Too Advanced for STA, Too Common for HST? Navigating NICE Appraisals of Gene Therapies

HTA337

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Introduction

- Gene therapies offer transformative potential for severe conditions but face particular health technology assessment (HTA) challenges due to high upfront costs, limited clinical data, and long-term outcome uncertainties.
- In the UK, the National Institute for Health and Care Excellence (NICE) appraises health technologies through either the Single Technology Appraisal (STA) route or the Highly Specialised Technologies (HST) route.
- The STA route is the default pathway for most technologies. It applies a standardised framework across therapeutic areas, typically requiring robust comparative evidence and cost-effectiveness thresholds of £20,000–£30,000 per quality-adjusted life year (QALY).
- The HST route is reserved for technologies targeting very rare and severe diseases. It incorporates tailored evaluation methods, greater evidentiary flexibility and higher cost-effectiveness thresholds (£100,000–£300,000/QALY). To qualify, technologies must meet the HST routing criteria which have undergone continuous refinement **(Figure 1).**[1-3]
- While both routes are used across therapeutic areas, the HST route may be better equipped to address the particular HTA challenges of gene therapies, such as reliance on single-arm trials and uncertainty regarding long-term durability of effect.

Objective: We aimed to compare gene therapy evaluations through the HST and STA routes, exploring decision drivers and implications for access.

Methods

- Gene therapies approved in the UK were identified via the EMA and MHRA databases.
- The NICE website was searched in June 2025 for completed up-to-date assessments of gene therapies approved in the UK. Incomplete and discontinued appraisals were excluded, while replaced appraisals were analysed in conjunction with their updates.
- For each eligible assessment, data were extracted on timelines, recommendation outcomes, indication restrictions, evidence base and associated criticisms, discount rates, use of severity modifiers, and managed access agreements (MAAs).
- Appraisals were categorised by route – STA vs HST (irrespective of routing criteria version) – and a comparative analysis was conducted to explore differences between pathways.

Figure 1. Current HST routing criteria (effective April 2025)

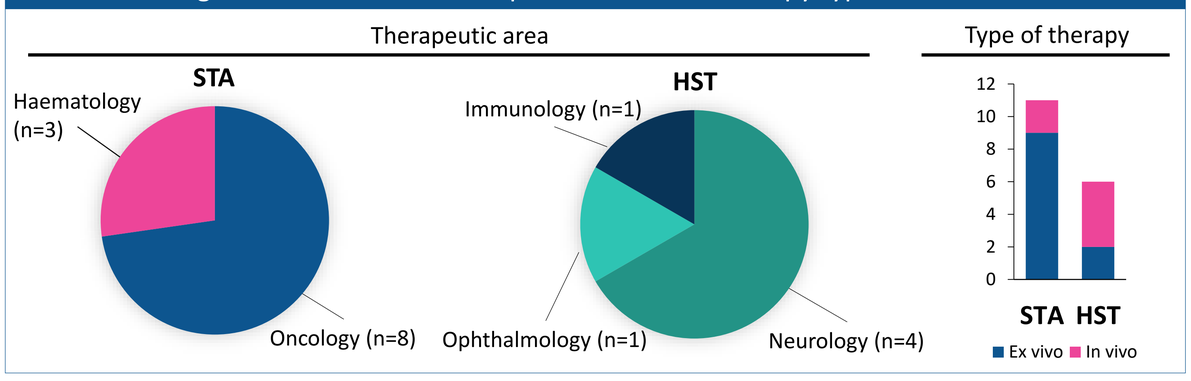
1 Rarity and severity	2 Innovation	3 Eligibility	4 Added benefit
The disease is **ultra-rare** and **debilitating** • **1:50,000** in England • **Lifelong** with exceptional negative **burden** for patients and caregivers	The technology is an **innovation** for the ultra-rare disease • Advanced therapy, new entity or drug-device combination • Not a repurposed technology	No more than **300 people in England are eligible** for the technology in its licensed indication • Not individualised medicine	The technology is likely to offer **substantial additional benefit** over existing clinical management is considered inadequate.
Key elements introduced in current version			
• Disease defined as ICD-11 diagnosis, excluding subgroups • Lifelong criterion added • No discretionary exceptions	New criterion	• Strict population cap (previously ≤500 patients across indications) • Individualised medicine exclusion	Clearer definitions of additional benefit and inadequacy of existing treatments.

