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Challenges that EUnetHTA21 will have to address to make a success of Joint Clinical Assessments

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Introduction

EUnetHTA21, a new consortium of 13 agencies, will play a crucial role in laying the groundwork for collaboration between HTA agencies in Europe. The new project is intended to "build on the achievements and lessons learned from the EUnetHTA Joint Actions and focus on supporting a future EU HTA system under the HTA Regulation."

A key part of the proposed work of EUnetHTA21 is to develop **Joint Clinical Assessments** (JCAs). These are defined in a regulation drafted by the Council of Europe and European Parliament and should cover the four clinical domains of the identification of a health problem and current technology, the examination of the technical characteristics of the technology under assessment, its relative safety, and its relative clinical effectiveness. All markets are meant to use the JCA as the basis of their decision-making process although they can undertake additional analyses if required. The JCAs will be piloted on oncology products initially.

Part of the reason for developing JCAs is to minimise the need for manufacturers to have to submit the same data to multiple HTA agencies. However, the joint clinical assessment report is meant to be purely factual and with no value judgement, or conclusions on the overall benefit.

The EUnetHTA21 has been tasked with developing a process for developing JCAs. The complexity of building a JCA that will be acceptable to all EU HTA agencies should not be underestimated. The EU in 2017 undertook a project that mapped HTA methodologies in the EU and Norway. They found **significant differences between HTA agencies in the choice of comparator, use of indirect comparisons, and the acceptance of surrogate endpoints**. This makes the job of EUnetHTA21 in designing a JCA which meets the needs of all EU HTA agencies challenging.

Objectives

To assess and analyse the different evidence interpretations and acceptance of European HTA in order to determine the extent and types of challenge that the divergence poses to development of EUnetHTA21 Joint Clinical Assessments.

Methods

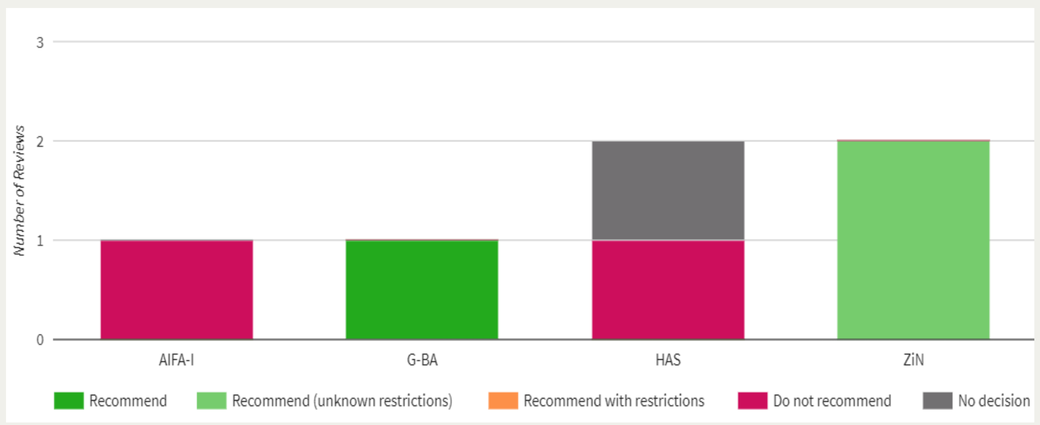
The Cortellis Context Matters Market Access Platform was searched to determine whether EU HTA agencies behave in a similar manner in their evaluations of oncology drugs. The database was filtered on various metrics, such as the clinical comparator used and final decision issued, across various cancers. When the database showed a divergence on the key metrics, the filters were applied to individual drugs used to treat the specific cancer. The most illustrative examples of the divergence are depicted.

The HTA decisions summarized by Context Matters were accessed through the platform and analyzed in order to determine the specific reasons for the divergence that was observed. The analysis was limited to oncology because cancer drugs will be the first drugs that are subject to the EUnetHTA21's Joint Clinical Assessments.

Results

The differing HTA outcomes of the review of diffuse large B-cell lymphoma (DLBCL) drug polatuzumab vedotin is an example of disagreement between the agencies regarding the validity of trial outcome measures. The agencies agreed that the primary endpoint (complete response) was not relevant, but had differing opinions of the secondary endpoint (overall survival). ZiN and G-BA recommended the drug on the basis of an 80-person clinical trial showing a 7.7 month improvement in survival vs. the comparator.

Figure 1: HTA decisions following assessment of polatuzumab vedotin to treat DLBCL



HAS did not make a decision on the cost-effectiveness of polatuzumab vedotin. All other reviews were clinical in nature.

