A Systematic Literature Review of the Mitigation Strategies to Overcome the Risk for Confounding of Overall Survival in Trials With Crossover/Treatment Switching Evaluated in Health Technology Assessments of Treatments for Select Tumors in Oncology

Poster HTA16

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Conclusions

- Our systematic literature review (SLR) demonstrates that overall, the acceptance of crossover trials in health technology assessment (HTA) submissions is contingent upon the robustness of survival, economic data, patient-reported outcomes, and safety
- Furthermore, the SLR demonstrates that it is the totality of evidence that helps in positive HTA decision-making
- Prespecifying the mitigation strategies and justification of any assumptions in the protocol or statistical analysis plan is viewed favorably by the HTA agencies
- Considerable variability exists in HTA adoption of mitigation strategies to address the impact of crossover or treatment switching on overall survival (OS) in oncology trials
- As crossover is an ethical approach to trial design for patients with life-threatening illnesses, it is important to align on approaches to inform HTA decision-making

Plain Language Summary

- Participants in clinical trials often switch treatment from the control to the experimental group. As a result, health technology assessment agencies find it difficult to interpret the main results from such trials, eg, how long the patients lived overall
- This review looked at how different agencies evaluate cancer trials in which participants switch from control to experimental treatment once their disease worsens
- The study found that agencies use different methods to evaluate such cancer trials. All agencies preferred that adjustment methods be included in the trial protocol and statistical analysis plan rather than being applied after the trial was completed
- Certain agencies considered analyses that were conducted after trial completion, such as real-world data, to try to predict what the treatment effect on patients' survival would have been if they had not switched treatments
- Even without a clear survival benefit, treatments could still be considered beneficial based on factors like improved quality of life, better safety, or economic advantages

Introduction

- Crossover, a type of treatment switching, is common in oncology trials, in which patients often change therapies from the control to the experimental arm upon disease progression due to ethical reasons and to aid recruitment
- While progression-free survival (PFS) remains unaffected, switching from the control to the experimental arm confounds postprogression end points, in particular OS
- Such confounding may overestimate the apparent benefit of the control arm and, consequently, undervalue the added benefit and cost-effectiveness of the experimental therapy
- Adjustment for crossover is necessary to resolve the HTA decision problem and support well-informed treatment recommendations

Objective

- This SLR assessed how HTA bodies have evaluated and critiqued mitigation approaches to address treatment switching impacting OS, and acceptance of unaffected end points (eg, PFS), in clinical trials studying advanced/metastatic cancer of lung (non−small cell; NSCLC), breast (BC), prostate (PC), renal (RCC), colorectal (CRC), and gastrointestinal stromal tumors (GIST). It focuses specifically on crossover as a distinct subtype, given that evaluation of all forms of treatment switching varies across different HTA bodies

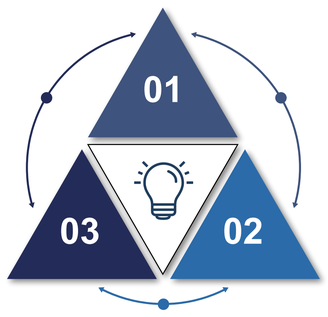
Methods

Search strategy and inclusion criteria

- The websites of the following HTA agencies, regulatory bodies, and clinical practice guidelines (CPG) were manually searched to retrieve published reports (manufacturer submission and final guidance) between January 1, 2013, and December 6, 2024:
  - HTA agencies:
    - Institute for Clinical and Economic Review (ICER) – United States (US)[1]
    - National Institute for Health and Care Excellence (NICE) – United Kingdom[2]
    - Haute Autorité de Santé (HAS) – France[3]
    - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); Federal Joint Committee (G-BA) – Germany[4]
    - Pharmaceutical Benefits Advisory Committee (PBAC) – Australia[5]
    - Canada's Drug Agency (CDA/CADTH) – Canada[6]
    - Agenzia Italiana del Farmaco (AIFA) – Italy[7]
  - Clinical practice guidelines:
    - National Comprehensive Cancer Network (NCCN) – US[8]
  - Regulatory bodies:
    - Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Spain[9]
    - US Food and Drug Administration - Oncologic Drugs Advisory Committee (FDA – ODAC) – US[10]
- **Figures 1** and **2** present the search strategy and inclusion criteria, respectively, for the SLR. The non-English HTA/regulatory documents (HAS, G-BA, AEMPS, and AIFA) were searched for keywords in their native language (eg, crossover, cross over, cross-over, switch, croisé, permuté, wechsel, cruzado, cambi, etc). Documents meeting the inclusion criteria were then reviewed to extract relevant information

