A comparison of the NICE highly specialised technology (HST) programme with assessment by the National Authority for Health (HAS; France) and the Federal Joint Committee (G-BA; Germany)

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Introduction

- NICE (England, UK) defines ultra-orphan drugs as those treating life-threatening or seriously debilitating conditions affecting ≤1:50,000 people[1,2].
- The NICE HST programme (HSTP) was introduced in 2013 to assess these drugs, which are unlikely to meet standard cost-effectiveness criteria due to the high acquisition costs required to recoup R&D costs for innovative technologies in small patient populations[3].
- The HSTP considers the following criteria:
  - Nature of the condition.
  - Impact of the new technology.
  - Cost to the NHS and personal social services.
  - Value for money.
  - Cost-effectiveness analysis (CEA) with £100,000/QALY threshold (introduced in April 2017).
  - Impact beyond direct health benefits.
  - Impact on the delivery of the specialised service.
- HAS (France) and the G-BA (Germany) also apply special criteria to the assessment of drugs for treatment of rare diseases[4,5].
- Table 1 summarises key criteria considered by NICE HSTP, HAS, and G-BA for ultra-orphan drugs.

Table 1: Criteria for assessment of ultra-orphan drugs by NICE HSTP, HAS, and G-BA

Criteria	NICE HSTP (England)	HAS (France)	G-BA (Germany)
Clinical benefit	Considered for patients and where relevant, carers.	SMR and ASMR considered proven at MA (if BI threshold met).	Additional benefit considered proven at MA (if BI threshold met). Extent of medical benefit assessed.
Costs	CEA, BI, and value for money.	BI threshold <€30 million per year.	BI threshold <€50 million per year.
Innovation	Considered.	Accelerated procedure.	Not mentioned.
Follow-up research	May be requested as part of MAA.	May be requested.	May be requested.

CEA, cost-effectiveness analysis; BI, budget impact; MA, market authorisation; MAA, managed access arrangement; PAS, patient access scheme; SMR, medical benefit; ASMR, additional medical benefit.

- If the budget impact (BI) threshold is exceeded:
  - HAS assess medical benefit (SMR; rated substantial, moderate, mild, or insufficient) and additional medical benefit (ASMR; rated I to V [major, important, moderate, minor, or no clinical improvement]).
  - The G-BA assess additional benefit over the relevant comparator and the extent of additional medical benefit (EAMB; rated major, considerable, minor, not quantifiable, no additional benefit, or less benefit).
- If the cost-effectiveness threshold is exceeded, NICE HSTP apply incremental weighting based on the QALY gain (weights of 1, 1 to 3, and 3 for incremental QALYs gained per patient [lifetime horizon] of ≤10, 10 to 30, and >30, respectively).

Objectives

- Compare the outcomes of NICE HSTP assessments of ultra-orphan drugs with assessments of the same technologies by HAS (France) and the G-BA (Germany).
- Explore the decision-making processes behind the recommendations made for ultra-orphan drugs by the three HTA organisations.

Methods

- A search was conducted on the NICE website (https://www.nice.org.uk/) for all HSTs that had guidance or final evaluation determinations (FEDs) published by 6th April 2018 (n=8).
- Searches were then conducted for evaluations of these technologies by HAS (https://www.has-sante.fr/portail) and G-BA (https://www.g-ba.de) (on 6th April 2018).

Results

- Eight ultra-orphan drugs had published guidance or FEDs from NICE HSTP by April 2018[6]. Excluding strimvelis, the assessments were conducted prior to the introduction of cost-effectiveness criteria to the HSTP.
- The outcome of assessment by NICE HSTP, HAS, and the G-BA for these drugs is presented in Table 2.
- All drugs received positive recommendations from NICE HSTP, HAS, and the G-BA, with the exception of sebelipase alfa, which was not recommended by NICE HSTP.
- Many of the recommendations are subject to re-evaluation after further data becomes available.

Table 2: Outcome of assessment of ultra-orphan drugs by NICE HSTP, HAS, and G-BA

Drug	Indication	NICE HSTP (England, UK)[6]	HAS (France)[7]	G-BA (Germany)[8]
Eculizumab	Atypical haemolytic uraemic syndrome	Recommended.	Recommended with request for supplementary data. SMR: substantial; ASMR: II	Accepted prior to routine benefit assessments.
Elosulfase alfa	Mucopolysaccharidosis type IVa	Recommended with MAA.	Recommended (re-evaluate in 5 yrs). SMR: substantial; ASMR: III	Recommended. EAMB: minor
Ataluren	Duchenne muscular dystrophy	Recommended with PAS and MAA.	Recommended (re-evaluate in 2021). SMR: mild; ASMR: V	Recommended. EAMB: minor
Migalastat	Fabry disease	Recommended with PAS.	Recommended (re-evaluate in 5 yrs). SMR: substantial; ASMR: IV	Recommended. EAMB: not quantifiable
Eliglustat	Type 1 Gaucher disease	Recommended with PAS.	Recommended. SMR: substantial; ASMR: V	Recommended. EAMB: not quantifiable
Asfotase alfa	Paediatric-onset hypophosphatasia	Recommended with MAA.	Recommended (re-evaluate in 3 yrs). SMR: substantial; ASMR: II	Recommended (valid until 1st Dec 2018. EAMB: not quantifiable
Sebelipase alfa	Lysosomal acid lipase deficiency	Not recommended (appeal underway).	Recommended with request for supplementary data. SMR: substantial; ASMR: III (infantile), V (juvenile)	Recommended with validity until 1st December 2018. EAMB: not quantifiable
Strimvelis	ADA-severe combined immunodeficiency	Recommended.	Not assessed.	Not assessed.

