Assessing criteria for NICE recommendation with the HST programme

Caroline Upton[1], James Wordsworth[1], David Cork[1], Alistair Curry[2], Georgia Hollier-Hann[1], **Stephen Ralston**[2]

[1]SIRIUS Market Access, Newcastle-upon-Tyne, United Kingdom. email: info@siriusmarketaccess.com

[2]SIRIUS Market Access, London, United Kingdom. email: info@siriusmarketaccess.com

256

Introduction

- Standard NICE technology appraisals (TAs) have strict criteria for cost-effectiveness, sometimes resulting in a negative recommendation despite clinical efficacy being demonstrated.
- In the case of rare conditions, cost-effectiveness can be even more difficult to demonstrate, due to the high acquisition costs required to recoup the costs of research and development, and the small population that will be eligible for treatment.
- Treatments for rare conditions are important to improve the prognosis of patients who otherwise experience low quality of life, morbidity, or early death.
- These medicines are often novel and innovative to target the rarity of the disease.
- In the UK, there are three main routes by which treatments for such interventions can be assessed for reimbursement; the Highly Specialised Technology Programme (HSTP), the Cancer Drugs Fund (CDF) and End of Life (EoL) criteria (Table 1).

Table 1: Summary of HSTP, CDF, and end of life schemes in the UK

	HSTP	CDF	EoL
Life expectancy	-	-	< 24 months
Life extension threshold	-	-	> 3 months
Cost effectiveness threshold	£100,000/ QALY. Weighting applies to drugs with higher ICERs (>£100,000) but a higher QALY gain.	£20-30,000/ QALY if EoL criteria not met. £50,000/ QALY if EoL criteria met.	£50,000/ QALY
Required follow-up research	Managed access agreement (MAA) may be agreed between key stakeholders, manufacturer, NHS, and patient groups to collect more data.	2 year MAA must demonstrate cost-effectiveness.	-

- The HSTP has existed since 2013 and takes into account factors specific to the technology such as:
  - Nature of the condition.
  - Impact of the new technology.
  - Cost (budget impact) to the NHS and personal social services.
  - Value for money, defined by the productive, technical and allocative efficiency of the treatment (not cost-utility analysis).
  - Impact of the technology beyond direct health benefits.
  - Impact of the technology on delivery of the specialised service.
- As of April 2017, cost-effectiveness evaluation was introduced to the HSTP, with the threshold for automatic funding set at £100,000/ QALY.
- Incremental weighting is applied based on the extent of the QALY gain for HSTs that cost >£100,000/ QALY (Table 2).

Table 2: Incremental weighting for HSTs > £100,000/ QALY

Incremental QALYs gained (per patient, lifetime horizon)	Weight versus 100k/ QALY
≤ 10	1
10 - 30	Between 1 and 3 (using equal increments)
> 30	3

Objectives

This work aimed to review the criteria by which HSTP assesses treatments for rare conditions, and to understand which key factors impacted on reimbursement decisions.

Abbreviations:
ADA, adenosine deaminase deficiency; CDF, Cancer Drugs Fund; EoL, End of life; FED, Final evaluation determination; HST(P), Highly specialised technology (programme); ICER, incremental cost effectiveness ratio; MAA, Managed access agreement; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, Patient access scheme; QALY, Quality-adjusted life year; QoL, Quality of life; RCT, Randomised controlled trial; TA, Technology appraisal

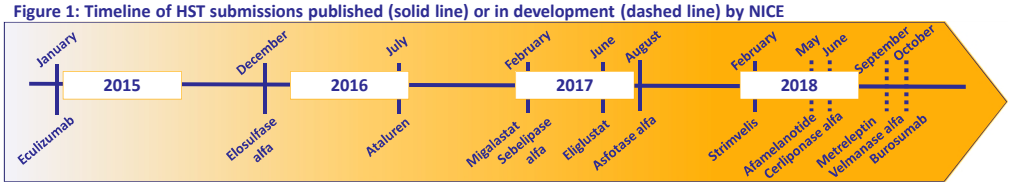
Methods

A search was conducted on the NICE website (www.nice.org.uk: accessed 6th April, 2018) for all HSTs with guidance published or expected to be published in 2018[1,2]. Those with final evaluation determinations (FEDs) were reviewed to assess the impact of factors such as budget impact, cost per patient, QALY gains, innovation, unmet need, and others associated with NICE recommendation.

Results

Eight treatments were identified with FEDs published by April 2018. A further five had guidance in development with expected publication in 2018. The number of HST submissions published by NICE increased between 2015 and 2018, with more than half published from 2017 onwards (Figure 1).

