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TO HST, OR NOT TO HST

– that is the question

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EXECUTIVE SUMMARY

NICE's Highly Specialised Technology (HST) route is seen by many manufacturers as critical for rare disease market access in the UK. Compared with the standard appraisal routing, HST is associated with a favourable willingness to pay, greater acceptance of uncertainty and consideration of the impact beyond direct health benefit. More often than not, these factors lead to a positive outcome, with 30 of 31 HSTs published to date resulting in a positive recommendation.

However, HST is reserved for a very small number of eligible medicines, with 31 HSTs published at the time of writing, compared with 1006 published appraisals via the standard single technology appraisal (STA) route. As of 2022, four HST criteria must be met during NICE topic selection in order to qualify for HST, relating to population size, severity of condition, and degree of added benefit. This analysis of data obtained from a Freedom of Information request by Cogentia provides the most comprehensive review of NICE topic selection to date.

Cogentia has conducted a detailed thematic analysis of all available HST topic selection decisions taken by NICE's Topic Selection Oversight Panel (TSOP), with the following objectives:

1. To explore the impact of routing decisions on the ultimate appraisal outcome
2. To establish the key contributing factors to treatments being routed via HST or STA
3. To better understand the topic selection decision-making process, including the interpretation of each criterion and the use of external sources to inform it
4. To provide recommendations to manufacturers with orphan medicines that they believe may be eligible for HST routing.

Of 23 appraisals where NICE's TSOP was required to make a determination (i.e. where a HST routing was plausibly an option), the ultimate decision is overwhelmingly to route to STA; just four medicines were successful in achieving HST routing. Outcomes for the 19 medicines routed to STA have been largely negative, with a number of appraisals either terminated, suspended, or resulting in protracted processes.

To conclude, our findings support the conventional wisdom that for manufacturers targeting ultra-rare conditions, there is no more critical step in a successful UK market access strategy than qualifying for HST. To optimise the likelihood of achieving HST routing, manufacturers may draw lessons from the detailed analysis presented here, as well as the associated recommendations detailed at the end of the article.

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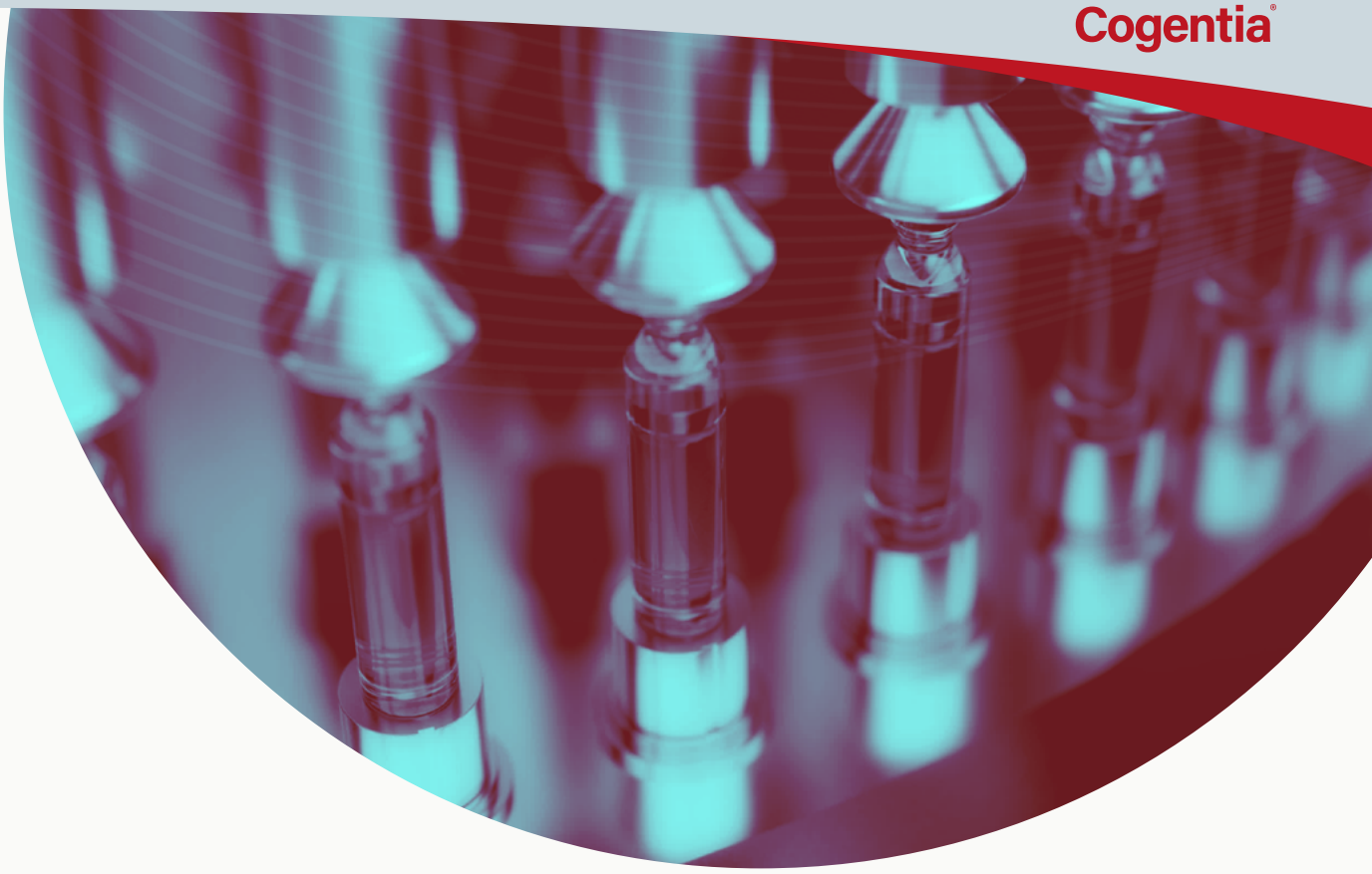


INTRODUCTION TO HST

Health Technology Assessment is conducted by the National Institute of Health and Care Excellence (NICE) in England. NICE makes recommendations on medicines that can be considered for routine commissioning by NHS England; the basis on which they make these decisions is through appraising clinical and cost-effectiveness evidence. With respect to cost-effectiveness, evidence is required that any incremental cost to acquire the new medicine is acceptable in relation to the benefits that are expected, and this is measured through calculating the number of Quality Adjusted Life Years (QALYs) gained, to determine a cost-effective price.

The majority of technologies are appraised through a single technology appraisal (STA), with NICE publishing their 1,000th STA in September 2024 (1). For a small subset of technologies treating very rare, severe conditions, there is an alternative route, the Highly Specialised Technology (HST) evaluation.

Compared with an STA, where the incremental cost-effectiveness ratio (ICER) threshold is £20,000 -£30,000 per QALY gained, appraisal via HST permits a far more generous ICER of £100,000 -£300,000, depending on the number of undiscounted QALYs gained. Other benefits of the HST process include a perceived willingness to accept greater uncertainty in the evidence package by the HST committee, and a consideration of the impact beyond direct health benefits, including taking a societal perspective. Given the relative lack of evidence available for ultra-rare conditions, the patient and carer perspective is also given greater focus in the HST process.

However, NICE is acutely aware that recommending a technology via HST results in the NHS allocating resources that would otherwise have been used on activities that would be expected to generate greater health benefits. As a result, the HST programme is designed to be used in exceptional circumstances. In fact, compared with 1006 published STAs, at the time of writing only 31 HSTs have been published. If we start the comparison at the time of HST1's publication, the number of published STAs is 677.

Given the reasons already outlined, the HST route is highly attractive to manufacturers. Of the 31 published HSTs, only one has resulted in a negative recommendation (HST27), resulting in a 96.7% success rate, far exceeding that of STAs; Clarke et al (2021) reported a success rate of just 67% for orphan medicines routed via STA between 2015 and 2020 (2).