SMR, medical benefit; ASMR, additional medical benefit; EAMB, extent of additional medical benefit; MAA, managed access arrangement; PAS, patient access scheme; ADA, adenosine deaminase deficiency.

- Key drivers in the decision-making process for each assessment are summarised in Table 3.
- NICE HSTP decisions were usually driven by BI, value for money, and unmet need. Clinical benefit, innovation, and quality of life (QoL) of patients and carers (where relevant) were also key factors in some assessments. Strimvelis was the first technology assessed under the HSTP cost-effectiveness threshold (applied April 2017).
- HAS considered clinical benefit (SMR and ASMR ratings), unmet need, target population size, and innovation as key drivers for decision-making. Costs were not discussed.
- The G-BA assessed clinical benefit (in the context of extent of additional medical benefit), target population size, annual treatment costs, and unmet need in decision-making.

Table 3: Factors that were key drivers in the decision-making process for each assessment by NICE HSTP, HAS, and G-BA

Criteria	Eculizumab			Elosulfase alfa			Ataluren			Migalastat			Eliglustat			Asfotase alfa			Sebelipase alfa			Strimvelis		
	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE	UK	FR	DE
Clinical benefit	✓	✓	NA	✓	✓	✓	-	✓	✓	-	✓	✓	-	✓	✓	-	✓	✓	-	✓	✓	✓	NA	NA
Patient QoL	✓	✓	NA	✓	-	-	✓	✓	-	✓	-	✓	✓	-	-	✓	-	-	-	✓	-	✓	NA	NA
Carer QoL	✓	-	NA	-	-	-	✓	✓	-	-	-	-	-	-	-	✓	-	-	-	-	-	✓	NA	NA
QALYs/ utilities	✓	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	✓	NA	NA
Unmet need	✓	✓	NA	✓	✓	-	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	-	✓	-	-	NA	NA
Budget impact	✓	-	NA	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	-	NA	NA
Value for money	✓	-	NA	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	-	NA	NA
Treatment cost	✓	-	NA	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	-	✓	-	NA	NA
Target pop. size	-	✓	NA	-	✓	✓	-	✓	✓	-	✓	-	-	✓	✓	-	✓	✓	-	✓	✓	-	NA	NA
Innovation	✓	✓	NA	-	-	-	✓	-	-	-	✓	-	-	✓	-	✓	-	-	-	-	-	✓	NA	NA
CEA	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	✓	NA	NA

QoL, quality of life; QALY, quality-adjusted life year; CEA, cost-effectiveness analysis.

✓ Key driver of decision; - Not a key driver of decision; NA No assessment available

Conclusion

- Clinical benefit and costs were key drivers of decision-making in the assessment of ultra-orphan drugs:
  - NICE HSTP considered BI and value for money more consistently than clinical benefit, likely reflecting uncertainty in available data due to small population sizes available for conducting clinical trials.
  - Although HAS assessments did not discuss costs, SMR and ASMR were assessed, indicating that the BI threshold of €30 million was exceeded in all cases.
  - The G-BA considered additional medical benefit proven at MA in all cases and assessed the extent of additional benefit, which suggests that the BI of each drug was not considered to exceed €50 million.
- Unmet need was a key driver in all countries, particularly in light of uncertain clinical evidence.
- As a key driver of costs, certainty around the target population size was frequently an important factor.
- Patient QoL was commonly a key driver for NICE HSTP and HAS, and infrequently for the G-BA. Carer QoL was a driving factor in some cases for NICE HSTP and HAS.
- All three bodies requested follow-up data and re-evaluations after a set timeframe in the majority of assessments, in order to manage uncertainty in available clinical data and costs to the health service.
- CEA was a key driver in one assessment (strimvelis), but will likely be central to future decisions by NICE HSTP.
- New criteria, such as the NICE HSTP cost-effectiveness threshold, may be necessary to manage combined BI as further high-cost ultra-orphan drugs are introduced.
- In conclusion, clinical benefit and unmet need are important drivers behind recommendations for ultra-orphan drugs by NICE HSTP, HAS, and the G-BA, but the uncertainty associated with clinical data commonly brings BI and other cost considerations to the forefront.

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