PharmaSUG China 2026 - Paper DS-228

Health Technology Assessment (HTA) Under EMA Framework: From Emerging to Mandatory Submission

Jun Zhai, Johnson & Johnson

ABSTRACT

Health Technology Assessment (HTA) is a multidisciplinary process that evaluates the clinical, economic, and social implications of health technologies to inform coverage and reimbursement decisions. The European Medicines Agency (EMA) has undergone significant shifts in its HTA alignment strategy, particularly following the implementation of the EU HTA Regulation (EUR) 2021/2282. Under the regulation, the HTA coordination group and its sub-groups, composed of national HTA bodies jointly conduct Joint Clinical Assessments of new medicines and certain high-risk medical devices, starting with new cancer medicine and advanced therapy medicinal product.

This paper examines current landscape of HTA submissions under EMA framework, identifies gaps and argues clearer direction for statistical programmers' involvement and responsibilities in HTA submission.

INTRODUCTION

WHAT IS HTA?

Health Technology Assessment (HTA) is a scientific, evidence-based process that systematically evaluates the properties, effects, and impacts of health technologies, including medicines, medical devices, and other interventions. It evaluates the added value of new health technologies by assessing whether a new technology works better, equally well, or worse than existing alternatives.

HTA aims to improve both quality and value for money, and to facilitate coverage decisions based on evidence-based information and other socioeconomic factors beyond clinical and cost-effectiveness alone.

HTA AROUND THE GLOBE

Nowadays more than 30 countries around the world have adopt with HTA frameworks. The way HTA is organized, conducted, and integrated into policy varies significantly across countries, reflecting differences in healthcare system structures, cultural values, and regulatory tradition. Understanding these variations is essential for pharmaceutical and biotech professionals involved in global drug development and market access strategies.

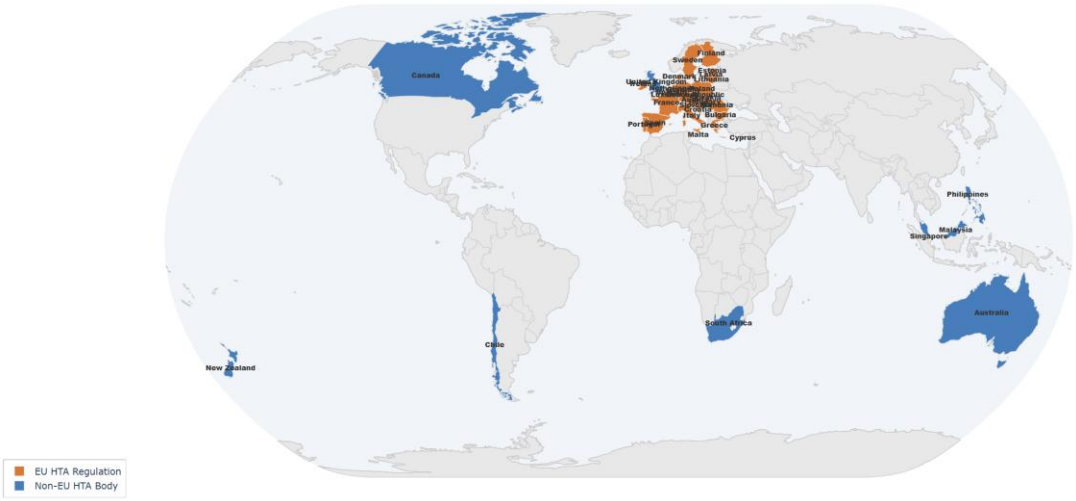

Figure 1. HTA Bodies Around the Globe

HTA UNDER EU REGULATION

Under the new EU HTA Regulation (entered into force January 2022, applied from January 2025), a Member State Coordination Group (HTACG) now oversees Joint Clinical Assessments (JCA) of new medicines and certain high-risk medical devices at the EU level. Starting January 2025, new cancer medicines and advanced therapy medicinal products (ATMPs) trigger Joint Clinical Assessments (JCA). Coverage will extend to orphan medicinal products by 2028 and all new medicinal products by 2030. Member States must give due consideration to Joint Clinical Assessments (JCA) reports in their national HTA processes while retaining responsibility for pricing and reimbursement decisions.

JCA VS MEMBER STATE HTA

The JCA is the EU-level shared clinical evidence synthesis; member state HTA is the national decision. They are complementary but distinct.

The JCA produces a single centralized clinical effectiveness report shared across all 27 EU member states, covering comparative clinical effectiveness vs. comparator(s), relative safety, and patient-relevant outcomes. It does not assess cost-effectiveness, budget impact, or make reimbursement decisions.

