Navigating RWE Strategies in HTA Submissions for Ultra-Rare Diseases in Key European Healthcare Systems

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Background and Objective

- Health Technology Assessment (HTA) agencies increasingly use real-world evidence (RWE) to evaluate medical products post-registration. Patient registries complement clinical trial data by providing insights into real-world practice.
- Ultra-rare diseases present unique challenges for conducting conventional clinical trials, making RWE essential for HTA submissions. RWE can bridge evidence gaps and support reimbursement decisions in key European markets.
- **OBJECTIVE:** This study aims to assess the acceptability of RWE by agencies for ultra-rare conditions, specifically focusing on NICE, HAS, and G-BA.

Methods

- We reviewed NICE evaluations of highly specialized technologies (HST) from 2021 to 2023 for medications treating ultra-rare conditions.
- Submissions for the same indications were examined in G-BA and HAS databases.
- Study designs included all types of RWE (e.g., natural history studies, observational studies, chart reviews) and indirect treatment comparison (ITC) techniques, such as population-adjusted methods (e.g., propensity score matching, inverse probability weighting).
- Two reviewers independently evaluated the submission justifications regarding the use of RWE strategies and the resulting recommendations.

Results

- Reports on fifteen drugs targeting ultra-rare conditions were reviewed across NICE, HAS, and G-BA. RWE studies, including historical cohorts, retrospective observational studies, registries and chart reviews, were accepted as evidence in submissions to NICE (13/15), HAS (12/15), and G-BA (12/15).
- Unadjusted comparison methods were predominantly used across submissions (NICE: 10/15, HAS: 11/15, G-BA: 11/15), whereas adjusted ITC methods, such as propensity score matching and inverse probability weighting, were applied less frequently (NICE: 4/15, HAS: 3/15, G-BA: 3/15).
- Most reports used natural history studies (70%) as external controls for RWE, followed by long-term real-world data (RWD) and patient-reported outcome (PRO) or surrogate endpoints (Table 1).
- Positive recommendations varied across agencies: NICE issued mostly positive recommendations (14/15), while HAS frequently recognized moderate ASMR III (6/15) or minor ASMR IV (6/15) added benefit. In contrast, G-BA was more selective, with a lower acceptance rate (6/15), often reflecting a demand for quantifiable evidence and concerns over patient-relevant endpoints in historical comparisons (Table 1).
- Furthermore, HTA agencies noted several limitations with the RWE strategies employed, including reliance on non-comparative methodologies, inadequate patient-relevant endpoints, and insufficient confounding adjustments. These findings highlight the need for more comprehensive real-world data to supplement short-term evidence and provide long-term findings.

Table 1: Inclusion of RWE in HTA for ultra-rare diseases and the outcomes of the assessment

Drug name (*Indication*)	RWE used			Naïve comparison			ITC			Type of RWE			HTA outcomes					
	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE
Afamelanotide (*EEP*)	✓	✓	✓	✕	✕	✕	✕	✕	✕	PRO endpoint			Not Recommended	ASMR IV	Low			
Asfotase alfa (*HPP*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Natural history study; Long-term RWD			Recommended	ASMR II	No added benefit			
Ataluren (*DMD*)	✓	✓	✓	✕	✓	✓	✓	✕	✕	Long-term RWD			Recommended	ASMR V	Minor			
Atidarsagene autotemcel (*MLD*)	✓	✓	✓	✕	✕	✕	✓	✓	✓	Natural history study			Recommended	ASMR III	Major			
Eladocagene exuparvovec (*AADC*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Natural history study			Recommended	ASMR III	No added benefit			
Elosulfase alfa (*MPS IV-A*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Natural history study			Recommended	ASMR IV	Low			
Givosiran (*AHP*)	✕	✕	✕	✕	✓	✓	✓	✕	✕	N/A			Recommended	ASMR II	Moderate			
Lumasiran (*PH1*)	✕	✕	✕	✓	✓	✓	✕	✕	✕	N/A			Recommended	ASMR III	No added benefit			
Metreleptin (*Lipodystrophy*)	✓	✓	✓	✕	✕	✕	✓	✓	✓	Natural history study; Surrogate endpoints			Recommended	ASMR IV	No added benefit			
Odevixibat (*PFIC*)	✓	✕	✕	✓	✓	✓	✕	✕	✕	Natural history study			Recommended	ASMR III	Minor			
Onasemnogene abeparvovec (*SMA*)	✓	✓	✓	✓	✕	✕	✕	✓	✓	Natural history study; Long-term RWD			Recommended	ASMR III	No added benefit			
Sebelipase alfa (*WD*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Natural history study			Recommended	ASMR III	No added benefit			
Selumetinib (*PN-NF1*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Natural history study			Recommended	ASMR IV	No added benefit			
Setmelanotide (BBS)	✓	✓	✓	✓	✓	✓	✕	✕	✕	PRO endpoint			Recommended	ASMR IV	No added benefit			
Velmanase alfa (*Alpha-mannosidosis*)	✓	✓	✓	✓	✓	✓	✕	✕	✕	Surrogate endpoints; Long-term RWD			Recommended	ASMR IV	No added benefit			