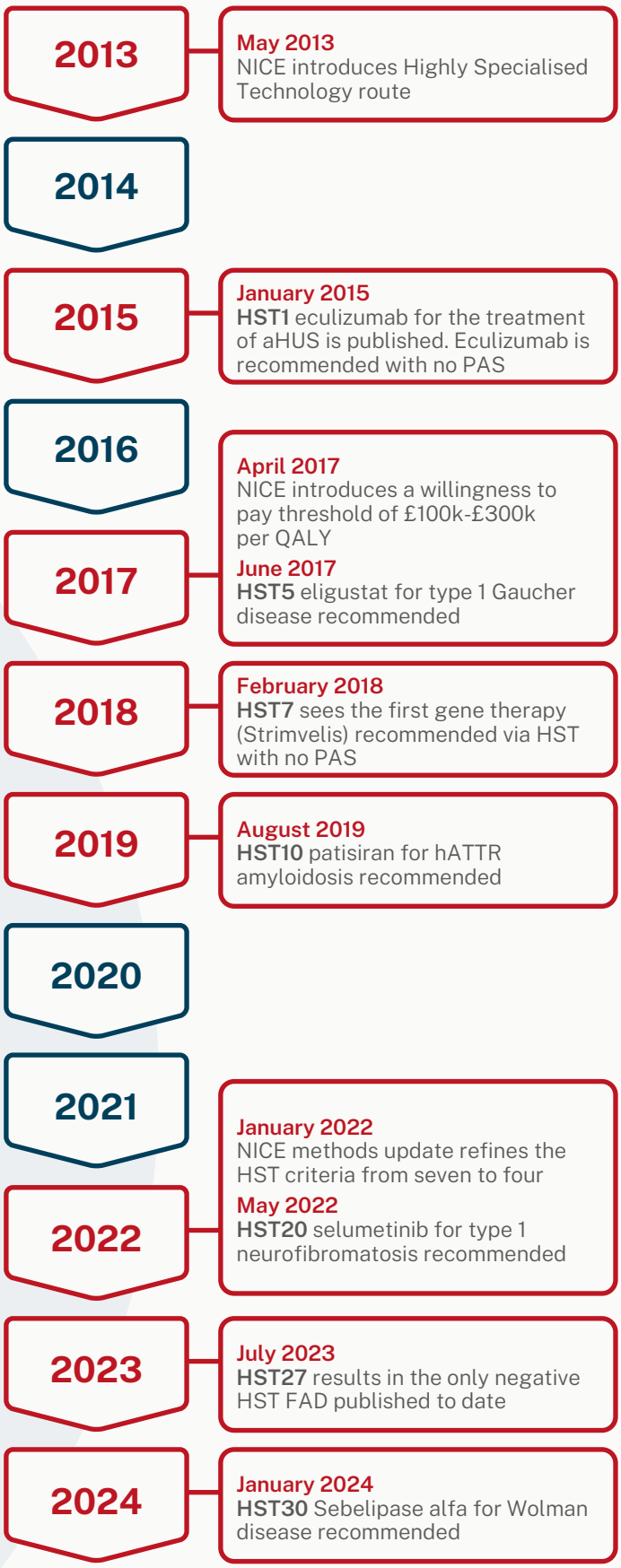
BRIEF HISTORY OF HST

The HST route was introduced by NICE in May 2013, taking over responsibility from the Advisory Group for National Specialised Services. The underpinning legislation described a HST as a health technology intended for use in the provision of services for rare and very rare conditions (3). As explained by NICE's Chief Executive Andrew Dillon at the time:

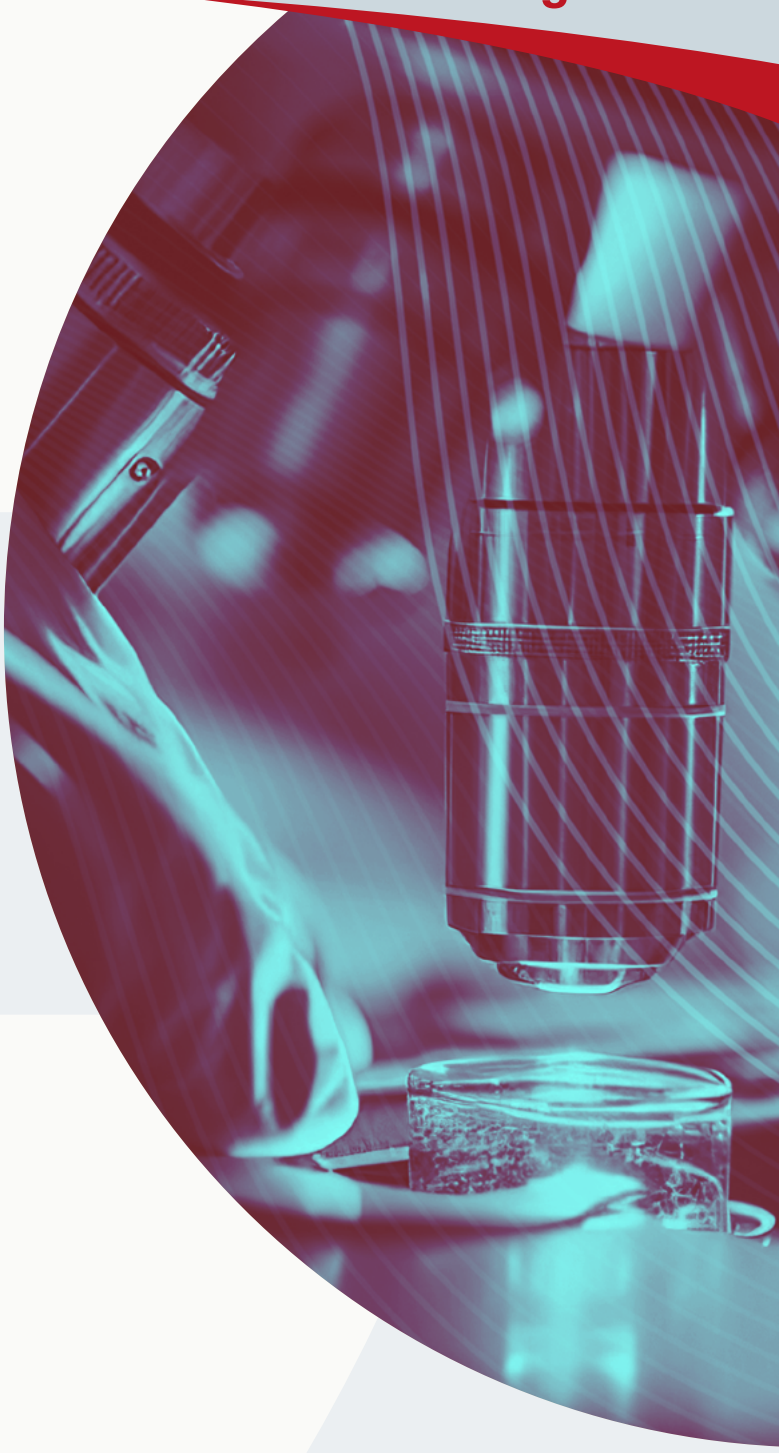
> *In evaluating [HST] drugs, NICE takes into account a greater range of criteria about the benefits and costs of HSTs than is the case with its appraisals of mainstream drugs and treatments. This is because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair.*

Figure 1 presents a timeline of the HST route since its introduction in 2013, highlighting some of the key milestones.

Figure 1: Highly Specialised Technologies: Key Milestones



Key: *aHUS, atypical haemolytic uraemic syndrome; FAD, final appraisal document; hATTR, hereditary transthyretin amyloidosis; PAS, patient access scheme*



Notable events include:

1. **The first published HST:** eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS). Incredibly, at least for those of us with experience engaging in negotiations with NICE and NHS England, eculizumab was recommended at list price, without the need for a confidential discount.

Sidebar: we note that having achieved list price in aHUS, Alexion did not provide an evidence submission in subsequent indications (TA636, TA647), perhaps in acknowledgement that a return to the negotiating table would likely result in a very different outcome. Alexion's (now AstraZeneca's) follow-on molecule, ravulizumab, has also only been recommended in paroxysmal nocturnal haemoglobinuria and aHUS, the two indications where eculizumab is recommended at list price, providing a relatively straightforward economic case.

2. **NICE introduces ICER thresholds:** in April 2017, NICE introduced an explicit ICER threshold for HST of £100,000-£300,000 per QALY. A threshold above £100,000 is determined by calculating undiscounted QALY gain for the technology under review, with a QALY gain of 10-30 corresponding to an acceptable ICER of £100,000 -£300,000. It is likely that the relatively generous pricing achieved in early HSTs (see point one) led NICE to realise a more robust mechanism for negotiation was required.