Results

Overview

- 17 HTAs of 12 gene therapies were identified, comprising 6 HST appraisals and 11 STAs.
- Oncology was the most common disease area (8 STAs), followed by neurology (4 HSTs), haematology (3 STAs), ophthalmology (1 HST) and immunology (1 HST).
- STAs predominantly assessed ex vivo gene therapies (9/11 STAs, most commonly CAR-Ts), whereas in vivo gene therapies were more common in HST appraisals (4/6).

Figure 2. Overview of therapeutic areas and therapy types evaluated



Timelines and recommendations

- On average, STA appraisals were associated with marginally shorter timelines from NICE submission to recommendation (12 months for STA vs 15 months for HST).
- 4 HST appraisals resulted in a full recommendation (in line with marketing authorisation), while 2 led to restricted recommendations on the basis of age and disease severity.
- STAs showed more restrictive reimbursement outcomes, including 6 full, 4 restricted (based on age, contraindications and disease-specific criteria), and 1 negative recommendation.

Figure 3. Evaluation timelines

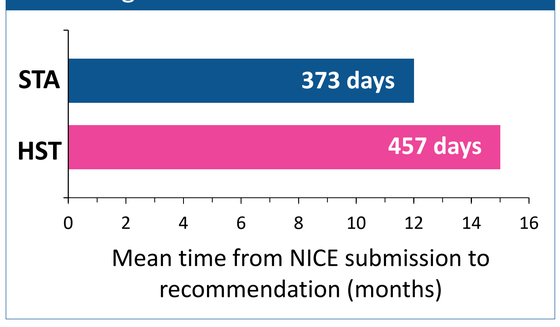


Table 1. Indication restrictions

Restrictions applied[a]	STA	HST
None (unrestricted recommendation)	6 (55%)	4 (67%)
Age	2 (18%)[b]	2 (33%)
Disease-specific criteria[c]	2 (18%)[b]	2 (33%)
Treatment suitability and contraindications	3 (27%)	0 (0%)
Treatment line	1 (9%)[d]	0 (0%)

[a]Categories are not mutually exclusive as multiple restrictions may apply per HTA.
[b]Includes one case (TA554) where restrictions were lifted upon re-evaluation (T975).
[c]Criteria included genotype, serology, disease severity, symptoms and relapse status.
[d]Includes one case (TA559) where restrictions were lifted upon re-evaluation (T872).

Evidence and criticisms

- Few submissions included randomised controlled trials (HST: 1/6; STA: 3/11), with most relying on single-arm studies.
- Indirect treatment comparisons (ITCs) were more frequent in STAs (6/11), most commonly matching-adjusted indirect comparisons (MAICs). Only one HST conducted an ITC (unadjusted unanchored comparison).
- Clinical evidence in both routes was often criticised for lack of comparative data, short follow-up, and concerns around generalisability to real-world UK clinical practice. HSTs were often limited by small sample sizes.
- Criticisms of economic evidence revolved around assumptions of long-term survival and cure fractions, utility values, and comparator cost inputs, leading to substantial uncertainty in final cost-effectiveness estimates.

Use of value modifiers and managed access

- The HST route showed more frequent use of a 1.5% discount rate (HST: 2/6; STA: 0) and QALY weighting (HST: 5/6; STA: 5/11).
- MAAs were more common among STAs, with 5 using the Cancer Drugs Fund (CDF) and 3 using the Innovative Medicines Fund (IMF). Only 1 HST included a bespoke MAA.
- Across both routes, MAAs were primarily used to address uncertainty around long-term clinical effectiveness, with data typically collected through ongoing clinical trials, real-world registries and NHS datasets.

Table 2. Overview of criticisms and outcomes in gene therapy appraisals conducted by NICE