Abbreviations: AADC: Aromatic L-amino acid decarboxylase deficiency, AHP: Acute hepatic porphyria, BBS: Bardet-Biedl syndrome, DMD: Duchenne muscular dystrophy, EPP: Erythropoietic protoporphyria, HPP: Paediatric-onset hypophosphatasia, MLD: Metachromatic leukodystrophy, MPS IV-A: Mucopolysaccharidosis type 4A, N/A: Not Applicable, PF-NF1: Plexiform neurofibromas associated with type 1 neurofibromatosis, PFIC: Progressive familial intrahepatic cholestasis, PH1: Primary hyperoxaluria type 1, SMA: Spinal muscular atrophy, WD: Wolman disease

Comparison with historic assessments

Previous HTAs for the same therapeutic indications and products were thoroughly evaluated for their outcomes. This retrospective analysis is particularly significant for HAS in France, where two products showed a decrease in their ASMR ratings :

- **Ataluren**: ASMR rating decreased from ASMR IV in 2015 to ASMR V in 2019
- **Elosulfase alfa**: ASMR rating decreased from ASMR III in 2014 to ASMR IV in 2023

RWE was used in both historical and current assessments, with no changes in the RWE data observed. This indicates that the decrease in ASMR ratings was not influenced by RWE. These outcome changes suggest that other factors, such as new clinical data or an evolving treatment landscape, may have played a more significant role in the reassessment.

Acceptance of ITC methods by HTA agencies (*Table 2*):

- **NICE:** Accepts all forms of ITC methods, with a preference for adjusted ITCs, but will consider unadjusted or other ITC techniques if a clear rationale is provided.
- **HAS**: Prefers adjusted ITC methods and is more selective about accepting other ITC methods.
- **G-BA**: Has limited acceptance of any ITC methods, particularly unadjusted ITCs, requiring strong justification.

Table 2: Acceptance of ITCs by NICE, HAS and G-BA

HTA body	Country	Adjusted ITCs	Unadjusted ITCs	Other ITCs
NICE	UK	✓	✓	✓
HAS	France	✓	—	—
G-BA	Germany	—	—	—

Conclusion

- This study reveals significant differences in RWE acceptance among major European HTA agencies. NICE and HAS demonstrate flexibility in evaluating treatments for ultra-rare diseases given data constraints, while G-BA maintains stringent criteria for robust evidence.
- Additionally, this analysis reveals that the same products may be valued differently across countries, highlighting significant variations in health authorities' perception of the added value of therapies, even when similar data sets are used.
- To address these disparities, harmonizing guidelines and enhancing RWE integration are essential to improve HTA processes and outcomes for ultra-rare diseases across Europe.
- Further research should focus on aligning HTA practices and optimizing the use of RWE in clinical and regulatory decision-making.

References

1. National Institute for Health and Care Excellence Appraisals (HST27, HST23, HST22, HST18, HST26, HST19, HST16, HST25, HST14, HST17, HST15, HST24, HST30, HST20, HST31, HST29);
2. Haute Autorité de Santé Appraisals;
3. Gemeinsamer Bundesausschuss Appraisals

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