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Differential appraisal of functional outcome measures by health technology assessment (HTA) agencies when reviewing therapies for rare muscular, skeletal and neurodegenerative disorders

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INTRODUCTION

- Despite recent advances in rare disease research, only 5% of identified rare diseases have an effective treatment option.[1]
- Obtaining market authorisation does not guarantee that the product will be reimbursed. Payers may require additional clinical and economic assessment via a health technology assessment (HTA) process.
- Rare diseases often result in a wide spectrum of disabilities. However, scientific information on how these disabilities occur mechanistically is lacking, which renders the evaluation of drugs aimed to treat such conditions challenging.
- Sensitive and valid clinical endpoints serve as essential tools to measure improvements in patients' physical and functional wellbeing, to capture multiple domains of complex and heterogeneous diseases. Payers evaluate these as a critical part of the HTA process to decide the overall effectiveness and value of a potential treatment.[2]

OBJECTIVES

- To understand how European HTA bodies appraise the applicability of functional measures to assess the following rare disease treatments: ataluren for Duchenne muscular dystrophy (DMD), elosulphase alfa for mucopolysaccharidosis type IVa (MPS IVa), and asfotase alfa for paediatric onset hypophosphatasia (HPP).

METHODS

- Targeted searches were conducted of publicly available appraisals from the UK (National Institute of Health and Care Excellence [NICE], All Wales Medicines Strategy Group [AWMSG], Scottish Medicines Consortium [SMC]), Spain (Spanish Agency of Medicines and Medical Products [AEMPS]), Sweden (Swedish Agency for Health Technology Assessment and Assessment of Social Services [SBU], The Dental and Pharmaceutical Benefits Agency [TLV], Västra Götaland Regional Council [VGR]), The Netherlands (National Health Care Institute [ZIN]), Germany (Federal Joint Committee [G-BA]), Italy (Italian Medicines Agency [AIFA]) and France (French National Authority for Health [HAS]) for the products ataluren, elosulfase alfa and asfotase alfa treating the above disorders.

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RESULTS

- European HTA bodies differentially appraised the benefit of ataluren, elosulfase alfa, and asfotase alfa (**Table 1**).
- The HTA bodies evaluated various functional measures differentially for their relevance and effectiveness (**Table 2**):[3–23]
  - The 6-minute walk test (6MWT) was considered an appropriate assessment tool by NICE and AEMPS, with TLV's experts indicating that the 6MWT has become an established measure of effectiveness. ZIN also recognised 6MWT as an important outcome measure in MPS IVa and DMD. The G-BA considered 6MWT a relevant outcome measure for DMD and MPS IVa, but not for HPP
  - Forced vital capacity (FVC) as a pulmonary function measure was accepted by NICE and considered an important determinant of clinical outcomes for MPS IVa
  - The 3-minute stair climb test (3MSCT) was considered a valid measure in MPS IVa by ZIN but was questioned by G-BA
  - The North Star Ambulatory Assessment (NSAA) and Time to Get Up and Stand (TTGUS) or 10-metre run are often used in clinical practice as per NICE documentation in the UK but considered less relevant than 6MWT in DMD by NICE.

Table 1. Reimbursement decision by HTA bodies

	Ataluren	Elosulfase alfa	Asfotase alfa
NICE	✓ *†	✓	✓
AWMSG	✓ †	✓	⊖
SMC	✓ ‡§	✗	⊖
AEMPS	✗	✗	✗
TLV	✓ **	⊖	⊖
VGR	⊖	⊖	⊖
ZIN	✗	✗	✓
G-BA	✓ †	✓ ††	✓ ‡‡
AIFA	⊖	⊖	⊖
HAS	✓ **	✓	✓

*Conditionally approved by NICE for 5 years in 2016.†DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged ≥5 years; ‡DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 2 to <5 years; §via ultra-orphan pathway; **DMD resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged ≥2 years; ††low additional benefit; ‡‡unquantifiable benefit.
✓, Accepted; ✗, Rejected; ⊖, The drug has not been assessed by the respective HTA.

Table 2. Summary overview of HTA judgement on functional measures[3–23]

Functional measure	HTA	Positive consideration	Negative consideration
6MWT	NICE	• Considered broadly appropriate to assess the benefits of treatment • Provides some indication of real-life treatment benefits in patients (MPS IVa) • Provides a broad measure of overall functioning in patients (MPS IVa) • Observed improvements in 6MWT during clinical trials correspond to real-world improvements in clinical outcomes and quality of life (MPS IVa)	• Not routinely used in clinical practice (DMD, HPP) • May not be relevant for assessing clinical outcomes or quality of life (HPP)
	SMC	• Considered broadly appropriate to assess the benefits of treatment • No other single endpoint with potentially greater sensitivity could be identified when the study was designed	• Provides an indirect measure of endurance and functionality in DMD and MPS IVa, but does not provide a direct measure of treatment efficacy on survival (MPS IVa)
	AEMPS	• Considered broadly appropriate to assess the benefits of treatment	• It has low specificity and can be influenced by external factors (DMD) • It has wide variability with respect to baseline values (DMD)
	TLV	• Considered broadly appropriate to assess the benefits of treatment	
	G-BA	• Considered a relevant treatment (DMD or MPS IVa)	• Cannot be used to assess treatment benefit (HPP)
	ZIN	• Considered broadly appropriate to assess the benefits of treatment • Recognised as crucial outcome measure (MPS IVa, DMD) • Routinely used in clinical practice (DMD) • Correlated with the physical domain of quality of life (DMD)	
FVC	NICE	• Important determinant of clinical outcomes for patients (MPS IVa)	
3MSCT	G-BA		• Considered unsuitable for patients (MPS IVa)
	ZIN	• Recognised as a crucial outcome measure (MPS IVa)	
Wheelchair use	NICE	• Informative outcome (MPS IVa)	
	AEMPS	• Particularly relevant to assess the impact on daily life, together with muscle strength and speed in performing certain tasks (DMD)	
	TLV		• Uncertainty increases when the effect of therapy is measured by wheelchair use instead of by improvement in walking ability with 6MWT (MPS IVa)
TTGUS or 10-metre run	NICE	• Used more often in clinical practice for DMD patients than 6MWT	• Not as clinically informative as the 6MWT (MPS IVa)
NSAA	NICE	• Routinely used in clinical practice (DMD)	• Not as clinically informative as the 6MWT (DMD)

LIMITATIONS

- Ongoing assessments and future reassessments of these drugs may change their future reimbursement status.
- The targeted search approach used for these analyses may be susceptible to selection bias.
- Not all the information about the acceptability or relevance of functional measures were available on HTA websites. Therefore, caution should be exercised when interpreting the provided findings.

CONCLUSIONS

- The 6MWT was the most frequently evaluated outcome used to assess treatment benefit in the rare disorders we investigated and was a generally accepted outcome measure by the HTA bodies. FVC and other functional measures like 3MSCT, NSAA, TTGUS/10-metre run were also considered applicable, but to varying extents. This targeted review highlights the wide range of opinions of European HTA bodies towards the same functional measures for the same therapies, and the challenge of developing an evidence package that meets all their specified requirements.
- European HTA bodies view the applicability of these functional measures differently. Despite negative comments from several HTA bodies, well-established functional measures such as 6MWT are routinely used in clinical practice for rare muscular, skeletal and neurodegenerative disorders.
- The development, acceptance, and subsequent distribution of new and innovative treatments for rare diseases will require overcoming a series of HTA-related challenges, including the lack of a tailored and uniform HTA evaluation method for functional measures and different levels of payers' hesitancy in considering them.

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