HTA293

Role of Real-World Evidence (RWE) in Pricing and Reimbursement Decisions for Rare Disease Health Technology Assessment (HTA) Submissions across EU4 + UK

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Background

- Rare diseases pose unique challenges for health technology assessment (HTA) including small patient populations, heterogeneous presentations, and limited evidence from randomized controlled trials (RCT). These constraints often lead to significant evidence gaps in demonstrating the clinical and economic value of emerging therapies.[1,2]
- Real-world evidence (RWE), derived from sources such as registries, electronic health records, and observational studies, has emerged as an important evidence source, complementing traditional clinical trial data.[3]
- RWE can provide insights into treatment effectiveness, long-term outcomes, quality of life, and healthcare resource utilization, thereby strengthening the evidence base for decision-making.[2]
- Increasingly, RWE is being incorporated into HTA submissions to support pricing and reimbursement (P&R) decisions, particularly in the context of rare diseases where conventional evidence may be insufficient.[2,4]
- Understanding how to incorporate RWE in HTA evaluations across different jurisdictions may result in timely patient access to innovative therapies for rare diseases.[5]

Objective

To assess the role of RWE in HTA decision making for rare disease therapies across EU4 (Germany, France, Italy, and Spain) and the United Kingdom (UK).

Methods

- **Data collection:** A targeted literature review was conducted from 2014–2025 for published HTA appraisals (national HTA agencies) and peer-reviewed PubMed articles across EU4 (France, Germany, Italy, and Spain) and the UK.[6-11]
- **Inclusion criteria:** Therapies with European Medicines Agency (EMA) orphan drug designation that explicitly incorporated RWE to inform P&R decisions.
- **Qualitative Analysis:** Data on the type and source of RWE (e.g., registries, observational studies, electronic health records) were extracted, and its use in HTA decision-making (e.g., clinical effectiveness, cost-effectiveness, budget impact) was evaluated, with cross-jurisdictional comparisons conducted to identify patterns in RWE sources, analytical approaches, and their impact on reimbursement decisions.

Results

- Sixteen rare disease therapies received approval for reimbursement across EU4 + UK (**Figure 1**), including NICE (UK, n=8), HAS (France, n=6), G-BA/IQWiG (Germany, n=6), AIFA (Italy, n=5), and AEMPS/AETS (Spain, n=7).
- Neurological disorders (**Table 1**) were the most common therapeutic indications (n=8). Gene therapies represented the largest proportion (n=4), followed by enzyme replacement therapies (n=3), and antisense oligonucleotides (n=3) (**Figure 2**).
- Key RWE sources included patient registries (n=10), natural history or historical comparator studies (n=6), and observational or post-marketing studies (n=5).
- These RWE sources were primarily used to provide external comparators for single-arm trials (n=9), demonstrate long-term effectiveness (n=3), safety/post-marketing effectiveness (n=2), utility/economic outputs (n=2).
- Two therapies achieved reimbursement in all five markets, supported in part by RWE: onasemnogene abeparvovec and elosulfase alfa.
- Since 2019, RWE use has increased to address clinical & economic uncertainties (drugs assessed, pre-2019: 6, post-2019: 10)
- In 44% of cases (n=7/16), RWE was pivotal for full or positive reimbursement; in others, it supported conditional reimbursement or restricted access (37%; n=6/16).
- NICE and AEMPS showed greater acceptance of RWE, incorporating natural history data and external comparators. AIFA leveraged RWE via outcome-based agreements and registries. HAS used RWE for re-evaluations or broad reimbursement, while G-BA remained more restrictive, accepting RWE mainly for ultra-rare conditions.

