-Comparator, the algorithm first prompts assessors to judge whether there are differences – in, for example, age, disease severity, intervention dose, clinician expertise or comparators - between the target and study PICOs. If there are differences, it asks whether biological or social factors are sufficiently similar to expect the same impact on the target outcome. The degree of dissimilarity then dictates whether to rate down once, twice, or not at all.

For Outcome, the algorithm focuses on two common sources of indirectness: surrogate outcomes and mismatches in outcome definition or timing. It directs assessors to judge how closely a surrogate links to the patient-important endpoint and whether the measurement aligns with what matters to patients. [3]

We anticipate this visual decision-support tool will improve consistency and transparency in indirectness assessments, enhance GRADE training, and serve as a reference for systematic reviewers, health technology assessors, and guideline developers.

Competing interests: None declared.

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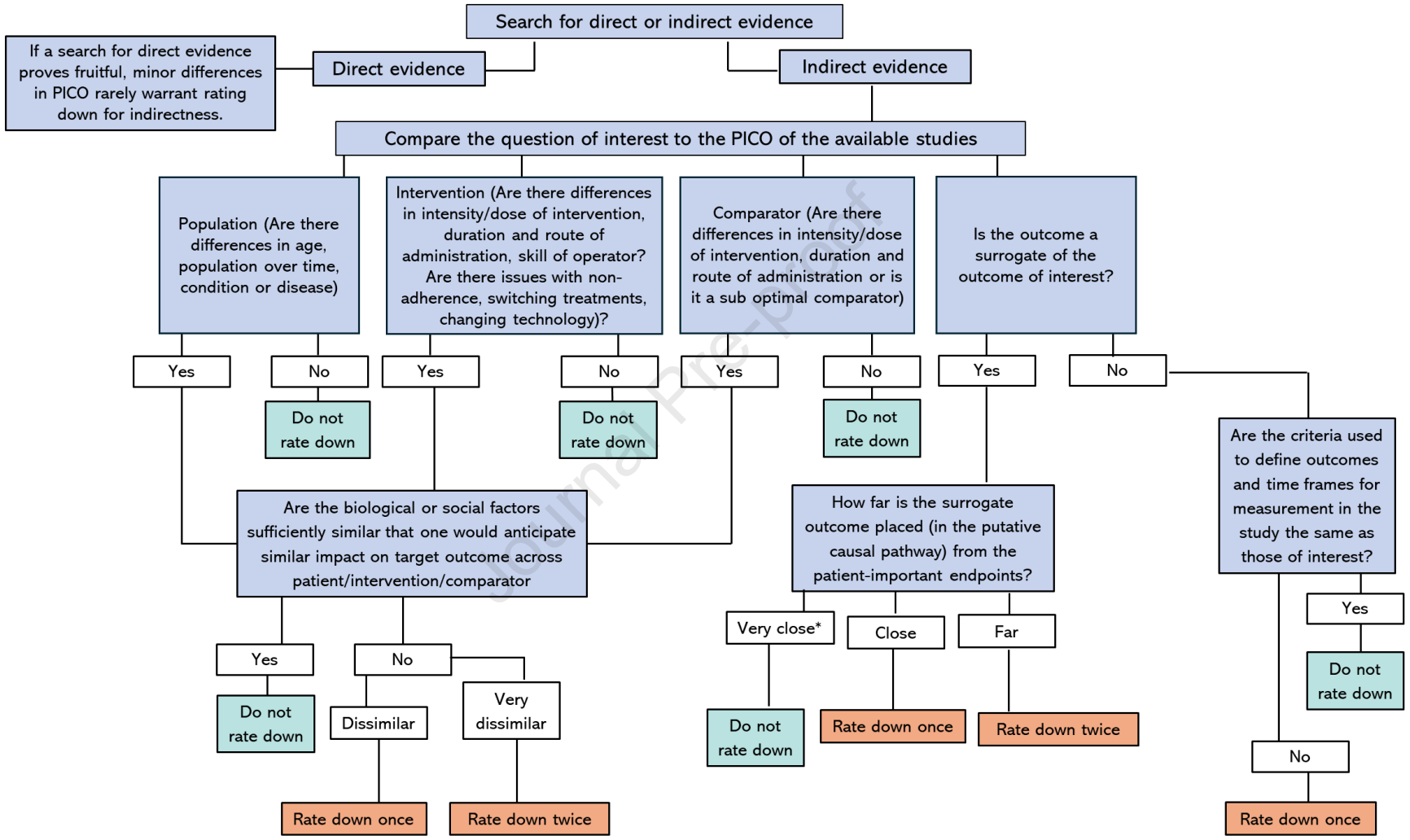
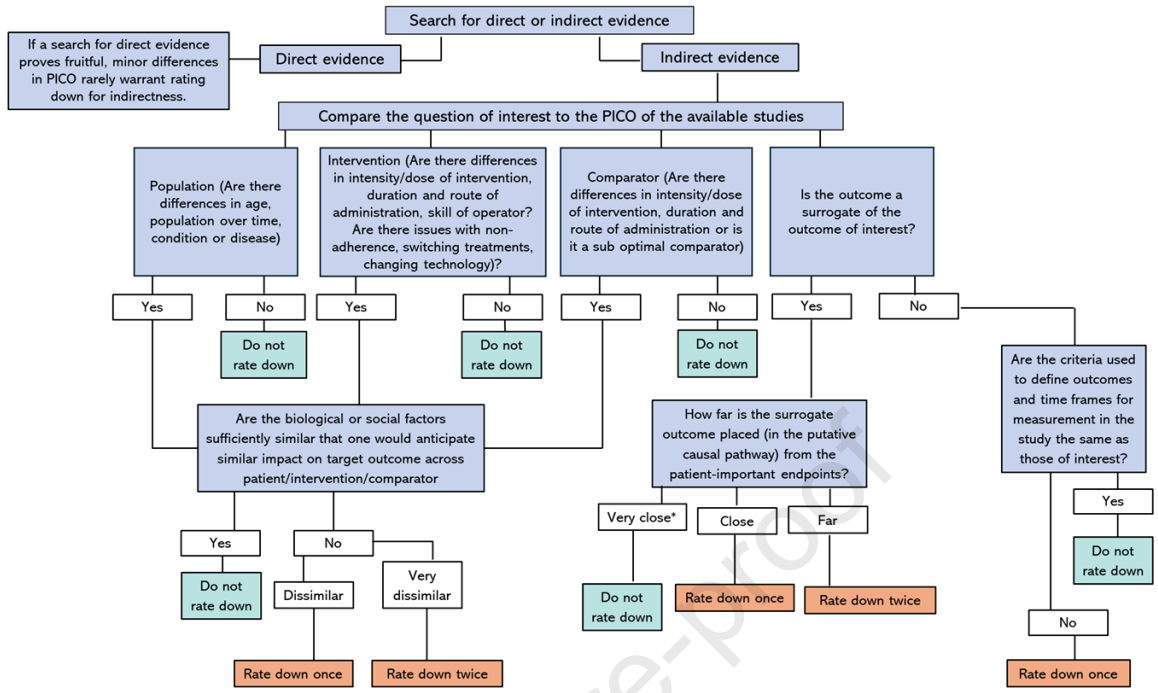
Figure legend:

Figure 1. Decision-algorithm for assessing indirectness in Core GRADE.



*Although some outcomes may be considered surrogates, they are so closely and directly linked to the disease process that they always represent a patient-important outcome. For example, a hip fracture diagnosed on radiograph inevitably leads to pain, immobility, and the need for treatment, and in malaria, treatment failure (recurrence or recrudescence) confirmed by uncorrected or corrected PCR is a patient-important outcome.



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Conflict of Interest Declaration

The authors declare that they have no conflicts of interest in relation to this submission. No financial, personal, or institutional relationships have influenced the development of this algorithm or the preparation of the accompanying letter to the editor