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Assessing the potential impact of NICE's updated HST routing criteria on ultra-orphan drugs

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Background and Objective:

What is the Highly Specialised Technology (HST) programme?

HST evaluations by the National Institute of Health and Care Excellence (NICE) in United Kingdom are designed to facilitate assessment of treatments for ultra-rare, debilitating conditions, given their unique challenges in evidence generation for very small patient populations.

In March 2025, NICE made changes to the HST routing criteria to improve their clarity and consistency without affecting the number of therapies assessed via the HST programme.[1]

The aim of this analysis was to understand how the updated routing criteria might affect the eligibility of new medicines for this programme in the future. We applied the updated HST routing criteria to previously conducted appraisals to understand their potential impact on future submissions.

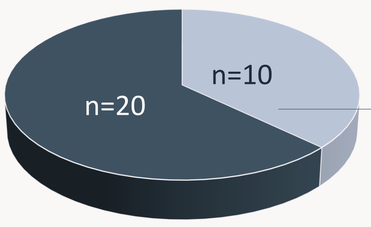
Methods:

All HST reports published by NICE until June 1st 2025, were extracted and benchmarked against each of the four updated routing criteria to assess their current eligibility status for the HST programme.

Results

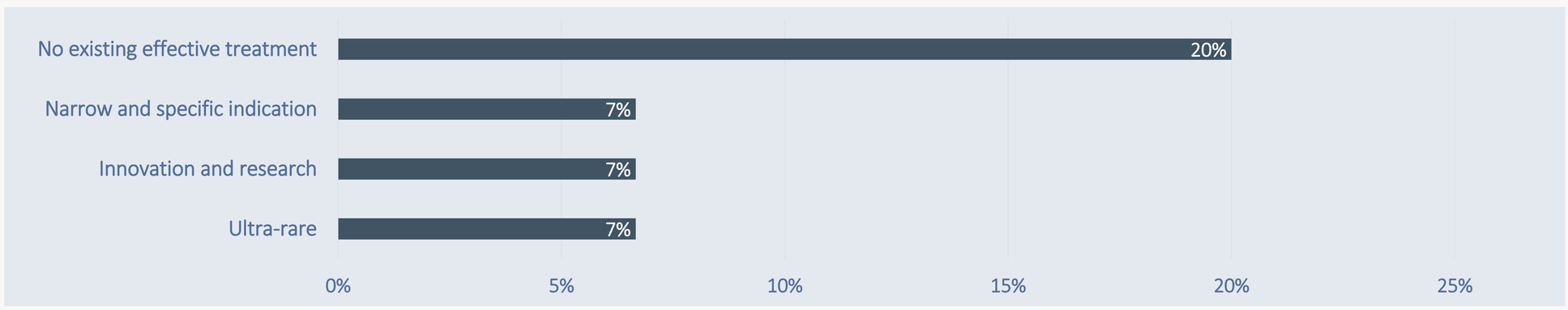
On March 19, 2025, changes to the routing criteria for HST were approved, with implementation starting from April 1, 2025.[1-2]

	Before the update	After the update
Ultra-rare & debilitating	Could be a subgroup based on genetic subtype	Only if the genetic subtype defines a unique clinically meaningful and distinct subgroup
Innovation and research	Considered innovative (not defined)	Must be innovative (e.g., ATMPs, new drug entities) and not a significant extension from another population or disease
Narrow and specific indication	Could be individualized medicine	Cannot be individualized medicine (i.e., developed based on a person's genome)
	Up to 500 people across all indications	No more than 300 people in England for the indication
No existing effective treatments	Likely offered substantial additional benefit over current standard of care	Likely offered substantial additional benefit over current standard of care and Existing clinical management must be inadequate



~33% (10/30) of legacy appraisals for 10 distinct therapies potentially may no longer meet either one (8/10) or two (2/10) of the four updated routing criteria for HSTs

Proportion of previously conducted HST appraisals (N=30) where the updated criteria might not be fulfilled



Eligibility of previously conducted HST appraisals evaluated against the newly updated HST criteria