Figure 1: Geographical distribution of reimbursed rare disease therapies

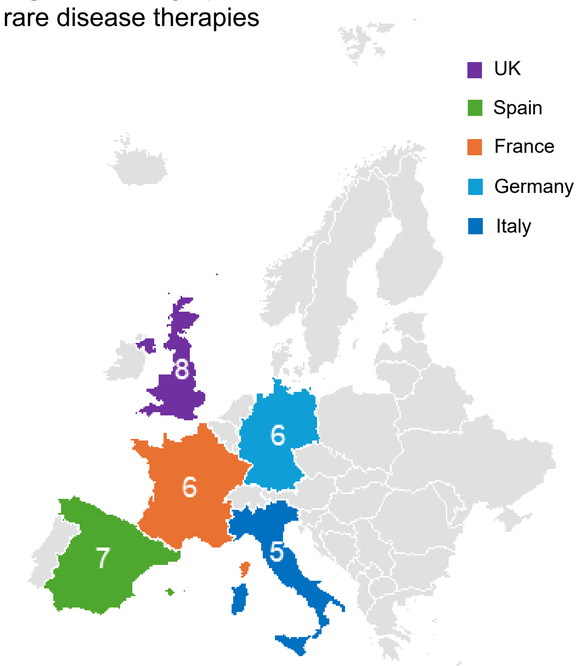

Figure 2: Therapeutic categories seen across reimbursed drugs

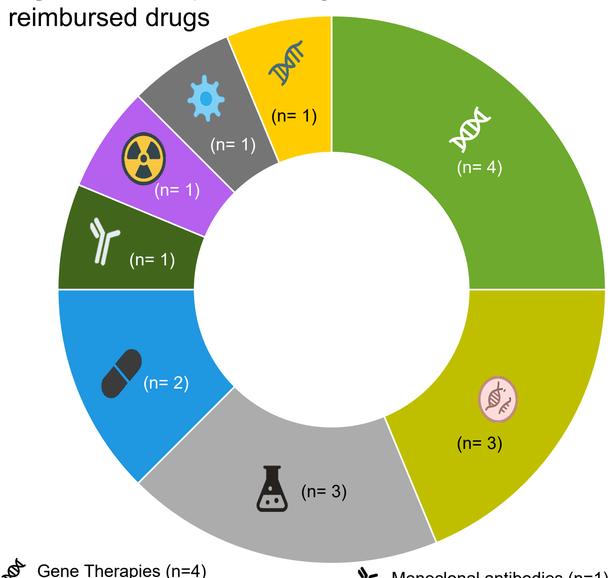

Table 1: Overview of drug therapies approved for reimbursement utilizing RWE evidence across EU4 + UK

