How is Real-World Evidence (RWE) Being Used in Health Technology Assessment (HTA) Decisions? Qualitative Insights from Comparisons of Three RWE Study Types Across Multiple Jurisdictions

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Background

- Real-world evidence (RWE) has been utilized in health technology assessment (HTA) submissions for decades with a focus on providing contextual information to reviewers (eg, disease burden, epidemiological studies, health economic models).
- The increasing access to real-world data (RWD) and data analytics tools, as well as advances in healthcare innovation, have increased the use of RWE in HTA submissions at both launch and re-assessment. There were 1,427 HTA global submissions involving RWE in 2011, which increased to 2,897 in 2021.[1]
- Certain types of RWE studies, such as external control arms, patient reported outcomes (PRO) studies, and retrospective studies, are increasing in use to support assessment of clinical benefit.
- However, we do not fully understand the role and impact of RWE in product recommendation, the methodological frameworks applied in evaluating RWE studies, or whether evaluation practices are common across key markets or are context specific.
- Furthermore, while countries such as the United Kingdom (UK), France, Germany, and Canada have issued guidance on RWE for HTA submissions, it is not clear to what extent HTA practices reflect these policies, and whether policies reflect recent practice.[2-5]

Objectives

- To understand HTA evaluation of three RWE study types (ie, external control study, PRO study, retrospective study) across key HTA markets.
- To identify and compare the role of these RWE study types of focus (SToF) and their evidence sufficiency/HTA treatment as factors influencing HTA product recommendations in key markets.

