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Beyond QALYs: Towards Fairer Cost-Effectiveness Analysis for Orphan Drug Populations

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Imagine a life-saving treatment being denied because it's not deemed to extend the life of someone who is already battling a rare disease. This happens due to the limitations of Quality-Adjusted Life Years (QALYs), a commonly used measure to assess healthcare interventions in cost-effectiveness analysis (CEA).[1,2] QALYs have limitations in capturing the true value people with disabilities find in their lives.[1,2] This disproportionately affects the access of vulnerable populations to necessary treatments. While the QALY remains a valuable tool, it is essential to recognize its limitations and embrace frameworks like the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Value Flower for fairer healthcare resource allocation. Alternative value frameworks are gaining traction globally, with institutions like ICER incorporating Equal Value of Life Years Gained (evLYG) alongside QALYs in their reports and announcing the piloting of Generalized Risk-Adjusted Cost-Effectiveness (GRACE) in September 2023. The UK's NICE is also actively exploring alternative frameworks as potential replacements.[3,4]

Treating Lives Unequally: The Bias Embedded in QALYs

Critics argue that relying solely on QALYs for resource allocation disproportionately disadvantages the elderly, disabled, and terminally ill, raising concerns about bias and discrimination due to its limitations in capturing the complexities of chronic illnesses and severe conditions.[2,3,5]

QALYs help compare well-being across patients, diseases, and treatments, but assigning health utility to patients with worse health raises distributional issues for resource allocation decisions. Patients with co-occurring illnesses or disability (because of more severe disease, disability, age, etc) may have lower quality of life (QoL) weights, resulting in fewer QALYs gained from

improving their health compared to healthy individuals. This distributional limitation arises due to the multiplicative nature of the QALY (life-years are multiplied by the utility).[6]

Take cystic fibrosis, for example. While QALYs might underestimate the daily struggles with breathing difficulties and limited lung function, effective treatments offering dramatic improvements in these areas, allowing patients to participate in activities they previously couldn't, are often undervalued. [5]

The "disability paradox" further complicates the picture. People with chronic conditions often rate their quality of life higher than the general population for the same health state. Yet, CEAs relying on general population preferences underestimate the burden of these conditions and undervalue lifesaving treatments. [5]

The current QALY framework assumes all life-years hold equal value, regardless of baseline health. This overlooks the concept of diminishing returns, where small improvements for someone with severe illness or limited life expectancy can hold vastly more significance than similar improvements for someone with better health. Treatments for these patients are potentially undervalued as a result. [5]

These limitations can have devastating consequences, denying access to life-changing treatments for individuals with chronic illnesses or those living with disabilities. In the UK, where QALYs hold significant influence, studies show that these patients disproportionately face restricted access to vital treatments. Recognizing these limitations, the US Inflation Reduction Act (IRA) prohibits the use of QALYs in drug price negotiations for Medicare and Medicaid.[2]

The ISPOR Value Flower Offers a Multifaceted Approach to Assessing Value

The ISPOR Value Flower (Figure 1) presents a multifaceted framework for understanding the full value of healthcare interventions. It expands beyond the limitations of QALYs by incorporating additional elements, both traditional and nontraditional, such as equity, caregiver burden, and scientific advancements. This comprehensive approach has the potential to provide a more comprehensive understanding of healthcare interventions, revealing the hidden value beyond traditional metrics.[7]

