

**Preamble:** The use of health technology assessment (HTA) to assess the value of pharmaceuticals has grown significantly more widespread in recent years. Payers in markets around the globe have established HTA bodies with a view to developing locally relevant assessments of the clinical and cost effectiveness of new treatments. Many emerging markets in Latin America and Asia have or are establishing HTA agencies that have a role in both pricing and reimbursement. In the United States, multiple value frameworks have emerged as a nascent form of HTA sponsored by non-governmental stakeholders. The European Union is moving toward harmonization of efficacy assessments and the early generation of real-world data to inform EU regulatory decisions and HTA, pricing, and reimbursement decisions for medicines at the Member State level.

As the importance and complexity of HTA continues to proliferate, it is crucial that both private and public bodies producing recommendations and evidence for consideration follow a common and transparent set of principles grounded in the practice of evidence-based health care. This should be underpinned by the latest and most appropriate use of current and established methodologies. Just as important, stakeholders with varying levels of expertise must be able to access and easily understand these reports to inform their decision making appropriately.

This document provides Merck's and MSD's perspective on current HTA issues and key elements of established HTA practice and utilization, to facilitate innovative and appropriate access to medicines for patients.

**Terminology:** HTA is a form of policy research that examines short- and long-term consequences of the application of a health care technology.<sup>1</sup> In this paper, the term HTA refers to both traditional HTA agencies, such as those that exist in many single-payer systems, and privately sponsored value frameworks, such as those that have arisen in the US.

## Principles for sound HTA practice and utilization

*Comprehensive assessment of treatment options.* In order to determine the most efficient use of healthcare resources, HTA should be applied not just to higher cost new technologies but to all relevant treatment options; local standards of clinical practice and non-clinical interventions should be assessed in order to identify system-wide inefficiencies.

*Broad perspective on value.* A broad definition of value is needed in order to capture the full range of benefits, risks, and cost impacts a treatment may have over the long-term throughout the health system and society. This should include clinical, economic, and humanistic effects, and should measure both direct and indirect effects on patients, families, caregivers, employers, and society as a whole.

*Separation of value and affordability considerations.* The assessment of treatment value, which is intended to measure long-term benefits relative to cost, must be kept separate and apart from considerations of affordability, which are typically dependent on stakeholder decisions about the appropriate short-term allocation of resources. Mixing affordability instruments such as thresholds and budget impact estimates with value assessment distorts the HTA process away from its primary purpose of assessing clinical and/or cost effectiveness.

- Thresholds are an expression of willingness to pay. The use of incremental cost-effectiveness ratio (ICER) thresholds in HTA processes superimposes an affordability criterion on value assessment, and whether a treatment is over that threshold carries over into the perception of treatment value.

<sup>1</sup> International Society for Pharmacoeconomics and Outcomes Research, <https://www.ispor.org/terminology/>

- In addition to distorting individual value assessments, on a system level, accepting budget impact as a component of treatment value wrongly suggests that curtailing pharmaceutical spending will solve system affordability issues and ignores the existence of numerous inefficiencies throughout health systems. It also discourages broader efforts to investigate health system waste and inefficiency that lower the quality of care and the potential for improved patient outcomes.

*Transparent, science-based methodology.* Analysis and conclusions should remain as close to the science as possible, and should adhere to the fundamental rules and established scientific method.

