Refinement of Highly Specialised Technologies Routing Criteria: Consultation Themes and Responses

Routing criterion 1:

Theme 1:

There is a perceived shift in language from rare to ultra-rare diseases noted by stakeholders. There is a risk of sending a negative signal to both patients and companies working in rare diseases.

Response:

The aim of the HST programme, since its inception, has been to evaluate technologies for ultra-rare diseases (previously referred to as ‘very rare’). Before this refinement work, routing criterion 1 was “the disease is very rare, defined by 1:50,000 in England”. Therefore, this change is an update to terminology without any change in the underlying calculation since the prevalence referred to is the same. Therefore, while the terminology has been updated to be consistent with that used in the broader rare disease landscape, this element of the criterion is objectively unaltered.

Theme 2:

Stakeholders commented that to estimate the point prevalence in ultra-rare diseases can be challenging and there may be conflicting literature or data. There are also concerns about operationalising this criterion, for example, how to estimate the point prevalence, where to obtain expertise and what sources of data to use. Therefore, a degree of flexibility in applying the 1:50,000 threshold was suggested.

Response:

NICE acknowledges that it can be challenging to estimate point prevalence precisely in ultra-rare diseases. However, the aims of this refinement of HST

routing criteria are to reduce differing interpretations and subjectivity, and to ensure predictable, consistent, and transparent routing decisions that align more closely with the HST programme's vision. Introducing flexibility will contradict the aims of ensuring more predictable and consistent routing decisions. Nevertheless, NICE will ensure relevant literature and data, and a range of views, are used to provide the most accurate point prevalence estimate for the NICE Prioritisation Board to consider in the application of this criterion.

Theme 3:

The definition for ‘prevalence’ should be amended to allow for the annual incidence of a disease to be considered, especially when a treatment is curative or given for a fixed duration.

Response:

NICE believes that point prevalence is the most appropriate estimate. When the technology is curative and given to patients at a specific time point, point prevalence and incidence are likely to be similar.

Theme 4:

Stakeholders were concerned that the prevalence threshold of 1:50,000 or less in England is focused on total disease population rather than treatable population, and that this impacts on equitable access for ultra-rare diseases. They suggest that the prevalence threshold should be applied to the treatable rather than the total disease population. Stakeholders also commented that this criterion should be focused on unmet patient need.

Response:

The aim of this criterion is to define what an ultra-rare disease is; it is not about the size of the treatable population or the level of unmet need. Treatable population is considered in criterion 3, and unmet need is considered in criterion 4.

Theme 5:

Stakeholders were concerned about the proposal to exclude 'relapsing-remitting' diseases from this criterion and therefore routing into the HST programme, with the perception that this would make the criterion more restrictive than is currently the case. They stated that some conditions can be relapsing-remitting but still require lifelong clinical management and have an exceptional negative impact on patients' lives. Additionally, stakeholders flagged that it is important to recognise that even if a person is in 'remission,' this does not mean that they are unaffected by subclinical or progressive impacts of the condition, such as progressive organ damage, or the distinct psychological impact of having a relapsing condition.

Response:

After consideration of stakeholders' comments, NICE has decided to remove relapsing-remitting from the definition of this criterion.

Theme 6:

Stakeholders expressed concern about the emphasis on ICD-10 or ICD-11 in the definition of an ultra-rare disease. They stated that many ultra-rare diseases do not have their own ICD-10 or ICD-11 code, but rather are part of a group code. Stakeholders are concerned that by utilising ICD codes to determine what an ultra-rare disease is, ultra-rare diseases that are recently identified or with unestablished status may be overlooked. They proposed an alternative source called Orphacodes.

Response:

ICD-10 and ICD-11 are internationally accepted and adopted disease classification systems. However, NICE acknowledges there are limitations in these two systems, therefore ICD-11 will only be used as a starting point tool to assist in defining ultra-rare diseases, not as a rule-based tool. Other expert sources will also be sought on a case-by-case basis.

Theme 7:

Stakeholders are concerned about the lack of information on how to assess whether an ultra-rare disease has an 'exceptional negative impact' on people living with it, and what would be the thresholds for the relevant quality of life (QoL) needed to satisfy this criterion. Stakeholders also stated that the assessment of an ultra-rare disease's negative impact should consider beyond the individual patient, since ultra-rare, debilitating diseases often have significant and lifelong impacts on carers and families, and the wider society and economy.

Response:

NICE acknowledges that 'exceptional negative impact' is to some degree a subjective and individual judgement due to the heterogeneity of ultra-rare diseases. To that end, it is very difficult to offer further guidance as to a precise threshold. NICE also recognises that if such thresholds were defined it may be difficult to provide evidence that they are met at the time of a routing decision. The Prioritisation Board will use information from the NICE single technology appraisal process as a gauge to support decision making. NICE also acknowledges the potential impact on carers and families, and so the impact on carers and families is now included in the definitions for assessing 'exceptional negative impact.'

