The Role Of Real-World Evidence In European HTA For Rare Diseases: Reducing Uncertainty In Reimbursements Decisions

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Introduction

Rare diseases are characterized by small, heterogeneous patient populations, limited understanding of natural history, and substantial variability in disease progression. These features, combined with ethical and logistical constraints, often make randomized controlled trials (RCTs) difficult or infeasible to conduct, resulting in incomplete evidence at the time of health technology assessment (HTA). [1,2] This uncertainty poses significant challenges for HTA bodies and payers when assessing the clinical and economic value of new rare disease treatments, particularly in Europe, where over 30 million people are affected. Rare diseases in this region are predominantly genetic, frequently manifest in childhood, and are associated with high morbidity, premature mortality, and substantial unmet medical need. [3]

Traditional trial designs may not adequately capture long-term effectiveness, safety, quality of life, or disease progression, limiting confidence in reimbursement and access decisions.[4] In response, real-world evidence (RWE) derived from sources such as patient registries, electronic health records, claims data, and observational studies has become an increasingly important complement to clinical trial data.[5,6]

This blog provides an overview of current practices, methodological challenges, and future opportunities for integrating RWE into rare disease HTA in Europe, with a focus on reducing uncertainty and informing reimbursement and coverage decisions.

Role of RWE to Address Evidence Gaps in Rare Disease HTA submissions

RWE plays a targeted and complementary role in rare disease HTA submissions by providing essential inputs where trial evidence is limited.[5] It complements traditional trial evidence by providing insights into disease progression, long-term outcomes, and patient-centered impacts. As summarized in **Table 1**, RWE enables external comparator cohorts, informs natural history studies, provides long-term effectiveness and durability data, and captures real-world treatment patterns, resource use, and patient-reported outcomes. These contributions improve model assumptions, economic inputs, and overall uncertainty in value assessments.[7-12]

Table 1: Key RWE Contributions to Rare Disease HTA Submissions

Evidence Gaps	Targeted RWE Contributions	HTA Submission Components Strengthened
Small, heterogeneous populations **[7]**	External comparator cohorts for single-arm trials	Comparative effectiveness assessment
Limited understanding of natural history **[8]**	Disease trajectory and progression insights	Model assumptions and extrapolation
Short-term trial follow-up/immature outcomes **[9]**	Long-term effectiveness, durability, safety, and adherence data	Extrapolation and uncertainty reduction
Lack of patient-centered outcomes **[10]**	Real-world quality of life, caregiver impact data	Patient-centeredness of HTA submission
Unclear treatment patterns and resource use **[11]**	Data on diagnostic pathways, treatment patterns, healthcare utilization	Economic modeling, cost inputs, health-state transitions
High uncertainty at approval **[12]**	Post-launch evidence generation, support for managed access	Decision readiness, reduced residual uncertainty

Together, these applications strengthen the completeness and decision readiness of rare disease HTA submissions by reducing residual uncertainty and improving the reliability of value assessments.

Landscape of RWE Use in Rare-Disease HTA Across Europe

Although RWE is becoming a priority globally, expectations and acceptance vary widely across European markets. **Table 2** below highlights acceptance level, study designs, methodological expectations, and rare disease specific considerations across different HTA bodies in Europe.

European HTA bodies are increasingly open to the use of RWE, though expectations vary considerably, with countries such as the UK, Sweden, Denmark, and Italy showing greater receptivity, while Germany remains the most conservative. External comparators are widely used to support single-arm trials in many jurisdictions, and post-launch evidence requirements often through registries or conditional access mechanisms are becoming more common. Strong registry ecosystems in the UK, Sweden, Denmark, Italy, and France facilitate high quality real-world data generation. Across all markets, transparency and rigorous methodology remain essential for ensuring that RWE is deemed credible and suitable for HTA decision making.

