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Addressing Bias in Indirect Treatment Comparisons: A Framework for Identifying Treatment Effect Modifiers and Prognostic Variables

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BACKGROUND

- In comparative effectiveness research, indirect treatment comparisons (ITCs) are employed to assess the relative efficacy of interventions in the absence of head-to-head trials.
- For unbiased results from an ITC, the distribution of treatment effect modifiers (TEMs) (described in **Table 1)** must be comparable across trials, also known as the similarity assumption.[1]
- When TEMs and/or prognostic variables (PVs) are imbalanced between studies in an ITC, the similarity assumption is violated.
  - Population-adjustment (PA) methods are recommended when the similarity assumption is violated. [1]

Table 1. Overview of TEMs and PVs impact in ITCs

	Treatment effect modifiers	Prognostic variables
Definition	Influence the magnitude or direction of treatment effect	Predict outcomes regardless of treatment
Impact on validity	Must be balanced across studies to uphold the similarity assumption	Imbalances can bias absolute outcomes, especially in unanchored ITCs
Adjustment required for	Anchored & Unanchored PA-ITCs	Primarily in Unanchored PA-ITCs
Role in outcome variation	Modify relative treatment effects	Affect baseline risk or prognosis

Abbreviations: PA-ITC = population adjusted indirect treatment comparison, PVs = prognostic variables, TEMs = treatment effect modifiers

- The validity of PA-ITC methods hinges on incorporation of all relevant TEMs/PVs.[1-3]
- Heightened methodological standards set out in the Health Technology Assessment Collaboration Group (HTACG) guidelines for EU Joint Clinical Assessment (JCA) advocate for rigorous, transparent, and reproducible practices for TEM and PV identification in ITCs to ensure clinical relevance and policy utility.[2,3]
- Best-practice procedures for TEM/PV identification need to be established to satisfy HTA requirements.

OBJECTIVES

- Evaluate current practices observed in recent HTA submissions, and related publications, to determine how TEM/PV identification is typically operationalised and documented.
- Develop a structured, actionable framework that integrates methodological rigour, statistical considerations, and clinical expertise to support transparent and reproducible TEM/PV identification in line with HTA expectations.

METHODS

Review of current guidelines

- ITC guidelines from HTACG for JCA and National Institute for Health Care Excellence (NICE) were reviewed, specifically for recommended methodologies in identifying TEMs and PVs.[2-4]

Evaluation of TEM/PV identification methods in HTA submissions

- NICE technology appraisals (TA) between April 2022 - March 2025 that included an ITC were reviewed for reporting of the methods used to identify TEM/PV.

Framework development: Practicality of TEM/PV identification

- A targeted review of HTA submissions, ITC publications, and published randomised controlled trials (RCTs) of a pre-specified indication within oncology was conducted to identify TEM/PV for consideration in an ITC.
  - Clinical experts were consulted to validate and rank the TEMs/PVs identified in the targeted review.
- Insights gleaned from this practicality assessment directly informed the development of the framework, ensuring its methodological feasibility and applicability to ITC contexts.

RESULTS

Recommendations from current guidelines

- Comprehensive reporting of TEM/PV identification is emphasized in both HTACG and NICE guidelines, however formal methodologies for TEM/PV identification remain unestablished.
- Common themes from the evidence base suggest an iterative approach:
  - Structured review of the literature, either systematic (SLR) or targeted (TLR)
  - Clinical consultation
  - Empirical analyses

