NICE National Institute for Health and Care Excellence

# ID6585 HST routing criteria (refined April 2025)

## Introduction

1. The NICE HST routing assessment checklist highlights when a technology meets or does not meet the criteria for routing it to the HST Programme. All 4 criteria need to be met for a technology to be routed to HST.

2. Anticipated marketing Authorisation (MA) wording:

   [redacted]

3. **Prioritisation Board routing discussion** 09/10/2025

4. **Description of the HST Programme's vision**

   **Criterion 1** - The rarer a disease is, the more challenging it is to do research and generate an evidence base that is robust enough to bring an effective technology to market. The HST Programme's vision aims to encourage research when it is most challenging.

   Not all ultra-rare diseases are debilitating. The vision focuses on ultra-rare diseases that cause ongoing debilitating symptoms and have an exceptional burden on the people with them, and on their carers and families. This is to justify prioritising access to HST technologies over overall population health.

| Criteria | Descriptions of how the criteria are met or not met through assessing the definitions |
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| **Criterion 1**<br>**The disease is ultra-rare, that is,**<br><br>• **1A: it is defined as having a point prevalence of 1:50,000 or less in England (NICE strategic principles for rare disease).**<br><br>**....and debilitating, that is,**<br><br>• **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.** | These definitions have been developed to help define what an ultra-rare disease is, and the debilitating nature of the disease. Relevant information should be collected during scoping by NICE (from the company, and other research or academic sources) to explain how each definition is considered by the NICE prioritisation board.<br><br>• 1A of routing criterion 1 is about defining the ultra-rare 'disease', not about the symptoms associated with the ultra-rare disease (regardless of whether the symptom or set of symptoms are the dominating feature). 1B of routing criterion 1 is about the characteristics of the ultra-rare disease.<br><br>• 'Disease' refers to a condition for which a diagnosis can be made using the International Classification of Diseases (ICD11) developed by the World Health Organization (WHO) as a guiding tool. Diagnosis is based on a unique set of signs and symptoms (characteristics) identified using:<br>  ○ clinical examination<br>  ○ patient history<br>  ○ imaging or laboratory tests that are, or can be made, available in the NHS in England.<br><br>• 'Disease' does not refer to subgroups based on age, sex, severity, or genetic subtype. These will only be considered if they are clinically meaningful.<br><br>• 'Point prevalence' refers to the point prevalence of the 'disease' in England. It counts the number of people with a diagnosis of the disease thought to be alive in England (numerator) on a given index date compared with the total population of England (denominator) at that time (NHS England). |

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| | **Has this criterion been met?**<br>Yes ☒<br>No ☐ |
| | **Notes and rationales:**<br>• The prevalence of FCS is around 1 to 2 per million people (HEART UK 2025)<br>• This equated to around 57 to 114 people in England in 2022 (ONS 2025)<br><br>**Prioritisation board conclusion: criterion 1A is met.** |
| | 1B of routing criterion 1 definitions:<br><br>• 'Lifelong' indicates that the disease needs ongoing clinical management, supportive care, or both.<br>• 'Exceptional negative impact' refers to shortened length of life or severely impaired quality of life. The precise assessment of this will require an element of subjective judgement. |
| | **Has this criterion been met?**<br>Yes ☒<br>No ☐ |
| | **Notes and rationales:**<br>• FCS is a lifelong condition as it is caused by loss-of-function mutations in genes involved in fat metabolism<br>• It is exceptionally debilitating and is associated with a range of symptoms that have a broad impact on morbidity and mortality, including unpredictable and recurrent episodes of acute pancreatitis<br>• Acute pancreatitis requires hospitalisation and intensive care unit stays, and can result in organ failure and mortality |

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| | • FCS also associated with unpredictable abdominal pain ranging from mild to incapacitating, as well as a wide range of other gastrointestinal symptoms<br>• There is also a substantial impact on mental health including anxiety, depression, fatigue, and impact on cognitive functioning<br>• The condition impacts on people's ability to participate in social activities, day to day activities, and enjoyment of life<br>• In HST13, the committee concluded that "FCS is a rare, serious and potentially life-threatening condition that can affect the lives of people with the condition, and their families and carers".<br><br>**Prioritisation board conclusion: criterion 1B is met.** |