Meanwhile each national HTA body retains full authority over cost-effectiveness analysis (e.g., NICE's QALY/ICER, HAS's SMR/ASMR, G-BA's benefit rating), pricing and reimbursement decisions, budget impact assessment, and contextual factors such as local disease burden and healthcare system priorities.

Before 2025, companies submitted a full clinical dossier separately to each national HTA body. From January 2025 (oncology/ATMPs), one JCA dossier covers the clinical part for all 27 member states simultaneously, after which companies submit only the economic and local evidence to each national body. This reduces duplication on the clinical side but requires the JCA comparator set and endpoints to satisfy 27 countries' needs simultaneously — a more demanding design challenge than a single-country submission.

GERMANY AND FRANCE HTA

Among all EU member states, no country holds formal dominance in the JCA process — the regulation is designed as consensus-based. In practice, however, Germany and France carry the greatest influence, owing to their market size, methodological maturity, and active role in shaping EU HTA governance.

Germany has a dual HTA system with two key national bodies:

- **G-BA** (Gemeinsamer Bundesausschuss): A regulatory body that is directly responsible for coverage and reimbursement decisions. G-BA's recommendations are legally binding, which means positive HTA recommendations lead directly to final funding decisions.
- **IQWiG** (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen): An advisory body that conducts independent scientific evaluations of the clinical benefit and cost-effectiveness of health technologies. IQWiG provides recommendations to G-BA to inform its decisions.

As the largest pharmaceutical market in the EU (approximately 25% of EU drug spend), Germany's benefit assessments effectively set reference signals for EU-wide price negotiations. When a product failing G-BA's assessment can trigger market withdrawal across Europe. G-BA representatives have been heavily involved in shaping JCA methodology within the Member State Coordination Group. Germany also has a very transparent price negotiation process comparing to other countries, which gives a clear reference for both HTA bodies from other countries as well as pharmaceutical companies.

France operates its HTA primarily through **HAS** (Haute Autorité de Santé), an advisory HTA body that assess technologies based on the comparative clinical benefit model. Although HAS recommendations are technically non-binding, they are considered equally impactful as binding in practice — they serve as a fundamental basis for both reimbursement decisions by the national insurance fund and pricing decisions by the Transparency Committee. HAS also played a central role during the EU HTA Regulation negotiations, pushing strongly to preserve national sovereignty over economic evaluation.

HTA MODELS

Each country may use mixed models of HTA assessments based on their national healthcare emphasis, but we can categorize them into two major considerations.

Comparative Clinical Benefit Assessment

Comparative clinical benefit assessment (CCBA) is a systematic methodology for evaluating whether a new medicine offers clinically meaningful advantages over the current standard of care, based exclusively on clinical evidence and independent of cost considerations. The assessment centers on patient-relevant outcomes — including overall survival, morbidity, and health-related quality of life.

A defining feature of CCBA is its categorical benefit rating. The German AMNOG framework, for instance, classifies added benefit as major, considerable, minor, non-quantifiable, absent, or negative. France employs the analogous ASMR scale (I–V).

The EU Health Technology Assessment Regulation (EU) 2021/2282 institutionalizes joint clinical assessment as a mandatory pan-European standard, while preserving member state autonomy over pricing and reimbursement.

Economic Evaluation

Economic evaluation in HTA is a systematic framework for assessing whether the clinical benefits of a new medicine justify its costs relative to existing alternatives. Unlike comparative clinical benefit assessment, it explicitly incorporates resource use alongside clinical outcomes, enabling decision-makers to allocate finite healthcare budgets efficiently.

The predominant analytical method is cost-utility analysis (CUA), in which health outcomes are expressed as quality-adjusted life years (QALYs), a composite measure integrating survival and health-related quality of life. The resulting incremental cost-effectiveness ratio (ICER), representing the additional cost per QALY gained, is compared against a willingness-to-pay threshold to determine whether coverage is justified. England's NICE applies an explicit threshold of £25,000–35,000 per QALY; Poland sets its threshold at three times GDP per capita. Other jurisdictions, including Sweden and the Netherlands, apply implicit thresholds modulated by disease severity.

> ***QALY = Years of Life × Utility Score***
>
> *Utility Score ranges from 0 to 1, usually derived from instruments such as EQ-5D*

> ***ICER = (Cost of New Treatment − Cost of Comparator) ÷ (QALYs of New Treatment − QALYs of Comparator)***

HTA VS CSR: WHAT'S THE DIFFERENCE

From a statistical design perspective, HTA submissions differ fundamentally from a standard Clinical Study Report (CSR). Whereas a CSR is principally concerned with demonstrating internal validity, establishing whether an intervention is efficacious and safe under controlled conditions; an HTA submission is concerned with external validity and value: whether the intervention represents a worthwhile use of healthcare resources relative to existing clinical practice.