3. **The only negative HST:** as of June 2024, 30 of 31 HSTs have resulted in positive recommendations, either for the full or restricted population. The one exception is HST27, afamelanotide, for treating erythropoietic protoporphyria, despite several committee meetings and two appeal panel hearings. Based on a brief review of the published documentation, the inability of the manufacturer to include a discount on the list price of this medicine likely caused this rejection.

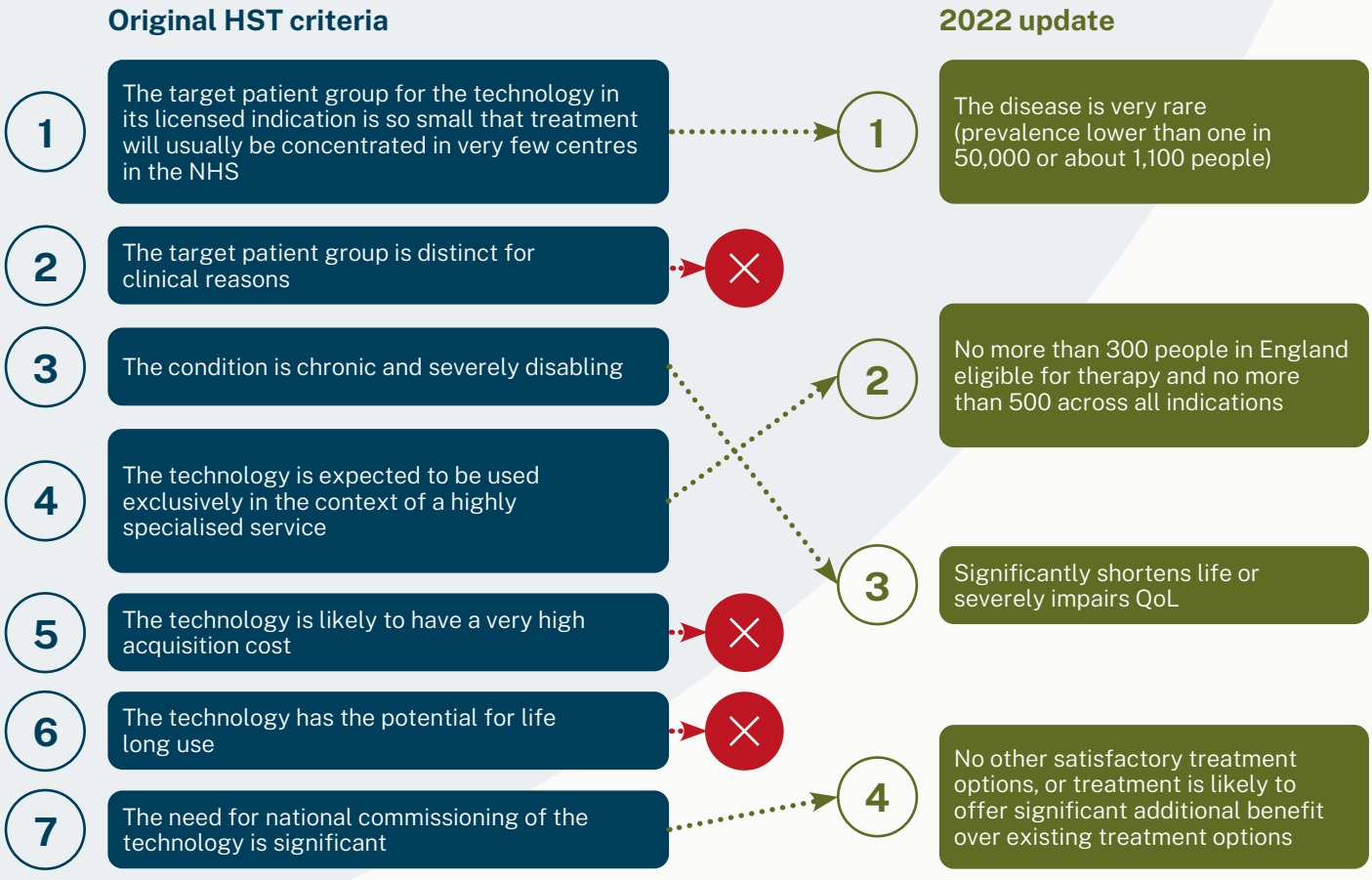
HST CRITERIA AND THE 2022 NICE METHODS UPDATE

To be routed via HST, technologies must satisfy all four of the following criteria:

1. The disease is very rare – defined as a prevalence of lower than one in 50,000, or about 1,100 people
2. Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications
3. The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life
4. There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.

Prior to the publication of NICE's updated methods manual in January 2022, medicines were assessed against seven criteria to determine HST eligibility. NICE explained at consultation that the criteria were refined to make 'routing decisions clearer, consistent, more transparent and precise to provide greater clarity, precision and predictability for the routing of topics through the Highly Specialised Technologies Programme'.

Figure 2: NICE Methods Update – HST Criteria Changes



THE TOPIC SELECTION OVERSIGHT PANEL

As part of its methods update, NICE established a new group, the Topic Selection Oversight Panel (TSOP). The TSOP consolidated the three existing topic selection decision-making groups into one, with the aim of promoting efficiency and consistency. Composed of senior NICE staff, and supported by external experts including from NHS England, the TSOP was the responsible party for determining whether new technologies should be routed to HST up until recently.

Note that as of May 2024, this role has been taken on by the NICE prioritisation board, although its remit as it relates to determining appropriate routing for potential HSTs is likely to remain the same, i.e. a NICE-led review of at least partially subjective criteria such as 'severe' and 'significant' to make a ruling on the appropriate routing.

The introduction of the TSOP in 2022 was accompanied by an increase in transparency relating to topic selection decisions. Prior to the NICE methods update, there was little information publicly available on why a treatment had been routed to STA or HST beyond making inferences based on the consultation on the draft scope. Following its establishment, where the TSOP has been asked to make a ruling on eligibility for HST, NICE routinely publishes the supporting documentation. This includes a narrative description of the TSOP's rationale, informing a decision as to whether each of the four criteria is met, partially met, or not met. NICE also used the methods update to formally introduce a process for stakeholders to appeal topic routing decisions – more on that later.

Although the introduction of the TSOP has greatly increased transparency of decision-making, the list of TSOP decisions regarding HST eligibility is not readily accessible on the NICE website. As a result, without prior knowledge, the only way to determine which appraisals required a TSOP decision would be to assess the individual pages of every TA published or in development since the start of 2022.

OBJECTIVES OF THIS ANALYSIS

In response to a Freedom of Information request to NICE topic selection, actioned on 23rd May 2024, Cogentia received a full list of the topics where the TSOP has made a ruling on eligibility for HST based on the streamlined four HST criteria introduced with the 2022 methods update. In total, there have been 23 such instances, starting with maralixibat for the treatment of cholestatic pruritus in Alagille syndrome (ID3941) in March 2022. In addition, there have been six appeals for five separate appraisals (the manufacturer appealed twice in ID3941, both times unsuccessfully).

It is important to note that all of these technologies will have been deemed to at least have plausible potential to be eligible for HST routing, as a prerequisite for referral into the TSOP to make a ruling. As such, a reasonable hypothesis is that where assessed technologies were routed via STA, the lower ICER threshold and limited flexibility for handling uncertainty would result in unfavourable outcomes for the manufacturer.

Cogentia has conducted a detailed thematic analysis of all available HST topic selection decisions taken by the TSOP that are based on the four HST qualifying criteria introduced in 2022, with the following objectives:

1. To explore the impact of routing decisions on the ultimate appraisal outcome
2. To establish the key contributing factors to treatments being routed via HST or STA
3. To better understand the topic selection decision-making process, including the interpretation of each criterion and the use of external sources to inform it
4. To provide recommendations to manufacturers with orphan medicines that they believe may be eligible for HST routing.

SUMMARY OF TECHNOLOGIES ASSESSED BY THE TSOP

A high-level summary of the 23 appraisals is presented in Table 1, with appraisals ordered from oldest to newest. Note that where companies appealed the initial routing decision, we have included only the outcome of the original TSOP decision for consistency. Further analysis of the appeals is presented in a later section.

Of the 23 appraisals, four of 23 (17.4%) were routed to HST, with the remaining 19 routed to STA. Note that as captured in the 'draft scope' column, NICE had only originally intended to appraise one of 23 (ID6264) by the HST route. As such, despite the limited number successfully achieving HST routing, the TSOPs intervention actually resulted in a higher proportion being routed to HST than may otherwise have been the case.