- Start with a well-defined objective and appropriate research questions, developed with broad stakeholder input, e.g., public health practitioners, health care professionals, patients, and industry representatives;
- Consider the spectrum of relevant comparators representing current clinical practice, including devices, procedures, diagnostics, pharmaceutical treatment options, alternative treatment strategies, comprehensive care management, and integrated health delivery systems.
- All relevant reliable data should be considered. Systematic reviews should collect data from all sources. In this spirit, open scientific exchange is needed to enable sponsors to share information, including published and unpublished clinical and non-clinical data, as well as the methods and results of their own internal cost-effectiveness modeling efforts. Assessment organizations should have procedures for protecting any confidential commercial data from public disclosure. Data should be ranked according to the quality of the source study, and the assessment of study quality should be based on standards that are disclosed by the assessment organization.
- Consider a broad range of methodologies, selecting those that are “fit for purpose,” ideally those that are peer-reviewed, and fully disclose the methodology chosen and the limitations of its execution.
- Acknowledge data and methodological limitations. Address generalizability and transferability of findings beyond study populations; include comprehensive and robust sensitivity analyses and disclose all sources of potential bias and uncertainty.
- Be sensitive to individual variation (heterogeneity of treatment effect). Studies used to inform HTA should be sufficiently powered to describe individual variation and individual patient or patient subgroup responses; analogously, HTA analyses should reflect variations among patient subgroups.

*Structural elements.* There is no single optimal model of value assessment – HTA must fit the local health care system. However, public and private entities that engage in the consideration of clinical and cost effectiveness should ensure all of the following:

- Independence of analysis. Entities that conduct or oversee HTA analysis should be independent from those that make clinical, budget, pricing, and reimbursement recommendations or decisions.
- Focus on priority healthcare issues. Assessments should focus on topics for which there are identified evidence gaps and which have the greatest importance for society (burden of disease, potential for effective treatment, variability in practice, ability to influence treatment and resource allocation decisions) based on broad stakeholder input.
- Transparency. HTA processes, timelines, and the basis for decisions should be open and accessible for all stakeholders, i.e. consultation periods, public comment dockets, etc., Should be clear.

- Broad stakeholder engagement. Those with a stake in HTA should be involved, including industry, healthcare providers and patients. In particular, industry involvement can facilitate the exchange of information in confidence to ensure the reviewer has complete clinical, epidemiologic, and economic information to formulate a review.
- Patient-centered. Patients' unique perspective on disease and the value of potential new treatments is invaluable in defining the objectives and key questions for HTA evaluations. Incorporating their views helps ensure HTA reviews and the clinical and financial decisions based upon them are patient-relevant.
- Periodic updating of reviews. Entities that develop and release HTA evaluations into the public domain should periodically review and update their findings as new evidence and methodologies are introduced that may affect the original conclusions. The results of these HTA "re-reviews" also should be made public.

*Non-transferability of HTA reviews.* HTA reviews are not wholly transferable among health systems. The variability of a number of factors, including availability of health care services, individual willingness to pay, economic circumstances, epidemiological contexts, patient populations, cultural norms, and other factors can cause wide variations in both value and affordability across health systems and payers, even those within the same country. The misapplication of existing HTA evaluations can cause undue delay in patient access to treatments and hamper improvements to care delivery, population health management, and efficient use of healthcare resources.

*Consensus approaches to handling uncertainty.* Flexible approaches to assessing medicines earlier in development can expedite patient access, however, the limited data packages used to fulfill regulatory requirements may not meet the expectations of HTA bodies. Although many regulators now approve products that address unmet needs in serious or life-threatening conditions on the basis of streamlined clinical development programs with the stipulation that some confirmatory data be generated in the post approval setting, these data may not capture the full value of innovative products. As payers struggle with how to incorporate these innovative products into their health systems, Merck and MSD support consensus approaches to handling uncertainty and flexible entry agreements.

*Ensuring adequate expertise and infrastructure.* Governments and payers should be committed to ensuring appropriate resources are devoted to improving the evidence base and infrastructure for medicines and vaccines evaluation, including the expertise needed to appropriately evaluate the evidence and methodologies used in health technology assessments.

*Ensuring uptake of HTA assessments.* The outcome of scientific value assessment procedures should be reflected in pricing and reimbursement decisions, as well as use in medical practice. Additional tools that are often used to influence cost parameters frequently distort original value assessments and undermine the scientific rigor under which they were applied.