Figure 1: Timeline of HST submissions published (solid line) or in development (dashed line) by NICE



- No single factor was important for all HST appraisal outcomes; each case was considered individually according to the strengths and limitations of its data. A summary of key drivers which contributed to the decision for each HST assessment is available in Table 3.
- Of the eight treatments with FEDs by April 2018, elosulfase alfa and ataluren were recommended with managed access agreements (MAAs); eculizumab, eliglustat, migalastat, and strimvelis were recommended without MAAs; asfotase alfa was recommended for a subpopulation with an MAA; and sebelipase alfa was provisionally not recommended.
- These outcomes did not reflect data quality; eculizumab offered only single-arm, non-randomised data, while sebelipase alpha was supported by RCTs.
- Recommendations also did not reflect QALY gains, as incremental QALYs gained with sebelipase alfa (6.64) were higher than migalastat (0.34-0.98). Additionally, babies presenting with lysosomal acid lipase deficiency did not survive longer than 12 months without sebelipase alfa, suggesting substantial unmet need.
- The annual budget impact, based on list prices, was highest for sebelipase alfa (5-year net £59 million). However, the £13.4 million impact for the subgroups not recommended for asfotase alfa was less than the £17.3 million for elosulfase alfa, indicating that the decision was made partially on efficacy grounds.
- With the exception of strimvelis, cost-effectiveness was not reported, but annual treatment costs (from list price) appear significant. Strimvelis had the greatest reported annual cost per patient of £505,000, followed by sebelipase alfa (£491,992 for an 11-year-old), compared with £211,000-£340,000 for eculizumab.
- Strimvelis was the first treatment assessed under the HSTP cost-effectiveness threshold (as applied to HST submissions from April 2017). Under the committee's preferred assumptions, the highest plausible ICER was £120,506/ QALY gained and a QALY weighting of 1.4 could be applied. The other HSTs assessed here may not have met the threshold of £100,000/ QALY.

Table 3: Factors which were key drivers of the decision for each HST assessment

Ref. (year)	HST1 (2015)[3]	HST2 (2015)[4]	HST3 (2016)[5]	HST4 (2017)[6]	HST5 (2017)[7]	HST6 (2017)[8]	ID737 (2017)[9]	HST7 (2018)[10]
Treatment	Eculizumab	Elosulfase alfa	Ataluren	Migalastat	Eliglustat	Asfotase alfa	Sebelipase alfa	Strimvelis
Indication	Atypical haemolytic uraemic syndrome	Mucopolysacc-haridosis type IVa	Duchenne muscular dystrophy	Fabry disease	Type 1 Gaucher disease	Paediatric-onset hypophosphate-asia	Lysosomal acid lipase deficiency	ADA-severe combined immuno-deficiency
HST assessment decision	Recommended.	Recommended with MAA.	Recommended with PAS and MAA.	Recommended with PAS.	Recommended with PAS.	Recommended with MAA, discount, and cost cap.	Not recommended.	Recommended.
Trial data	✓	✓	-	-	-	-	-	✓
Budget impact	✓	✓	✓	✓	✓	✓	✓	-
QALY gains (preferred estimate)	✓ (10.14)	- (5.04)	- (3.05)	- (0.34)	- (1.05 – 1.06)	✓ (14 – 25)	- (6.64)	✓ (14.0-19.6)
Innovation	✓	-	✓	-	-	✓	✓	✓
Other important factors considered during TA	• Expert opinion. • Patient QoL. • Carer QoL and cost burden. • Treatment duration.	• Expert opinion. • Patient QoL. • Confounding variables. • Surrogate endpoint.	• Expert opinion. • Patient QoL. • QoL and cost burden on families.	• Expert opinion. • Patient QoL.	• Patient and clinical expert opinion. • Patient and carer QoL.	• Expert opinion. • Patient and carer QoL. • Model design. • Juvenile vs. paediatric subgroups.	• Expert opinion. • Patient and carer QoL. • Limitations in the MAA.	• Expert opinion. • Patient and carer QoL. • Cost/ QALY (<£120,506). • QALY weight of 1.4-1.96.

✓ Key driver of the HST assessment decision; - Not a key driver of the HST assessment decision

Conclusions

- HST recommendations do not directly reflect treatment efficacy, which is frequently associated with substantial uncertainty. Annual treatment cost and budget impact are more likely to be the key drivers behind HST assessment decisions prior to April 2017.
- Patient and clinical expert opinion are extremely important, as well as patient and carer quality of life.
- Clinical trial data, whilst important, is often not pivotal in HST decisions, due to small patient populations and the difficulties associated with conducting RCTs.
- Reimbursement of HSTs by NICE frequently depends on the implementation of an MAA or a PAS.
- HSTs are very expensive; HSTs assessed prior to April 2017 may not have met the HSTP threshold of £100,000/ QALY. As a gene therapy, the one-off expense of strimvelis was offset by potentially large QALY gains, ensuring that the cost/ QALY was acceptable, despite the highest plausible ICER being >£100,000/ QALY.
- Orphan diseases can be expensive to treat, potentially posing a significant risk to healthcare budgets. Therefore a budget impact threshold is important in ensuring that cost-effective treatments are reimbursed.

References
1. NICE guidance and advice list: published (2018) National Institute for Health and Care Excellence. Accessed 6th April 2018.
2. NICE guidance and advice list: In development (2018) National Institute for Health and Care Excellence. Accessed 6th April 2018.
4. NICE [HST2] (2015). Elosulfase alfa for treating mucopolysaccharidosis type IVa.
5. NICE [HST3] (2016). Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene.
6. NICE [HST4] (2017). Migalastat for treating Fabry disease.
7. NICE [HST5] (2017). Eliglustat for treating type 1 Gaucher disease..
8. NICE [HST6] (2017). Asfotase alfa for treating paediatric-onset hypophosphatasia
9. NICE [ID737] (2017). Sebelipase alfa for treating lysosomal acid lipase deficiency.
10. NICE [HST7] (2018). Strimvelis for treating adenosine deaminase deficiency-severe combined immunodeficiency.

SIRIUS MARKET ACCESS