All of the appraisals routed to HST fulfilled all four criteria, as expected. As previously mentioned, to warrant referral into the TSOP all 23 will have been deemed to have the plausible potential to be suitable for HST; they are likely to treat small numbers of patients, in severe conditions, with limited treatment alternatives, or a clear added benefit. As such, and as demonstrated in Table 1, routing to STA poses a considerable challenge for these medicines.

Three of the four technologies to be routed to HST are still awaiting their first committee meeting, with the fourth, setmelanotide for Bardet Biedl syndrome (HST31), recommended for routine commissioning with a simple discount.

Of those routed to STA, outcomes have been overwhelmingly negative, with a number of appraisals either terminated, suspended or requiring protracted processes. This is not surprising given the more stringent ICER threshold and lower acceptance of uncertainty that characterise STA. Recall that any technology not routed to HST will be appraised via STA (with a few exceptions). These medicines are being assessed in the same process that any prevalent disease treatment, such as those for type 2 diabetes or asthma, would be.

Of the 19 technologies routed to STA, two are still at the early stages of appraisal, with the manufacturer no longer pursuing Medicines and Healthcare products Regulatory Agency (MHRA) approval for another (this is for reasons unrelated to the STA routing). Of the remaining 16, six (37.5%) have been recommended to date, all with a simple discount. Analysis of the remaining ten appraisals demonstrates the negative implications of routing via STA, and difficulties for manufacturers initially coming to terms with, and then navigating, the STA process:

- **One** of **ten** has not been recommended by NICE. ID3988 received a negative recommendation in August 2024, despite the committee accepting a severity modifier of 1.7x may apply
- **One** of **ten** has been suspended. ID3767 was suspended by NICE in September 2024 based on feedback from the manufacturer
- **Two** of **ten** have been terminated. Ravulizumab for neuromyelitis spectrum optica disorder (NMOSD) (TA941) and tabelecleucel for post-transplant lymphoproliferative disorder caused by the Epstein-Barr virus (TA923)
- **Four** of **ten** are awaiting further developments following routing to STA, which took place between September 2023 and January 2024. In this sense they may be considered suspended pending further update from the manufacturer
- **Two** of **ten** have faced extensive delays, with further detail below:
  - **ID547:** awaiting next steps following a negative draft guidance issued in May 2024. ACM2 originally June 2024 but delayed pending further update
  - **ID3941:** after an original topic selection decision in March 2022, two further unsuccessful appeals and a brief period suspended, appraisal committee meeting (ACM) 1 took place in July 2024, with a negative draft guidance issued on 31st July

Table 1: Summary of TSOP Outcomes and Current Status of Appraisals

Topic ID	Technology	Indication	TSOP outcome published	Draft scope	HST or STA?	Number of criteria met	Topic selection challenged?	Challenge successful?	Current status
ID3941	Maralixibat	Cholestatic pruritis in Alagille syndrome	Mar-22	STA	STA	2.5	Yes, twice	No	Negative draft guidance issued in July 2024
HST31	Setmelanotide	Bardet Biedl syndrome	May-22	STA	HST	4	N/A	N/A	Positive recommendation May 2024
TA912	Cipaglucosidase alfa	Late-onset Pompe disease	May-22	STA	STA	2.5	No	N/A	Positive recommendation August 2023
TA915	Pegunigalsidase alfa	Fabry disease	Aug-22	STA	STA	1.5	No	N/A	Positive recommendation October 2023
TA923	Tabelecleucel	EBV+ Post-transplant lymphoproliferative disorder	Nov-22	STA	STA	1	No	N/A	Terminated appraisal
ID3988	Ganaxolone	Seizures caused by CDKL5+ deficiency	Nov-22	STA	STA	3	No	N/A	Negative recommendation published in August 2024
ID1664	Omburtamab	Relapsed neuroblastoma	Nov-22	STA	STA	3	No	N/A	Company no longer pursuing MHRA approval
ID3932	Belzutifan	Tumours associated with von Hippel-Lindau disease	Dec-22	STA	STA	1	Yes	No	Positive recommendation issued August 2024
TA948	Ivosidenib	Advanced cholangiocarcinoma	Jan-23	STA	STA	2	No	N/A	Positive recommendation January 2024
TA949	Belumosudil	Chronic GvHD after 2+ systemic treatments	Feb-23	STA	STA	1	No	N/A	Positive recommendation February 2024
TA941	Ravulizumab	AQO4+ neuromyelitis optica spectrum disorder	Mar-23	STA	STA	2	No	N/A	Terminated appraisal
TA1002	Evinacumab	Homozygous familial hypercholesterolaemia	Mar-23	STA	STA	1	No	N/A	Positive recommendation issued September 2024
ID3767	Tofersen	SOD1 amyotrophic lateral sclerosis	Jun-23	STA	STA	3	Yes	No	Suspended in September 2024
ID3959	B-VEC	Dystrophic epidermolysis bullosa	Jun-23	STA	STA	2	Yes	No	No update since routing to STA in January 2024
ID4024	Vamorolone	Duchenne muscular dystrophy	Aug-23	STA	STA	2	No	N/A	Awaiting next steps following ACM3 in June 2024
ID547	Idebenone	Leber's hereditary optic neuropathy	Aug-23	STA	STA	2	No	N/A	Awaiting next steps following negative draft guidance May 2024
ID4029	Pegzilarginase	Arginase-1 deficiency	Sep-23	STA	HST	4	N/A	N/A	Negative draft guidance issued in August 2024
ID6181	Odevixibat	Cholestatic pruritis in Alagille syndrome	Sep-23	STA	STA	2	No	N/A	No update since routing to STA in September 2023
ID6130	Leniolisib	Activated phosphoinositide 3-kinase delta syndrome	Sep-23	STA	HST	4	Yes	Yes	Submission delayed due to regulatory expectations
ID3818	Maralixibat	Progressive familial intrahepatic cholestasis	Sep-23	STA	STA	3	No	N/A	No update since routing to STA in September 2023
ID6264	Fosdenopterin	Molybdenum cofactor deficiency type A	Oct-23	HST	HST	4	N/A	N/A	Awaiting next steps following ACM1
ID3903	Leriglitazone	Adrenoleukodystrophy	Oct-23	STA	STA	2	No	N/A	No update since routing to STA in October 2023
ID1001	Sodium thiosulfate	Cisplatin-related ototoxicity solid tumours	Feb-24	STA	STA	2	No	N/A	ACM1 took place in September 2024

Notes: *A score of 0.5 indicates the TSOP determined the criterion was partially met. Colour coding for current status is subjective, but loosely determined as follows: green, recommended; blue, too early to determine whether process has been favourable/unfavourable; amber, unfavourable protracted process that may yet result in a recommendation; red, appraisal terminated; grey, MHRA approval no longer being pursued. Current status as of 12th September 2024.*

It is clear from the previous page that routing to STA has a substantial negative impact on the outcome. As mentioned previously, 30 of 31 published HSTs have been positive. Compared to this, of the 16 appraisals routed to STA where sufficient time has elapsed to draw conclusions, only six have been recommended to date. In explaining their decision to terminate their appraisals, Alexion (AstraZeneca) and Pierre Fabre directly attributed the withdrawal to routing via STA, and concerns around value recognition. In withdrawing Ultomiris in the NMOSD indication, Alexion/AstraZeneca stated that:

"Assessment of rare disease medicines through the STA process, presents significant challenges to demonstrate the value a product delivers in the treatment of rare conditions."