Table 2: Landscape of RWE use in rare disease HTA submissions across Europe

Country	RWE Acceptance	Accepted Study Designs	Methodological Expectations	Rare Disease Considerations
Denmark; DMC	High	Registry based cohorts, comparative effectiveness, external controls	Causal inference, PSM/IPTW, Bayesian methods	MEAs leverage longitudinal RWE
Italy; AIFA	High	Post-marketing registries, external comparators, hybrid RCT-RWE	Bayesian models, transparency	RWE essential for MEAs and long-term follow-up
Sweden; TLV	High	Registry cohorts, external comparators, longitudinal observational	Advanced modeling, confounding control	Registries enable decades long follow-up
United Kingdom; NICE	High	External comparator arms, target trial emulation, hybrid evidence	Causal inference frameworks, Bayesian borrowing	CDF/IMF institutionalize RWE for HST
Belgium; NIHDI / RIZIV	Moderate-High	Registry studies, MEA monitoring, external comparators	Transparency, bias adjustment	Outcome based agreements highly RWE-driven
France; HAS	Moderate-High	PAS, registries, external controls, natural history	PSM/IPTW, sensitivity analyses	Flexibility for ultra-rare diseases
Netherlands; ZIN	Moderate-High	Registry based studies, pragmatic trials	PSM, IPTW, Bayesian models	Conditional reimbursement relies on RWE
Spain; AEMPS	Moderate	Observational registry/ EHR, contextualization of single-arm data	Confounding adjustments	RWE supplements limited trial evidence
Germany; G-BA, IQWiG	Low-Moderate	High quality observational, natural history, limited external controls	Strong preference for RCTs, bias validation	Orphan/ultra-orphan flexibility; required single-arm justification

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios; AIFA: Agenzia Italiana del Farmaco; CDF: Cancer Drugs Fund; DMC: Danish Medicines Council; EHR: Electronic Health Record; EMA: European Medicines Agency; EHDS: European Health Data Space; G-BA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; HES: Hospital Episode Statistics; HST: Highly Specialized Technologies; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MEAs: Managed Entry Agreements; NDRS: National Disease Registries Service; NIHDI / RIZIV: National Institute for Health and Disability Insurance (Belgium); NICE: National Institute for Health and Care Excellence; OMPs: Orphan Medicinal Products; PAS: Post-Authorization Studies; PSM: Propensity Score Matching; RWE: Real-World Evidence; RWD: Real-World Data; TLV: Tandvårds- och Läkemedelsförmånsverket (Sweden); ZIN: Zorginstituut Nederland (Netherlands)

Case studies

Table 3 presents selected rare disease therapies in Europe which secured either full or conditional reimbursement utilizing RWE evidence. The examples illustrate the diversity of therapeutic areas, data sources, and HTA approaches, highlighting how RWE can strategically address evidence gaps such as providing comparators for single-arm trials, demonstrating long-term effectiveness, and capturing patient-centered outcomes.[13]

These case studies also underscore evolving HTA trends across Europe, including the increasing acceptance of RWE for managed access, conditional reimbursement, and pricing decisions. For manufacturers and policymakers, they offer actionable insights on the types of RWE most likely to strengthen submissions, reduce uncertainty, and support evidence-driven coverage decisions in the rare disease space.

Table 3: Overview of drug therapies reimbursed utilizing RWE evidence across Europe

Drug	Country	Indication	RWE Source	Outcome	Result
Atidarsagene autotemcel	UK	MLD	Natural history studies	Comparator for survival and cognitive decline	Conditionally reimbursed (MEA)
Elosulfase alfa	Germany, France, UK, Spain, Italy	Morquio A	International/ registry cohorts, observational studies, post-marketing	Demonstrate long-term effectiveness & functional improvement	Reimbursed, but benefit often uncertain or restricted
Givosiran	UK	AHP	Global Porphyria Registry	Baseline attack rates, utility values	Recommended for routine use
Strimvelis	Italy	ADA-SCID	Historical registry cohort	Comparator due to single-arm trial	Reimbursed with pricing discount
Tegsedi	France	HTA	Real-world follow-up, TTR-FAP registry	Supplement long-term and indirect comparisons	Conditional reimbursement (ASMR IV, SMR important)

