Use of RWE in HTA Submissions:

A Systematic Review of Case Studies Across Three HTA Agencies Reveals Continued Concerns Around Internal Validity and Unmeasured Confounding

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Introduction

An increasing number of targeted therapies have been developed for rare diseases and / or oncology indications. For these indications, randomized controlled trials (RCTs) are often not feasible due to small patient populations or ethically challenging because of the absence of established alternative treatments and the curative potential of the new therapies. In this context, real-world evidence (RWE) is increasingly used to establish the comparative effectiveness of new drugs, either by generating an external control arm (ECA) or by providing data for the intervention at reassessment. In response, HTA agencies have defined strict evidence requirements and specific situations in which they accept RWE. Prior research shows that while there are select success cases of RWE positively influencing HTA decisions, most often RWE falls short of meeting HTA evidence requirements. Therefore, it is critical to gain a better understanding of the most common critiques from HTA agencies regarding RWE submissions as well as to draw learnings from positive cases to guide more robust and impactful RWE generation in the future.

Objective

This study aimed to provide a comprehensive analysis of the most common critiques raised by HTA agencies and the impact of RWE submissions on HTA decisions in two key contexts:

1. When RWE was submitted to construct external control arms (ECAs)
2. When RWE was used as primary data source for the intervention in HTA reassessments

Method

HTA cases involving RWE submissions from 2020-2024 in these two contexts were systematically identified. The analysis focused on three European HTA agencies: G-BA, NICE, and HAS. A total of 42 relevant cases were included. Specific critiques from HTA reports were identified and evaluated against a predefined catalogue of methodological critiques developed based on RWE guidelines and existing literature. Cases were then assessed on whether RWE was considered for the HTA decision and the extent of impact on the final HTA outcome.

Results

All identified cases where RWE was submitted to HTA bodies involved either orphan or oncology drugs, or both. While most ECA cases were retrospectively planned (81%), RWE studies submitted for the intervention in reassessments were all prospectively planned (100%). Most RWE submissions included adjusted comparisons (56%). Acceptance of RWE differed substantially across agencies, with NICE considering RWE in 93% of cases, compared to 21% at G-BA and 14% at HAS. However, the impact on outcomes was limited, with RWE submissions having a visible positive impact on HTA decisions only in 36% (NICE) and 14% (G-BA and HAS) of all cases reviewed. Most frequent critiques were unmeasured confounding (57%) and concerns about internal validity (55%). Comparing criticisms across HTA agencies revealed a high level of agreement among HTA agencies with both most frequent and least frequent critiques being the same across all three agencies. No other relevant differences among the two cases of RWE submissions were identified.

Figure 1. Most frequent critiques across both ECA and reassessment cases. Absolute frequency of critiques shown. Number of cases per HTA agency was 14.