HTA ID	Technology	Disease area	Main criticisms of clinical evidence	Main criticisms of economic evidence	Discount rate	QALY weight	MAA used	Outcome
HST 7	**Strimvelis** (Autologous CD34+ enriched cells)	SCID due to ADA deficiency	Evidence from small, uncontrolled trials with limited follow-up; potentially outdated historical control; patient characteristics limit UK generalisability; long-term safety remains uncertain.	Major uncertainty in survival, utility, lifelong impairment, travel, screening, and rescue costs; oversimplified treatment pathway; model overestimates cure and long-term QALY gains.	1.5%, 3.5%	1.4		✓
HST 11	**Luxturna** (Voretigene neparvovec)	Retinal dystrophy	Small sample size, short follow-up, minimal RCT data and lack of PRO data; narrow trial eligibility criteria limit generalisability.	Model relies on proxy utilities and unvalidated extrapolation of treatment effect, leading to major uncertainty in long-term value.	3.5%	1.2		✓
HST 15[a]	**Zolgensma** (Onasemnogene abeparvovec)	Spinal muscular atrophy	Evidence from open-label, single-arm trials with small sample sizes and short follow-up; patient and supportive care differences in US-based external control; long-term efficacy uncertain.	Model relies on unanchored comparisons and untested assumptions for motor milestone transitions, long-term effectiveness and utilities; omits direct HRQoL and caregiver data.	1.5%	ND	Bespoke	✓
HST 24[a]	**Zolgensma** (Onasemnogene abeparvovec)	Spinal muscular atrophy	Data from single-arm, small trials; uncertainty if motor milestone gains are sustained lifelong; uncertain NHS generalisability.	Model sensitive to loss of milestones and unclear social care costs; proxy utilities; ICER varies by SMN2 copy number.	3.5%			✓
HST 18	**Libmeldy** (Atidarsagene autotemcel)	Metachromatic leukodystrophy	Studies have very small sample sizes, baseline heterogeneity, short follow-up, and few adult patients, limiting generalisability.	Model sensitive to lifetime extrapolation, utility estimation method, response subgroup definition, discount rate, and carer costs.	3.5%	ND		✓
HST 26	**Upstaza** (Eladocagene exuparvovec)	AADC deficiency	Uncertainty from small, single-arm trials, high attrition, imputed milestone data, and lack of long-term (>10 yr) outcomes.	Model highly sensitive to QALY modifier, discount rate, proxy utility values, motor milestone persistence, and survival assumptions.	3.5%	ND		✓
TA 410	**Imlygic** (Talimogene laherparepvec)	Metastatic melanoma	Trial population and comparator evidence not matching NHS context. Indirect comparison methods add uncertainty.	Model is highly sensitive to OS extrapolation, progression utility and PAS impact, comparator validity and discounting assumptions.	3.5%[b]			✓
TA 677	**Tecartus** (Brexucabtagene autoleucel)	Mantle cell lymphoma	Single-arm trial; generalisability issues (younger, fitter population); limited comparator data; immature survival curves.	Model assumptions for long-term survival, quality-of-life, administration costs, and naïve comparator results add uncertainty.	3.5%	ND	CDF	✓
TA 872	**Yescarta** (Axicabtagene ciloleucel)	Large B-cell lymphoma	Comparative evidence shows excessive reliance on SCHOLAR-1, search limitations; lack of robust adjustment and UK relevance.	ICER sensitive to OS and PFS extrapolations; lack of sensitivity analysis for survival or cure rate uncertainty.	3.5%[b]	ND	CDF[c]	✓
TA 893	**Tecartus** (Brexucabtagene autoleucel)	B-cell leukaemia	Single-arm, small, non-UK trial; risk of bias in MAIC and naïve comparisons due to inadequate adjustment methods.	Drug costing inaccuracies, survival extrapolation, comparator dosing, cure utility, AE costs, SCT exclusion and MAIC impact ICER.	3.5%	ND	CDF	✓
TA 894	**Yescarta** (Axicabtagene ciloleucel)	Follicular lymphoma	ZUMA-5 trial is single-arm, non-UK, shows differences in prior therapy, short follow-up; use of SCHOLAR-5 comparator adds uncertainty due to design and patient differences.	Major uncertainty from non-randomised OS/PFS extrapolation, long-term survivor assumption, utility sources, and treatment cost modelling approaches.	3.5%[b]			✗
TA 895	**Yescarta** (Axicabtagene ciloleucel)	Large B-cell lymphoma	ZUMA-7 trial has short follow-up, unknown cure fraction, high rate of cross-over to CAR-T in SOC arm, uncertain UK generalisability due to population and pathway differences.	ICER uncertainty due to choice of cure fraction, OS extrapolation, cross-over adjustment method, post-event utility selection, and cost assumptions for subsequent SCT and adverse events	3.5%		CDF	✓
TA 975	**Kymriah** (Tisagenlecleucel)	B-cell leukaemia	Potentially exaggerated benefits due to EFS definition, pooled non-randomised data; comparator evidence has limited UK relevance.	ICER highly sensitive to dataset, OS/EFS extrapolation, utility values, IVIg costs, comparator selection, and cure fraction assumptions.	3.5%	1.7	CDF[c]	✓
TA 989	**Hemgenix** (Etranacogene dezaparvovec)	Haemophilia B	Single-arm trial; risk of COVID-related bias; external comparator efficacy and suitability uncertain; durability data limited.	Cost-effectiveness hinges on durability, threshold for restarting IV FIX, utility differences, and small number of non-responders.	3.5%		IMF	✓
TA 1003	**Casgevy** (Exagamglogene autotemcel)	Beta-thalassaemia	Small, single-arm trial with short follow-up. Uncertainty regarding durability of transfusion independence and long-term safety.	ICER sensitive to relapse, model structure, mortality, HRQoL, withdrawal rates, transfusion frequency and discounting.	3.5%		IMF	✓
TA 1044	**Casgevy** (Exagamglogene autotemcel)	Sickle cell disease	Single-arm, small, short-term trial. Uncertain NHS generalisability due to few UK patients. Long-term outcome uncertainty.	Model lacks Markov structure, dropout costs, key adverse events and robust sensitivity analyses; inappropriately use of VOC data.	3.5%	1.2	IMF	✓
TA 1048	**Breyanzi** (Lisocabtagene maraleucel)	Large B-cell lymphoma	TRANSFORM trial population, prior/subsequent therapies, and CAR-T sequencing differ from NHS care, so UK applicability and efficacy estimates are uncertain.	Model structure, survival extrapolation, subsequent and bridging therapy distributions, UK-specific AE costs, and health state utilities are not robustly validated or fully aligned with UK context.	3.5%			✓