PRIMARY QUESTION

CSR: The primary objective is to demonstrate efficacy and safety against a protocol-specified comparator (commonly placebo), employing a pre-specified primary endpoint within a formal hypothesis-testing framework.

HTA: The primary objective is to establish comparative effectiveness relative to the prevailing standard of care within each jurisdiction's healthcare system. In the absence of direct head-to-head trial evidence, indirect treatment comparisons are required.

SUBGROUP ANALYSES

CSR: Pre-specified and exploratory subgroup analyses are conducted primarily to assess consistency of treatment effect in support of the primary result.

HTA: Subgroup analyses serve a fundamentally different function; they delineate the reimbursable population and directly inform coverage restriction decisions. To be considered credible, subgroup analyses must be pre-specified, supported by formal interaction tests, and adequately powered. HTA bodies (G-BA, NICE, HAS) frequently stipulate required subgroup definitions within their assessment scoping documents.

ENDPOINT SELECTION

CSR: accept disease-specific clinical or surrogate endpoints to establish efficacy, e.g. progression-free survival (PFS), objective response rate (ORR), biomarker response.

HTA: prefer final patient-relevant outcomes; accept surrogates only with demonstrated biological and epidemiological justification and translate into health value for payers and society.

E.g. For oncology studies, NICE, IQWiG, and CADTH all have specific published guidance requiring validation of PFS-to-OS correlation before surrogate data can inform economic models.

E.g. For cardiovascular disease, blood pressure, LDL, and HbA1c have a long tradition as surrogates in trials, but HTA bodies generally require hard cardiovascular outcome trial (CVOT) data such as MACE, cardiovascular death, hospitalization for heart failure. Where CVOTs are unavailable, surrogate-to-outcome mapping is required but is often challenged.

PREFERRED STATISTICS

All major HTA bodies require the presentation of both relative and absolute effect measures, neither is considered sufficient in isolation. Relative measures establish the direction and magnitude of treatment effect, whilst absolute measures contextualize clinical and public health relevance.

For example, HTA bodies may require risk ratio (RR) or odds ratio (OR) to be reported alongside the absolute risk difference (RD) for binary outcomes; For survival analysis, a single HR summary statistic may be insufficient, non-proportional hazards must be addressed.

REAL-WORLD EVIDENCE (RWE)

CSR: RWE does not constitute part of the primary regulatory submission package.

HTA: RWE is increasingly integrated into the submission, serving to substantiate the external validity of trial population and address evidence gaps as well as directly inform treatment effect estimates.

PROGRAMMING CHALLENGE IN HTA

COLLABORATION MODEL

In a standard CSR, the statistical programmer's primary collaboration model is relatively contained — working within a clinical study team alongside Biostatisticians, Data Managers, and Medical Writers to deliver analysis datasets and outputs against a pre-specified SAP. The functional boundaries are well-defined, and the evidence package is largely self-contained within the sponsor's own trial data.

HTA submissions operate under a substantially more complex collaboration structure. Because the submission must address the value of the technology within specific healthcare systems, the programming deliverables are shaped by inputs from a broader set of stakeholders, often spanning multiple countries and functional disciplines simultaneously. A typical HTA programming workstream may involve Market Access, HEOR, Regulatory Affairs, local affiliate teams, etc.

This collaborative complexity has direct implications for programming timelines and specifications. Moreover, the stakeholders from post-market teams may not be familiar with documents and processes from pre-market, programmers must therefore maintain flexibility and robust practices to collaborate effectively among team members, and also maintain consistency and integrity between global CSR and HTA-specific analyses.

OVERLAPPED TIMELINE

In HTA submissions, programming timelines often overlap with clinical study reporting and regulatory submission activities. Effective planning requires early alignment between statistical programming, clinical operations, and regulatory teams to ensure that data deliverables (e.g., analysis datasets, TFLs, and submission-ready packages) are produced on time despite concurrent workstreams. Also to keep consistency between CSR and HTA analyses, regular consistency check between mocks, codes and outputs are required for programming team.

AUTOMATIC PROGRAMMING

Since a substantial portion of HTA outputs are subgroup analyses derived directly from CSR outputs, and given the strict consistency requirements across overlapping timelines, programming teams typically automate rather than rebuild from scratch.

