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HTA8

A Long and Winding Road: An Evaluation of NICE HST Appraisals Taking Longer Than Two Years for Guidance Publication

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Background

The National Institute for Health and Care Excellence (NICE) Highly Specialised Technology (HST) programme is designed to evaluate innovative technologies that address the high unmet need in ultra-rare diseases with debilitating symptoms

These conditions have an exceptional negative impact and burden on the people living with them, and on their carers and families, for whom timely access to new treatments is key.

However, events that extend the health technology assessment (HTA) process such as consultations, appeals, and additional committee meetings can push back publication of NICE final guidance, delaying patients' access to treatment.

Methods

Publicly available HST appraisal data were collected from programme inception to May 2025.

The duration of the appraisal process was calculated as the length of time from Final Scope (FS) to Final Evaluation Determination (FED).

For appraisals taking longer than 2 years, the main critiques from the committee and External Assessment Group (EAG) were extracted and qualitatively analysed.

"In the NICE HST appraisals taking >2 years, what are the common critiques?"

Results

Of the 30 HST appraisals published between January 2015 and May 2025, 2 resulted in the appraised technologies not being recommended, and were excluded from subsequent analyses.

Mean duration of the 28 HST appraisals culminating in a positive recommendation was 81 weeks. For the 6 appraisals taking longer than 2 years, several common issues were observed (Table 1; Figure 1):

1. Lack of coherence between the company strategy and the presented clinical trial evidence
2. Questionable selection and interpretation of outcome measures
3. Limited description of ancillary studies
4. Incomplete review of previous evidence
5. Model assumptions that were not aligned with current clinical guidance and practice
6. Methodological limitations of the statistical analyses and/or the economic model

***Figure 1**. Main themes and common critiques identified*

***Table 1**. Selected examples of common themes and main critiques*

Theme	Supporting quotes
Strategy and clinical trial evidence	About 48% of patients [in the pivotal trial] had a higher (…) than the recommended dosage stated in the SmPC.[1] [The committee] concluded that, because of the higher dosing in trials, volanesorsen's effect on clinical and safety outcomes may have been overestimated in the short term and that, given the lack of evidence, its effect in the long term at any dose is uncertain.[2]
Selection and interpretation of outcome measures	[The] score appeared to be insensitive to changes in disease status, so did not reflect differences between the treatments seen in the [trial].[1] [A] one-off questionnaire might not fully capture the effect of FCS on quality of life.[2]
Description of ancillary studies	The committee was concerned about the robustness of the vignettes used to elicit the utility values [due to] lack of details on the study methodologies, such as recruitment, description of health states and the ordering of questions asked.[2] [A] critical analysis of the GL/PL natural history study (…) was not provided in the clinical section and included a population different to the metreleptin studies.[3]
Review of previous evidence	The company included utility decrements for carers in the economic model [from] a NICE submission (…) [The] source of the carer utility decrement, and the committee's view of it, in the [previous] submission was unknown.[2] [The] submission did not include any search term for comparators, and […] there was no attempt to do indirect comparisons to study the effects of established clinical management.[3]
Model assumptions	[There] was considerable evidence to suggest that substantially lower doses of ERT are used in practice, so the higher dose of ERT assumed in the model overestimated [its] acquisition cost.[1] The committee noted that the incremental QALYs gained for patients who had cerliponase alfa estimated in the company's base case was 30.42. [An] analysis [incorporated] assumptions that [the committee] did not consider to be realistic.[4]
Statistical analysis and modelling methods	[The] estimates of mean decline in the natural history controls varied depending on the statistical method used, with more sophisticated methods (…) resulting in lower estimates.[4] The utility values for the base case were derived from a vignette study commissioned by the company (…) [which] did not distinguish between patients who were on treatment and those who were not, but instead by [low or high risk].[2]

Abbreviations: ERT, enzyme replacement therapy; FCS, familial chylomicronaemia syndrome; QALY, quality-adjusted life year; SmPC, Summary of Product Characteristics.

Discussion

Limited materials were used in the analyses, as potentially relevant components of the HST dossier, such as appendices and technical engagement documents (when applicable), are not publicly available.

The thematic analyses were limited to HST appraisals that took longer than 2 years. Further research could consider what features contributed to rapid decision-making in appraisals for which the submission process was the shortest.

Our advice:

I. Engage early with HTA bodies and payers
II. Build relationships with patient and physician groups
III. Develop a cross-functional evidence generation plan
IV. Map out a methodologically robust analysis plan

References

1. NICE, Eliglustat for treating type 1 Gaucher disease. 2017.
2. NICE, Volanesorsen for treating familial chylomicronaemia syndrome. 2020.
3. NICE, Metreleptin for treating lipodystrophy. 2021.
4. NICE, Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. 2019.
5. NICE, Elosulfase alfa for treating mucopolysaccharidosis type IVa. 2022.
6. NICE, Velmanase alfa for treating alpha-mannosidosis. 2023.

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