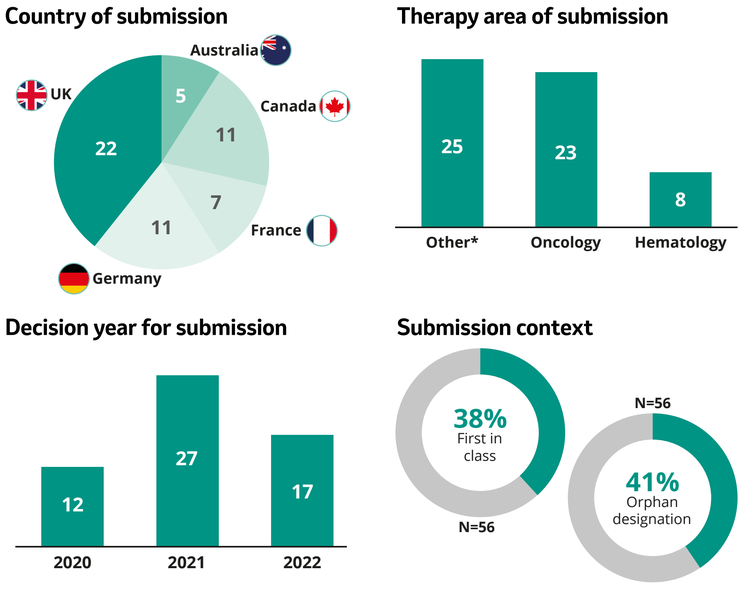
Methods

- This hybrid, 2-phase study was conducted from September–December 2022.
- Phase I consisted of a collective case study of HTA submissions across five countries/HTA agencies:
  - Australia (Pharmaceutical Benefits Advisory Committee, PBAC)
  - Canada (Canadian Agency for Drugs and Technologies in Health, CADTH, including pan-Canadian Oncology Drug Review, pCODR; Institut national d'excellence en santé et en services sociaux, INESSS)
  - France (Haute Autorité de Santé, HAS)
  - Germany (Gemeinsamer Bundesausschuss, GBA, including Institute for Quality and Efficiency in Health Care, IQWiG)
  - UK (National Institute for Health and Care Excellence, NICE)
- A database of over 22,000 HTA records covering more than 100 agencies globally (IQVIA's HTA Accelerator) was used to identify completed HTA decisions on single-drug assessments over the 5-year period of January 2018–August 2022. This was followed by a review of publicly available HTA reports and policies, in-depth coding for each case, and synthesis of study results.
- Cases were screened by RWE SToF, submission date, country, and submission type (ie, initial HTA assessment, extended indication, resubmission). Products submitted to <3 countries were excluded from the analysis. The following variables were extracted for each review case: title and date, issuing body, country/countries of submission, product, company, therapy area, reviewed indication and treatment modality, HTA submission context, and for each RWE study, the type of study, the rationale for submission, type(s) of RWD source(s) utilized, and whether and why the study was deemed not fit-for-purpose or evidentially sufficient/insufficient.
- Case review determined whether the study was explicitly cited by the HTA body as a factor in its product recommendation and whether it positively or negatively influenced the recommendation.
- Cases included RWE used for several purposes, including economic, clinical effectiveness and pharmacovigilance.
- Given the context of use and low number of 1:1 product matches across the countries of submission, a direct comparison across countries was not possible.
- Phase II consisted of twelve 1-hour telephone interviews with country-level HTA experts, selected based on their expertise and experience in HTA policies and practices in the past 5 years.
- Experts confirmed and provided context to the secondary data collected in Phase I. The interviews aimed to understand the use and role of RWE SToF in HTA product recommendations, and factors influencing these recommendations.

Results

- 49 cases (totalling 56 SToF) involving 17 products were identified: 18 cases with external control studies, 23 cases with PROs, and 15 cases with other retrospective studies (7 cases included both external control and PRO studies) (**Figure 1**).

Figure 1. Case distribution.

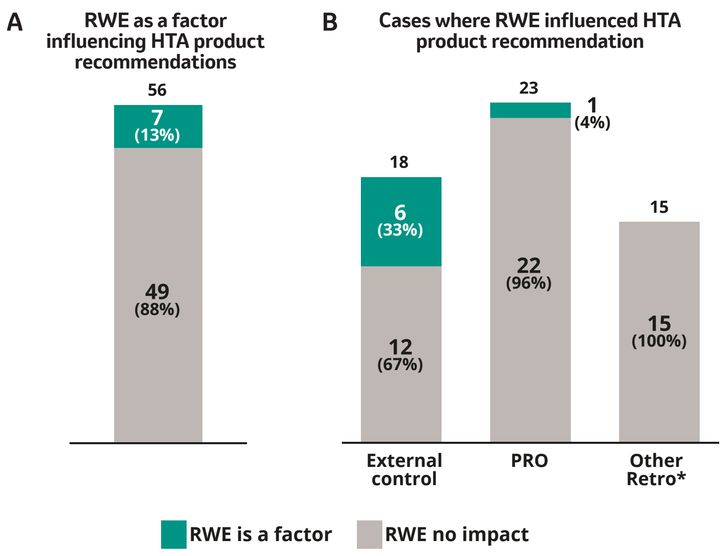


*"Other" therapy area includes atypical hemolytic uremic syndrome, anemia, desensitization prior to kidney transplant, heart failure, migraine, multiple sclerosis, treatment resistant depression, osteoporosis, and spinal muscle atrophy.

Role of Study Types of Focus in Product Recommendations

- RWE from the 3 SToF was cited as a factor in HTA product recommendations in 13% of cases; this was further confirmed through expert interviews (**Figure 2A**).
- As expected, external control studies were more likely to be cited as a factor in decision making (33% of those cases) than other SToFs (**Figure 2B**).

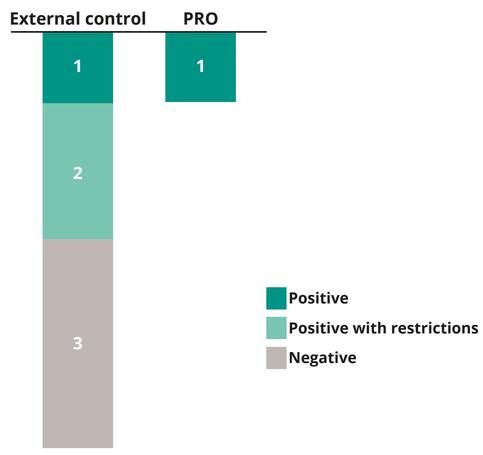
Figure 2. RWE influence on HTA product recommendations.