For metadata and mock shell preparation, when changes are limited to titles, footnotes, and column layouts, Python or VBA tools can batch-edit specification documents and perform automated comparison against CSR specs, ensuring alignment without manual reconciliation.

For TFL generation, a growing ecosystem of published and open-sourced R packages, Shiny applications, and SAS macros allows programmers to produce subgroup analyses by extending existing CSR programs with an additional population filter layer, rather than authoring new code. This reuse of validated CSR infrastructure reduces both development effort and the validation burden, while maintaining traceability between the CSR and HTA deliverables.

REFERENCES

[1] World Health Organization. (2015). *Global survey on health technology assessment by national authorities*. https://www.who.int/health-technology-assessment/en/

[2] Banta, D. (2003). The development of health technology assessment. *Health Policy*, *63*(2), 121–132. https://doi.org/10.1016/S0168-8510(02)00059-3

[3] Fontrier, A.-M., Visintin, E., & Kanavos, P. (2022). Similarities and differences in health technology assessment systems and implications for coverage decisions: Evidence from 32 countries. *PharmacoEconomics - Open*, *6*, 315–328. https://doi.org/10.1007/s41669-021-00311-5

[4] Angelis, A., Lange, A., & Kanavos, P. (2018). Using health technology assessment to assess the value of new medicines: Results of a systematic review and expert consultation across eight European countries. *European Journal of Health Economics*, *19*(1), 123–152. https://doi.org/10.1007/s10198-017-0871-0

[5] European Commission. (2021). *Regulation (EU) 2021/2282 of the European Parliament and of the Council on health technology assessment*. https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment_en

[6] IntuitionLabs. (2026, April 30). *HTA dossiers: A guide to submissions for NICE, CADTH & ICER*. https://intuitionlabs.ai/articles/hta-dossier-submission-guide

[7] National Institute for Health and Care Excellence. (2022). *Process and methods guide PMG36: Developing NICE technology appraisal guidance*. https://www.nice.org.uk/process/pmg36/chapter/developing-the-guidance-2

[8] Kaltenthaler, E., Tappenden, P., Paisley, S., & Squires, H. (2012). Identifying and reviewing evidence to inform the conceptualisation and measurement of the impact of single technology appraisals on clinical practice in England. *BMC Health Services Research*, *12*(1). https://pmc.ncbi.nlm.nih.gov/articles/PMC3277905/

[9] Value in Health. (2024). HTA67: Tackling heterogeneity in indirect treatment comparison (ITC): A comparative review of NICE submissions in oncology versus non-oncology. *Value in Health*, *27*(Suppl.). https://www.valueinhealthjournal.com/article/S1098-3015(24)04755-7/fulltext

[10] Phillippo, D. M., Ades, A. E., Dias, S., Palmer, S., Abrams, K. R., & Welton, N. J. (2024). The use of real-world data for estimating relative treatment effects in NICE health technology assessment submissions: A review. *PharmacoEconomics*. https://link.springer.com/article/10.1007/s40273-024-01449-w

[11] Grigore, B., Furtado, V., & Milbers, K. (2025). Clinical equivalence and non-inferiority within health technology assessment. *PharmacoEconomics*. https://pubmed.ncbi.nlm.nih.gov/40506597/

[12] Phillippo, D. M., et al. (2024). The use of real-world data for estimating relative treatment effects in NICE HTA submissions. *PharmacoEconomics*. https://link.springer.com/article/10.1007/s40273-024-01449-w

[13] Canada's Drug Agency. (2022). *CADTH pharmaceutical reviews update — Issue 28*. https://www.cda-amc.ca/cadth-pharmaceutical-reviews-update-issue-28

[14] Institute for Clinical and Economic Review. (n.d.). *Methods and process: Value assessment framework*. https://icer.org/our-approach/methods-process/

[15] National Institute for Health and Care Excellence. (n.d.). *Technology appraisal submission templates and supporting documents*. https://www.nice.org.uk/what-nice-does/our-guidance/about-technology-appraisal-guidance/technology-appraisal-submission-templates-and-supporting-documents

[16] Cencora. (2025). *EU HTA 2025 readiness: Key methodological updates and practical tips on statistical guidelines*. https://www.cencora.com/resources/pharma/eu-hta-2025-key-methodological-updates-and-practical-tips-on-statistical-guidelines

ACKNOWLEDGMENTS

I would like to give sincere thanks to my programming lead Daphne Vuurstaek for her support and valuable feedback during HTA programming activities and preparation of the presentation.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Jun Zhai
Johnson & Johnson
jzhai@its.jnj.com