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Implications of EU HTA on Future Relevance of Surrogate Outcomes in National Assessment

Objectives

Acceptance of surrogate outcomes is one key challenge in HTA. EU HTA will set new standards for HTA on the European level and will be more closely connected to the regulatory process. This study analyzes
(1) the current problems in accepting surrogate endpoints in (national) HTAs,
(2) the methods set out by EUnetHTA, and
(3) the implications for upcoming national assessments post 2025.

Methodology

German HTA will be analyzed here, as this can currently be considered the most rigorous national HTA within the EU. Relevant surrogate outcomes are identified by screening G-BA resolutions since 2011, excluding orphan drug assessments. Reasons for acceptance or non-acceptance are extracted and categorized. EU HTA standards on surrogate outcomes are extracted from respective guidelines.

Results

- Both the Gemeinsamer Bundesausschuss (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG), the bodies defining the German HTA process, accept surrogate outcomes once they have been validated beforehand by means of appropriate statistical methods within a sufficiently restricted patient population and within comparable interventions[1,2]. However, fulfilling the formal requirements for such a validation is challenging.
- IQWiG considers correlation-based procedures for surrogate validation, with estimation of correlation measures at the trial and the individual level as an adequate validation approach[2].
- So far, only disease-free survival (DFS) in breast cancer and the virologic response in HIV infection have been accepted as surrogate endpoints by the G-BA.
- Other attempts to validate surrogates have been declined by G-BA, mainly due to inconsistencies between the patient population that was used for the validation and the target population in which the surrogate was assessed.

- EUnetHTA 21's final guideline on outcomes was published in January 2023[3]. It states that surrogate outcomes such as biomarkers or intermediate outcomes can be requested by the member states in addition to patient-centered outcomes where relevant for Joint Clinical Assessments (JCAs).
- Preferably, the validity of the surrogate has been established in previous JCAs or in other literature on the same indication. The strength of the association between the surrogate outcome and the patient-centered outcome and the treatment effect should be demonstrated. This is often done via regression analysis for single studies, or meta-regression in the case of multiple studies. Ideally, the association will be demonstrated at both the individual and the trial level. Scientific literature which demonstrates the link can also be provided[3].
- EUnetHTA 21's recent PICO exercises demonstrated the ambivalent behavior of HTA bodies across the EU member[4-6]. The consolidated PICO for both Pluvicto® and Ebvallo® included surrogate endpoints such as progression-free survival (PFS) and radiologically assessed response endpoints (see table).

- While methodological requirements defined by G-BA and EUnetHTA seem to be similar, their practical implementation in real life remains to be seen.
- By G-BA standards, the surrogate endpoints that have been requested in EUnetHTA's PICO exercises have not yet been validated adequately. Consequently, the G-BA would not assess and accept these endpoints in a national HTA procedure due to their lack in patient-relevance.
- Clearly, other HTA bodies have a different opinion on that matter since they saw the corresponding results as integral part of the PICO exercises.
- With a publicly available JCA report that assesses surrogate outcomes, acceptance of such endpoints on the national level might be re-considered in order to meet one of the overall aims of EU HTA: the harmonization of clinical assessments across Europe.
- It is expected that countries with a well-established national HTA may stick to their own assessment standards where possible to ensure procedural consistency. This holds true especially for the rigorous German HTA. However, accepted surrogate outcomes on a European level that are based on a high methodological and reporting standard may be difficult to reject on a national level.
- Hence, a joint methodological approach for the validation of surrogate outcomes that is commonly accepted should be aimed for.

Requested surrogate outcomes during EUnetHTA 21's PICO exercises and their acceptance by the G-BA

	Pluvicto®	Ebvallo®	Pombiliti®	Acceptance by G-BA
ORR overall response rate	–	✓	–	✗
DOR duration of response	✓	✓	–	✗
PFS progression-free survival	✓	✓	–	✗
EFS event-free survival	–	✓	–	✗
Laboratory parameters	✓	–	–	✗

✓ requested by EUnetHTA 21 – not requested by EUnetHTA 21 ✗ not accepted by G-BA

Conclusion

It is anticipated that the upcoming EU HTA, running in parallel to the regulatory EMA process, will force HTA bodies to rethink their stance on surrogate outcomes. The general skepticism of the G-BA towards these endpoints is not equally met in other European HTA bodies. The need to align on a stringent EU HTA procedure in combination with a harmonized methodology in terms of surrogate validation might lead to increased acceptance of surrogates, which are essential determinants for the clinical efficacy. Consequently, this may also enrich the available set of instruments for evidence demonstration within the national German HTA framework.

References

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