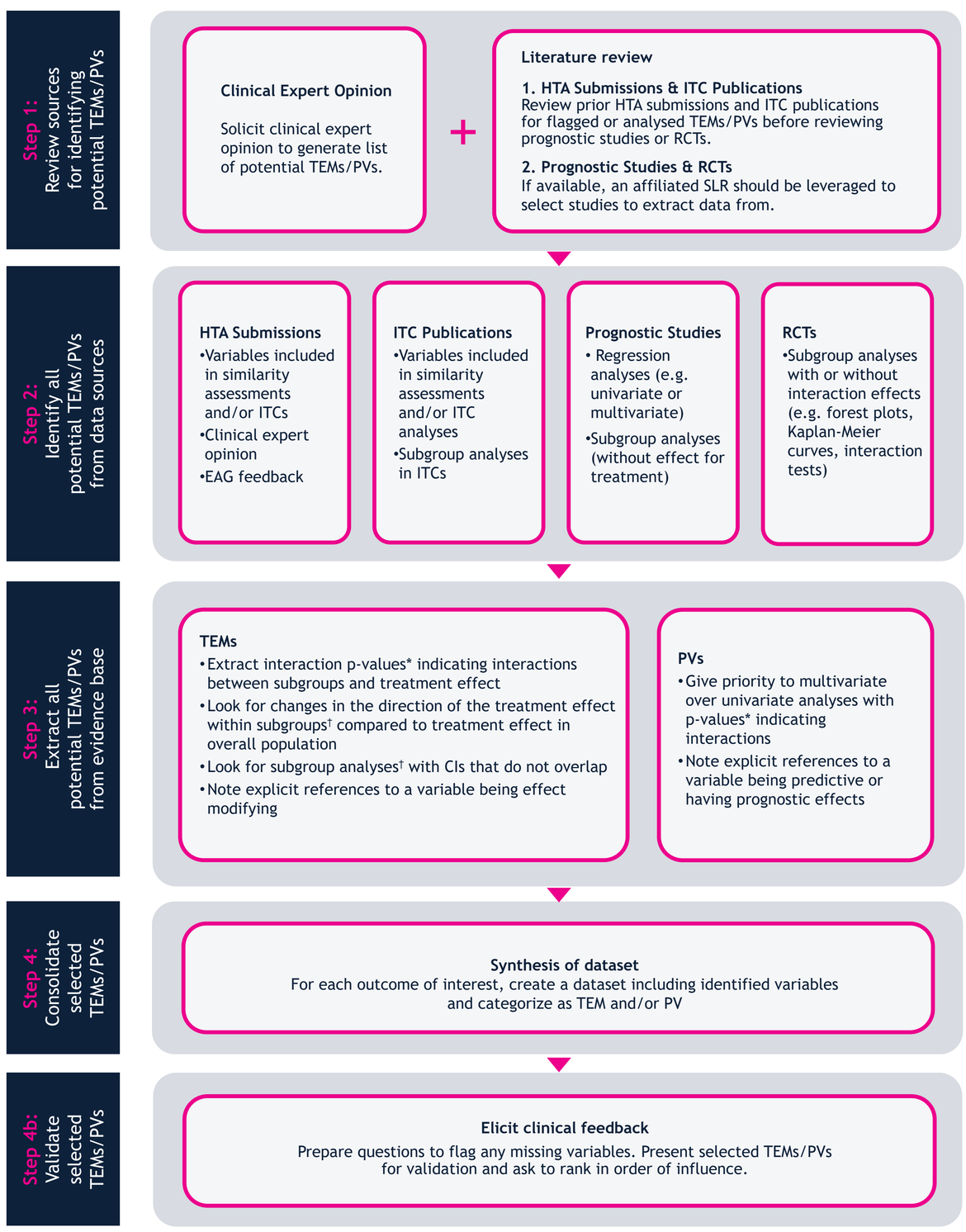
Evaluation of TEM/PV identification methods in HTA submissions

- TEM/PV identification methods were reported in 73 of 112 NICE TAs reviewed.
- Of the 73 TAs, 43 reported conducting a literature review, 52 reported consulting clinical experts, and 16 reported using empirical analyses to identify TEM or PV; however, only 10 included details on how these methods were undertaken.

Framework for TEM/PV identification

- A five-step framework for systematic TEM/PV identification is proposed in **Figure 1**. Each stage is designed to enhance transparency, reproducibility, and methodological rigour.

Figure 1. Framework for identification of TEMs/PVs for ITCs



*Modest thresholds (e.g. ≤ 0.20-0.25) are recommended for inclusion/exclusion to capture all potential TEMs/PVs.[5]
†Consideration for sufficient sample size, both overall and within subgroups, is essential and context-dependent.[6]
Abbreviations: CI = confidence intervals, EAG = Evidence Assessment Group, HTA = health technology assessment, ITC = indirect treatment comparison, PVs = prognostic variables, RCT = randomised controlled trial, SLR = systematic literature review, TEMs = treatment effect modifiers

CONCLUSIONS & RECOMMENDATIONS

- The framework presented here offers a practical and evidence-based approach for identifying a comprehensive list of TEMs and PVs for ITCs in HTA submissions.
- Integrating systematic evidence review, quantitative analysis, and clinical validation helps to ensure that the most influential variables are identified and appropriately accounted for, thus minimising bias.
- Early involvement of clinical experts, use of predefined inclusion criteria, and transparent documentation of decision pathways are key enablers of robust population-adjusted analyses.
- Adoption of structured frameworks such as this can help align future ITCs with evolving HTA and JCA expectations, ultimately enhancing the credibility, reproducibility, and policy relevance of comparative effectiveness research.
- Although the importance of comprehensive reporting of the TEMs/PVs identification process is emphasised in both HTACG and NICE guidelines, formal methodologies are unestablished. This underscores the value of adopting transparent and systematic approaches such as the one proposed here.

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