Theme 8:

Stakeholders are concerned that current definitions exclude subgroups of patients, including genetic subtypes when defining ultra-rare diseases. Stakeholders disagree with excluding these subgroups without further clarifying the definition of 'clinically meaningful.'

Response:

Clinically meaningful is likely to be disease specific and as such it is difficult to provide a general definition. The Prioritisation Board may need to apply a

level of subjectivity to its assessment of whether or not a disease meets this criterion based on the information available. Such deliberations may need to consider, for example, the unique and identifiable distinct clinical features of any subgroups and the relevancy of those subgroups for separate medical coding and research purposes.

Routing criterion 2:

Theme 1:

Stakeholders perceive criterion 2 as restrictive, and called for it to be removed entirely. They criticised:

restrictions in relation to repurposed technology and significant license extensions, claiming technology that even if it is repurposed or with license extension from another disease to an ultra-rare disease is still innovative for that specific ultra-rare disease, and should be assessed by the Prioritisation Board on this basis.

restriction in relation to the requirement for the technology to not be involved in ongoing clinical trials for other indications in different populations, stating that not all clinical trials will succeed, and that this restriction is not aligned with the science of product development.

Response:

The motivation behind routing criterion 2 is to ensure that the vision and aims of the HST programme are transparently addressed to justify the cost displacement associated with HST in the wider NHS. The aims of the HST programme are to encourage innovation in technology and innovation for ultra-rare diseases when there are challenges in generating an evidence base that is robust enough to bring the product to market. We do not believe a repurposed technology, or a significant extension of an existing licenced indication, is innovation in technology that warrants an exceptional departure from the usual ICER used in NICE evaluations. Also, a technology that is being repurposed or has a significant licence extension is a technology that is

already in the market, and hence not aligned with the vision of the HST programme. Repurposed medicines and treatments seeking a significant licence extension will have already gone through some level of safety and toxicity testing. Also, it is likely that there would be clinical experience with the treatment and knowledge around its mechanism of action.

However, we agree with stakeholders' criticism of the restriction that the technology not be involved in ongoing clinical trials for other indications in different populations, and hence we have removed this specific definition from routing criterion 2.

Routing criterion 3:

Theme 1:

Stakeholders comment that there is a lack of clarity as to how routing criterion 1 interacts with routing criterion 3, and why there is discrepancy between 1,100 people in England (point prevalence of 1:50,000 or less in routing criterion 1) and the population that is less than 300 in this criterion.

Response:

The purpose of the NICE HST programme is to evaluate technologies for ultra-rare diseases. Therefore, the aim of criterion 1 is to assess whether the disease of interest is indeed an ultra-rare disease, with a point prevalence of 1:50,000 or less (e.g. total patients 1100 or less in England). Then, after the ultra-rare disease is identified (criterion 1), criterion 3 assesses the treatable population (indication for the technology) within that ultra-rare disease. The treatable population within the defined ultra-rare disease needs to be smaller than 1100 to ensure an appropriate balance between facilitating access to the treatment and the inevitable reduction in overall health gain across the NHS that results from the higher ICER threshold for evaluation that is used in the HST programme. The acceptable treatable population size here is set at 300 as before.

Theme 2:

Stakeholders request that there should be flexibility in applying the 300-person threshold if the cap of no more than 500 for multiple indications is removed.

Response:

The HST programme is designed to be used in exceptional circumstances, to evaluate technologies for ultra-rare diseases that have small numbers of patients, and where there are significant challenges for research and difficulties in collecting evidence because of the rarity of the disease. We continue to apply 300 patients as the threshold because we believe this is an appropriate number for the treatable population. Altering this threshold would likely change the number of technologies routed to HST, which is not the intention of this refinement work. Furthermore, introducing the concept of flexibility creates ambiguity in decision-making thresholds; clarity on the definition of the treatable population supports consistency and predictability in HST routing decision making.

Theme 3:

Stakeholders question the reason why individualised medicines (n of 1) are excluded from the HST programme. And if these are excluded, how will individualised medicines be assessed. They also question how treatments that require a single dose, such as gene therapies, would be considered.

Response:

The HST programme was not set up for individualised medicines (n of 1) and we do not believe the HST programme is suitable for evaluating these technologies. We are working with system partners to consider how best to address the challenges associated with (n of 1) medicines and hope to be able to say more about this in due course. Regarding a single dose curative therapy, this will be considered for HST routing if the single dose of curative therapy is not an individualised medicine (n of 1).

Theme 4:

Stakeholders are concerned about the definition that the technology must be the first treatment for the 'licensed indication' under consideration. They state that while it is unusual for there to be multiple treatment options in development for conditions considered eligible for the HST Programme, if this situation arises the application of the criterion should not prevent a competitor technology from being permitted the same evaluation approach, unless the first in class has become established clinical practice (which would mean criterion 4 would not be met).

Response:

NICE acknowledges that this definition may be perceived as unfair to the manufacturers of any follow-on technologies indicated for the same patients, however NICE is required 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 that results. The follow-on technology could still be evaluated under the single technology appraisal programme, and if recommended, more than one technology will be made available for clinicians to determine which is most suitable for their patients.

