Selection of Appropriate Endpoints for the EU JCA and National Assessments in Select Member States and England for ATMPs

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HTA35

Background

- The assessment of relative effectiveness and safety in the Joint Clinical Assessment (JCA) is a fundamental aspect of EU Health Technology Assessment (HTA) Regulation.
- Although EU guidelines on outcomes are available,[1] with a stated preference for clinical endpoints (defined as a characteristic or variable that reflects how a patient feels, functions, or survives[2]). However, the use of surrogate endpoints to demonstrate the clinical benefit in trials of Advanced Therapy Medicinal Product (ATMPs) in absence of mature data from clinical endpoints is of increasing importance for HTA as therapies that are potentially curative or long-term clinical benefits are developed.
- However, the use of surrogates is associated with limitations, as they do not directly measure final clinical outcomes. With the first wave of JCAs fast approaching, and considering current guidance, our research aimed to explore differences between JCA and local EU methods for the assessment of endpoints to find areas of harmonization and divergence as Health Technology Developers (HTDs) prepare for a new landscape in Europe.

Objectives

- To review the methodological requirements for endpoint selection for selected European HTA processes and the JCA.
- To identify areas of harmonization and divergence in European guidelines on the acceptance of surrogate endpoints.
- To identify possible areas of challenge in the acceptance of surrogate endpoints for the assessment of ATMPs in the JCA and member states' national HTA processes.

Methods

- We conducted a targeted review of methodological guidelines from the EU and European HTA bodies: the EU's EUnetHTA21,[1] Germany's Institute for Quality and Efficiency in Health Care (IQWiG),[3] France's Haute Autorité de Santé (HAS),[4] and England's National Institute for Health and Care Excellence (NICE).[5]
- These bodies were selected to provide a range of approaches to HTA based on their established role in development of methodological guidelines and influence in other markets, population size, and geographic location.
- The most recently available guidelines from each organization were reviewed to identify areas of harmonization and differences between EU and member state HTA methods for selection of endpoints and use of surrogate outcomes. The reviewed guidelines are listed in the reference list below.

Results

Relevant Outcomes

- All guidelines stated a preference for clinical endpoints that measure how a patient feels, functions, or survives.[2] These endpoints are preferred to surrogates as they are considered more informative, given they directly measure the benefit of a treatment on patients. Additionally, any uncertainty in the association between a surrogate and clinical endpoint are viewed to carry a risk to healthcare budgets if the expected clinical benefits are not realized.
- EUnetHTA guidelines were unique in their stated preference for all-cause mortality (being objective, easy to measure, and definite). Other guidelines did not express a preference between outcomes for mortality, morbidity, or health-related quality of life (HRQoL). However, French and German guidelines expect a treatment to improve survival in serious or life-threatening diseases. In such cases, an improvement in HRQoL without improving mortality or morbidity would not be accepted.

Table 1. Summary of Methodological Guidelines

	METHODOLOGICAL CONSIDERATION		
	DEFINITION OF RELEVANT OUTCOMES FOR DECISION MAKING	ACCEPTANCE OF SURROGATE ENDPOINTS	VALIDATION OF SURROGATE ENDPOINTS
EU	Long-term or final outcomes (i.e., the occurrence of an irreversible event of primary interest such as death, all-cause mortality) are preferred.	A validated surrogate outcome can be accepted if there is evidence of a strong association or correlation of the effects of the surrogate outcome with the final outcome. Surrogates should only be used to replace a final patient-centered outcome of interest if absolutely necessary, and where possible only validated surrogate outcomes should be requested.	Meta-analysis of several randomized-controlled trials (RCTs) and evidence of biological plausibility should be provided. Ideally, the association between the surrogate and final outcome will be demonstrated at the individual and trial levels. Deliverable 4.4 on Endpoints states this demonstration is often done via regression analysis or meta-regression (single vs multiple studies, respectively). The company can also provide scientific literature to demonstrate the link.
FR	The primary outcome of a study must be a relevant clinical endpoint wherever it is possible to collect one.	The use of a surrogate endpoint is acceptable if a link with a clinical endpoint for mortality or morbidity has been demonstrated in the concerned disease.	The Transparency Committee Doctrine does not include details on the approach to validation.
DE	The assessment of patient-relevant medical benefit and harm should assess outcomes for mortality, morbidity, and HRQoL.	Surrogate endpoints are only considered in the benefit assessments if they have been validated using appropriate statistical methods in an appropriate patient population with comparable interventions.	Correlation-based procedures are preferred, using a meta-analysis of randomized studies that investigate the surrogate endpoint and patient-relevant outcome. Alternatively, if a surrogate endpoint cannot be conclusively validated, the surrogate threshold effect concept can be applied.
UK	NICE refers to appropriate clinical endpoints as those including a validated relationship with the overall survival and quality of life of the patients, allowing for quantification that translates into quality-adjusted life years (QALYs).	The use of a surrogate endpoint is acceptable, with 3 levels of evidence: • **Level 3**: Biological plausibility of relation between surrogate endpoint and final outcomes. • **Level 2**: Consistent association between surrogate endpoint and final outcomes derived from epidemiological or observational studies. • **Level 1**: The technology's effect on the surrogate endpoint corresponds to commensurate effect on the final outcome as shown in the RCT.	Preferably, evidence of the relationship between the surrogate and final outcomes comes from a meta-analysis of level 1 evidence (RCTs) that reported the surrogate and final outcomes, using recommended meta-analytic methods. The validation of a surrogate outcome is specific to the population and technology type under consideration.