5. **Description of the HST Programme's vision**

**Criterion 2** - This criterion is designed to uphold the HST Programme's vision to encourage innovation and research into ultra-rare and debilitating diseases for which there is poor service provision within the NHS (for example, delay in diagnosis, no treatment options beyond supportive care). Without these incentives from the HST Programme, the technology may not be available either after launch, or during development or testing of the technology in England. The availability of the innovation can also reshape NHS services and advance awareness.

| Criteria | Descriptions of how the criteria are met or not met through assessing the definitions |
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| **Criterion 2**<br>**The technology is an innovation for the ultra-rare disease.** | These definitions have been developed to help define an innovative technology. Information about the technology should be collected by NICE from relevant sources (for example, the Medicines and Healthcare products Regulator Agency [MHRA], ongoing trials, registries) to explain how each definition is considered. |

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| | • 'Innovation' refers to a technology or medicine such as an advanced therapy medicinal product (ATMP), a new chemical or biological entity, or a novel drug device combination that brings additional health gains to people with the ultra-rare disease (compared with existing treatment or best supportive care).<br>• To ensure the technology is an innovation for the ultra-rare disease:<br>  ○ the technology should not be a repurposed technology<br>  ○ the indication for the technology should not be a significant extension of an indication from another population or disease.<br><br>• A repurposed technology means new uses for medicines that are outside the scope of the existing licence for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for human use for a particular condition and then using it to treat another condition. This can also include generic treatments or treatments that have had marketing authorisation withdrawn and the developer is seeking a new indication. |
| | **Has this criterion been met?**<br>Yes ☒<br>No ☐ |
| | **Notes and rationales:**<br>• Both treatments (volanesorsen and olezarsen) target apolipoprotein CIII (APOC3), but the mechanisms of action are different<br>• Volanesorsen and olezarsen are both anti-sense oligonucleotides (ASOs) targeting APOC3 mRNA, but olezarsen is GalNAc3 derivative of volanesorsen ASO<br>• Olezarsen's mechanism of action has been used in other drugs for other conditions, but not in a treatment for FCS<br>• Olezarsen offers a lower dose and extended dosing interval compared with volanesorsen, which is expected to improve adherence – olezarsen is administered every month whereas volanesorsen is administered every 2 weeks |

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| | • Because of the improved mechanism of action, olezarsen does not carry the same risk of low platelet counts/thrombocytopenia as volanesorsen (see criterion 4). Therefore, frequent platelet monitoring is not required<br>• Following conversations with clinical experts, it is our understanding that most people who would start olezarsen would be those switching from volanesorsen because of side effects or those wanting a lower treatment burden<br>• Olezarsen is not currently licensed in any other indication<br>• Olezarsen is a designated orphan medicine<br><br>**Prioritisation board conclusion: criterion 2 is met.** |

6. **Description of the HST Programme's vision**

**Criterion 3** - This criterion is designed to establish the acceptability of the technology as an effective use of NHS resources, considering the significantly higher ICER threshold. So, the eligible population needs to be small. This is to strike a balance between the desirability of supporting access to treatments for ultra-rare diseases and the inevitable reduction in overall health gain across the NHS because of a higher ICER threshold. A small subpopulation within a population with a common disease would not be suitable for the HST Programme.

| **Criteria** | **Descriptions of how the criteria are met or not met through assessing the definitions** |
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| **Criterion 3**<br>**No more than 300 people in England are eligible for the technology in its licensed indication, and** | These definitions have been developed to help define what kind of licensed indication is suitable for a technology to be considered for routing to the HST Programme, and to help explain what an individualised medicine is. Relevant information about the licensed indication of the technology should be collected by NICE to explain how each definition is considered.<br><br>• 'Eligible' refers to everyone who could have the technology under its marketing |

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| **the technology is not an individualised medicine** | authorisation (obtained or in the process of being obtained) in England.<br><br>• The 'technology' should only be developed for the ultra-rare disease, so the eligible population is small. The technology:<br><br>  ○ has to be the first licensed treatment indicated for the ultra-rare disease under consideration<br>  ○ should not be an extension of an indication from another:<br>  • related population or disease, or<br>  • subgroup of people with the same ultra-rare disease under consideration<br>  ○ is unlikely to be suitable for other subgroups of the population with the ultra-rare disease in the future who are outside of its first indication.<br><br>• 'Individualised medicine' refers to a medicine that is developed based on a person's unique genetic profile (n of 1), or on the genetic profile of monozygotic twins or triplets. |
| | **Has this criterion been met?**<br>Yes ☐<br>No ☒ |
| | **Notes and rationales:**<br>• The number expected to be eligible for treatment will not be greater than the number with the condition (as per criterion 1a)<br>• As per criterion 1a, the number with the condition is around 57 to 114 people in England<br>• In HST13, there were thought to be around 80 to 100 people with FCS eligible for treatment with volanesorsen in the UK.<br>• However, this criterion also specifies that the technology has to be the first licensed treatment indicated for the ultra-rare disease under consideration. Volanesorsen is already licensed in this disease area. |

