'Kaleidoscope (QALY-in-scope)': A Conceptual Framework for Contextualizing Value through Dynamic Cost-Utility Thresholds

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INTRODUCTION

Cost-utility analysis (CUA) is increasingly integral to health technology assessment (HTA) worldwide, promoting value-based pricing. The cost-utility threshold (CUT), i.e. the willingness-to-pay (WTP) for an additional health outcome, expressed in quality adjusted life years (QALY), profoundly influences the pricing and accessibility of medical interventions.

Rare diseases pose a significant burden, often with severe symptoms and limited treatment options, impacting patients' quality of life and straining healthcare resources. Orphan drugs are designed to meet critical clinical needs within small patient populations, yet they often attract limited investment due to their narrow potential market size. As such, orphan drugs typically have higher price tags and do not meet standard cost-effectiveness thresholds. Such traditional static thresholds may inadequately account for nuanced factors affecting societal value judgments, particularly affecting rare diseases.

It's crucial to balance efficiency and equity in resolving the Welfarist-Rawlsian tension affecting orphan drug availability. CUA builds on the Welfarist theoretical foundation, concerned with maximizing the population health within constrained resources. Under such approach, the objective of a healthcare system is to generate as many units of health outcomes as possible (i.e. maximizing QALY gains) for its population. Underlying this philosophy is the principle of "QALY egalitarianism", which upholds the notion that each QALY has equal value, irrespective of who benefits, limiting the consideration for societal or ethical priorities (Schlander, et al. 2014). In contrast, Rawlsianism emphasizes fairness and equity, advocating that resources should prioritize improving the well-being of the least advantaged. In orphan drug pricing and reimbursement (P&R) decisions, this debate is crucial as balancing these perspectives helps decision-makers ensure equitable yet efficient resource allocation (Postma, et al. 2022). At the core, the challenge is to align equity considerations with rational resource allocation, ensuring that vulnerable populations are not neglected while avoiding perverse incentives for the pharmaceutical industry. If systems bend too much toward favouring orphan drugs with higher cost-per-QALY, it could prompt pharmaceutical companies to exploit these policies, inflating prices for minimal innovation.

Value-based pricing encourages investment in transformative medicines that address unmet needs and deliver substantial clinical benefits. To ensure optimal access to orphan drugs, the concept of value could be contextualized by adjusting WTP thresholds to specific contextual factors related to the decision problem. There is a trend by which HTA agencies are introducing methods to increase CUT for highly specialized treatments or orphan drugs such as dynamic thresholds. Different dimensions (often named "modifiers") are being considered, among which: disease severity (e.g. NICE's disease severity modifier), evidentiary uncertainty, disease prevalence (e.g. TLV's recent proposal), etc. Whether such modifiers are being considered and affecting the outcome of decision-making is not easy to determine, especially when it comes to qualitative modifiers (Radu, et al. 2024).

Often, HTA consider modifiers implicitly without formal guidance (Radu, et al. 2024). This may create variability and potential biases that compromise the reliability, consistency, and fairness of assessments. Implementing clear guidelines helps standardize criteria and reduce the influence of individual interpretation, enhancing the accuracy and credibility of the assessment process. Nonetheless, there is no consensus among health economists and decision-makers on which criteria should be considered and how such considerations should be quantified.

OBJECTIVE

The objective was to develop a conceptual framework for configuring a dynamic CUT, designed to tailor the CUT to the specifics of the decision problem, with a particular focus on orphan drugs.

METHODS

First, a targeted literature review was conducted, focused on the CUT literature and on the societal preferences on P&R decisions of orphan drugs. Secondly, a conceptual framework for a dynamic CUT was developed.

Methodological guidance of the following agencies was reviewed: AEMPS (Spain), AIFA (Italy), CADTH (Canada), HAS (France), INFARMED (Portugal), NICE (England), PBAC (Australia), TLV (Sweden) and ZIN (Netherlands).