Treatment	Indication	HST criteria met				Rationale
		Ultra-rare	Innovation and research	Narrow and specific indication	No existing effective treatments	
Setmelanotide	• Obesity and hyperphagia in LEPR or POMC deficiency • Obesity and hyperphagia in Bardet-Biedl syndrome (BBS)	✓	✗	✓	✓	Setmelanotide's original indication for 2021 was extended to include BBS, which would not meet the criterion that the technology must not have an indication extension from another disease.
Birch bark extract	Epidermolysis bullosa (EB)	✗	✓	✗	✓	• EB is usually diagnosed in babies and children and is thought to affect 1 in 17,000 births with around 5,000 people affected in the UK, which is above the specified prevalence for the ultra-rare criterion of ≤1 in 50,000. • EB is estimated to affect 5,000 people which is beyond the threshold set for the narrow and specific indication criterion requiring that only ≤300 people in England must be eligible for the treatment.
Afamelanotide	Erythropoietic protoporphyria (EPP)	✓	✓	✗	✓	There were 390 patients with EPP as of 2006, with estimates of 500-600 patients accounting for underdiagnosis, which does not meet the specified threshold of only ≤300 people in England who are eligible for treatment.
Selumetinib	Symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis (NF1) in children aged 3 and over	✗	✓	✓	✓	Prevalence of NF1 is 1 in 4,560, which is above the specified threshold for the ultra-rare criterion of ≤1 in 50,000.
Patisiran	Hereditary transthyretin amyloidosis	✓	✓	✓	✗	Two competing therapies exist (patisiran and inotersen). Additionally, tafamidis is indicated but not available in England due to a negative recommendation while diflunisal is another off-label option in use, albeit it is not suitable for many patients due to its contraindications.
Inotersan		✓	✓	✓	✗	
Strimvelis	Adenosine deaminase deficiency-severe combined immunodeficiency	✓	✓	✓	✗	Enzyme Replacement Therapy (ERT) with PEG-ADA is a preferred treatment if a matched donor is available and is also curative, hence it might not meet the "no existing effective treatments" criterion.
Eliglustat	Type 1 Gaucher disease	✓	✓	✓	✗	ERT is preferred for treating type 1 Gaucher disease and substrate replacement therapy may be considered in patients who do not tolerate or cannot receive ERT, which might not meet the "no existing effective treatments" criterion.
Migalastat	Fabry disease	✓	✓	✓	✗	Treatments such as ERT date back to 2001. Migalastat was first approved in 2016 and is a different category "chaperone" drug, hence it might fail to meet the "no existing effective treatments" criterion.
Eculizumab	Atypical hemolytic uremic syndrome	✓	✗	✓	✗	• Plasma therapy is an available treatment option and though response to it is variable, up to 40% of patients may die or progress to ESRD, which makes qualifying the "no existing effective treatments" criterion uncertain. • Eculizumab is also used for other indications such as PNH, aHUS, myasthenia gravis, and NMOSD, thus it might fail to meet the newly revised "innovation and research" criterion too.

Conclusion:

The updated NICE HST routing criteria may facilitate benchmarking of new therapies against a set of better-defined eligibility metrics. However, without some flexibility in the application of these criteria, innovative ultra-orphan drugs in the future might find it harder to obtain patient access via the HST assessment pathway.

Given the small number of HST assessments conducted annually, it will take considerable time to establish whether these new routing criteria have any undesirable real-world consequences for ensuring timely patient access to highly specialized innovative treatments.

Abbreviations

aHUS, atypical hemolytic uremic syndrome; ATMP, advanced therapy medicinal products; EB, epidermolysis bullosa; EPP, erythropoietic protoporphyria; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplantation; HST, Highly specialised technology; LEPR, leptin receptor; NF1, type 1 neurofibromatosis; NICE, National institute for Health and Care excellence; NMOSD, neuromyelitis optica spectrum disorder; PEG-ADA, polyethylene glycol- modified adenosine deaminase; PNH, paroxysmal nocturnal hemoglobinuria; POMC, proopiomelanocortin

References

1. NICE-wide topic prioritisation: the manual. NICE process and methods. Published: 29 May 2024, Last updated: 31 March 2025 https://www.nice.org.uk/process/pmg46/resources/highly-specialised-technologies-nice-prioritisation-board-routing-criteria-15301445581/chapter/hst-routing-criteria
2. Highly specialised technologies: NICE prioritisation board routing criteria. Published: 31 March 2025. https://www.nice.org.uk/process/pmg46/resources/highly-specialised-technologies-nice-prioritisation-board-routing-criteria-pdf-19830673472965

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