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Reassessing NICE's Highly Specialised Technologies (HST) Criteria: A Retrospective Review of Completed Appraisals Using the Revised Framework

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Aims

- To evaluate how the UK National Institute for Health and Care Excellence's (NICE) revised routing criteria for the Highly Specialised Technologies (HST) pathway would apply retrospectively to evaluations of technologies for rare and ultra-rare conditions completed between 2020 and 2025.
- To assess alignment of completed HST and Single Technology Appraisal (STA) evaluations with the revised framework and examine consistency of NICE's interpretation of key eligibility criteria.

Background

- NICE has different routes or pathways of evaluation for different healthcare technologies. The majority of new medicines are evaluated via the STA route; the HST programme evaluates new medicines for very rare conditions.[1]
- From the HST programme's introduction in 2013 to February 2022, NICE applied seven criteria to determine eligibility. In 2022, the number of criteria was reduced to four, centred around the following themes: ultra-rare condition; small patient population; substantial disease burden; and unmet need with likelihood of significant benefit (Box 1).
- All four criteria had to be met for a technology to be routed down the HST evaluation pathway, failing which the technology would be routed to the STA programme. The criteria were a mix of objective and subjective criteria, with various aspects potentially open to different interpretation (see Box 1).
- The criteria were updated and refined in March 2025 "to ensure consistent, predictable, and transparent decisions for routing technologies" to the HST pathway (Box 2).
- The HST routing decision is important for new technologies for several reasons, but primarily:
  - The higher willingness-to-pay (WTP) threshold of £100,000/quality-adjusted life year (QALY) applies,
  - There is greater flexibility when considering uncertainty in the evidence base, and
  - There is the opportunity to negotiate commercial and managed access schemes that go beyond a simple price discount.

Methods

- A retrospective review was conducted on two cohorts of NICE evaluations, completed and published between 2020 and April 2025:
  1. Completed HST evaluations (N=22)
  2. A subset of STAs for rare and borderline ultra-rare diseases identified through consultation feedback or stakeholder commentary as potential HST candidates.
- Each included appraisal was reassessed against the 2025 eligibility criteria using HST routing checklists (where available), scoping documentation, and final guidance.
- Thematic analysis was then applied to evaluate how the routing criteria had been applied previously compared with how the revised criteria would apply in the future.
- Four themes were considered: (i) definition of a "debilitating" disease, (ii) innovation, (iii) prevalence and patient number thresholds, and (iv) likelihood of "substantial additional benefit".

Box 1: HST eligibility criteria (2022-2025)*

1. The condition must be ultra-rare (<1 in 50,000 prevalence in England)
2. The technology must be for a small patient population (**normally** <300 eligible patients in England for the licensed indication or up to 500 patients across all indications)
3. The disease **significantly shortens life** or **severely impairs** quality of life;
4. No other **satisfactory** treatment option exists or the technology is **likely to offer significant benefit** over existing options

*Words in bold are subjective and/or open to different interpretations

Limitations

- This was a non-exhaustive review of completed appraisals based on selected documents in the public domain and a limited number of themes chosen by the authors as being of particular interest. A more systematic, comprehensive review might yield different insights.
- HST routing checklists were only available for three of the 22 HST evaluations completed during the period of interest (HST21, HST28, HST33) as well as other potential HST candidates since 2022. As such, the authors' interpretation of key eligibility criteria may differ from that of decision-makers.

Results

Definition of "debilitating"

- According to the clarified criteria, a disease is "debilitating" if it is "lifelong" and has an "exceptional negative impact and burden", which in turn is described as shortened length of life or severely impaired quality of life. NICE acknowledges that the precise assessment of these terms will require an element of subjective judgement.
- Previous routing decisions suggest that the disease does not necessarily need to be life-threatening or life-limiting in and of itself to qualify for the HST programme. For example, final HST guidance for volanesorsen (familial chylomicronaemia syndrome, HST13[2]) and setmelanotide (obesity caused by LEPR or POMC deficiency, HST21[3]; obesity and hyperphagia in Bardet-Biedl syndrome, HST31[4]) focus primarily on the significant burden and impact on the quality of life of patients, their families and carers. Conversely, decision-makers concluded it was unclear whether Pompe disease, an ultra-rare inherited genetic metabolic disorder, significantly shortened life or severely impaired quality of life, thus routing cipaglucosidase alfa for STA evaluation.[5]