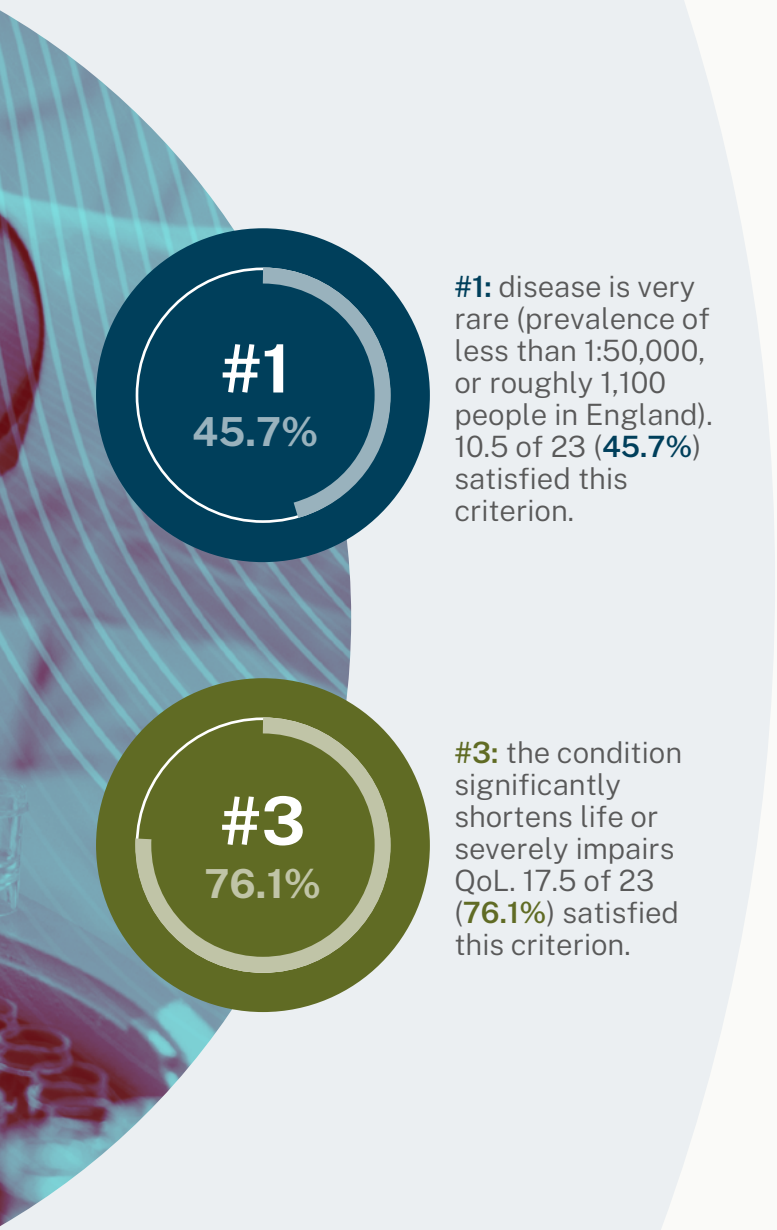
With Pierre Fabre citing similar concerns:

"We do not believe that the STA process is the appropriate routing for this technology and as such will review our position at a later point in time in order to ensure the value of this transformative technology can be appropriately accounted for."

It is of course very possible that some of the remaining ten will eventually be recommended, but if they are, it will be after a protracted process.

Detailed analysis of the HST vs STA decisions

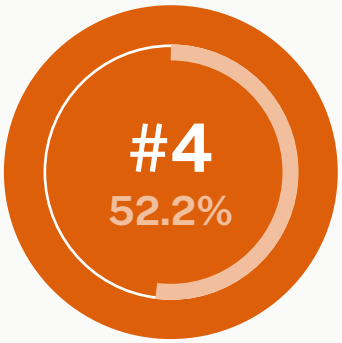
Having summarised the outcomes for technologies considered by the TSOP, we then reviewed the supporting documentation for each appraisal, assessing TSOP deliberations and rationale for assessing whether each HST criterion was met or not. For the purpose of this analysis, we included only original decisions. Our analysis is presented in Table 2, followed by a deep dive. Criterion #3 was the most commonly met criterion, with criterion #1 being least commonly satisfied, primarily owing to the TSOPs' interpretation of how the condition is defined. Note that where a half score (0.5) has been given, this indicates the criterion was partially met.



#1: disease is very rare (prevalence of less than 1:50,000, or roughly 1,100 people in England). 10.5 of 23 (**45.7%**) satisfied this criterion.

#2: no more than 300 people in England are eligible in this indication, no more than 500 across all indications. 14.5 of 23 (**63%**) satisfied this criterion.

#3: the condition significantly shortens life or severely impairs QoL. 17.5 of 23 (**76.1%**) satisfied this criterion.



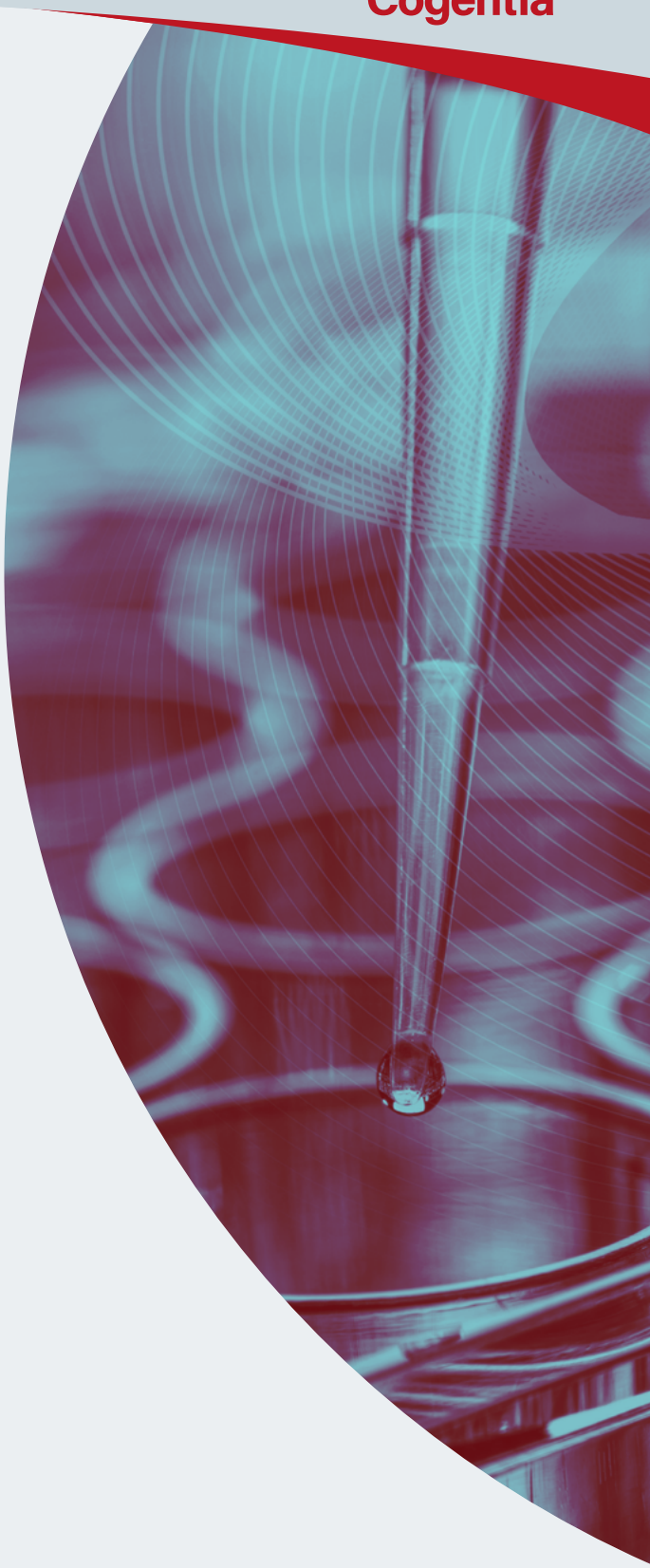
#4: no other satisfactory treatments/significant additional benefit if existing options available. 12 of 23 (**52.2%**) satisfied this criterion.

Our analysis suggests that appraisals may be referred to TSOP for a decision primarily based on perception of disease severity. This makes sense; determination of incidence and how the condition is defined, likely eligible patients, and extent of added benefit / lack of alternatives are all likely to require more detailed analysis and calculation compared with a face value assessment of the severity of the condition in question.