Figure 1. Search Strategy to Identify HTA Submissions

Keyword search for drugs
- PBAC (Australia)
- FDA-ODAC (US)
- HAS (France)
- AIFA ((Italy)

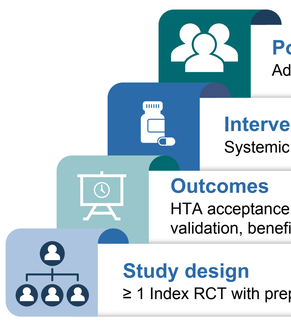


Keyword search for cancer types
- IQWiG/G-BA (Germany)
- NICE (UK)
- CDA/CADTH (Canada)
- ICER (US)
- NCCN (US)
- AEMPS (Spain)

Compile a list of drugs
A list of drugs and their corresponding indications was retrieved

AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; CDA/CADTH, Canada's Drug Agency; FDA-ODAC, Food and Drug Administration - Oncologic Drugs Advisory Committee; HAS, Haute Autorité de Santé; ICER, Institute for Clinical and Economic Review; IQWiG/G-BA, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen/Federal Joint Committee; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee.

Figure 2. PICOS Criteria for Inclusion in the SLR



Population
Adult patients (≥ 18 years) with advanced/metastatic BC, NSCLC, CRC, GIST, RCC, and PC, in any line of therapy

Intervention and comparator
Systemic anticancer treatments

Outcomes
HTA acceptance for reimbursement, approaches for mitigating and their acceptability, application of surrogate modeling and counterfactual validation, benefit rating, factors driving HTA decision, unmet needs and their impact on HTA decision-making, stakeholder engagement

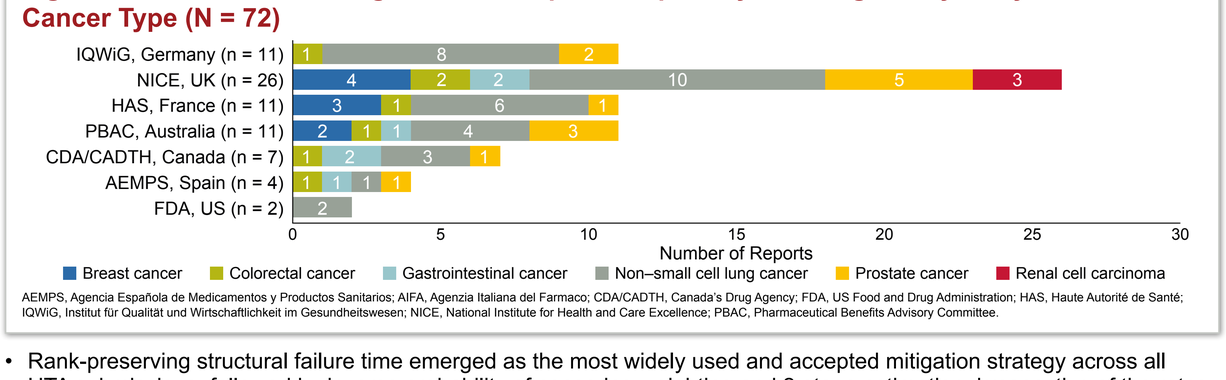
Study design
≥ 1 Index RCT with preplanned or spontaneous crossover

BC, breast cancer; CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HTA, health technology assessment; NSCLC, non−small cell lung cancer; PICOS, population, intervention, comparator, outcomes, study design; RCC, renal cell carcinoma; RCT, randomized controlled trial; SLR, systematic literature review.

Results

- Of the 1653 records screened, 162 product submissions permitting treatment switches were included (HTA: 147; product label: 11; CPG: 4), of which 72 reported the use of formal mitigation techniques to adjust the impact of crossover on OS
- **Figure 3** reports the distribution of submissions reporting mitigation strategies by HTA/regulatory body and cancer type. Of the 72 submissions, 26 were submitted to NICE, followed by 11 each to IQWiG, HAS, and PBAC; 7 to CDA; 4 to AEMPS; and 2 to the FDA
  - The majority of submissions were for NSCLC (n = 34), followed by PC (n = 13), BC (n = 9), CRC (n = 7), GIST (n = 6), and RCC (n = 3)
- A total of 40 submissions were in the first-line setting, followed by 14 in second line, 8 in second line and beyond, 4 in third line, 3 in third line and beyond, and 2 in fourth line and beyond