Innovation

- Innovation has been a factor that NICE evaluation committees have taken into consideration since the HST programme was first introduced, but the 2025 revisions have elevated innovation so that it constitutes a routing criterion in its own right. Under the clarified criteria, the technology will be considered an innovation if it is an advanced therapy medicinal product (ATMP), a new chemical or biological entity, or a novel drug combination that brings additional health gains.
- In several previous HSTs, the NICE committee accepted that the technology was innovative because it represented a "step change" in the management of the ultra-rare disease in question (givosiran for acute hepatic porphyria, HST16[6]; metreleptin for lipodystrophy, HST14[7]; setmelanotide, HST21[3]; onasemnogene abeparvovec for spinal muscular atrophy, HST15[8]).
- According to the clarified innovation criterion, the technology must be the first treatment for the "licensed indication" for the ultra-rare disease under consideration. As a result, technologies that are first-in-class (but second to market for a particular indication), have a different mechanism of action, or which claim to change the treatment paradigm may not qualify for the HST pathway in the future.

Point prevalence and maximum patient numbers

- Before 2025, HST routing was restricted to technologies licensed for a "small patient population, normally <300 in England". No definition was given of "normally" and we identified a small number of examples of previous HSTs where the threshold was exceeded, and which would likely not meet the revised criteria today. The givosiran HST identified 560 patients in England with acute hepatic porphyria, of which 35 experienced recurrent attacks.[6]
- Conversely, we found examples where innovative technologies to treat rare conditions were routed to the STA pathway instead of HST because they did not satisfy the strict condition of ultra-rarity. Routing checklists or scoping documents confirmed that the other criteria of significant burden of disease, unmet need, and likelihood of substantial additional benefit were generally met (see Table 1).
- Another example is spesolimab[11], a treatment for generalised pustular psoriasis (GPP). During scoping, the manufacturer reported GPP prevalence of 2.16:100,000 (i.e. just above the 1:50,000 cut-off for HST evaluation) and an estimated diagnosed patient population in England of 290 patients, and argued that GPP was a rare, severe, clinically heterogenous disease suitable for HST evaluation. NICE disagreed.
- In future, the boundary on estimated patient numbers will be determined by the marketing authorisation, not the (sometimes narrower and smaller) target patient population for which the submitting manufacturer is seeking reimbursement in England or the proportion who might be eligible for the treatment in clinical practice.
- This is important, because it means that some rare diseases, conferring equally significant burden and impact as some ultra-rare conditions, and where innovative, first-in-class treatments have the potential to offer substantial additional clinical and quality of life benefits, could be denied access to the HST programme (and increased WTP threshold) based on the prevalence and patient number criteria alone.

Substantial additional benefit

- In previous HST recommendations, laboratory-based and surrogate endpoints have been considered relevant for decision-making. In HST25 (lumasiran for primary hyperoxaluria type 1[9]), the committee noted that clinical trial evidence suggested that lumasiran plus standard of care reduced oxalate levels compared to standard of care (SoC) alone. In HST14[7], evidence from clinical trials and indirect comparisons suggested that metreleptin improved HbA1c, triglyceride levels and liver enzyme levels, as well as acute pancreatitis and hyperphagia. In the odevixibat evaluation (HST17[10]), the primary outcome in the PEDFIC1 trial for Europe and the rest of the world was the proportion of people who had a reduction of at least 70% in the serum bile acid level from baseline or levels that reached 70 micromol/litre or less.
- Based on the clarified criteria, it is unlikely that surrogate endpoints alone will suffice in future to demonstrate that the technology is likely to offer substantial additional benefits over current management options. Instead, "substantial additional benefit" means that the technology, at the point of routing, is likely to demonstrate clinically relevant outcomes, such as patient-reported outcomes measures or improved mortality.

