

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.



Key aspects of KOL consultation for ITCs

KOL selection

Objective, transparent eligibility criteria should be defined to ensure that only the most appropriate clinical experts contribute.

Input areas/questions

Questions should address specific knowledge gaps related to TEMs and PVs in the ITC.

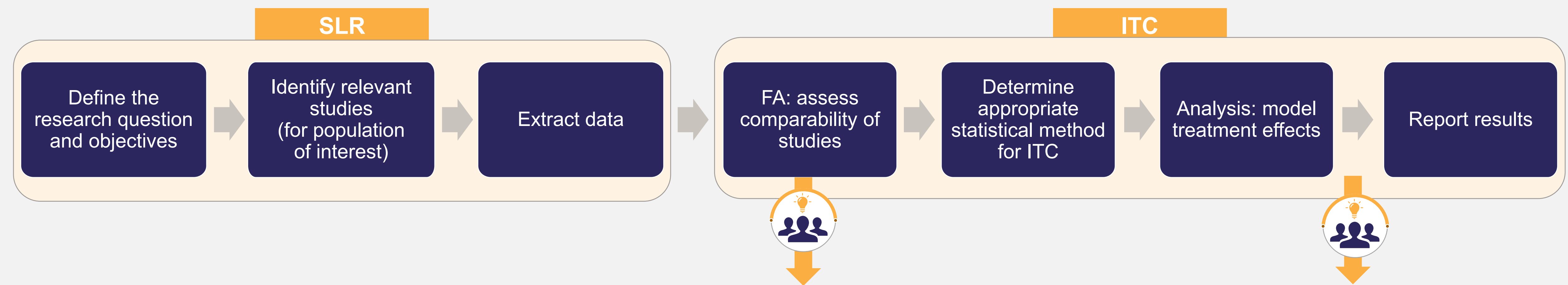
Timing

Expert opinion should be solicited throughout the ITC process, including early on, rather than on an "as-needed" basis.

Format

Effective methods for engaging KOLs should be employed (e.g., advisory boards, 1:1 interviews, and questionnaires).

Proposed timepoints for KOL involvement



- Provide KOLs with a list of potential TEMs/PVs from the literature to determine if any variables are missing.
- Using the complete list of potential TEMs/PVs, request that KOLs rank the magnitude of importance of the variables (i.e., high, medium, low) for inclusion in the analysis.
- Where applicable, determine if there are thresholds that should be set for the TEMs/PVs to define clinically meaningful differences (e.g., performance status score, organ function tests).
- Present KOLs with a summary of differences across studies in terms of study and patient characteristics to determine if the populations are sufficiently homogeneous.
- Facilitate discussions concerning the inclusion of comparator studies if important TEMs/PVs are not available.
- Provide an opportunity for KOLs to suggest specific subgroup and sensitivity analyses.

- Consult with KOLs to review the validity of ITC results and suggest any additional sensitivity analyses.

Formats for eliciting KOL feedback



Advisory boards

Pros

- Efficient use of time in a single session where all KOLs attend
- Live discussion may elicit additional feedback
- Can be held in-person or remotely
- Consensus building among KOLs

Cons

- Difficult to coordinate availability for multiple KOLs
- Can be expensive depending on the number of KOLs
- Limited time and agenda – less room to explore tangents
- Strong personalities can dominate the discussion



1:1 interviews

Pros

- Easier to explore a topic in-depth without interruption
- Can tailor questions based on responses
- Typically less expensive
- Some KOLs may feel more comfortable sharing their opinions in private
- Easier to schedule

Cons

- No dynamic interactions/discussions among KOLs
- Difficult to identify trends or divergence until after synthesis
- Takes more time to gather and analyze input from multiple interviews



Questionnaires

Pros

- Can reach a large number of KOLs quickly
- KOLs complete on their own time
- Cost-effective
- Easy to compare and analyze responses

Cons

- Limited ability to explore reasoning behind responses
- Follow-up to clarify misunderstandings or go deeper on interesting points is not immediate
- Response rates can be poor if the survey isn't well incentivized or too long
- Quality depends heavily on how well the questions are written

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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