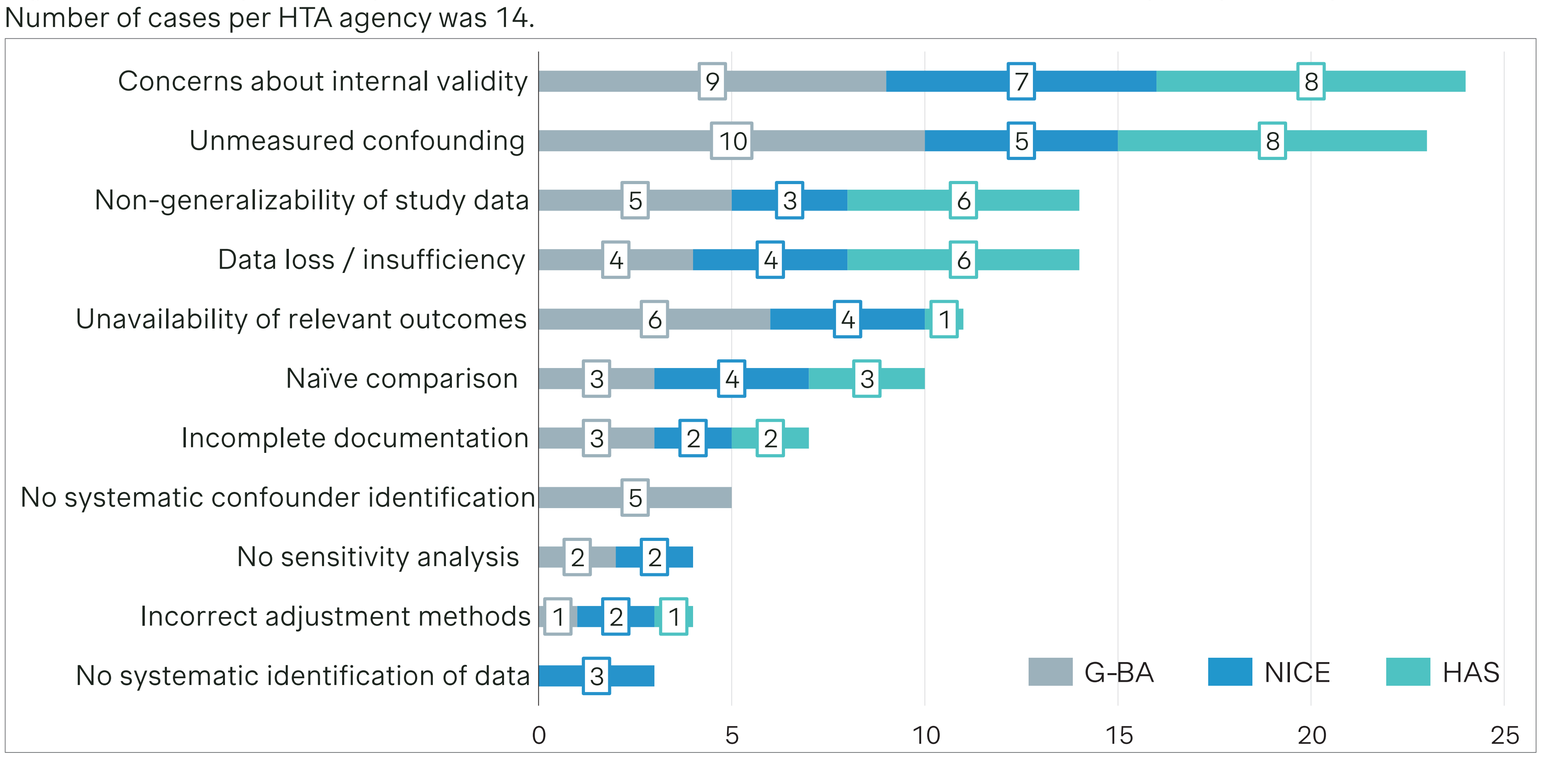
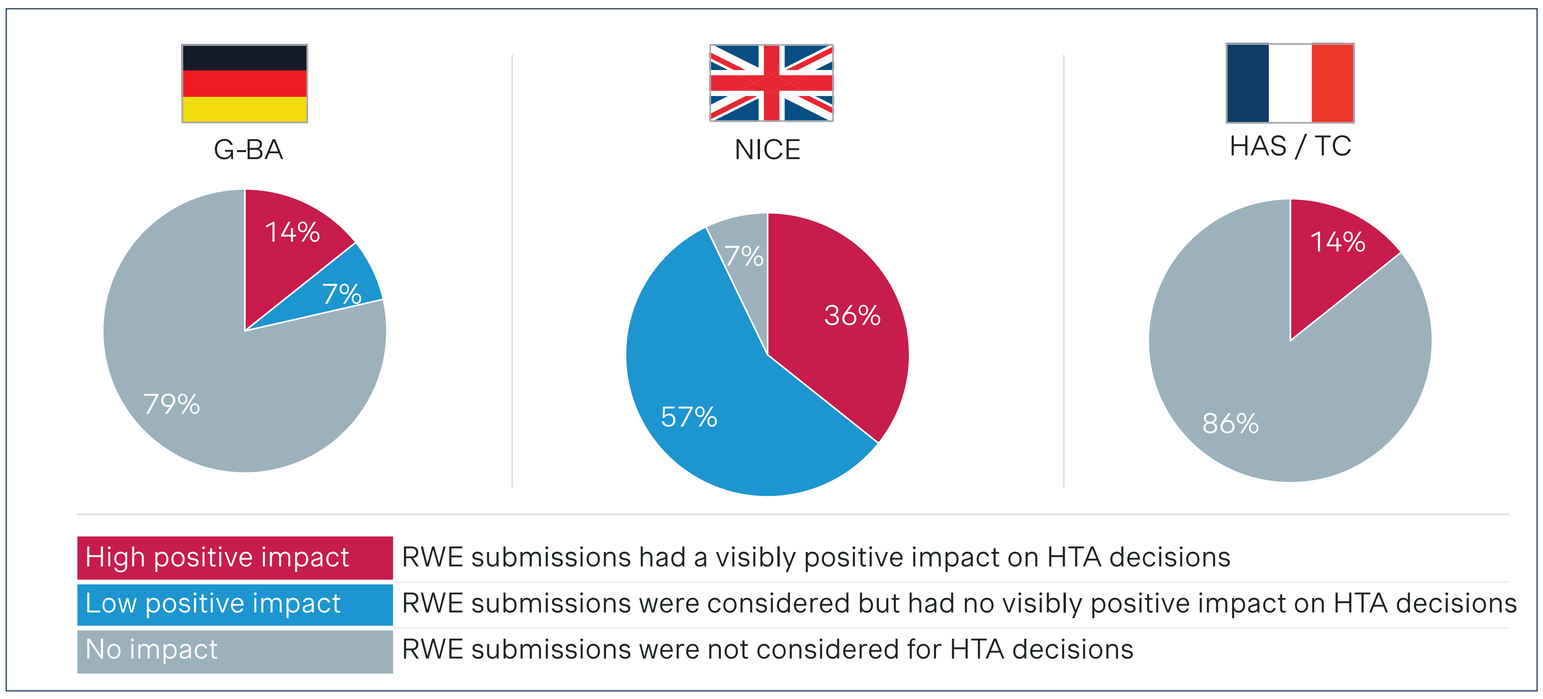