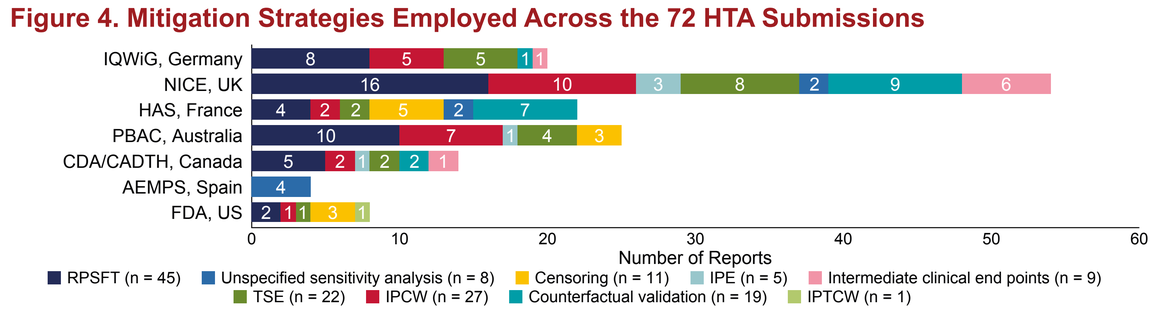
Figure 3. Distribution of Mitigation Techniques Adopted by HTA/Regulatory Body and Cancer Type (N = 72)



AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; CDA/CADTH, Canada's Drug Agency; FDA, US Food and Drug Administration; HAS, Haute Autorité de Santé; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee.

- Rank-preserving structural failure time emerged as the most widely used and accepted mitigation strategy across all HTA submissions, followed by inverse probability of censoring weighting and 2-stage estimation, irrespective of the rates and definition of crossover (**Figure 4**)

Figure 4. Mitigation Strategies Employed Across the 72 HTA Submissions



AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; CDA/CADTH, Canada's Drug Agency; FDA, US Food and Drug Administration; HAS, Haute Autorité de Santé; IPCW, inverse probability of censoring weighting; IPE, iterative parameter estimation; IPTCW, inverse probability of treatment and censoring weighting; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; RPSFT, rank-preserving structural failure time; TSE, 2-stage estimation.

Surrogate End Point

- Nine submissions reported the use of intermediate clinical end points such as PFS and postprogression survival
  - However, their formal validation as a surrogate end point was not reported (NICE, n = 6; CDA, n = 2). The 6 technology appraisals from NICE with intermediate clinical outcomes were not used in the economic model
  - One submission to IQWiG/G-BA found that the confidence intervals of radiological PFS from indirect comparisons exceeded the surrogate threshold effect, indicating no evidence of effect on the patient-relevant end point and no evidence for surrogacy; however, further rationale or commentary was not provided by the company

Counterfactual Validation

- Validation of the treatment effect on OS was reported within the cost-effectiveness–focused payer archetype to support decision-making
- OS validation of suitability of the comparator arm using real-world evidence was most reported in HAS (n = 7), followed by NICE (n = 5) and CDA/CADTH (n = 1) submissions; these real-world datasets included only patients treated with standard chemotherapy and excluded those treated with investigational agents

Receptivity to Mitigation Strategies

- The manufacturer's approach, as specified in the protocol or statistical analysis plan, was accepted by the reviewing body in 29 of 72 submissions
- In 5 submissions, the investigational agent used as crossover treatment in the comparator arm was an established standard of care, thus negating the need for adjustment
- When OS data are not favored after mitigation, positive HTA decisions may instead be based on quality of life (IQWiG/G-BA, n = 2), safety (HAS, n = 2), and economic outcomes (NICE, n = 4; CDA/CADTH, n = 4; PBAC, n = 2)

Strengths and Limitations

- This is the first comprehensive SLR highlighting the similarities and differences in approaches to mitigate confounding through therapy crossover that are adopted by different HTA bodies, and the key drivers of HTA decisions
- The SLR was not restricted to English language and included publications in other languages such as German, French, Spanish, and Italian, reducing selection bias
- A multidimensional perspective was explored in this SLR, covering not only mitigation strategies but also other aspects such as economic modeling, surrogate end point use, and counterfactual validation
- Valuable insights were derived into how payer archetypes (cost-effectiveness vs clinical-effectiveness focus) influence HTA decisions
- The HTA submissions that did not explicitly mention crossover or switching in their reports may have been missed in this SLR. Furthermore, several HTA reports contained redacted or missing information

References:
1. ICER: https://icer.org/
2. NICE: https://www.nice.org.uk/guidance/
3. HAS: https://www.has-sante.fr/jcms/
4. IQWiG/G-BA: https://www.iqwig.de/
5. PBAC: https://www.pbs.gov.au/pbs/home
6. CDA/CADTH: https://www.cda-amc.ca/
7. AIFA: https://www.aifa.gov.it/en/
8. NCCN: https://www.nccn.org/
9. AEMPS: https://www.aemps.gob.es/edicamentosUsoHumano/
10. US FDA: https://www.fda.gov/

All reference links were accessed on October 7, 2025.

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