NICE National Institute for Health and Care Excellence

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.

Marketing Authorisation (MA) wording: Zanidatamab is indicated for the treatment of adults with [redacted].

2. **Prioritisation Board routing discussion** 07/05/2025

3. **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

Criterion 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 (NICE strategic principles for rare disease).**
 	
• **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.
	
	Definition 1A:
	
	• 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.
	
	• '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:
	  ○ clinical examination
	  ○ patient history
	  ○ imaging or laboratory tests that are, or can be made, available in the NHS in England.
	
	• 'Disease' does not refer to subgroups based on age, sex, severity, or genetic subtype. These will only be considered if they are clinically meaningful.
	
	• '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).

	Definition 1B: • 'Lifelong' indicates that the disease needs ongoing clinical management, supportive care, or both. • '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? Yes ☐ No ☒
	Notes and rationales: **Definition 1A:** Condition being assessed: Biliary tract cancer (BTC) (instead of the HER2+ subset of the condition) **Point prevalence** of biliary tract cancer as a whole according to EMA orphan designation documentation = 1.6 in 10,000 (around 8 in 50,000) (EMA, 2021). Prevalence in England is also likely above the threshold for this criterion: • Current population of England in mid-2023 according to ONS = 57,112,500 • Size of disease population in England needed to meet point prevalence of 1:50,000 or less: 57,112,500/50,000 = 1,142 people or fewer • No England-specific prevalence estimates, but current incidence of BTC: 2,800 people diagnosed with cholangiocarcinoma (CCA), 1,100 people diagnosed with gallbladder cancer (GBC) and 500 people were diagnosed with ampullary cancer (AoV) (2021) – 4,300 altogether (NHS Cancer Registration Statistics, 2021) • Company estimate from literature of cases of BTC is 3,865 annually (Tataru et. al, 2024)

	Population incidence for BTC is already significantly above population size needed to meet criteria (and the incidence estimates above of 4,300 only account for new cases annually). Point prevalence in England is likely greater than 1 in 50,000 - definition 1A of criterion 1 is not met. **Definition 1B:** BTC significantly shortens length of life – the prognosis is extremely poor for BTC and net survival is low according to Tataru et. al (2024): • 1 year survival CCA: 25.1% (95% CI 24.7-25.6), 27.6% (95% CI 26.8-28.4) for GBC and 58.3% (95% CI 57.1-59.5) for AoV cancer. • 3-year survival CCA: 7.7% (95% CI 7.4-8.1%), 12.9% (95% CI 12.3-13.5) for GBC and 32.3% (95% CI 31.1-33.4) for AoV cancer. Estimated survival estimates at 5 years are also poor and range from 7-20% (Qurashi 2025). Estimates for 5-year survival are comparable with estimates from NHS of cancers with particularly poor prognoses including brain, lung, and oesophageal cancers in NHS England – all of which have 5 year survival estimates below 20% (NHS England, 2023) Quality of life is significantly impacted by progression of disease due to burden of symptoms and decline in physical function as well as psychological impacts on well-being – this is particularly the case in advanced biliary tract cancer (Hunter 2021) BTC needs ongoing clinical management and supportive care, and significantly shortens length of life as well as causing severe impairment to quality of life, so definition 1B of criterion 1 is met. **Criterion 1 overall conclusion**

	BTC is lifelong after diagnosis with current treatment, and has an exceptional negative impact and burden on people with the condition, but the point prevalence of BTC as a whole is likely greater than 1:50000. Therefore, based on definition 1A, criterion 1 is not met.

4. 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

Criterion 2
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.
	• '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).
	• To ensure the technology is an innovation for the ultra-rare disease:
	  ○ the technology should not be a repurposed technology
	  ○ the indication for the technology should not be a significant extension of an indication from another population or disease.

	• 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? Yes ☐ No ☒
	Notes and rationales: • Zanidatamab is not a repurposed technology and not a significant extension of an indication from another population or disease. It does not have a licence for any other indication in the UK. • Zanidatamab is a bispecific antibody that targets the HER2 protein. HER2 is a commonly exploited target in the oncology space – for example, in solid tumours, breast cancer, and gastric cancers as well as BTC (Ayasun 2023,Britte 2024) and therefore the drug mechanism is not novel. • Other treatments are available beyond best supportive care for this population in the UK at an earlier stage - NICE technology appraisal guidance 944 recommends durvalumab with gemcitabine and cisplatin as an option for treating locally advanced, unresectable, or metastatic biliary tract cancer in adults. Zanidatamab would be an additional systemic therapy available to people with BTC and would be an option after durvalumab with gemcitabine and cisplatin. Therefore, the technology is not an innovation for BTC since it would be an addition to the other treatments available in the care pathway for BTC. The mechanism of the drug is not novel and is not innovative since there are other options beyond best supportive care available for people with BTC – so criterion 2 is not met.

