



Access in all areas? A roundup of developments in market access and health technology assessment: part 6

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In this update, we discuss an article covering the implementation challenges of the upcoming European Union Health Technology Assessment regulation, particularly focusing on the complexity of population, intervention, comparator and outcomes requirements across member states; a user guide to applying generalized cost-effectiveness analysis for broader value assessment and finally highlight an ongoing debate surrounding National Institute for Health and Care Excellence's severity modifier implementation.

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The implementation of the Health Technology Assessment (HTA) Regulation in the European Union (EU-HTA) represents a significant shift in the evaluation of health technologies across Europe, starting in January 2025 [1]. The regulation introduces a framework for joint clinical assessments (JCAs) and joint scientific consultations (JSCs), initially focusing on oncology and advanced therapy medicinal products. Central to these assessments is the population, intervention, comparator and outcomes (PICO) framework, with the JCA dossier containing manufacturers' responses to consolidated PICO questions defined by member states. The quality of this evidence is key to the evaluation, as the EU-HTA dossier focuses solely on evidence, without value judgments. However, a recent analysis by van Engen *et al.* underscores the complexity of aligning PICOs across member states [2]. Their study, focusing on two oncology indications: first-line non-small-cell lung cancer (NSCLC) and third-line multiple myeloma, revealed an unexpected proliferation of requirements. Using the European Network for Health Technology Assessment (EUnetHTA) guidance on the key steps for defining and consolidating PICOs, 10 PICOs were identified for NSCLC and 16 for multiple myeloma. The majority of these would require indirect treatment comparisons due to limited head-to-head trial data (and whether these would be accepted by decision makers as robust evidence is another matter [3,4]). Importantly, these PICOs would require 280–720 analyses per product (covering the various permutations of population, comparator and outcome), potentially increasing exponentially with any additional outcome measures, subgroups and/or safety analysis requests. This substantial analytical workload stems from varying national demands for subgroup and safety analyses, many of which may only be relevant to one country but applied to all PICOs which could result in hundreds of analyses that few stakeholders requested or would use. The complexity and volume of analyses required within tight assessment timeframes raises serious concerns about the workability of the process and the quality of submissions. Van Engen *et al.* propose pragmatic solutions to address these challenges:

- Early and meaningful engagement between manufacturers and HTA bodies to harmonize requirements.
- Streamlining evidence demands through evidence-based selection of populations and comparators.
- Adopting member-state-specific analyses, reducing the need for universal inclusion of all data points in EU submissions.

The success of the EU HTA regulation hinges on balancing the rigorous scientific standards of JCA with practical implementation. Manufacturers must prepare to navigate these demands by enhancing organizational analytical capabilities while proactively participating in discussions that shape future processes. Achieving this balance is vital to fulfilling the regulation's goal of harmonizing HTA across Europe without introducing unsustainable burden.

As HTA bodies grapple with harmonizing assessment processes, there is also growing recognition that traditional value assessment frameworks need to evolve. The traditional cost–effectiveness analysis (CEA) framework used to assess the value of medicines is increasingly being recognized as being too narrow in scope, focusing primarily on direct health system costs while overlooking broader societal impacts [5]. In 2016, the Second Panel on Cost Effectiveness recommended best practices for value assessment, including the consideration of a societal perspective by including additional value elements, such as productivity costs [6]. In 2018, an International Society of Pharmacoeconomics Outcomes Research (ISPOR) special task force developed the ISPOR value flower, which highlights value elements traditionally excluded from traditional cost–effectiveness analyses in a visual format [7]. Researchers face methodology challenges when integrating novel or broader value elements into cost–effectiveness models and the literature to date mainly offers either broad, high-level overviews or highly detailed applications for quantifying single value elements in isolation. The recent publication by Shafrin *et al.*, thus provides a much-needed user guide for implementing generalized cost–effectiveness analysis (GCEA). ‘Generalized’ refers to inclusion of all societal costs and benefits in cost–effectiveness models and builds upon previous value frameworks (e.g., ISPOR, Second Panel). The GCEA incorporates value elements (or ‘petals’) beyond those in the ISPOR value flower and organises them into four categories: uncertainty, dynamics, beneficiary and additional value components. The uncertainty category aims to move beyond the outcomes for the average patient by also considering the distribution of outcomes and how changes in uncertainty may impact patient well-being, and the petals include outcome certainty (which combines the “value of reducing outcome uncertainty” and “value of hope”), disease risk reduction (classified as “insurance value” in the ISPOR value flower), and the value of knowing (for diagnostics). The dynamics category petals account for the evolution of real-world treatment value and includes drug pricing trends, particularly due to genericization, changes in disease prevalence, option value, scientific spillover and different rates of discounting. The beneficiary category accounts for the fact that value can vary depending on who is benefiting. This includes disease severity, health equity, family and caregiver spillover. Finally, GCEA incorporates additional broader sources of value, including community spillovers, patient productivity losses, adherence-improving factors and direct non-medical costs of illness. The manuscript provides guidelines for calculating each petal in practice and examples are provided. A checklist is provided which can be used to describe which GCEA petals were incorporated (and why some were not) and how petals were quantified. GCEA addresses the well-documented limitations of conventional CEA and provides an approach to holistically valuing medicines. The authors, however, acknowledge several limitations and areas needing further development. These include methodological challenges in measuring certain societal impacts, and the need to establish standards for incorporating these additional value components into decision-making processes (e.g., is there potential double counting and do cost–effectiveness thresholds need to be altered for GCEA?). Health technology assessment (HTA) bodies still remain hesitant to broaden value assessment, frequently citing implementation challenges [8]. For pharmaceutical manufacturers, GCEA provides an opportunity to demonstrate the societal value of their medicines to HTA bodies and payers and by generating more data on societal impact of medicines, they can help shape the dialogue on future changes to value assessment. This is becoming increasingly important as some HTA organizations are starting to explore a broader value lens (e.g., CDA-AMC) [9] and policy makers are seeing the economic value of good health [10].

