Understanding the role of real-world evidence in health technology assessment for orphan drugs

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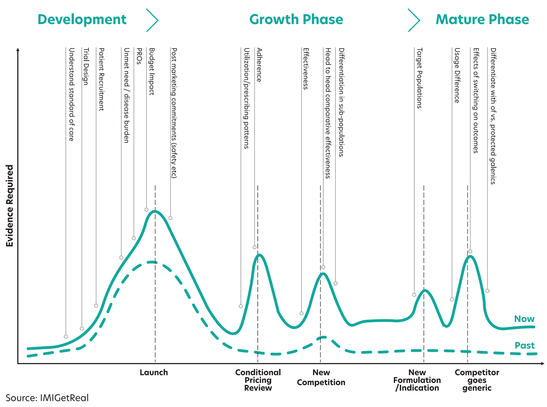
Background

Real word evidence (RWE) is data that are collected from sources other than randomized controlled trials (RCTs) or trial evidence-syntheses.

Historically, RWE was seen as 'weaker' than RCT data. However, use and acceptance of RWE has increased and broadened in scope in recent years (Figure 1). RWE is valued by regulators as a basis for regulatory decision-making, including approval of new indications for licensed drugs, as seen in the 21st Century Cures Act (2016)[1], and EMA adaptive pathways[2]. RWE is accepted by health technology assessment (HTA) agencies and payers in HTA submissions. Pharmaceutical companies increasingly use RWE to provide effectiveness or safety data in HTA submissions or reimbursement negotiations.

Figure 1: RWE throughout product lifecycle



Source: IMIGetReal

RWE is often especially useful for orphan drug HTA because data in the literature or collected as part of RCTs can be sparse. RWE can supplement evidence from conventional RCTs or non-controlled trials, or act as an alternative if RCT data are not available.

Objective

This study sought to understand the positioning of HTA guidance documents and current role of RWE in HTA for orphan drug/highly specialized technology (HST) submissions.

Method

The UK National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH) guidance documents on use of RWE[3,4] were reviewed.

Orphan drug HTA case studies in asfotase alfa (AA) for pediatric-onset hypophosphatasia and elosulfase alfa (EA) for mucopolysaccharidosis type IVa were compared to explore how guidance was being implemented. These case studies were chosen as they had clear RWE included in both the NICE and CADTH submissions, and also included managed entry agreements (MEAs) that included a requirement to collect RWE.

Results

HTA guidance

Draft CADTH guidance notes that RWE has value in supporting regulatory and reimbursement decision-making. It identifies situations within orphan drug development where RCT evidence may not be available and RWE could be a suitable alternative.

NICE guidance notes that RWE can be an acceptable source of evidence to inform estimates of treatment effect for cost-effectiveness analysis, as a complement to RCTs or as the sole source of data.

HTA outcomes

The NICE technology appraisals for EA and AA were undertaken via the HST pathway. In Canada, both products underwent the CADTH Common Drug Review. Both NICE and CADTH accepted EA and AA with restrictions, additional criteria, or MEAs (Table 1).

Table 1: Orphan drug HTA case studies

Drug	Agency and assessment details	Assessment and outcome
Asfotase alfa	NICE (United Kingdom) HST6[5] August 2017vv	Recommended with an MEA and confidential commercial terms
	CADTH (Canada) SR0443[6] July 2015	Recommended with clinical criteria and conditions
Elosulfase alfa	NICE (United Kingdom) HST2[7] December 2015	Recommended with an MEA
	CADTH (Canada) SR0389[8] March 2015	Rejected
	CADTH (Canada) SR0456[9] May 2016	Recommended with clinical criteria and conditions

The RWE accepted by NICE and CADTH is summarized below.

Table 2: RWE included in HTA submissions

Drug	Agency	Natural history study	Survey
Asfotase alfa	NICE (United Kingdom)	Three natural history studies	
	CADTH (Canada)		
Elosulfase alfa	NICE (United Kingdom)	Natural history observational study	Surveys of patients and their families
	CADTH (Canada)		

The NICE Evidence Review Group concluded that using natural history data for AA was necessary in economic modelling, but adjustment for potential biases was required. Similarly, the natural history observational study used in submissions for EA provided demographic and disease characteristics for cost-effectiveness modelling for both NICE and CADTH.

In the NICE submission for EA, surveys of patients and their families contributed quality-of-life, caregiver burden, and cost data. The RWE was accepted by NICE as an evidence source to calculate utility scores.

Managed entry agreements

In the cases of both EA and AA, NICE's recommendations were conditional on the collection of additional RWE within MEAs, and evidence development to inform subsequent re-assessment. For EA, the MEA specified collecting data via a 12-year disease registry specified by the European Medicines Agency as part of marketing authorization. In contrast, the MEA data collection strategy for AA was designed specifically for the HTA agency's requirements, to assess the clinical impact of AA on patient outcomes.

CADTH also specified RWE collection for EA, through a manufacturer-sponsored registry.

Discussion

RWE can help gain a better understanding of the population who will receive a medicine, *i.e.*, patient and disease characteristics. It can also provide information on the relative effectiveness of medicines for both patients and their carers, including impacts on quality-of-life and activities of daily living.

MEAs – often coupled with conditional reimbursement and a risk-sharing agreement - are frequently developed due to uncertainty in the data package. MEAs collect RWE to better understand these areas of uncertainty, with the intention to monitor performance in the real world or reassess the technology after evidence is generated.

Conclusions

The use of RWE is important for reimbursement decisions and market access. Its use now goes beyond the historical focus on epidemiological, resource-use, and cost data.

RWE is valuable in both initial HTA assessment of a medicine presented by the sponsor, and/or may be collected after reimbursement (*i.e.*, through an MEA).

References

1 US Government. *PUBLIC LAW 114–255—13* December 2016

2 EMA. *Final report on the adaptive pathways pilot*. 28 July 2016

3 NICE DSU. *Technical support document 17: the use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data*. May 2015

4 CADTH. *Defining decision-grade real-world evidence and its role in the Canadian context: A design sprint: summary report of a workshop*. October 21, 2018

5 NICE. *Asfotase alfa for treating paediatric-onset hypophosphatasia. HST6*. 2 August 2017

6 CADTH. *Asfotase alfa. SR0443-000*. 20 July 2015

7 NICE. *Elosulfase alfa for treating mucopolysaccharidosis type Iva. HST2*. 16 December 2015

8 CADTH. *Elosulfase alfa. SR0389*. 5 August 2014

9 CADTH. *Elosulfase alfa. SR0456-000*. 1 October 2014

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