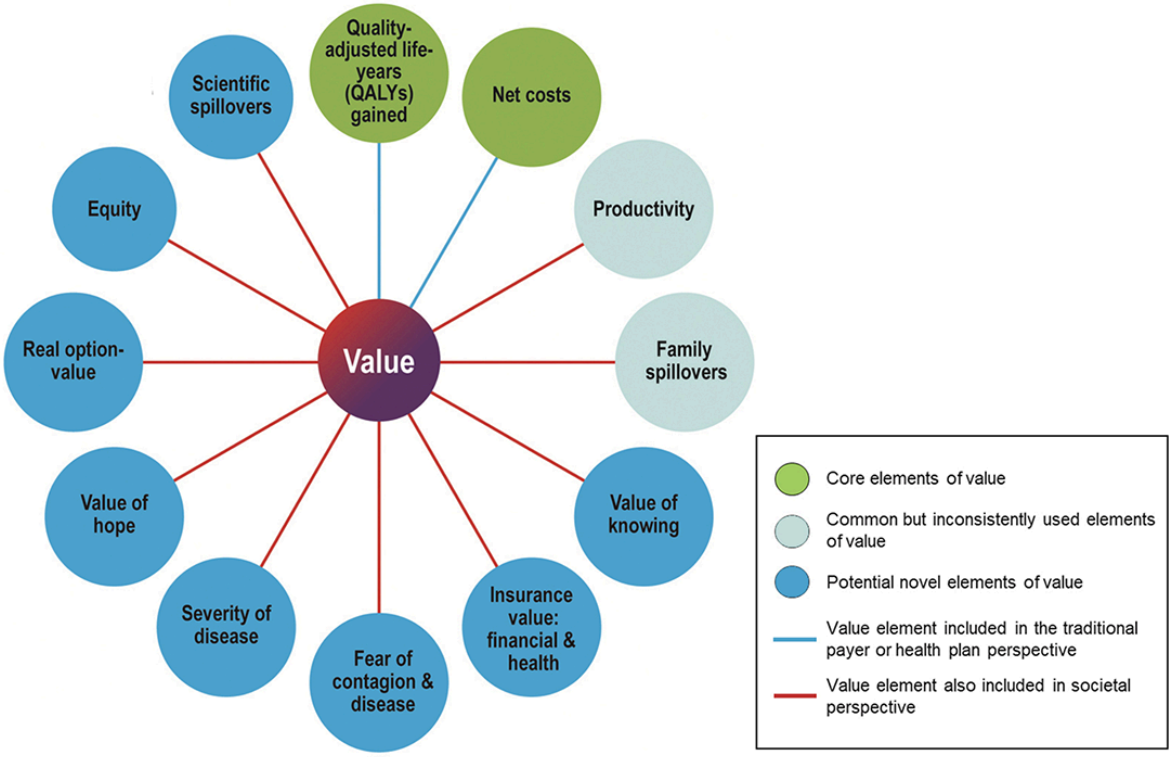

Figure 1 The ISPOR Value Flower. Adapted from Lakdawalla et al.[8]

Emerging Alternatives to QALYs in Healthcare Decision-Making

Emerging frameworks like Equal Value of Life Years Gained (evLYG), Healthy Years in Total (HYT), and Generalized Risk-Adjusted Cost-Effectiveness (GRACE) offer promising alternatives to QALY-based CEA by addressing its limitations and capturing additional aspects of healthcare value (Table 1).

- Equal Value of Life Years Gained (evLYG): Introduced in 2018 by the Institute for Clinical and Economic Review (ICER), evLYG assigns equal weight to gains in life expectancy, regardless of initial QoL, aiming to address concerns of undervaluing life extension for individuals with chronic illnesses or disabilities. However, its critics argue it neglects QoL improvements, potentially disadvantaging severely ill patients.[2]
- Healthy Years in Total (HYT): This newer alternative utilizes a modified QALY and an additive approach to separately assess life expectancy and QoL effects. This potentially

better reflects the benefits of life-extending interventions for individuals with lower QoL. However, it has been criticized for not directly addressing distribution issues like prioritizing populations with greater health needs or inequities. [2,3]

- Generalized Risk-Adjusted Cost-Effectiveness (GRACE): Perhaps the most comprehensive alternative, GRACE addresses potential bias against severe illnesses and disabilities through disease-specific risk adjustments and higher cost-effectiveness thresholds for more severe cases. It incorporates "Generalized risk-adjusted QALY" to account for uncertainty and diverse risk preferences, making it a more flexible and patient-centered approach.[2,9] ICER's piloting of GRACE in September 2023 further highlights its potential.[10] While ICER's recent pilot testing shows promise,[10] further analysis is needed to ensure fairer QALY implementation within GRACE

Table 1 provides a comparative overview of these alternative frameworks compared to traditional QALY-based CEA. Each framework presents unique strengths and weaknesses, prompting ongoing discussions and research to refine their implementation and address remaining challenges. For each situation, it is crucial to carefully evaluate the disease context, ethical implications, and resource allocation impacts, while also taking into account health technology assessment (HTA) guidelines , in order to select the framework that will best serve healthcare decision-making.