Drug	Countries (Year of approval)	Regulatory Agency	Indication	CC	RWE Source	Outcome	Result
Alglucosidase alfa	France (2020), Germany (2006 & 2020)	HAS, GBA	Pompe disease	Neurological	French Pompe registry, disease registries, natural history cohorts	Long-term outcome and disease progression vs. untreated populations	Reimbursed/added benefit acknowledged (with limitations)
Ataluren	Germany (2014, reassessed 2018)	GBA	nmDMD	Neurological	Longitudinal registry data	Support delay in functional decline vs. natural history	No added benefit recognized
Atidarsagene autotemcel	UK (2022)	NICE	MLD	Neurological	Natural history studies	Comparator for survival and cognitive decline	Conditionally reimbursed (Managed Access Agreement)
Cerliponase alfa	UK (2019), Italy (2019), Spain (2019)	NICE, AIFA, AEMPS/AETS	CLN2 Batten disease	Neurological	DEM-CHILD, CLN2 registries (EU/US)	Natural history comparators for progression	Reimbursed with restrictions/conditional agreements
Eculizumab	Germany (2014), France (2015), Spain (2016)	GBA, HAS, AEMPS/AETS	aHUS	Hematologic/immunologic	Global/International aHUS registry, historical controls	Comparator for renal outcomes, dialysis use, TMA events	Added benefit recognized; reimbursed
Elosulfase alfa	Germany (2015), France (2015), UK (2020), Spain (2015), Italy (2016)	GBA, HAS, NICE AEMPS/AETS, AIFA	Morquio A	Metabolic syndrome	International/registry cohorts, observational studies, post-marketing	Demonstrate long-term effectiveness and functional improvements	Reimbursed, but benefit often uncertain or restricted
Givosiran	UK (2020)	NICE	AHP	Metabolic syndrome	Global Porphyria Registry	Baseline attack rates, utility values	Recommended for routine use
Lutetium (177Lu) Oxodotreotide	Spain (2017+)	AEMPS/AETS	GEP-NETs	Oncology	ERASMUS cohort (1,200+ patients)	Real-world safety and effectiveness post-launch	Reimbursed, supported by RWE
Nusinersen	Germany (2018), France (2018), Spain (2018), UK (2019)	GBA, HAS, AEMPS/AETS, NICE	SMA Types 1–3	Neurological	Global SMA registry (TREAT-NMD), expanded access, national cohorts	Reinforce survival and motor function benefits; supplement limited trial data	Accepted/reimbursed, mostly conditional with reassessment
Onasemnogene abeparvovec	Germany (2020), France (2020), Italy (2021), Spain (2021), UK (2021)	GBA, HAS, AIFA, AEMPS/AETS	SMA Type 1	Neurological	SMA registries (PNCR, TREAT-NMD)	External comparators for survival/milestones due to lack of RCTs	Reimbursed (conditional, outcome-based in Spain)
Strimvelis	Italy (2017)	AIFA	ADA-SCID	Hematologic/immunologic	Historical registry cohort	Comparator due to single-arm trial	Reimbursed with pricing discount
Tabelecleucel	Spain (2023–24)	AEMPS/AETS	EBV+ PTLD	Oncology	EAP RWD; retrospective/natural history	Effectiveness and safety in RW setting	Conditional approval based on RWE
Tegsedi	France (2019)	HAS	HTA	Mixed	Real-world follow-up, TTR-FAP registry	Supplement long-term and indirect comparisons	Conditional reimbursement (ASMR IV, SMR important)
Viltolarsen	UK (2022)	NICE	DMD (exon 53 skipping)	Neurological	CINRG & natural history registries	External control for motor outcomes	Not recommended
Volanesorsen	UK (2021)	NICE	FCS	Lipid disorder	UK EAP, case series	Frequency of pancreatitis, QOL impact	Not recommended
Voretigene neparvovec	Italy (2020)	AIFA	RPE65-mediated inherited RD	Neurological	AIFA Monitoring Registries + clinical cohort	Post-marketing follow-up	Reimbursed with follow-up obligation

ADA-SCID: Adenosine deaminase severe combined immunodeficiency; AHP: Acute Hepatic Porphyria; aHUS: Atypical Hemolytic Uremic Syndrome; CC: Clinical category; CINRG: The Cooperative International Neuromuscular Research group; DEM-CHILD: Patient database; EAP: Early Access Program; EBV: Epstein-Barr Virus; ERASMUS: EU programme for education, training, youth and sport; FCS: Familial Chylomicronaemia Syndrome; GEP-NETs: Gastroentero-pancreatic neuroendocrine tumors; HTA: Hereditary Transthyretin Amyloidosis; MLD: Metachromatic Leukodystrophy; Morquio A: Mucopolysaccharidosis IVA; nmDMD: Duchenne Muscular Dystrophy; PNCR: Pediatric Neuromuscular Clinical Research Network; PTLD: Post-Transplant Lymphoproliferative Disorder; SMA: Spinal Muscular Atrophy; QOL: Quality of Life; RCTs: Randomized Controlled Trials; RD: Retinal dystrophy; RW: Real world; RWE: Real world evidence; TMA: Thrombotic Microaniopathy; TREAT-NMD: Global network of experts in the neuromuscular field; UK: United Kingdom; US: United States

Neurological · Lipid disorder · Oncology · Metabolic syndrome · Hematologic/immunologic

Conclusions

- HTA bodies primarily accept RWE to inform external comparator analyses or to supplement clinical effectiveness data in rare disease therapies.
- However, the degree of acceptance varies across agencies and may become more harmonized with the implementation of the EU Joint Clinical Assessment (EU-JCA).

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