Why Current HTA Frameworks Fall Short for Anti-Cancer Combination Therapies: Toward Equitable Value Attribution and Policy Reform

HTA370

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INTRODUCTION

Combination therapies (CTs) are increasingly used in oncology to enhance clinical efficacy, expand therapeutic options, and reduce toxicity compared to high-dose monotherapy. However, existing health technology assessment (HTA) frameworks are largely designed for single-agent evaluations and lack mechanisms to disaggregate and assign value to individual components in a combination. This structural limitation presents challenges for fair pricing and reimbursement, particularly when multiple manufacturers are involved. Without robust value attribution tools, the development and adoption of innovative CTs may be disincentivized, despite their growing clinical relevance.

OBJECTIVES

This study aims to:

1. Describe the conceptual underpinnings and mathematical structure of the Towse segmented attribution model, an outcome-based approach to valuing individual agents within CTs;
2. Compare this framework against the limitations of traditional HTA practices, particularly their inadequacy in fair value division among CT components;
3. Identify key practical and policy-level barriers to implementing segmented value attribution, drawing from a scoping review and insights from the 2024 Office of Health Economics (OHE) stakeholder survey

METHODS

A structured literature review was conducted using PubMed and Ovid MEDLINE databases as of March 26, 2025, focusing on value attribution frameworks specific to combination therapies. Search terms included "combination therapy," "value attribution," and "health technology assessment." A total of 660 records were screened, and 10 relevant publications were selected for full-text review. Two principal methodological approaches emerged from the literature:
(1) Briggs' negotiation-based framework, and
(2) Towse's outcome-based attribution framework.

While both offer potential solutions to the shortcomings of traditional HTA in CTs, this study focuses on describing and evaluating the Towse model due to its explicit mathematical structure and alignment with QALY-based valuation.

To complement the literature, relevant grey literature from organizations such as National Institute for Health and Care Excellence (NICE), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the OHE was reviewed to gather policy insights.

In parallel, findings from the 2024 OHE stakeholder survey were analyzed. The survey captured industry perspectives on feasibility, legal and evidentiary barriers, and the perceived fairness of segmented value attribution in real-world reimbursement settings.

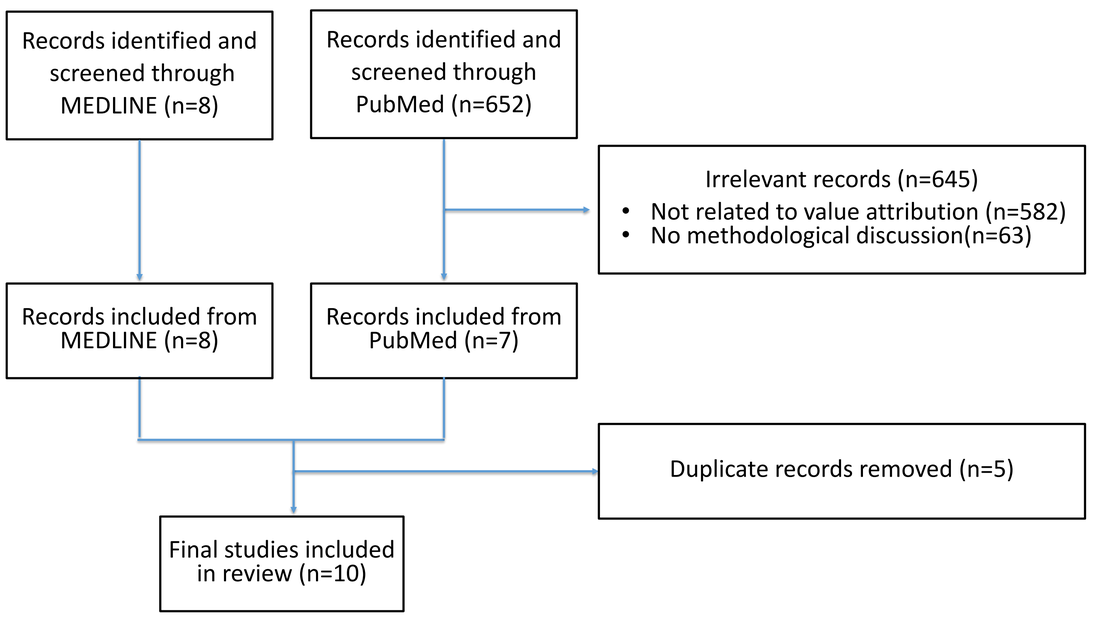


Figure 1. Flowchart of literature selection process

RESULT

The scoping review identified two primary frameworks for value attribution in combination therapies: negotiation-based models such as the Briggs framework, which allow for flexible value-sharing through deliberative processes, and outcome-based models such as Towse's segmented attribution model. This study focuses on the Towse model due to its mathematical transparency, fairness, and alignment with health economic principles.

The Towse model partitions the total QALY-based incremental benefit of a combination therapy into three segments:

1. Segment 1 – Shared value: The overlapping benefit attributed jointly to both drugs.
2. Segment 2 – Backbone-specific value: The incremental benefit of the backbone drug compared to the add-on alone.
3. Segment 3 – Add-on-specific value: The incremental effect of the add-on compared to the backbone alone.