Table 2: Summary of TSOP Decisions Per HST Criterion

Topic ID	Technology	Indication	HST or STA?	TSOP outcome published	Criterion #1 Prevalence <1:50k	Criterion #2 <300 people	Criterion #3 Severe condition	Criterion #4 No alternatives
ID3941	Maralixibat	Cholestatic pruritis in Alagille syndrome	STA	Mar-22				
HST31	Setmelanotide	Bardet Biedl syndrome	HST	May-22				
TA912	Cipaglucosidase alfa	Late-onset Pompe disease	STA	May-22				
TA915	Pegunigalsidase alfa	Fabry disease	STA	Aug-22				
TA923	Tabelecleucel	EBV+ Post-transplant lymphoproliferative disorder	STA	Nov-22				
ID3988	Ganaxolone	Seizures caused by CDKL5+ deficiency	STA	Nov-22				
ID1664	Omburtamab	Relapsed neuroblastoma	STA	Nov-22				
ID3932	Belzutifan	Tumours associated with von Hippel-Lindau disease	STA	Dec-22				
TA948	Ivosidenib	Advanced cholangiocarcinoma	STA	Jan-23				
TA949	Belumosudil	Chronic GvHD after 2+ systemic treatments	STA	Feb-23				
TA941	Ravulizumab	AQO4+ neuromyelitis optica spectrum disorder	STA	Mar-23				
TA1002	Evinacumab	Homozygous familial hypercholesterolaemia	STA	Mar-23				
ID3767	Tofersen	SOD1 amyotrophic lateral sclerosis	STA	Jun-23				
ID3959	B-VEC	Dystrophic epidermolysis bullosa	STA	Jun-23				
ID4024	Vamorolone	Duchenne muscular dystrophy	STA	Aug-23				
ID547	Idebenone	Leber's hereditary optic neuropathy	STA	Aug-23				
ID4029	Pegzilarginase	Arginase-1 deficiency	HST	Sep-23				
ID6181	Odevixibat	Cholestatic pruritis in Alagille syndrome	STA	Sep-23				
ID6130	Leniolisib	Activated phosphoinositide 3-kinase delta syndrome	HST	Sep-23				
ID3818	Maralixibat	Progressive familial intrahepatic cholestasis	STA	Sep-23				
ID6264	Fosdenopterin	Molybdenum cofactor deficiency type A	HST	Oct-23				
ID3903	Leriglitazone	Adrenoleukodystrophy	STA	Oct-23				
ID1001	Sodium thiosulfate	Cisplatin-related ototoxicity solid tumours	STA	Feb-24				

Notes: *Colour coding for each criterion is as follows: green, met; amber, partially met; red, not met. This analysis relates to TSOP decisions aligned to the four HST criteria introduced in 2022 only, as such decisions based on the original seven criteria are excluded.*



Trends over time

By presenting decisions over time, Table 2 also permits an assessment of trends, with a few interesting ones apparent.

1. TSOP was content to rule a criterion 'partially met' early on, with four partially met decisions in the first five decisions. However, for the subsequent 18 assessments, there were no partially met rulings. This makes sense. Where uncertainty exists, either applying discretion and ruling 'met', or ruling 'not met' and allowing the opportunity of appeal helps to reduce the ambiguity inherent in the process.

2. Of the first 12 TSOP decisions, only two of 12 satisfied criterion #4, relating to lack of satisfactory alternatives / demonstration of added benefit. For the final 11, ten of 11 satisfied this criterion. The limited number achieving this criterion may have been fed back to NICE, permitting a re-think of NICE's process for referral into the TSOP. For instance, where NICE has appraised a technology in the indication before, it is possible this is used as an exclusion filter to better tailor referrals into TSOP.

3. Of the first 16 TSOP decisions, only one of 16 was routed to HST. For the most recent seven, three have been routed to HST. Whilst small sample sizes limit the interpretation, it could be speculated that over time, NICE are improving the process for filtering referrals into TSOP, resulting in more suitable candidates. This links nicely to point #2.

TSOP rationale per criterion and sources used

Having summarised outcomes for technologies routed to HST vs STA, and provided an overview of TSOP decisions per HST criterion, we now present a deep dive into the underpinning rationale for those decisions. Before getting into the detail, to avoid confusion please note that where we refer to analysis based on a sample of 23 decisions, this relates to original decisions from the TSOP. Where we refer to a sample of 29, this includes all decisions, including the 23 original decisions, and six appeal decisions.

#1

Criterion #1: The disease is very rare, defined as a prevalence of lower than one in 50,000, or about 1,100 people

This criterion was the hardest to achieve, with the TSOP considering this met for less than half (10.5 of 23) of appraisals. It is clear from a thematic analysis that a key stumbling block here is the interpretation of 'the disease'. Although many of the technologies considered not to have met this criterion are indicated for a subpopulation of a condition, unless this subpopulation is considered 'clinically distinct and well defined', the TSOP used the full population to inform the prevalence estimate. A number of examples of this, as well as the TSOP's rationale, are presented in Table 3. As noted, the two successful examples, in green below, were originally not met, requiring an appeal to overturn.

The examples of leniolisib and B-VEC, highlighted in green in Table 3 provide an example of the TSOP determining that the subset was well defined, resulting in the criterion being met, albeit after an appeal. This supports a point raised later in this article that, given the subjective challenge of determining whether a subset of a condition is 'clinically distinct', criterion #1 may provide the greatest basis for appeal.

Based on a review of all 29 decisions (23 original decisions and six appeal decisions), it is clear that the TSOP most commonly relied on literature (20 of 29) to inform a decision on criterion #1. This typically took the form of a natural history or registry study to support an estimate of incidence. Note that for all four criteria, the TSOP had a strong preference for more recent, UK-specific literature, with sources cited rarely older than 2015 throughout. Other sources commonly cited in support of this criterion included clinical expert validation (five of 29), and European Medicines Agency (EMA) orphan designation documents (five of 29).

Table 3: Select Examples of TSOP Application of HST Criterion #1

Topic ID	Technology	Indication	Population considered for criterion #1	Rationale
ID3932	Belzutifan	Tumours associated with von Hippel-Lindau disease	von Hippel-Lindau disease	For this criterion, the disease is von Hippel-Lindau, as the genetic condition targeted by the therapy.
TA948	Ivosidenib	Advanced cholangiocarcinoma	Cholangiocarcinoma	Cholangiocarcinoma is a subset of bile duct cancer and is the disease considered here as opposed to the indication-specific population, which is considered in the next criterion.
TA1002	Evinacumab	Homozygous familial hypercholesterolaemia	Familial hypercholesterolaemia	If the full population is considered (homozygous and heterozygous familial hypercholesterolaemia), the criterion is not met. NICE applies this criterion to the full population.
ID3767	Tofersen	SOD1 amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis	TSOP considered stakeholder feedback and concluded that currently, SOD1 is not perceived to be different to other forms of amyotrophic lateral sclerosis and is treated in the same way.
ID1001	Sodium thiosulfate	Cisplatin-related ototoxicity solid tumours	Solid tumours	A condition is not defined by treatment received such as cisplatin.
ID3959*	B-VEC	Dystrophic epidermolysis bullosa	Epidermolysis bullosa	The COL7A1 subtype can be diagnosed through genetic testing, so can be clinically distinguished from other subtypes, and B-VEC would only benefit these patients.
ID6130*	Leniolisib	Activated phosphoinositide 3-kinase delta syndrome	Activated phosphoinositide 3-kinase delta syndrome	It was highlighted that genetic testing is standard practice in the UK, and that a specific PID diagnosis must be established; activated phosphoinositide 3-kinase delta syndrome is a distinct and well-defined condition.

**On appeal. Original decision was not met.*

#2

Criterion #2: Normally, no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications

Criterion #2 was more commonly met than criterion #1, with 14.5 of 23 (63%) achieving criterion #2 compared with 10.5 of 23 (45.7%) for criterion #1. This makes sense in light of the rationale described above relating to whether a subset is clinically distinct. In addition, inclusion of the word 'normally' in this criterion does appear to permit ultimate discretion on the part of the TSOP.

For some decisions on criterion #1, the TSOP considered a wider population than that in the anticipated regulatory label, whereas for assessment of the eligible population the TSOP always accounted for any relevant restrictions in its epidemiological cascade calculations. Indeed, rationale for the decision on this criterion was often framed around an epidemiological cascade, that moved from total population through to eligible population, including both incidence and prevalence.

Where medicines did not satisfy this criterion, TSOP often leaned heavily on comments from clinical experts, where for instance they had suggested that they would offer the treatment to all eligible patients, or that prevalence estimates from the literature were likely underestimates. It is clear from a narrative review that clinical expert opinion formed a critical part of decision-making where used, often overriding literature or registry-based estimates.

Where manufacturers were able to present a detailed epidemiological cascade that filtered down to a number just below the (apparently arbitrary) threshold of 300, as was the case for HST31, the TSOP appeared willing to take this into consideration for making its own estimates.

While having an approved treatment already available makes HST qualification challenging (see criterion #4), it can support a positive decision on criterion #2. For ID3818, maralixibat for progressive familial intrahepatic cholestasis, NHS England was able to provide prescription data on an approved treatment, odevixibat, to demonstrate eligible patient numbers are likely well below 300. The UK has historically held a reputation for relatively slow uptake of innovative medicines; in this way, data on currently available treatments can help to demonstrate that a theoretical addressable population does not translate into an actual treated population, potentially swaying a decision in the manufacturers favour where it is 50:50.