ADA-SCID: Adenosine deaminase severe combined immunodeficiency; AHP: Acute Hepatic Porphyria; HTA: Hereditary Transthyretin Amyloidosis; MEA: Managed Access Agreement MLD: Metachromatic Leukodystrophy; Morquio A: Mucopolysaccharidosis IVA; TTR-FAP: Transthyretin Familial Amyloid Polyneuropathy; UK: United Kingdom

Challenges in Using RWE for Rare Disease HTA Submissions

Despite its growing role, the use of RWE in rare disease HTA submissions faces several challenges.[2,14]

- **Fragmented and inconsistent data:** Rare disease registries often lack standardization, completeness, and interoperability, making cross country analyses difficult.
- **Small samples and missing data:** Limited patient numbers and incomplete follow-up reduce statistical power and the robustness of conclusions.
- **Confounding and bias risks:** Non-randomized study designs require careful adjustment; without rigorous methods, HTA bodies especially in conservative markets like Germany may discount findings.
- **Divergent regulatory expectations:** Countries differ in methodological and evidentiary requirements, creating a complex landscape for manufacturers preparing multi-market submissions.
- **Resource-intensive evidence generation:** High quality RWE often requires substantial time, investment, and coordination (e.g., new registries, chart reviews, prospective observational studies), potentially delaying submissions.

Best Practices for Incorporating RWE in Rare Disease HTA Submissions

To support consistent, high-quality submissions, manufacturers could confirm several best practices for generating and presenting RWE in rare disease HTA dossiers. **Table 4** summarizes key principles that help enhance methodological credibility, jurisdictional relevance, and overall acceptance by HTA bodies.

Table 4: Best Practices for RWE in Rare-Disease HTA Submissions

Practice	Key Action
Early Engagement	Align early with regulators and HTA bodies on study design, endpoints, and methods
High Quality Data	Prioritize robust registries and standardized, validated datasets
Methodological Transparency	Clearly report populations, confounders, statistical adjustments, and sensitivity analyses
Evidence Integration	Combine RWE with clinical trial data to reinforce comparative and long-term evidence
Jurisdictional Tailoring	Adapt analyses to country specific HTA expectations (e.g., France: post-launch data; Germany: design justification)
Patient-Centered Outcomes	Capture PROs, HRQOL, and caregiver burden where feasible

Collectively, these practices help ensure that RWE is generated, analyzed, and presented in a way that aligns with HTA expectations, reduces uncertainty, and strengthens the overall value proposition for rare disease therapies.

Future Outlook: The Evolving Role of RWE in Rare Diseases

The regulatory and HTA landscape is evolving, positioning RWE as increasingly central in rare disease decision making. EU-level initiatives, such as the European Health Data Space, aim to standardize and facilitate cross-border healthcare data use, enhancing RWE availability and quality.[15] The expansion of digital health technologies, including wearables and remote monitoring, will generate high frequency real-world data suited to diseases with variable progression.[16] Hybrid evidence packages integrating RCT data with RWE through Bayesian or mixed models are gaining acceptance by regulators and HTA bodies.[17] RWE is also expected to play a larger role in conditional approvals and managed access programs, supporting post-launch monitoring and pricing reassessments. Finally, patient advocacy and co-created registries are increasingly generating natural history and outcomes data, improving relevance, completeness, and patient-centered insights, further strengthening the evidence base for rare disease therapies.[17]

Conclusion

RWE is rapidly reshaping how rare disease therapies are evaluated across Europe, helping fill persistent evidence gaps and strengthen HTA decision making. While expectations and methodological requirements vary across jurisdictions, the trend toward increased acceptance is clear. As regulators and HTA bodies continue to refine their expectations, high quality data, transparent methods, and early engagement will remain essential. With emerging data infrastructures, digital health tools, and growing acceptance of hybrid evidence packages, the role of RWE will only expand supporting timelier, informed, and patient-focused access to innovative treatments for rare diseases.

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