Health technology appraisals of gene therapies appraised through NICE highly specialised technology route

J. Noble-Longster, A. Strickson, C. Worsley, K. Tolley

Tolley Health Economics Ltd., Buxton, UK.

Poster No. HTA35

Background

- A rare disease is one that affects fewer than 1 in 2,000 people;[1] around 80% have a genetic cause.[2] Rare diseases often present with a range of symptoms and can affect just one or a range of organs and systems in the body. The symptom burden is often vast with substantial impact on the patient, their families, and the healthcare system.
- Gene therapies alter the genes inside human cells to prevent and treat disease, by replacing a disease-causing gene with a healthy copy, inactivating a disease-causing gene, or introducing a new gene to treat a disease.[3,4] They include single-dose therapies with lifelong benefit, as well as enzyme-replacement therapies, which introduce an additional, healthy copy of a gene into the cells, and are normally administered at regular intervals, long-term.[5,6]
- Gene therapies offer the potential to address high unmet need in rare diseases by providing a therapy where there are sometimes limited or no treatment options.
- At NICE, the rarest diseases are generally appraised through the highly specialised technology (HST) route. A high price and inherent uncertainty in the long-term clinical efficacy and safety data of gene therapies create challenges for health technology assessment bodies, including NICE, in assessing their cost-effectiveness.

Objectives

This research aimed to analyse previous HST appraisals by NICE, as a case study, to highlight the challenges associated with cost-effectiveness assessments of gene therapies for rare diseases.

Methods

- Previous gene therapies appraised through the NICE HST process were examined in a targeted review, performed by a single reviewer.
- Data were assimilated from the summary of evidence information for each appraisal, made publicly available via the NICE website.

Results

- As of May 2024, NICE had appraised eight gene therapies through the HST route, and all received positive recommendation: five single-dose therapies and three enzyme replacement therapies with long-term dosages (**Table 1**).
- All eight therapies received positive recommendation from NICE, however most had a Patient Access Scheme (PAS) which remained confidential, so it is not clear what discounts were required for the therapies to be considered cost-effective.
- The comparator(s), source of data, and economic model type utilised are summarised for each appraisal in **Table 2**.
- Several areas of uncertainty were identified through analysis of the NICE appraisal documentation for the eight gene therapies (**Figure 1**).

Figure 1: Themes of uncertainty across prior NICE HST appraisals of gene therapies

Long-term treatment effect

- Although treatment effect is expected to last decades, the trial follow-up time was often limited, creating substantial uncertainty
- Case study: HST11 Luxturna - trial evidence showed no loss of efficacy after 7.5 years of follow-up, but the economic evaluation assumed a treatment effect of 40-years. Experts confirmed clinical plausibility and committee considered 40-year duration "uncertain but reasonable"

Evidence source

- Main source of evidence in most appraisals was from single-arm trials, with comparator evidence from natural history or real-world studies
- Case study: HST18 – clinical evidence of Libmeldy came from single-arm trials and expanded access programmes so a naïve comparison was performed with a natural history cohort. The EAG had concerns about the natural history evidence, however the committee concluded that when Libmeldy was effective, it had a substantial clinical benefit compared with the natural history cohort

HRQoL

- The majority of the trials informing the submissions did not collect EQ-5D; the NICE preferred preference-based HRQoL measure. Some of the appraisals therefore performed vignette utility elicitation studies
- Case study: HST26 – committee submitted evidence for Upstaza from 3 clinical trials, none of which collected HRQoL data because the patients were too young, had a language impairment, or a severe cognitive impairment and therefore could not communicate effectively. The base case utilities were elicited through a TTO of vignettes in the UK general population. The committee considered these utilities to be conservative and therefore appropriate.