While discussions continue about broadening value assessment frameworks, recent changes to the National Institute for Health and Care Excellence (NICE)’s approach to valuing severity have highlighted specific challenges in implementing such reforms. The severity modifier, introduced by NICE in February 2022, replaced the previous end-of-life modifier and provides additional weighting to the ‘value’ of medicines that treat severe conditions [11]. While the end-of-life modifier only considered life-extending treatments for terminal conditions, the new severity modifier uses both absolute shortfall (AS) and proportional shortfall (PS) measures to assess severity [11]. This broader approach was designed to consider both quality of life and survival impacts across a wider range of conditions, not just end-of-life scenarios. Under NICE’s current criteria, patients who lose a substantial amount of their future health can qualify for a value ‘multiplier’ of either 1.2 or 1.7. NICE applies this multiplier to health gains when calculating the cost–effectiveness of a treatment. This means the quantity of quality-adjusted life years (QALYs) gained with treatment appears larger, and the effective cost per QALY gained appears lower, making NICE more likely to recommend these treatments compared with those for conditions that do not qualify for the modifier.

To receive a multiplier of 1.2, patients must be expected to lose between 85 and 95% of their expected lifetime quality-adjusted life years (QALYs) or between 12 and 18 QALYs compared to someone without the disease. A multiplier of 1.7 is given when patients are expected to lose more than 95% of their expected lifetime QALYs or more than 18 QALYs compared to someone without the disease. The implementation of the severity modifier in February 2022 has however generated significant debate regarding its effectiveness in facilitating appropriate access to medicines for severe conditions [12]. Recent research by the Office of Health Economics (OHE) attempted to benchmark NICE's implementation approach and public preferences in England and Wales [13]. The OHE study found that the public considers that 'severe' health states started around 50% PS (compared with NICE's 85%) and that 'very severe' health states begin around 65% PS (compared with NICE's 95%), suggesting NICE's thresholds may be overly restrictive [13]. Further, the Association of the British Pharmaceutical Industry's (ABPI) Continuous NICE Implementation Evaluation (CONNIE) data also provides evidence that the modifier is being applied more conservatively than intended [14]. CONNIE showed an average QALY weighting of just 1.09 across evaluated technologies up to July 2023, which fell below NICE's target benchmark of 1.119 that was calculated to maintain cost neutrality with the end-of-life modifier [14]. CONNIE evaluations up to July 2023 highlighted that out of 20 topics reviewed, only four received severity modifiers – two with a 1.2× weight and two with a 1.7× weight [14]. This represents severity modifier application in just 20% of cases, compared with NICE's original estimates that suggested around 38.7% of topics should receive some form of modifier. The ABPI argues that this conservative implementation means some patients may be missing out on treatments that would have previously been approved under the end-of-life criteria. The industry association suggests that given the existence of overall medicine budget controls through the Voluntary Scheme for Branded Medicines Pricing and Access (VPAG), there is scope for more flexible application of the severity modifier without compromising system sustainability (i.e., there is no need to maintain cost-neutrality with the previous end-of-life modifier). NICE however maintains that the modifier is operating as designed, citing that it has approved a broader range of conditions including non-cancer indications like cystic fibrosis and chronic hepatitis D [15]. Their September 2024 review concluded no changes were needed, committing only to further research over a 2-year timeline [15]. The controversy highlights fundamental tensions between maintaining strict cost control frameworks and ensuring appropriate access to innovative medicines for severe conditions. While NICE's modifier represents progress in considering severity beyond just end-of-life scenarios, current evidence suggests refinement may be needed to optimize patient access. Continued monitoring of the impact of the severity modifier on patient access to treatment is warranted.

The future of health technology assessment continues to evolve, from the practical challenges of implementing harmonized European assessments, to expanding how we capture value, to ensuring assessment criteria align with societal preferences. Success in each of these areas will require continued dialogue between stakeholders to shape processes that are both workable and scientifically robust. Ultimately, getting these aspects right is crucial for ensuring appropriate patient access to innovative medicines while maintaining sustainable healthcare systems and drug development.

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