For this criterion, TSOP relied much less on literature. Only ten of 29 decisions cited literature, primarily in the form of chart reviews and genetic screening studies. Instead, clinical experts had a particularly key involvement here, informing decisions on 13 of 29 occasions. As noted, a comment from clinicians along the lines of, 'I would like to offer this treatment to all eligible patients', or noting data provided by the company, literature or patient organisations was likely an underestimate, had a key influence on TSOP decision-making. Even a reasonably vague comment like, 'registry data likely underestimates prevalence by around 10%', was then carried forward as a quantitative input by the TSOP.

Other key sources here were UK registry data, often provided by patient associations (nine of 29), and NHS England / NHS Digital (six of 29).

#3

Criterion #3: The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life

This criterion had by far the highest success rate, with 17.5 of 23 appraisals meeting this criterion. The TSOP typically framed this criterion in terms of life expectancy where possible, and if not on a short summary of the impact the condition has on patients. The TSOP made extensive use of the literature here, with 22 of 29 decisions informed by literature. Types of literature used include natural history studies, systematic literature reviews of clinical burden, and registry studies. Unsurprisingly, the TSOP also made use of clinical experts (nine of 29), patient experts (four of 29) and disease associations (four of 29) to support this. The lower use of patient experts than expected may be due to the fact that the majority of treatments satisfied this criterion, and so the TSOP did not need to further seek input to be comfortable with considering it met.

It is interesting to consider the context within which the TSOP is making this decision. Many of these ultra-rare conditions have very limited evidence to support an accurate estimate of life expectancy and quality of life. In this regard, the TSOP has shown a willingness to acknowledge these challenges, even on occasions accepting circumstantial evidence, e.g. 'not many patients with the condition are known to be alive beyond X years of age'.

For the few that did not meet this criterion, it was usually due to the heterogeneous presentation of the condition.

#4

Criterion #4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options

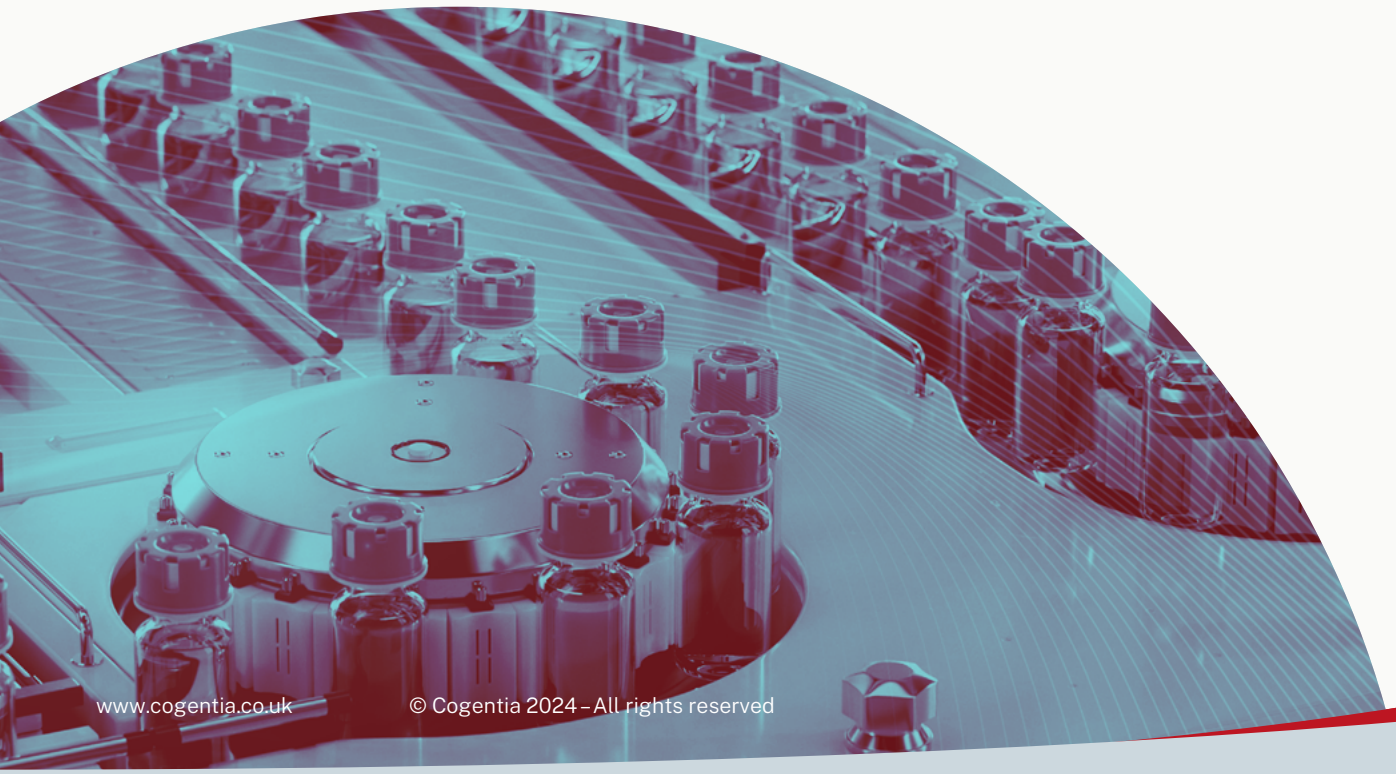
Criterion #4 was the second most challenging to satisfy, with 12 of 23 appraisals meeting this criterion. There are two elements here, for which only one needs to be satisfied. The TSOP considers the use of approved and unapproved treatments in its consideration of satisfactory treatment options. Where NICE has appraised a medicine previously, this part of the criterion is very difficult to meet, though if your technology is considered to offer a significant additional benefit (as with B-VEC for dystrophic epidermolysis bullosa, ID3959), it is still possible to meet criterion #4.

However, ID3959 is the exception. Success against criterion #4 was overwhelmingly driven by a lack of other satisfactory treatment options, with TSOP only explicitly stating a belief that the technology under review offers, or may offer, significant additional benefit on three occasions.

This criterion generally relied on a subjective view of the TSOP, often without citing external sources. This is perhaps unsurprising given that terms like 'satisfactory' and 'significant additional benefit' are highly subjective. The sources most commonly relied on to inform its decision included clinical expert opinion (nine of 29), literature (seven of 29) and data from the pivotal trial (six of 29).

A key feature of the TSOP approach to criterion #3 and #4 in particular, but also for others is the application of discretion. Ultimately, and as defined in the topic prioritisation manual, decisions on satisfaction of each criterion are subjective. Terms such as 'satisfactory' 'significant' and 'severely' in the context of HST criteria are not defined, such that the TSOP can apply reasonable discretion.

As further detailed below, discretion is a key theme at appeal. Where other criteria are clearly met, and where the criterion under review is potentially met, the TSOP is willing to apply discretion where appropriate.



ANALYSIS OF APPEALS

The outcomes of the five appraisals where the manufacturer appealed an initial STA decision are summarised in Table 4.

Table 4: Topic Selection Routing Appeals and Outcomes

Topic ID	Technology	Indication	Stage	TSOP outcome published	Criterion #1 Prevalence <1:50k	Criterion #2 <300 people	Criterion #3 Severe condition	Criterion #4 No alternatives
ID3941	Maralixibat	Cholestatic pruritis in Alagille syndrome	Original	Mar-22				
			Appeal 1	Dec-22				
			Appeal 2	Sep-23				
ID3932	Belzutifan	Tumours associated with von Hippel-Lindau disease	Original	Dec-22				
			Appeal	Aug-23				
ID3767	Tofersen	SOD1 amyotrophic lateral sclerosis	Original	Jun-23				
			Appeal	Sep-23				
ID3959	B-VEC	Dystrophic epidermolysis bullosa	Original	Jun-23				
			Appeal	Jan-24				
ID6130	Leniolisib	Activated phosphoinositide 3-kinase delta syndrome	Original	Not reported				
			Appeal	Sep-23				

Notes: *Data for the original decision on ID6130 are not available, with NICE stating this information is exempt from disclosure under section 41 of the Freedom of Information Act. As such, presented results are based on interpretation of the appeal documentation, where the rationale for criterion #1 indicates this was reassessed and overturned. Colour coding for each criterion is as follows: green, met; amber, partially met; red, not met.*

Of the appellants, only Pharming was successful in its appeal for leniolisib (ID6130). Data on the original TSOP decision is not available on NICE's website, with NICE stating this information is exempt from disclosure under section 41 of the Freedom of Information Act. However, based on a review of the appeal documentation, it can be inferred that it was the first criterion that was originally not met, and overturned at appeal. The TSOP states in its rationale that it 'considered the comments from stakeholders about this being a more severe primary immunodeficiency'. It can be reasonably assumed from this that the original decision was not met due to the TSOP using a broader definition of the condition to inform incidence estimates.

