

Guidance for the role of key opinion leaders in the identification and validation of treatment effect modifiers and prognostic variables in indirect treatment comparisons

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Background

- When data from head-to-head randomized controlled trials (RCT) are not available, indirect treatment comparisons (ITC) can be used to evaluate the comparative effectiveness of different therapeutic options, which is crucial in making informed decisions.
- In ITCs, the validity of results is dependent on the assumption that the populations for comparison have homogeneous distributions of covariates that may influence the outcomes.
- These covariates can be treatment effect modifiers (TEM; variables that influence the direction or magnitude of the treatment's effect on an outcome) or prognostic variables (PV; variables that affect the outcome of patients regardless of the treatment they receive).
- Typically, relevant TEMs and PVs are identified through literature reviews, statistical approaches, and expert opinion. Key opinion leaders (KOL) are often consulted for clinical relevance of TEMs and PVs; however, their roles remain unstructured in formal guidance.
- In a review of methodological approaches of identifying TEMs in ITCs, only 17 of 511 (3.3%) ITCs included a description of the selection process for TEMs and PVs; literature reviews and expert opinion were the most commonly cited sources.¹
- Although there are well-documented methods for identifying TEMs/PVs using literature reviews or statistical approaches, there is no accepted guidance or processes for the crucial role of KOLs in selecting TEMs/PVs.

Objectives

- The objective of this work was to provide a stepwise framework for consulting KOLs on PVs and TEMs during ITCs, addressing the lack of standardized procedures for clinical validation of these variables.

Methods

- Review of relevant documents published by health technology assessment (HTA) bodies and non-payer organizations were searched for guidance regarding identification of TEMs for conducting ITCs (N = 11).
- A pragmatic review was conducted to identify existing guidance on the selection of KOLs and timing of TEM/PV identification (Table 1).
- No guidance was identified on the format or types of questions that should be proposed to KOLs.

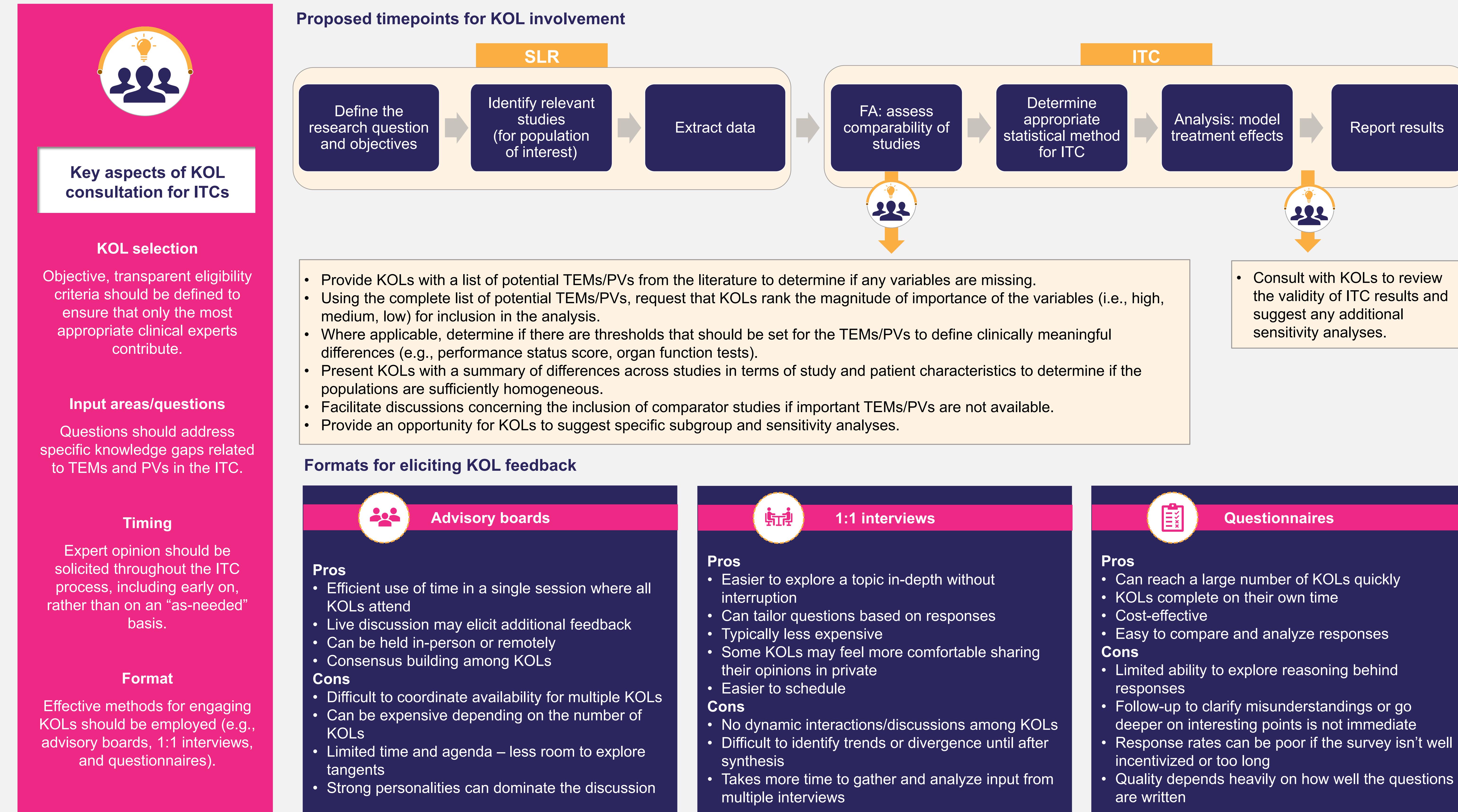
Table 1. Existing guidance on KOL engagement for ITCs

	Year	KOL mentioned?	Definition	Timing provided?
EU HTA CG ²	2024	Healthcare professionals	Knowledge of the disease area	A priori
NICE ³	2023	Experts	In the clinical discipline	Before data analysis
NICE ⁴	2016	Experts	Clinical expertise or with prior empirical evidence	Prior to analysis
NICE ⁵	2012	Experts	None	No
Cochrane ⁶	2024	No	None	No
PRISMA Group ^{7,8}	2015	No	None	Prespecified

Abbreviations: HTA CG, Health Technology Assessment Coordination Group; EU, European Union; KOL, key opinion leader; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses

Results

The review of existing guidance from relevant HTA and non-payer organizations highlighted a significant gap in terms of clear guidelines that outline when and how to integrate KOL input for ITCs. The proposed framework aims to bridge this gap by addressing key aspects of KOL consultation for ITCs.



Abbreviations: FA, feasibility assessment; ITC, indirect treatment comparison; KOL, key opinion leader; SLR, systematic literature review

Conclusions

- The accurate identification of TEMs can significantly influence the reliability of ITC outcomes. Without consistent frameworks, there is a risk that KOL input is either underutilized or inconsistently applied, affecting both the credibility and applicability of findings.
- The lack of guidance highlights the need to explore effective approaches in the absence of standardized methodologies for KOL engagement. Addressing this gap is essential for improving the reliability of ITC results and supporting informed healthcare decision-making.
- This framework offers a systematic approach to KOL consultation for validating PVs and TEMs in ITCs, potentially improving the accuracy and relevance of treatment comparisons in the absence of head-to-head RCTs.

References

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