ANALYSIS OF NICE ASSESSMENTS FOR ORPHAN MEDICINES AND KEY DRIVERS FOR DECISION-MAKING

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INTRODUCTION

- For a medicine to qualify for orphan designation in the UK, the prevalence of a life-threatening or chronically debilitating condition must be ≤5 in 10,000.[1]
- Small patient numbers present challenges for collecting clinical data in rare patient populations, often leading to clinical uncertainty, making it more difficult for payers to make decisions for treatments which are often expensive/higher than the traditional cost-effectiveness threshold, despite high clinical need.[2]
- For ultra-rare illnesses, NICE have a Highly Specialised Technologies (HST) pathway with a higher acceptable ICER threshold (£100,000 per QALY gained), however, not all orphan medicines meet the criteria:[3]
  - The condition is "ultra-rare", defined by 1 in 50,000 in England, and debilitating (exceptional negative impact and burden)
  - The technology is an innovation for the ultra-rare disease
  - No more than 300 people in England are eligible for the technology in its licensed indication, and the technology is not an individualised medicine
  - The condition significantly shortens life or severely impacts quality of life
  - The technology is likely to offer substantial additional benefit over existing established clinical management (which is considered inadequate)
- In addition to the HST pathway, NICE has multiple mechanisms by which uncertainty can be addressed, such as Managed Access Agreements (MAA) and the Cancer Drugs Fund (CDF), or to allow greater flexibility in cost-effectiveness estimates, such as severity modifiers, and previously, End-of-Life criteria.
- The objective of this study was to understand orphan medicine decision-making in England and Wales.

METHODS

- Medicines with UK orphan designation were identified through the MHRA orphan register.[4] Medicine names and therapeutic indications were recorded.
- The NICE website was searched (up to 9th January 2025) for technology appraisal (TA) and HST guidance for medicines identified through the MHRA orphan register.[5]
- Guidance publication dates, therapeutic indications, decision outcomes, commercial arrangements, MAAs, and key decision drivers were extracted from publicly available final guidance documents.

RESULTS

Medicines & Healthcare products Regulatory Agency

144 medicines with current orphan designation in the UK

- 144 medicines with orphan designation in the UK were identified via the MHRA orphan register, of which 41 (29%) were oncology drugs.
- There were 102 NICE appraisals for medicines identified on the MHRA orphan register (including single TA [STA] and HST); 97 (94%) were recommended.
- 9 appraisals were in development at the time of analysis: 6 STAs and 3 HSTs.

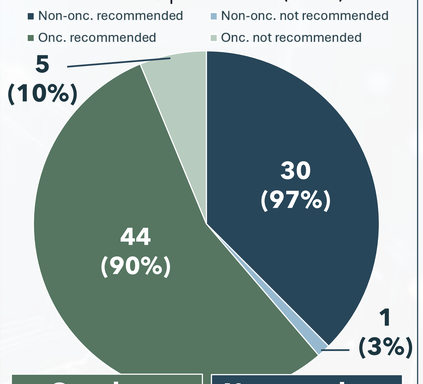
RESULTS

NICE National Institute for Health and Care Excellence

102 NICE appraisals for medicines currently with MHRA orphan designation

80 STAs

74 Recommended (93%)
>> 27 Optimised* (37%)



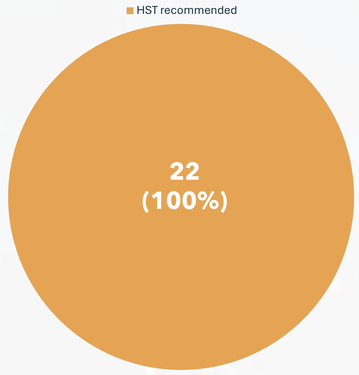
Oncology	Non-oncology
40 (91%) simple discount PAS **3 (7%)** recommended via CDF; **5 (11%)** reviews of CDF data	**23 (77%)** simple discount PAS **3 (10%)** MAA i.e. recommended while further data collected