Acceptance of Surrogate Endpoints

- The guidelines included in the research differ in the level to which they will accept surrogate endpoints. NICE prescriptively outlines three levels of acceptable evidence of increasing strength, while HAS's acceptance of surrogate endpoints corresponds only to level 1 (strongest) evidence in NICE's scale.
- German and EU guidelines take a similar view with acceptance depending on a "strong association or correlation or link" between surrogate and final outcomes. German methods also state this link should be established for the appropriate patient population and interventions, while EU methods state the association should ideally be established at the individual and trial levels.
- EUnetHTA21, NICE, and HAS guidelines acknowledge that there are circumstances where the collection of clinical outcomes are not feasible within a clinical trial. These include diseases with a long-term survival and subsequent lines of therapy.

Survival

- The acceptance of progression-free survival (PFS) as a surrogate of overall survival (OS) highlights the difference in approaches across HTA bodies.
- The Appendix for EUnetHTA21's Deliverable 4.4 on Endpoints, which is specific to oncology outcomes, specifies that demonstrating improvement in OS is not always possible and highlights that the correlation between PFS and OS is not always confirmed in final results. However, the deliverable does not contain details on use cases where PFS would be acceptable. On the other hand, the Transparency Committee Doctrine in France highlights PFS can be used if OS cannot be documented in short or medium term.

Discussion

- Generally, HTA methods are aligned in their preferences for final endpoints, but several bodies state surrogates are appropriate in certain circumstances. Some of them, such as HAS, provide specific examples on when surrogates may be acceptable (e.g., in the context of oncology, infectious diseases, and rare diseases).
- The current guidelines for EU HTA may lead to some uncertainties in the selection of appropriate endpoints to provide evidence for relative effectiveness ahead of JCA submissions. Further, they currently offer limited pragmatic solutions to meet the objectives of EU HTA Regulation and ensure appropriate and timely access for EU patients.
- The lack of EU guidance on the acceptance of surrogate endpoints during the assessment of orphan drugs and ATMPs represents a missed opportunity for developing a structured and predictable approach to handling uncertainty in challenging therapy areas.
- Companies should proactively seek to identify the likely JCA scoping requests in terms of outcomes to undertake the validation of any surrogate endpoints early on. As seen with NICE methods, this can be done via the generation of real-world evidence to demonstrate the association between the surrogate and final outcomes. Companies should plan this prediction early in the development program of novel assets, particularly when they fall under the orphan drug and/or ATMP categories.

Conclusions

- Our review identified a few areas of harmonization, including the preference for final clinical endpoints and use of meta-analyses of randomized controlled trials to validate surrogates. However, the level of acceptance of surrogate endpoints and the level of guidance provided on cases of use for surrogates varied between HTA bodies.
- Further research is required to understand how EUnetHTA21 guidelines will be interpreted by different assessors at the time of a JCA, especially for unique circumstances where alternative methods may be accepted by HTA bodies at a national level.

References

1. EUnetHTA21. D4.4 – Outcomes (Endpoints). 2023. Accessed April 23, 2024. Available from https://www.eunethta.eu/wp-content/uploads/2023/01/EUnetHTA-21-D4.4-practical-guideline-on-Endpoints-v1.0.pdf.
2. Biomarkers Definitions Working Group. *Clin Pharmacol Ther*. 2001;69(3):89-95.
3. IQWiG. General Methods version 7.0. 2023. Accessed April 23, 2024. Available from https://www.iqwig.de/methoden/general-methods_version-7-0.pdf.
4. HAS. Doctrine de la commission de la transparence (CT). 2023. Accessed April 23, 2024. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2021-03/doctrine_ct.pdf#page=32.
5. NICE. Introduction to health technology evaluation [PMG36]. 2022. Last updated October 31, 2023. Accessed April 23, 2024. Available from https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.

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