Carer disutility

- Treatments that have a large impact on survival can result in an increase in the total amount of caregiving required and will therefore likely be a consideration for many gene therapies
- Case study: HST15/ 24 - Zolgensma for SMA reduced carer burden in the short-term but prolonged life and therefore increased the total amount of caregiving required over a lifetime horizon, having an adverse impact on the ICER

Table 1: Overview of NICE HST appraisals of gene therapies

NICE HST	Therapy	Therapeutic area	Recommendation
HST6 replaced by **HST23** following MAA	**Strensiq** (Asfotase alfa) Alexion Pharma UK	Paediatric onset hypophosphatasia	Positive
HST7	**Strimvelis** (Autologous CD34+ enriched cell fraction) GlaxoSmithKline	SCID due to adenosine deaminase deficiency	Positive
HST11	**Luxturna** (Voretigene neparvovec) Novartis	Retinal dystrophy	Positive
HST15 updated to include pre-symptomatic SMA in **HST24**	**Zolgensma** (Onasemnogene abeparvovec) Novartis	SMA	Positive
HST18	**Libmeldy** (Atidarsagene autotemcel) Orchard Therapeutics	Metachromatic leukodystrophy	Positive
HST26	**Upstaza** (Eladocagene exuparvovec) PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency	Positive
HST29	**Lamzede** (Velmanase alfa) Chiesi	Alpha-mannosidosis	Positive
HST30	**Kanuma** (Sebelipase alfa) Alexion	Wolfman disease	Positive

Table 2: Data sources and models used in NICE HST appraisals of gene therapies

NICE HST	Therapy	Comparator	Clinical efficacy data source	Economic model type
HST6/ HST23	Strensiq	BSC	4 trials and 2 real-world studies with 4-year FU collected under MAA	Markov model
HST7	Strimvelis	HSCT	Clinical trials presented as an "integrated population" Named Patient Programme	Decision tree/Markov model
HST11	Luxturna	BSC	2 clinical trials	Markov model
HST15/ HST24	Zolgensma	BSC and Zolgensma*	Clinical trial; natural history studies and published data for BSC	Markov model
HST18	Libmeldy	BSC	Clinical trials, natural history data	Markov model approximating a partition survival model
HST26	Upstaza	BSC	Clinical trial; natural history data	Cohort model
HST29	Lamzede	BSC	Clinical trial and real-world evidence	Markov model
HST30	Kanuma	BSC	Clinical trial and natural history data	Markov model

***In the HST24 update appraisal to include pre-symptomatic SMA, the EAG thought that Zolgensma should also be considered in part of the comparator arm when pre-symptomatic SMA develops into type 1 SMA**

Conclusion

- NICE have demonstrated proficiency to date in appraising a relatively small number of gene therapies in rare diseases. However, there will likely be increased pressure with more gene therapies expected to reach the market, including those for rare diseases that do not meet HST criteria.
- Submitting companies of novel gene therapies should try to address the key areas of uncertainty identified in this analysis in advance of HTA, to improve efficiency and reduce time to access for patients.
- Alternative payment models may be adopted by some healthcare systems to address long-term uncertainty and reimbursement issues, however, to date, simple discounts have dominated and can be expected to continue to be preferred by NICE.

Abbreviations: BSC, best supportive care; EAG, evidence assessment group; EQ-5D, EuroQoL 5-dimension; FU, follow-up; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplant; HST, highly specialised technology; ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; SCID, severe combined immunodeficiency; SMA, spinal muscular atrophy; TTO, time trade-off.

References: 1. GOV.UK. The UK Rare Diseases Framework. 2021 01/06/2022]; Available from: https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework. 2. European Commission. Rare diseases. 15/05/2024]; Available from: https://health.ec.europa.eu/european-reference-networks/rare-diseases. 3. Toumi, M., *et al*., Recommendations for economic evaluations of cell and gene therapies: a systematic literature review with critical appraisal. Expert Rev Pharmacoecon Outcomes Res, 2023. 23(5): p. 483-497. 4. Alnasser, S.M., Review on mechanistic strategy of gene therapy in the treatment of disease. Gene, 2021. 769(15). 5. FDA. What is Gene Therapy? 2018 2024]; Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy. 6. EMA. Advanced therapy medicinal products: Overview. May 2024]; Available from: https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview.

tolley
Trusted **HTA consultants** from **beginning** to **end**

Presented at ISPOR Europe, November 2024, Barcelona, Spain