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| | **Prioritisation board conclusion: criterion 3 is not met.** |

7. **Description of the HST Programme's vision**

**Criterion 4 -** This criterion is designed to address the lack of effective treatment and access to NHS services for some ultra-rare diseases. To justify prioritising treatment access for ultra-rare diseases over overall population health, the technology under consideration should be anticipated to provide substantial health benefits to people with the disease over existing clinical management and supportive care.

| Criteria | Descriptions of how the criteria are met or not met through assessing the definitions |
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| **Criterion 4**<br>**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.** | These definitions have been developed to help define what is substantial additional benefit, and to help to explain the meaning of no other treatment options. Relevant information should be collected by NICE to explain how each definition is considered.<br><br>• 'Substantial additional benefit' means that the technology is likely to:<br>  ○ significantly redress the reduced length of life, or<br>  ○ is likely to demonstrate substantial improvements in the severely impaired quality of life attributable to the ultra-rare disease, as exemplified by research data on clinically relevant measures, for example, patient-reported outcome measures (PROMs).<br><br>• 'The technology' means that:<br>  ○ if the technology is a disease-modifying treatment (including curative treatment), there is no other disease-modifying treatment available in the NHS in England for the same ultra-rare disease at the time of the routing decision, or<br>  ○ if the technology treats a symptom or set of symptoms unique to the ultra-rare disease, there is no other treatment available in the NHS in England for the same symptom for which the technology is indicated at the time of the routing decision. |

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| | **Has this criterion been met?**<br>Yes ☐<br>No ☒ |
| | **Notes and rationales:**<br>• There is already a disease-modifying treatment for FCS recommended by NICE (volanesorsen [HST13])<br>• Nearly all people with FCS would be eligible for volanesorsen (see criterion 3), but many people choose not to have volanesorsen and continue to be managed by an extremely restrictive low-fat diet<br>• The key reasons people choose not to start treatment with volanesorsen include:<br>  - Intensive monitoring – people are required to have blood tests at least every 2 weeks, and often more frequently, to monitor platelet count<br>  - Safety concerns around the risk of thrombocytopenia<br>  - Requirement to self-inject<br>• Following conversations with clinical experts, it is our understanding that around 2/3 of people with FCS start treatment with volanesorsen, but often, people have dose reductions and pauses or discontinue because of side effects<br>• Estimates of discontinuation from clinical experts varied greatly, possibly due to small numbers of people seen in practice, but roughly up to 50% of those who start treatment would discontinue overall and 50% or more would be treated effectively<br>• Volanesorsen is effective for people can tolerate treatment at the recommended dose<br>• As per criterion 2, olezarsen does not carry the same risk of low platelet counts/thrombocytopenia as volanesorsen and monitoring requirements and injection frequency are reduced<br>• Because of this, adherence is expected to improve, which could potentially result in better efficacy outcomes (**Note:** No efficacy data comparing olezarsen to volanesorsen was presented by stakeholders)<br>• As per criterion 2, it is expected that most people who start olezarsen will be those switching from volanesorsen because of side effects or those wanting a lower treatment burden |

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| | • Although olezarsen has an improved mechanism of action and is considered innovative in the treatment of FCS as per criterion 2, there is already a treatment available to people with FCS (volanesorsen)<br>• People at high risk of pancreatitis are eligible for volanesorsen, but some people choose not to start treatment, or stop treatment because of issues with tolerability<br>• Although there are benefits in reducing injection frequency and a likely reduction in side effects, olezarsen has not demonstrated “substantial” additional benefits compared with volanesorsen in terms of increasing length or quality of life<br><br>**Prioritisation board conclusion: criterion 4 is not met.** |

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| **Routing decision** | **Overall routing decision:**<br>HST☐<br>STA☒ |