Box 2: HST eligibility criteria (revised and clarified March 2025)*

1. The disease is **ultra-rare** and **debilitating**, that is,
   - ***1A:*** it is defined as having a point prevalence of 1:50,000 or less in England
   - ***1B:*** it is lifelong after diagnosis with current treatment, and has an **exceptional negative impact and burden** on people with the ultra-rare disease, and their carers and families.
2. The technology is an **innovation** for the ultra-rare disease
3. No more than 300 people in England are eligible for the technology in its licensed indication, and the technology is not an individualised medicine.
4. The technology is **likely to offer substantial additional benefit** for people with the ultra-rare disease over existing established clinical management, and the existing established clinical management is **considered inadequate**.

*Words in bold are subjective and/or open to different interpretations

Table 1: Examples of HST routing checklists

	Oleogel-S10 for treating skin wounds associated with epidermolysis bullosa (HST28)	**Omaveloxolone for treating Friedreich's ataxia** (TA1061, terminated)	**Setmelanotide for obesity and hyperphagia in Bardet-Biedl syndrome** (HST31)	**Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years** (TA1033)	**Leniolisib for activated phosphoinositide 3-kinase delta syndrome in people 12 years and over** (HST33)	**Vamorolone for treating Duchenne muscular dystrophy** (TA1031)
1. Condition is ultra-rare	✓ Met	✓ Met	✓ Met	✓ Met	✓ Met	✗ Not Met
2. Technology is for a small patient population (normally <300 in England)	✓ Met	✗ Not Met	✓ Met	✓ Met	✓ Met	✗ Not Met
3. Disease significantly shortens life or severely impairs quality of life	✓ Met	✓ Met	✓ Met	✓ Met	✓ Met	✓ Met
4. No other satisfactory treatment option exists or the technology is likely to offer significant benefit	✓ Met	✓ Met	✓ Met	✗ Not Met	✓ Met	✓ Met

Conclusion

- The NICE routing decision is important given the vastly different WTP thresholds for the STA and HST routes.
- Our review suggests that several technologies for rare diseases previously evaluated via the STA route would likely meet the revised HST criteria, were it not for the prevalence threshold of <1:50,000.
- Between 2020 and early 2025, innovative technologies for rare conditions associated with significant unmet need, exceptional clinical burden and negative quality of life impact have missed out on an HST evaluation because the condition is not sufficiently rare to meet both prevalence and patient number thresholds. It will be interesting to see how rigidly these thresholds are applied to future routing decisions.
- Conversely, some technologies or diseases previously evaluated via the HST route may no longer meet the threshold for "substantial additional benefit" or "exceptional burden" under the revised criteria.
- While the revised HST criteria and their accompanying descriptions aim to bring greater clarity, consistency, and fairness to the appraisal process for ultra-rare conditions, there remains scope for different interpretation around key eligibility terms such as "innovative", "substantial additional benefit" and "exceptional negative impact and burden".
- Our findings underscore the need for clear operational guidance, and consistency of application, tempered with a degree of pragmatism, especially where criteria are still open to varying interpretations.

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References:
1. NICE, 2025. https://www.nice.org.uk/what-nice-does/our-guidance/about-highly-specialised-technologies-guidance; 2. https://www.nice.org.uk/guidance/hst13; 3. https://www.nice.org.uk/guidance/hst21; 4 https://www.nice.org.uk/guidance/hst31; 5. https://www.nice.org.uk/guidance/ta912/documents/supporting-documentation; 6. https://www.nice.org.uk/guidance/hst16; 7. https://www.nice.org.uk/guidance/hst14; 8. https://www.nice.org.uk/guidance/hst15; 9. https://www.nice.org.uk/guidance/hst25; 10. https://www.nice.org.uk/guidance/hst17; 11. https://www.nice.org.uk/guidance/ta1070.