Table 1 Comparative overview of alternative frameworks compared to traditional QALY-based CEA; EQ-5D-5L, The US 5-level EuroQol 5-dimensional questionnaire

	Traditional CEA[2]	evLYG[2,3,6]	HYT[2,3,6]	GRACE[2,9]
Approach	Combines life expectancy with QoL adjustments (0-1) to capture overall health benefit.	Assigns equal value to any year of life gained, regardless of age or health state.	Modifies the QALY and combines it with life expectancy into a single metric	Allows incorporation of combinations of novel value elements and introduces diminishing returns to health related QoL (HRQoL)
Value Elements	QALYs gained	Equity, Disease severity, HRQoL	Equity, Disease severity, HRQoL, Option Value	Many of the Value Flower elements
Applicability	Widely used for various diseases and interventions	Best for acute scenarios or general population comparisons, less ideal for chronic diseases	Useful for scenarios emphasizing lifespan extension, less ideal for chronic diseases with varying QoL	Suitable for chronic diseases with diverse populations and risk profiles
Limitations	Vulnerable to societal biases in QoL weighting, potentially discriminatory for certain conditions	● QALY derivative ● Ignores differences in quality of life, undervaluing improvements for severely ill patients	● Does not consider QoL differences, potentially favouring interventions with short, low-quality life extension ● Methodologically complex (requires establishing a counterfactual to calculate a modified QALY)	● Complex calculations and data requirements ● Relies on data limitations like "representative individual" health utilities, potentially overlooking health inequities
Advantages	Standardized metric, balances quantity and quality of life	Easy to understand and interpret, avoids valuing life based on QoL	Easy to understand and interpret, emphasizes life extension	More equitable for patients with different risk profiles, considers risk variation

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Conclusions

The rise of frameworks like evLYG, HYT, and GRACE suggests a shift towards a more inclusive and ethical approach to healthcare resource allocation. However, it is important to carefully assess their effectiveness, unintended consequences, and ethical implications as research and piloting continue. Successfully navigating this evolving terrain demands an adaptable strategy that prioritizes ethical principles, acknowledges the diverse requirements of stakeholders, and guarantees equitable access to quality healthcare services for every individual.

How IMAC Can Help

International Market Access Consulting (IMAC; www.imarketaccess.com), a boutique company of senior consultants who are recognized as industry leaders with decades of experience, offers invaluable assistance to clients navigating alternative frameworks for economic models beyond the traditional QALY approach. In today's globalized and dynamic healthcare landscape, nuanced perspectives that extend beyond standardized metrics, may drive successful HTA for orphan therapeutics in vulnerable populations and beyond. By collaborating with IMAC, clients gain access to a breadth of expertise that includes innovative economic models and strategic solutions designed to capture a broader spectrum of patient experiences and treatment outcomes. This tailored approach ensures that clients can navigate complexities efficiently, optimizing market access strategies for diverse markets.

Furthermore, IMAC's expertise fosters innovation and adaptation in an ever-evolving healthcare landscape. By challenging the status quo and exploring novel approaches to HTA, our team helps clients anticipate future trends proactively. This anticipatory stance not only enhances market access strategies but also fosters a culture of continuous improvement and responsiveness to emerging challenges. Through close collaboration and strategic guidance, IMAC equips clients with the tools and insights needed to navigate complexities successfully, ensuring sustainable market access and competitive advantage in diverse global markets.

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