5. 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**

Criterion 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
	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.
	
	• 'Eligible' refers to everyone who could have the technology under its marketing authorisation (obtained or in the process of being obtained) in England.
	
	• The 'technology' should only be developed for the ultra-rare disease, so the eligible population is small. The technology:
	
	  ○ has to be the first licensed treatment indicated for the ultra-rare disease under consideration
	  ○ should not be an extension of an indication from another:
	  • related population or disease, or
	  • subgroup of people with the same ultra-rare disease under consideration
	  ○ 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.

	• '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? Yes ☒ No ☐

	Notes and rationales:
	
	Population eligible under MA: [redacted]
	
	• Current incidence of biliary tract cancer - 2,800 people were diagnosed with cholangiocarcinoma, 1,100 people were diagnosed with gallbladder cancer and 500 people were diagnosed with ampullary cancer (2021) = 4,300 in total (NHS Cancer Registration Statistics, 2021)
	  ○ Current population of England in mid-2023 according to ONS = **57,112,500**
	  ○ Tataru et. al (2024) paper examining BTC across England from 2001-2018 indicated that there were 3,865 cases diagnosed in 2018. The same paper indicated that 60-65% of people present with locally advanced or metastatic disease
	• Company estimation of people with metastatic/late-stage disease (mBTC) is 2,038 (Valle 2017)
	• Proportion of people with HER2+ BTC – estimation from final scope is 4-16%. Applying this to the range of BTC cases (3,865 to 4,300) suggests that there are 155 (4% of 3865) to 600 (16% of 4300) people with HER2+ BTC.
	• Approximately 25% of people go on to receive 2L therapy following disease progression (Vogel 2023). Based on the estimated range (155-600 people with HER2+ BTC), this [redacted] (company estimate is [redacted]).

	There are no currently approved treatments available for HER2+ BTC – so zanidatamab would be the first licensed treatment indicated for this population. Zanidatamab does not currently have any other indications for use and is not an individualised medicine. Since fewer than 300 people in England are considered eligible for zanidatamab in its licensed indication and the technology is not an individualised medicine, criterion 3 is met.

6. 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**

Criterion 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.
	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.
	
	• 'Substantial additional benefit' means that the technology is likely to:
	  ○ significantly redress the reduced length of life, or
	  ○ 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).
	
	• 'The technology' means that:

	○ 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 ○ 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.
	Has this criterion been met? Yes ☐ No ☒
	Notes and rationales: • The intervention offers some additional benefit over existing established clinical management – according to clinical trial estimations from the company, the median progression-free survival (PFS) was 5.5 months (95% CI: 3.6, 7.3), and the median overall survival (OS) was 15.5 months (95% CI: 10.4, 18.5). • Standard median OS in comparison is normally 6-7 months with chemotherapy (Brieau, 2015; Fornaro, 2015; Lamarca, 2014; Lamarca, 2021) and prognosis is thought to be worse in HER2+ BTC (Lee 2025). • A study of outcomes associated with HER2 positivity in BTC indicated HER2-positive patients who did not receive HER2-targeted therapy had significantly poorer prognosis compared to HER2-negative patients (median OS 8.1 vs. 17.1 months, HR=2.46, 95% CI=1.73 to 3.48), while those receiving HER2-targeted therapy had comparable overall survival (OS) to HER2-negative patients (median OS 18.2 vs. 17.1 months, HR=0.95, 95% CI=0.71 to 1.27) (Lee 2025) • Analysis of HERIZON-BTC-01 (n=80) reported that people responding to zanidatamab reported improved pain scores and lower opioid use (Pant 2024) Despite the clinical benefit of zanidatamab, the size of this benefit is not large enough to qualify as substantial additional benefit in line with the HST criteria.

	There are multiple interventions available at various points in the treatment pathway for BTC. NICE technology appraisal guidance 944 recommends durvalumab for gemcitabine and cisplatin as an option for treating locally advanced, unresectable, or metastatic biliary tract cancer in adults – this would be available to this population in practice as a first line option. Following progression after first line treatment, chemotherapy (usually folinic acid, fluorouracil and oxaliplatin (FOLFOX) is available at second line (and is a relevant comparator in this appraisal). Zanidatamab is unlikely to offer substantial additional benefit for people with the ultra-rare disease over existing established clinical management and established clinical management is not sufficiently inadequate for criterion 4 to be met.

Routing decision	**Overall routing decision:** HST☐ STA☒ **Other comments:** Population eligible under marketing authorisation is small, but wider prevalence of condition as a whole does not meet the point prevalence criteria. HER2+ targeting is not innovative and although the intervention may offer clinical benefit, this benefit is not substantial enough to meet the HST criteria and there are other treatments available which suggests that established clinical management is not inadequate.