Figure 2. Impact of RWE submissions on HTA outcomes across both ECA and reassessment cases.



Conclusions

Use of RWE for comparative effectiveness remains largely confined to orphan and oncology drugs. Frequently raised methodological concerns around unmeasured confounding and internal validity continue to hinder its acceptance and influence in HTA decisions. Most ECAs are still planned retrospectively, lacking similarity to the single-arm trial population and key prognostic factors needed for robust adjusted comparisons. To strengthen future evidence generation, ECAs should be prospectively planned at the time of pivotal (single-arm) trial design, ensuring identification of high-quality data sources, alignment of inclusion criteria, and systematic selection of confounders for adjusted comparisons. Early engagement with HTA agencies is essential to confirm methodological expectations. Post-launch, registry-based evidence generation is often constrained by missing data and poor recording of relevant prognostic factors, limiting its value in HTA reassessments. Manufacturers should therefore ensure that registries are set up in a way that all relevant prognostic factors are captured to enable for robust adjusted comparisons. They should also explore the feasibility of randomized registry trials (R-RCTs), as they are encouraged by HTA agencies, carry lower risks of methodological critiques and may therefore deliver greater impact in HTA reassessments.

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Key references
Vanier et al. (2022); Wieseler et al. (2023); Akehurst et al. (2023); Jaksa et al. (2023); De Pouvourville et al. (2023); Orsini et al. (2020); Thompson (2021)