Meanwhile, AIFA and HAS deemed the trial to be of insufficient quality, citing the small sample size, lack of non-inferiority hypothesis, and concerns that comparator group had more favorable disease prognostic factors. In addition, HAS said it expected quality of life data, stated that the comparator is rarely used in France, and rejected the matching-adjusted indirect comparison (MAIC).

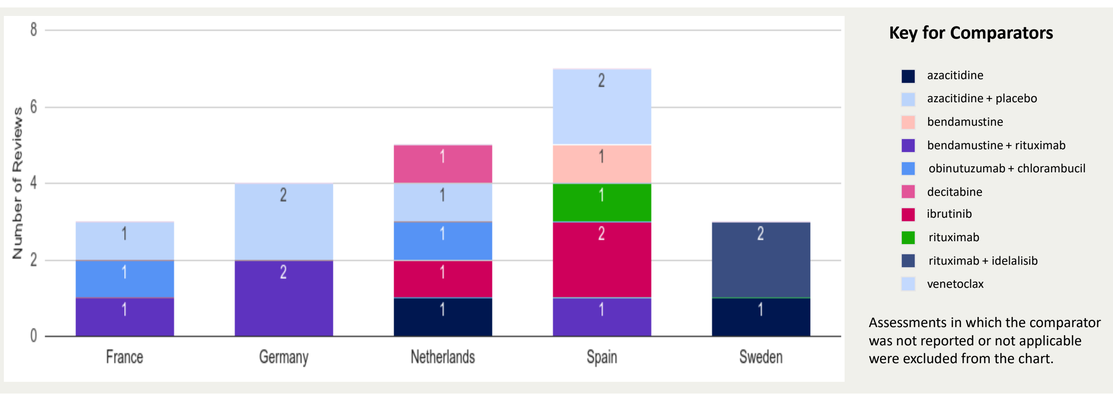
Interestingly, G-BA and ZiN noted many of the same weaknesses, but still recommended polatuzumab vedotin (though ZiN seeks a price below the reference value due to the "very low" trial quality), suggesting that the divergence stems from the agencies' unique values and desires, rather than differences between the sponsor's submitted evidence package or their objective interpretation of the data.

For example, a key area of divergence between HTA agencies noted in the 2017 mapping exercise was the in the way in which surrogate endpoints, such as progression-free survival (PFS), are valued. G-BA typically does not accept PFS as an endpoint for either mortality or morbidity because it is not seen as patient relevant. G-BA has a standard phrase used in HTA assessments:

"The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component "mortality" was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively by means of imaging procedures (according to RECIST 1.1). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint."

Another common point of divergence that contributes to the variety of HTA opinions issued on the same drug is the choice of comparator used. The inconsistency stems in part from differences in the standard of care across countries. Figure 2 shows that 10 different comparators were used across five EU countries to assess the hematological cancer drug venetoclax. Moreover, the agencies used different comparators to assess the drug in the same or similar chronic lymphocytic leukemia (CLL) indications. For instance, HAS compared venetoclax + obinutuzumab (V+O) to obinutuzumab + chlorambucil when used among certain 1L patients with CLL, while G-BA used bendamustine + rituximab as the comparator to V+O when used among the same patient cohort.

Figure 2: Comparators used in HTA assessments of venetoclax by country



Conclusion

The Joint Clinical Assessments are meant to reduce the need for multiple evidence submissions to individual HTA agencies. However, member states can still ask for additional analyses or evidence relating to patient groups, comparators, or outcomes, or even request use of a different methodology than that performed in the JCA. Our analysis found significant differences regarding the acceptance of clinical trial endpoints, desired evidence, and comparators across HTA agencies in their assessment of oncology drugs. In scenarios where the agencies make divergent recommendations, companies may be asked to submit additional evidences to obtain coverage from the dissenting agencies. It will be a challenge for EUnetHTA21 to design JCAs that simultaneously satisfy all HTA agencies. Despite the presence of JCAs, there is a risk that companies will still have submit analyses, data and evidence to multiple HTA agencies.

References

1. Context Matters. *Dashboard* Clarivate Analytics;
2. Regulation (EU) 2021/2282 on health technology assessment https://health.ec.europa.eu/publications/regulation-eu-20212282-health-technology-assessment_en
3. European Commission, Directorate-General for Health and Food Safety, Børlum Kristensen, F., Mapping of HTA methodologies in EU and Norway, Publications Office, 2018, https://data.europa.eu/doi/10.2875/472312