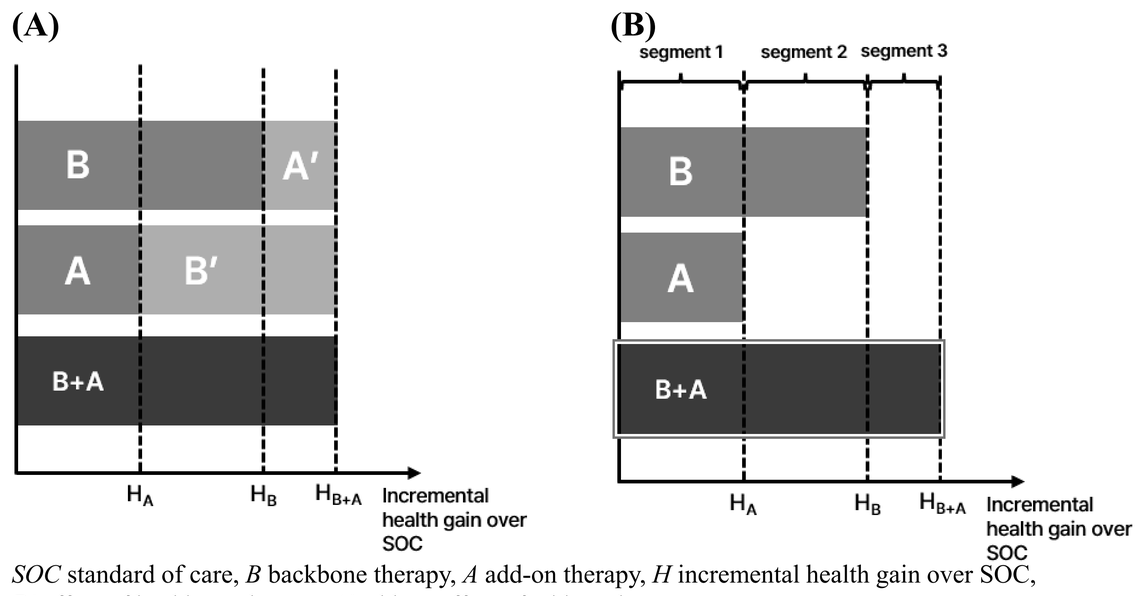
This structure improves upon simple average or monotherapy ratio methods by recognizing both absolute and differential contributions and remains technically accurate under sub-additive and super-additive efficacy conditions.

Stakeholder insights from the 2024 OHE survey further contextualize the practical implications.

- 67% of stakeholders perceived the generalized Towse model as the fairest attribution method, noting its symmetry and alignment with clinical logic (OHE 2024, Section 3.1.1).
- It was also perceived as the only technically correct method under non-constant additivity assumptions.
- However, 88% of stakeholders rated the Incremental Value(IV) model as more feasible due to the Towse model's heavy data requirements, including monotherapy comparator arms, which are rarely available (OHE 2024, Section 3.1.2-3.1.3).
- Concerns were also raised around input uncertainty, particularly when estimating effects for newly developed or indication-specific add-ons.

These findings underscore the trade-off between conceptual robustness and operational feasibility, highlighting the need for parallel policy mechanisms to support the model's real-world adoption..

Figure 2. Illustration of Towse's Segmented Value Attribution Model: Monotherapy and Incremental Contributions (A), and Value Segmentation Structure (B)



SOC standard of care, *B* backbone therapy, *A* add-on therapy, *H* incremental health gain over SOC, *B'* effect of backbone therapy, *A'* add-on effect of add-on therapy

CONCLUSION

The increasing clinical relevance of CTs calls for HTA frameworks that can fairly recognize the contribution of individual components. The Towse segmented attribution model provides a theoretically sound and mathematically transparent solution to this challenge. Its alignment with QALY-based logic, fairness under additive and non-additive conditions, and neutrality regarding market entry order make it a compelling option for future reimbursement frameworks.

However, real-world feasibility remains a major barrier. The model's reliance on full efficacy data from monotherapy comparators—often unavailable in oncology trials—limits its practical application. Furthermore, regulatory constraints on inter-manufacturer pricing discussions and the lack of adaptive pricing mechanisms hinder its broader adoption.

To operationalize the Towse model or any similarly structured value attribution framework, reforms are needed across multiple dimensions of the policy environment. These include:

- Flexible evidentiary thresholds to accommodate uncertainty or partial data;
- Legal exemptions or safe harbor provisions to enable collaborative value-sharing discussions between companies;
- Indication-based pricing systems to reflect context-specific therapeutic value;
- Provisional reimbursement mechanisms that allow early adoption with retrospective adjustment as more data emerge.

Ultimately, the choice of attribution method must be accompanied by procedural safeguards, institutional readiness, and regulatory flexibility. Without such enabling conditions, even the most robust frameworks risk remaining underutilized. This study supports embedding segmented models into HTA processes, not as fixed formulas, but as part of a more adaptive, transparent, and innovation-supportive reimbursement system for complex combination therapies.

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