Theme 5:

Stakeholders disagree with the definition 'the technology should not be for a subgroup of people with the ultra-rare disease,' as this appears to duplicate the definition of 'disease' under criterion 1. The consideration of a HST should be about the eligible (treatable) patient population. It is also contradictory to FAQ#4 in the supporting information, which says the patient population has to be a subgroup of the ultra-rare disease because the number of eligible patients must be ≤300.

Response:

To improve clarity, this definition has been reworded to ‘the technology should not be an extension of an indication from another subgroup of people with the same ultra-rare disease under consideration.’ This is to avoid a perverse incentive whereby the technology could have benefited a wider population living with the ultra-rare disease, but a manufacturer chooses to restrict the initial indication to meet the 300 treatable population requirement and therefore make it eligible for an HST routing.

Routing criterion 4:

Theme 1:

Stakeholders comment that NICE should provide clear guidance outlining the types of data, evidence, and expert opinions that could be considered in determining 'substantial additional benefit', defining what is "inadequate" existing clinical management, and defining "no other treatment available.”

Response:

NICE acknowledges that it is challenging to precisely define all these elements in criterion 4, and the criterion therefore states ‘likely to offer’, rather than ‘need to offer’. However, it is equally challenging to provide universal guidance on what constitutes 'substantial additional benefit', "inadequate" existing clinical management, and "no other treatment available” because of the heterogeneity of ultra-diseases. The types of data, evidence, and expert opinions that are required will depend on the epidemiology, symptomology, clinical characteristics, patient baseline quality of life and treatment or management currently available in the NHS for that specific ultra-rare disease. We are therefore unable to provide guidance that can be applied consistently in all cases. Nevertheless, NICE will look to enhance the scoping process of technology appraisals to ensure the appropriate types of evidence and data, expert opinions and patient experiences are sufficiently elicited during scoping to inform the NICE Prioritisation Board’s routing decision.

Theme 2:

Stakeholders are concerned that collecting robust data and QoL assessments for this criterion can be highly challenging due to the inherent uncertainties associated with very small patient populations in ultra-rare diseases, and also the skewed prevalence of ultra-rare diseases in children, in whom robust data is difficult to obtain. Data on the additional benefit a technology can offer is also unlikely to be available at the routing stage. Stakeholders also stressed that clinical outcomes should not be ruled out and should be considered alongside patient reported outcome measures (PROMs). Finally, stakeholders recommended that patient and expert clinical input is sought to inform the Prioritisation Board's judgement of the inadequacy of existing treatments and that the rationale for the decision is transparently communicated to all stakeholders.

Response:

NICE acknowledges that it can be highly challenging to collect robust data due to the inherent uncertainties associated with very small patient populations in ultra-rare diseases. NICE also recognises the opportunity to improve the scoping process of technology appraisals to ensure the right level of detail and appropriate types of evidence and data, expert opinions and patient experiences are appropriately elicited during scoping to inform the NICE Prioritisation Board's routing decision. We acknowledge clinical outcomes could be appropriate in certain circumstances and have changed the definition to reflect that PROMs are only examples, not essential.

Theme 3:

Stakeholders ask NICE to clarify whether the definition of 'existing established clinical management' in this criterion includes off-label treatments, as this is not clearly stated under the criterion's definitions. Stakeholders are concerned that demonstrating substantial additional benefits over existing clinical management, with the inclusion of off-label treatments, may present challenges due to these treatments not being subject to the same regulatory scrutiny as licensed therapies and could discourage research and development in ultra-rare diseases. The inclusion of off-label treatments as

standard of care could also disincentivise companies from launching rare disease products in the UK and prevent patients from accessing innovative, licensed treatment options.

Response:

The definition of ‘existing established clinical management’ in this criterion refers to all treatments, which includes off-label treatments if the off-label treatments provide adequate clinical management to patients with the ultra-rare disease. NICE does not accept that there is a rationale to specifically exclude off-label treatments as existing established management from other established management. This is in line with methods for technology evaluation where off-label treatments are often used as established management or a comparator in the analysis.

Theme 4:

Stakeholders highlight that replacing the word ‘or’ in the current criterion 4 with ‘and’ in the proposed refinement may restrict eligibility for the HST Programme, which is not the aim of this work. Stakeholders urge NICE to revert to the current language for this criterion.

Response:

The proposal is in line with the aim of the criteria refinement. As stated in the vision, the HST programme is designed to be used in exceptional circumstances, with the purpose of evaluating technologies for ultra-rare diseases that have ‘limited or no treatment options’. If existing clinical management is adequate or effective, then a new technology that offers additional benefit should be routed to STA because it does not meet the vision of ‘limited or no treatment options’. We therefore think ‘and’ better reflects the HST vision here. NICE’s retrospective routing analysis indicates that the suggested refinements result in no change to the number of technologies that would be routed to the HST programme. We believe that this change will enhance the predictability of the application of this criterion.