

Additional File 5A: Illustrations of the GRADE approach

Table AF5A-1: The outcome-centric approach in GRADE

Source	PICO question	Outcomes evaluated ^a	Outcome importance ^b	Systematic review	Recommendation formulation
				Certainty of a body of evidence ^c	Overall certainty of evidence ^d
Hanson 2019 ¹ and Crocket 2012 ²	Should lubiprostone be used in the management of opioid-induced constipation in patients with non-cancer pain?	Spontaneous bowel movement response	Critical	Low ⊕⊕○○	Low
		Reduction in severity of straining	Important	Moderate ⊕⊕⊕○	
		Adverse effects leading to discontinuation of treatment	Important	Moderate ⊕⊕⊕○	
Lantos 2021 ³	In patients following a high-risk tick bite, should prophylactic antibiotic therapy be used <i>versus</i> observation?	Clinical evidence of Lyme disease after treatment	Critical	Moderate ⊕⊕⊕○	Moderate
		Seroconversion	Important	Low ⊕⊕○○	
		Serious adverse events	Important	Moderate ⊕⊕⊕○	

^aSee original citations for a complete list of outcomes that are reported in the GRADE evidence profiles;

^bMultiple stakeholders participate in defining which outcomes are critical and important. This is an early step in the process for developing clinical recommendations;

^cDetermined by consideration of factors that affect confidence in an estimate of effect.⁴ See Table 5.1 in main text for the specific reasons for upgrading and downgrading the certainty of evidence;

^dFor recommendations, overall certainty across outcomes is determined by the lowest certainty of evidence for any outcome rated as critical.⁵

Table AF5A-2: Statement of conclusions on evidence certainty reached with and without application of GRADE^a

Topic of interest: <i>Should treatment (X) be used to treat (condition) in (population)?</i> Critical outcomes: <i>Quality of Life (QoL), significant adverse events (AEs)</i> Systematic review research question: <i>Is treatment X more effective than usual care for improving QoL in (condition)?</i>	
Without application of GRADE	With application of GRADE
Treatment X compared to usual care leads to statistically significant improvements in QoL.	There is (<i>high, moderate, low, very low</i>) certainty evidence that Treatment X compared to usual care improves QoL in (population) with (condition).
Treatment X was not associated with significant AEs compared to usual care.	There is (<i>high, moderate, low, very low</i>) certainty evidence that Treatment X does not cause more frequent AEs compared to usual care in (population) with (condition).
There is sufficient evidence to suggest Treatment X over usual care for improving QoL in (condition).	There is (<i>high, moderate, low, very low</i>) certainty evidence that Treatment X is more effective for improving QoL compared to usual care in (population) with (condition).

^aThe example is a hypothetical systematic review. Adapted from Samuniak and colleagues.⁶

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