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Implications of EU HTA on Future Relevance of Real-World Evidence in National Assessments

Objectives

Acceptance of real-world evidence (RWE) is one key challenge in HTA. The upcoming European HTA will set new standards on the European level. Hence, recently published guidelines by EUnetHTA 21 on RWE might have an impact on the national level. This study analyzes (1) the current problems in accepting RWE in (national) HTAs with the focus on clinical registry data, (2) the methods that are set out by EUnetHTA 21, and (3) the implications for upcoming national appraisals post 2025. German HTA will be analyzed here, as it can be considered one of the most rigorous national HTA within Europe.

Methods

The following analysis focuses on registry data as an example for RWE. Submitted registry data is identified by screening German HTA body (G-BA) justification of resolutions since 2011 by using the German search terms *"Registerstudie"* (study registry) and *"Registerdaten"* (registry data). The search has been conducted in March 2023. Hits were screened for relevant cases, i.e. HTA assessments in which registry data have been submitted. Reasons for acceptance or non-acceptance are extracted and categorized. European HTA standards on RWE are extracted from recently published guidelines by EUnetHTA 21.[1-4]

The conducted search does presumably not cover all assessments in which registry data have been submitted as this would require a more exhaustive search strategy, but it provides a decent overview on the handling of registry data in the German HTA context.

Figure 1: Flowchart of the conducted search for submitted RWE

Results

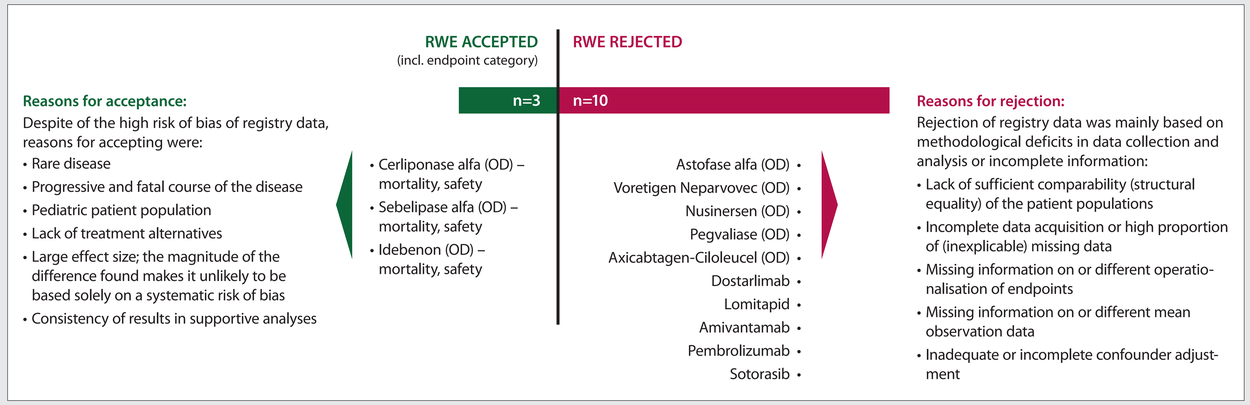

Figure 2: Overview on the 13 relevant assessments including the reasons for acceptance and non-acceptance of RWE according to G-BA[5] (OD: Orphan drug)

- The search for *"Registerstudie"* (study registry) as well as *"Registerdaten"* (registry data) yielded 22 and 18 potential assessments, respectively.
- Screening of these hits revealed 13 relevant assessments of medicinal products, for which registry data have been submitted for the German benefit assessment (8 orphan drugs, 5 non-orphan drugs).
- RWE has been predominantly presented as additional supportive data (9 assessments) or as source for unadjusted indirect comparisons (4 assessments).
- In 3 of 13 assessments (23 %), RWE has been accepted by G-BA. All three cases were orphan medicinal products (Figure 2).
- RWE has been accepted for endpoint categories mortality, morbidity and safety.

Key messages on RWE based on EUnetHTA 21 guidelines[1-4]

- The current guidelines by EUnetHTA 21 acknowledge RWE as possible data source for HTA.
- The different types of RWE, their potentials, weaknesses and methodological limitations are discussed. Few methodological guidance is provided.
- In particular, the use of registry data is encouraged by the "D5.1 Submission Dossier Guidance" document, which explicitly demands the search for relevant data in study registries and information based on these registries shall be provided in the dossier.
- As important methodological limitations for the use of RWE in HTA, the risk of bias as well as data validity are discussed in more detail.

The current EUnetHTA 21 guidelines do not give a conclusive picture of the role of RWE in the upcoming European assessments, however, its potential role is acknowledged.

Conclusion

- Acceptance of RWE in German HTA is rather the exception than the rule. Registry data, for example, have only been accepted in specific settings (e.g. rare diseases, progressive and fatal course of the disease, pediatric patient population). In the majority of cases (73 %) registry data have been rejected due to methodological aspects.
- In contrast to the "General Methods" paper by IQWiG[6], which provides the general framework for the German HTA, the EUnetHTA 21 guidelines discuss RWE as potential source for the HTA in more detail highlighting its chances and limitations including few methodological recommendations.
- Despite the known limitations of RWE data, the European HTA may open new routes of evidence demonstration, possibly influencing subsequent national HTA – at least for some countries.
- It is expected that countries with a well-established national HTA may stick to their own procedures and specifications where possible to ensure procedural consistency. This holds true especially for the rigorous German HTA.
- It remains to be seen how the European HTA will deal with RWE and whether and how this will affect national HTA.
- However, it would be very surprising to see a specific set of RWE being rejected on the national level due to methodological concerns, once it had been endorsed in the joint clinical assessment (JCA) report.

References

1: EUnetHTA 21 - Individual Practical Guideline Document, D4.3.1 Direct and Indirect Comparisons, Version 1.0, 16.12.2022, 2: EUnetHTA 21 - Individual Practical Guideline Document, D4.3.2 Direct and Indirect Comparisons, Version 1.0, 29.07.2022, 3: EUnetHTA 21 - Individual Practical Guideline Document, D4.6 Validity of Clinical Studies, Version 1.0, 16.12.2022, 4: EUnetHTA 21 - Guidance, D5.1 Submission Dossier Guidance, Version 1.0, 16.12.2022., 5: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/, 6: IQWiG – General Methods, Version 6.1 of 24 January 2022, https://www.iqwig.de/methoden/general-methods_version-6-1.pdf