What HTA Bodies Criticize in Indirect Treatment Comparisons for Advanced Cancers: A Thematic Analysis of Recent HTA Reports in Solid Tumors

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HTA45

Background and Objectives

- Methods for conducting indirect treatment comparison (ITC) have evolved substantially in recent years, as has awareness of sources of bias within ITCs. Therefore, health technology assessment (HTA) bodies expect robustly conducted and reported ITCs.
- In this context, we aimed to qualitatively characterize themes in HTA critiques of ITCs in recent oncology reimbursement submissions.

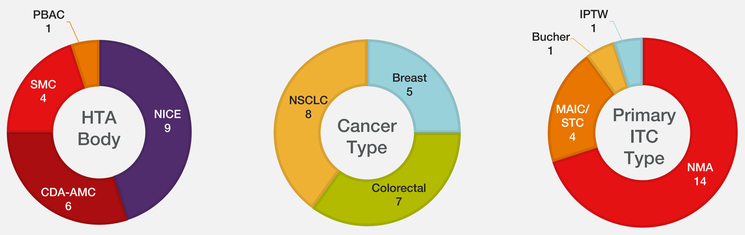
Methods

- We performed an artificial intelligence (AI)-assisted rapid review of 20 randomly selected, publicly available English-language HTA reports from the National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Canada's Drug Agency (CDA-AMC), and Pharmaceutical Benefits Advisory Committee (PBAC) in January 2026.
- We included HTA submissions of systemic anticancer therapies in advanced or metastatic non-small cell lung cancer (NSCLC), breast cancers, and colorectal cancer that included at least one ITC in the main clinical and/or economic evidence package and were published from May 2024 through November 2025.
- With a prespecified extraction template and codebook, we extracted the ITC method, role in the submission, and verbatim HTA critiques via ChatGPT Enterprise. Extractions were validated by a human reviewer.
- Critiques were classified by theme and subtheme. Critiques mentioned as part of the overall HTA decision were classified as having an impact on the decision. Findings were narratively synthesized by HTA body and ITC method.

Results

- Twenty HTA submissions[1-20] were reviewed and 71 critiques were catalogued:
  - Thirty-eight additional critiques catalogued by ChatGPT Enterprise were removed during validation due double-counting critiques; 24 critiques were added during validation.
- There was a median of three critiques cited per submission (range: 0–7).
- Characteristics of the submissions, by HTA body, cancer type, and ITC type are shown in **Figure 1**.
- Sixteen submissions were accepted (six with specific conditions) and four were rejected.
  - Seven submissions cited the ITC in a positive decision.
  - Eleven submissions cited ITC uncertainty or limitations and generally resulted in no recommendation (four submissions) or a positive decision (five submissions).
  - Two did not mention the ITC with respect to decision-making.
- The most common critiques were related to comparability and heterogeneity, problematic survival data, and model implementation and transparency (**Figure 2**). The types of sub-themes are described in **Table 1**.
- All types of theme categories were cited in at least one submission as contributing to the decision. The subthemes most commonly contributing to HTA decisions, as they related to the ITC, were unadjusted differences in population characteristics and risk-of-bias insufficiently assessed/reported (**Table 1**).
- All ITC methods were subject to some criticism. NMAs were subject to the largest variety of critiques, although this was expected as there were a larger volume of NMAs assessed. However, criticisms related to model implementation/transparency and treatment switching/subsequent therapy were observed primarily for NMA submissions (**Figure 3a**).
- The number of critiques per submission were similar across the five HTA bodies assessed.
- The CDA had more critiques on model implementation and transparency than other HTA bodies while interpretation and model choice critiques were most frequently recognized by the SMC. Problematic survival data and data limitations were most frequently criticized by NICE (**Figure 3b**).

Figure 1. Characteristics of HTA Submissions



Abbreviations: CDA-AMC = Canada's Drug Agency; HTA = health technology assessment; IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; STC = simulated treatment comparison; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium.