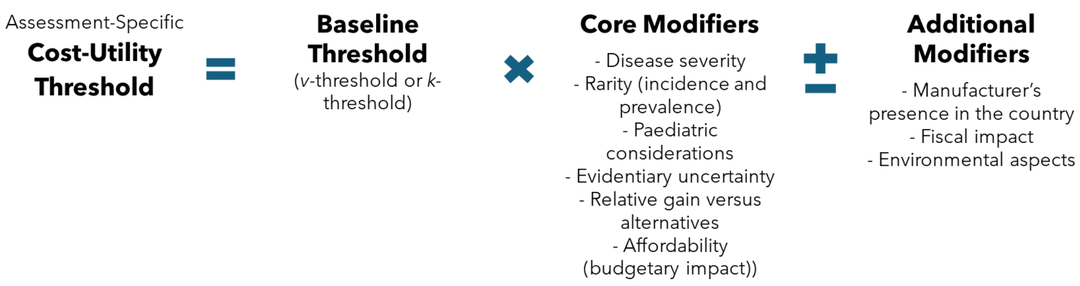
RESULTS

Many agencies adopt a flexible, qualitative approach, enabling decision committees to assess these factors within a broader deliberative framework (Zhang & Garau, 2020).

The modifiers considered by HTA agencies include the severity of the disease, rarity, unmet need, innovation, and end-of-life criteria, being the first two criteria the primary ones. These modifiers are implemented either quantitatively and with clear guidance, or qualitatively, as discretionary factors during the decision-making process (Radu, et al. 2024).

A conceptual framework was developed to estimate a dynamic CUT for specific assessment contexts. Feasibility in terms of observable and quantifiable criteria was considered. The following dimensions were included: **disease severity, rarity** (incidence and prevalence), **paediatric considerations, evidentiary uncertainty, relative gain versus alternatives and affordability** (budgetary impact).

Figure 1. Outline of *"Kaleidoscope (QALY-in-scope)"*: A conceptual framework for contextualizing value via dynamic cost-utility threshold



- There are already proposed methods available for considering disease **severity** and **rarity**, for instance NICE's and TLV's methods, respectively.
- **Paediatric consideration** could be easily considered by eliciting a societal weight function of age.
- **Evidentiary uncertainty** may be tackled by means of available tools such as the GRADE approach and quantifying the uncertainty by means of deterministic and probabilistic sensitivity analyses (e.g. by linking the ICER dispersion in PSA to a multiplier). High uncertainty is inherent in rare diseases, so the framework should avoid excessive penalties. Chronic conditions may also face greater long-term evidence gaps in comparison to acute or short-term conditions.
- The **relative gain** versus alternatives may become a key aspect to favour specially underserved populations, where there's no treatment alternatives or these bring very limited benefits. A quantitative method could be though off to express such variable and calibrated according to social preference.
- Finally, the **budget impact** could also play a role in the CUT, as affordability is a crucial concern for payers and to the financial sustainability of all health care systems. As an example, one could propose a function between CUT and budget impact, acting as upper cap.

Additional economically impactful factors beyond the listed criteria could also be considered, incorporating a broader societal perspective and including aspects such as manufacturer's presence in the country, fiscal impact, and environmental aspects.

CONCLUSIONS

Navigating the Welfarist–Rawlsian tension is crucial to ensure equitable access to orphan drug. The proposed conceptual framework allows decision-makers to consider the assessment context (decision problem) and other factors that are relevant in setting a relevant CUT for the assessment of an intervention, while promoting transparent, consistent and equitable decision-making in HTA processes.

This framing represents a nuanced and flexible approach to valuing health outcomes in perspective and may provide a health economic rationale for higher value-based CUT for orphan drugs, aligned with societal equity preferences.

Further research to develop empirical tools to quantify each criterion is needed. Moreover, eliciting societal preferences will be key to determine inclusion/exclusion of each specific criterion and its respective relative weight in this framework.

In ensuring equitable and optimal access to innovation to all patients in need, we should reject the QALY egalitarianism. A QALY's value should always be viewed through the lens of a kaleidoscope, contextualizing each QALY and warranting varied WTP that adapt to contextual nuances. "Kaleidoscope (QALY-in-scope)" offers a conceptual framework for determining such context-sensitive CUT.

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