Key drivers†

6 (8%) Severity Modifier
End-of-Life **15 (20%)**
1 (1%) Lower discount rate of 1.5%
Unmet need **70 (95%)**
19 (26%) Innovation
Family QoL **16 (22%)**
40 (54%) Clinical uncertainty
Economic uncertainty **31 (42%)**

22 HSTs

22 Recommended (100%)
>> 6 Optimised* (27%)



20 (91%) simple discount PAS

4 (18%) MAA i.e. recommended while further data collected

Key drivers†

12 (55%) QALY weighting
1 (5%) Lower discount rate of 1.5%
Unmet need **20 (91%)**
16 (73%) Innovation
Family QoL **11 (50%)**
17 (77%) Clinical uncertainty
Economic uncertainty **19 (86%)**

CONCLUSION

- NICE recommended 94% of orphan medicines assessed via either pathway; 32% of these recommendations were optimised i.e. a narrower patient population than allowed by the marketing authorisation.
- 87% of recommendations required a PAS, and a further 9% were recommended subject to further data collection to address uncertainty.
- Clinical and economic uncertainty was discussed in over 75% of HST appraisals, which is to be expected when considering rare diseases and the difficulty in collecting comparative long-term data. Through a combination of higher ICER thresholds, QALY weighting, PAS and MAA, uncertainty did not inhibit patient access to important treatments.
- Clinical and economic uncertainty was highlighted less frequently by the committee in STA appraisals; the severity modifier and former End-of-Life process allowed greater flexibility in cost-effectiveness estimates.
- Unmet need was a key contributor to the committee's decision-making in both pathways, while innovation was more frequently discussed in HST appraisals, reflecting the HST pathway criteria.
- These data suggest that assessment of orphan medicines via the NICE STA pathway (rather than HST) is not necessarily a significant barrier to reimbursement, and greater cost-effectiveness flexibility in HST appraisals is working as intended to ensure patient access to orphan medicines.
- Methodological updates such as the severity modifier and non-reference-case discount rates are likely to play an increasingly important role in the appraisal of rare diseases, particularly as expensive gene and cell therapies come to market. Greater utilisation of MHRA's Innovative Licensing and Access Pathway (relaunched March 2025) and NICE's Innovative Medicines Fund could support the ongoing difficulty of demonstrating value for rare disease medicines. Furthermore, adapting the criteria for non-reference-case discounting would give greater weight to long-term QALY gains and help justify high upfront costs (e.g. one-off gene therapies).
- Whilst we found that almost all orphan drugs were recommended by NICE, many orphan medicines approved by the FDA in 2024 have not yet attained EMA approval (79 vs 46). Therefore, manufacturers, regulators and payers must work together to ensure European patients with rare diseases are able to access the newest and most effective treatments.[6]

*optimised = narrower patient population than the marketing authorisation; †percentages of recommended appraisals.

Abbreviations: CDF, Cancer Drugs Fund; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HST, Highly Specialised Technology; ICER, incremental cost-effectiveness ratio; MAA, Managed Access Agreement; PAS, Patient Access Scheme; QALY, quality-adjusted life year; QoL, quality of life; STA, single technology appraisal. **References:** (1) Gov.uk (2025). Guidance: orphan medicinal products. Accessed at: https://www.gov.uk/guidance/orphan-medicinal-products-in-great-Britain; (2) Fehr, A. & Prütz. F (2023). Rare diseases: a challenge for medicine and public health. *J Health Monit.*, 8(4):3-6. doi: 10.25646/11826; (3) NICE (2025). NICE-wide topic prioritisation: the manual. Accessed at: https://www.nice.org.uk/process/pmg46/resources/highly-specialised-technologies-nice-prioritisation-board-routing-criteria-15301445581/chapter/hst-routing-criteria; (4) Gov.uk (2025). Orphan register. Accessed at: https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register; (5) NICE (2025). Published: Guidance, quality standards and advice. Accessed at: https://www.nice.org.uk/guidance; (6) Coronado Research (2025). The Future for Orphan/Rare Illnesses: Time for a New Approach? Accessed at: https://coronado-research.com/insight/the-future-for-orphanrare-illnesses-time-for-a-new-approach