For the unsuccessful appeals (n=5), there were two cases where the TSOP changed its decision from unmet to met for one criterion, two cases where a partially met criterion was changed to unmet, and one case where no change was made. Decisions typically added ~8-9 months to the process (i.e. from publication of original decision to appeal decision), although for tofersen ID3767 this was just 3 months.

Only on one occasion did an appeal lead to a successful change of routing. As already described, the TSOP has to make somewhat subjective calls to come to a decision on eligibility for HST. The TSOP has demonstrated willingness to apply discretion where appropriate but is ultimately bound by the definition of each criterion.

The positive changes that ultimately did not result in a change to the routing decision were an acknowledgement of a subtype of the whole indication as being clinically distinct in ID3959, thus satisfying criterion #1, and an acceptance that despite uncertainty, the condition is likely to significantly reduce life expectancy in ID3932, thus satisfying criterion #3.

For ID3941, where appealing resulted in a backward step (i.e. 2.5 of four criteria being met

down to two of four), the TSOP identified a recent source that it felt best reflected incidence data, changing its estimate from a range of 1:30k-1:70k to settling on 1:30k.

At appeal, the TSOP consistently presented more detailed analysis and rationale for the criteria that had not been met in the original decision, whereas for criteria already considered met the presented rationale did not change, suggesting TSOP did not use the appeal process to revisit previously positive decisions.

Whilst noting that drawing conclusions from the appeal procedures above is confounded by the limited sample size, it is reasonable to suggest that the criterion where an appeal may be most justified is number one, specifically in relation to whether a subset of a condition is clinically distinct.

With the introduction of the NICE prioritisation board (see the following section), the appeal process has been amended, and is now referred to as clarification. Despite this change in the wording, it is not immediately apparent that this will result in any meaningful change in the appeal process, and as such the findings and analysis here are likely to remain applicable for manufacturers considering recourse after an STA routing.

NICE PRIORITISATION BOARD

We note that the NICE-wide topic prioritisation manual was published on 29th May 2024, with the NICE prioritisation board taking over the role of making topic decisions on HST eligibility from the TSOP. Additionally, there is a further review and consultation on the HST criteria planned for 2024. However, NICE is clear that the objective is to further clarify the HST criteria and their application, rather than to change them in any meaningful way.

In this sense, the process of topic selection for HST routing is likely to remain the same – a group of experts overseen by NICE making somewhat subjective decisions on whether medicines should be routed to HST, using the same criteria as currently, albeit perhaps with a little more clarity.

CONCLUSIONS

The HST route, with its more favourable willingness to pay, acceptance of uncertainty in the evidence package, and consideration of impacts beyond direct health benefit, is seen by many manufacturers as critical for market access for rare disease medicines in the UK. The statistic that 30 of 31 published HSTs have resulted in a positive recommendation illustrates this point, but also raises another – that very few technologies are routed to HST.

In this context, it is critical that manufacturers have an early view on how the extent to which their medicine meets the criteria for HST, as well as a strong understanding of the methodology underpinning determination of whether each of the four qualifying criteria are met. Benefiting from NICE's increasing transparency on topic selection, introduced as part of the 2022 methods update, as well as data received from NICE as part of a Freedom of Information request in May 2024, this analysis provides the most comprehensive review of NICE topic selection decision-making to date.

Of the 23 appraisals where the TSOP was required to make a determination, just four were successful in achieving HST routing. This demonstrates that even where NICE considers a HST routing as plausible — a prerequisite for referral into the TSOP — the ultimate decision is overwhelmingly to stick with the status quo and route the technology via STA. Even upon appeal of the decision, only one topic successfully changed the decision from STA to HST.

Fundamentally, it must be acknowledged that the TSOP — and now the NICE prioritisation board — are making subjective decisions, based on criteria, particularly criteria #3 and #4, which intentionally leave key terms such as 'significant' and 'severe' undefined. The TSOP applied reasonable discretion where appropriate but is doubtless aware of NICE's position that in making a decision to route a technology via HST, resource is diverted away from activities that would be expected to generate a greater health benefit.

For technologies considered for HST but ultimately routed to STA, our analysis shows that outcomes are overwhelmingly negative. While some manufacturers responded to an STA routing by terminating the appraisal entirely, more common was a prolonged period of delay in the appraisal — tantamount to a suspension — as UK access teams likely had to re-calculate achievable price, and gain sign-off from global pricing committees for an undoubtedly eyewatering level of discount.

It should be noted that of the 19 technologies routed to STA, there are six that have received a positive recommendation for routine commissioning. Notably, two of these had expensive enzyme replacement therapy comparators, supporting their economic proposition. Likewise, for many of the other 13 STAs, it is not unreasonable to assume a majority will eventually be recommended by NICE. However, it is clear that if this is to be the case, it will be after protracted negotiations, and that recommendation may be met more with a sigh of relief than celebration by the relevant manufacturers.

Although change is on its way, with the TSOP passing the topic selection baton to the NICE prioritisation board, and NICE committing to further clarify the application of the HST criteria later in 2024, the overall premise of a group of experts making decisions on qualification for HST based on at least partially subjective criteria remains the same.

To conclude, our findings support the conventional wisdom that for manufacturers targeting ultra-rare conditions, there is no more critical step in a successful UK market access strategy than qualifying for HST. To optimise the likelihood of achieving HST routing, manufacturers may draw lessons from the analysis presented here. To support this, we provide recommendations on the next page.

RECOMMENDATIONS FOR MANUFACTURERS

In conducting the extensive analysis informing this article, Cogentia has distilled our findings into a number of recommendations for manufacturers that feel they have an asset suitable for HST.

1. **Be clear on whether the condition is clinically distinct:** Where a medicine is targeting a subtype of a wider indication (for instance SOD1 amyotrophic lateral sclerosis), be ready to provide supporting rationale for the subtype being clinically distinct. This may include routine genetic testing being available, a specific diagnosis being required, different outcomes compared with the broader population, or the mechanism being directed specifically at the mutation relevant to that subtype.

2. **Do your homework on epidemiology data:** Review recent literature on epidemiology of disease, ideally in a systematic way. Companies that had a strong understanding of the latest data on incidence and prevalence, particularly in UK-based studies, were better able to influence the choice of source for criterion #1. The TSOP typically used the selected source in criterion #1 to inform the epi cascade for criterion #2, further reinforcing the critical importance of this step.

3. **Engage with clinical experts:** Clinical expert engagement is a critical part of preparation for the topic selection process. Expert opinion had an enormous impact on outcome, particularly in relation to eligible population, the severity of the condition, and availability of alternative treatments.

4. **Engage with patient advocacy groups:** Similar to recommendation #3, patient advocacy groups are important stakeholders for topic selection, championing the unmet need in the condition. They may also be able to provide registry or other contemporary data that can be used as an input into scoping consultation.

5. **Be clear on the treatment landscape:** If a NICE approved medicine is already available in the indication you are pursuing, it is highly unlikely a HST routing will be made without a clear expectation of added benefit. Should there be no NICE recommended alternative, it is critical to demonstrate that available treatments, including those used off-label, are not satisfactory. As with point three, clinical expert input on the treatment landscape is also critical.

6. **Be aware of potential discretion:** In a subjective process like HST vs STA routing, high confidence on two+ criteria can support a willingness to apply discretion on another. Assess the extent to which your technology meets each criterion, if two+ are likely met with high confidence, prepare to make a compelling case for those that are less clear, with reasonable expectation that the prioritisation board may apply discretion.

These recommendations are based on the analysis presented herein, as well as Cogentia's extensive experience supporting manufacturers with all aspects of UK market access, including topic selection routing. For more information on how Cogentia can support you in UK market access, email mark.orchard@cogentia.co.uk.

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