*"Other retro" includes retrospective chart review, retrospective electronic health record (EHR) analysis, retrospective claims analysis, retrospective cohort, and retrospective registry analysis.

- In cases where RWE was cited as a factor in HTA product recommendations, the cases were approximately evenly distributed around whether they positively or negatively influenced the recommendation (**Figure 3**).

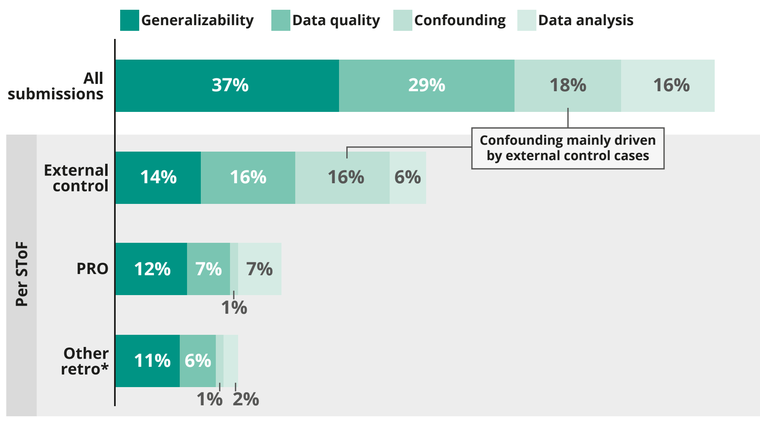
Figure 3. Product recommendations where RWE was cited as a factor by the HTA.



HTA Evaluation of RWE Studies

- 61% of external control studies, 22% of PROs, and 7% of retrospective studies were judged by the HTA to be not fit-for-purpose or otherwise analytically insufficient.
- Countries varied in the proportion of cases in which RWE studies were deemed evidentially sufficient: Australia (80%, n = 5), France (57%, n = 7), UK (50%, n = 22), Canada (45%, n = 11), and Germany (36%, n = 11).
- Generalizability and data quality were the most cited critiques across SToF (**Figure 4**).

Figure 4. Critique categories in HTA documents.