[a] HST24 is a partial update of HST15, focusing on presymptomatic disease. Therefore, HST15 and HST24 are shown sequentially but considered separately. [b] As discount rate was not disclosed, the standard rate was assumed. [c] MAA was used as part of the original appraisals, TA559 (replaced by TA872) and TA554 (replaced by TA975).

Abbreviations: AADC, aromatic L-amino acid decarboxylase; ADA, adenosine deaminase; AE, adverse event; CAR-T, chimeric antigen receptor T-cell; COVID, coronavirus disease; EFS, event-free survival; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV FIX, intravenous factor IX; IVIg, intravenous immunoglobulin; ND, not disclosed; OS, overall survival; PAS, Patient Access Scheme; PFS, progression-free survival; PRO, patient-reported outcome; RCT, randomised controlled trial; SCID, severe combined immunodeficiency; SCT, stem cell transplant; SMN2, survival motor neuron 2; SOC, standard of care; VOC, vaso-occlusive crisis.

Used Not used ✓ Full Recommendation ✓ Restricted Recommendation ✗ Not recommended

Conclusions

Findings

- While both HST and STA pathways have enabled access to gene therapies in the UK, key differences exist in how uncertainty is managed.
- HST appraisals demonstrated greater flexibility in applying favourable modifiers and discount rates and were more likely to result in unrestricted recommendations.
- Technologies evaluated through the STA route faced tighter scrutiny of clinical evidence and economic assumptions, often resulting in restricted access and MAAs to address uncertainty.

Implications

- NICE's recently updated HST routing criteria reinforce the requirement that technologies must be innovative and target ultra-rare, lifelong and debilitating conditions.[1]
- The revised framework could result in a greater proportion of gene therapies being assessed through the STA route, especially in cases of more prevalent or less severe conditions.
- Considering the stricter evidentiary requirements and cost-effectiveness thresholds associated with the STA route, MAAs are expected to play an increasingly critical role in enabling timely access while addressing uncertainty.

References: *(1) NICE.* Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes. *Available at*: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf. *Accessed October 27, 2025. (2) NICE.* NICE publishes new combined methods and processes manual and topic selection manual. *Available at:* https://www.nice.org.uk/news/articles/nice-publishes-new-combined-methods-and-processes-manual-and-topic-selection-manual-for-its-health-technology-evaluation-programmes. *Accessed October 27, 2025. (3) NICE. Changes approved to the routing criteria for highly specialised technologies. Available at: https://www.nice.org.uk/news/articles/changes-approved-to-the-routing-criteria-for-highly-specialised-technologies. Accessed October 2, 2025.* ***Declaration of funding:*** *This project has been funded in full by Symmetron Limited.*