Figure 2. Number Critiques By Theme

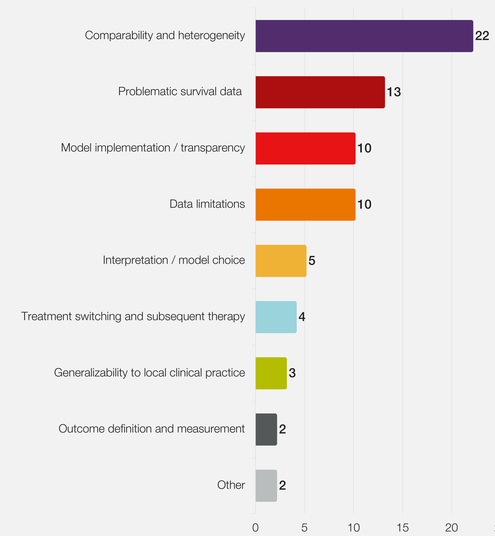
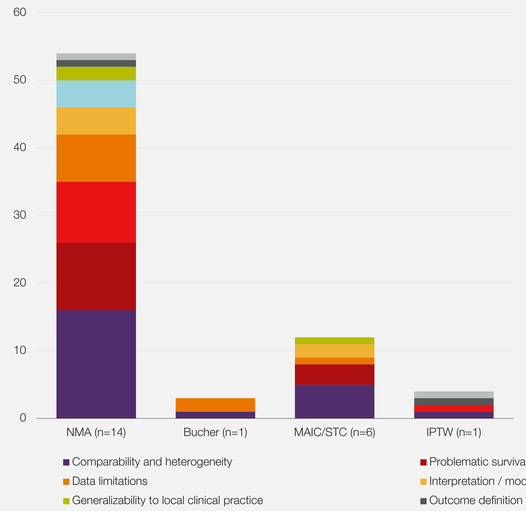
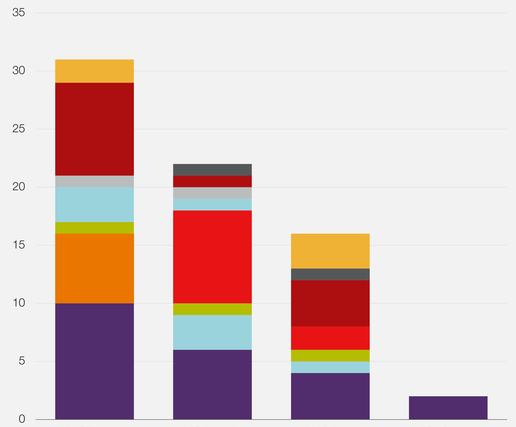


Figure 3a. Types of Critiques by ITC Type



Note: Two submissions presented different ITC methods
Abbreviations: IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; STC = simulated treatment comparison

Figure 3b. Types of Critiques by HTA Body



Abbreviations: CDA = Canada's Drug Agency; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium

Table 1. Subthemes by Critique Category and Contributions to HTA Decisions

Critique Themes Category	Subthemes (# Contributing to Decision / Total)	
Comparability and heterogeneity	• **Unadjusted differences in population characteristics (7/13)** • **Insufficient adjustment/missing factors (1/3)** • **Unclear/unknown heterogeneity (1/3)**	• Differences in study design characteristics (0/1) • **Imbalance after adjustment (1/1)** • **Including irrelevant comparators (1/1)**
Data limitations	• **Sparse network (2/4)** • **Small sample sizes (1/3)**	• **Subgroup availability (1/2)** • No quality-of-life/safety in ITC (0/1)
Generalizability to local clinical practice	• **Comparator availability/relevance (1/3)**	
Model implementation / transparency	• **Risk-of-bias insufficiently assessed/reported (4/5)** • **FE model choice (2/3)**	• **Unclear criteria for excluding studies (1/1)** • Follow-up not reported (0/1)
Treatment switching and subsequent therapy	• **Insufficient adjustment for crossover / subsequent therapy (2/2)** • Post-progression treatments not assessed across trials (0/1) • Subsequent therapy in trials not generalizable to local market (0/1)	
Problematic survival data	• **Potential proportional hazards assumption violation (2/8)** • **Immature OS (1/2)** • **Averaged time-varying HRs (1/1)**	• Lack of constant HR ITC (0/1) • Subjective cut-offs (0/1)
Outcome definition and measurement	• PFS assessment schedules (0/1) • **RWE monitoring/measurement (1/1)**	
Interpretation / model choice	• **Under-interpreting non-significant results (1/2)** • FE vs. RE model consistency (0/2) • Over-interpreting non-significant results (0/1)	
Other	• **Residual confounding (RWE / high risk-of-bias) (1/1)** • Discordance: PFS gain did not translate to OS (0/1)	

Bold = theme/subtheme contributing to at least one HTA decision
Abbreviations: FE = fixed effects; HR = hazard ratio; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; RE = random effects; RWE = real-world evidence

Conclusions

- Critiques of oncology ITCs in recent HTA reports were common, recurrent, and often decision-relevant. The most frequent concerns centered on comparability/heterogeneity, survival data, and model implementation/transparency, and were observed across all ITC methods.
- These findings suggest that HTA acceptability depends not only on the analytic approach selected, but on transparent reporting, explicit justification of assumptions, and robust assessment of uncertainty, bias, and cross-trial differences.
- Variation across HTA bodies further suggests that ITC design and reporting may need to be tailored to agency expectations.

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