SToF: Study Type of Focus

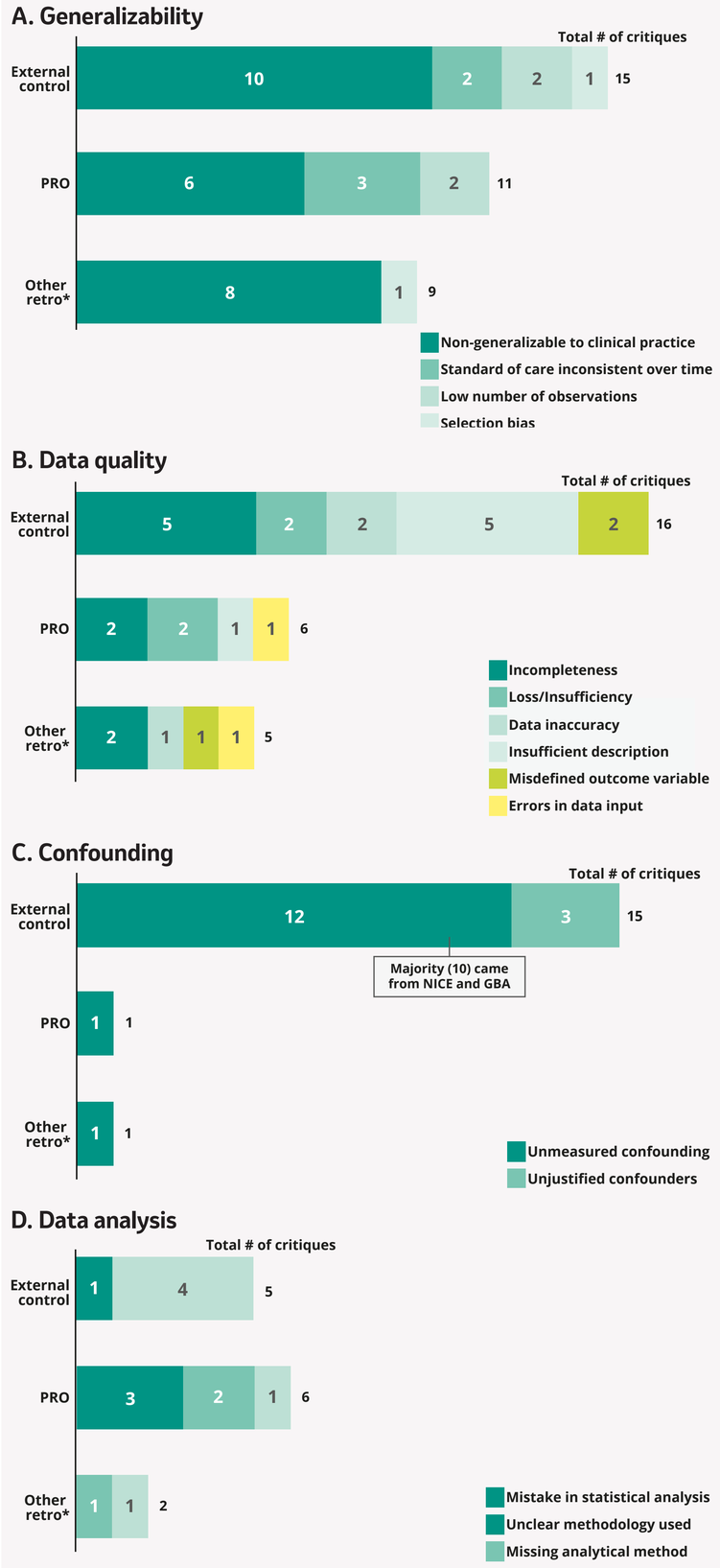
N=56. Seven of the 49 cases include more than one study type of focus and SToF is counted as such.

SToF can have more than one critique; as such, total number of concerns per SToF exceeds the number of cases.

*"Other retro" includes retrospective chart review, retrospective EHR analysis, retrospective claims analysis, retrospective cohort, and retrospective registry analysis.

- Generalizability concerns focused on the importance of matching country-specific patient cohorts and alignment with current local clinical practice (**Figure 5A**).
- Data quality concerns highlighted the importance of submitting complete and sufficiently described data—particularly for external control studies (**Figure 5B**).
- Analyzed cases and interviews confirmed that insufficient mitigation of confounding may decrease the value of external control studies in HTA review (**Figure 5C**).
- Mistakes and missing information in statistical analyses were also commonly cited as concerns (**Figure 5D**).

Figure 5. HTA critique categories.



*"Other retro" includes retrospective chart review, retrospective EHR analysis, retrospective claims analysis, retrospective cohort, and retrospective registry analysis.

Conclusions and implications

- The role and impact of RWE in HTA decisions largely depends on the study type, specific context of the submission, and the extent to which studies meet HTA expectations regarding confounding, generalizability, and data quality/analysis.
- While HTA policies regarding RWE highlight common concerns, RWE planning for HTA is encumbered by a need for greater alignment on specific issues, including acceptable study designs and data fitness-for-purpose.
- As policy and practice evolve, further research focused on a single study type and/or methodological area may allow for a deeper understanding of HTA RWE needs.
- Our findings suggest that early and iterative engagement between sponsors and HTA bodies is crucial to ensure that HTA decisions are informed by the highest-quality RWE.

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