BIA response to NICE consultation on refinements to its Highly Specialised Technologies (HST) routing criteria

The BIA has responded to the National Institute for Health and Care Excellence (NICE)'s consultation on proposed changes to its Highly Specialised Technologies (HST) routing criteria.

The consultation closed on 30 January 2025. For further details about the consultation, please visit the consultation page on the NICE website.

Summary of BIA response and key recommendations:

- The BIA welcomes NICE's intention to increase the clarity, predictability and transparency of the HST routing criteria. We also support the aims of NICE's HST vision to encourage research and innovation in ultra-rare diseases and to secure equitable access to treatments for these conditions.
- However, the proposed changes would make the criteria significantly more restrictive, which contradicts the intention of the consultation and will reduce the number of products routed to HST.
- Greater clarity is needed around the definition of a disease in criterion 1 which excludes genetic subtypes when these are not 'clinically meaningful'.
- We strongly recommend NICE removes criterion 2 as it directly contradicts the HST vision and could act as a significant barrier to patient access to treatments.
- The BIA recommends that a more pro-innovation approach should be applied to the HST criteria to ensure alignment with the HST vision, the UK Rare Disease Framework and wider Government ambitions related to growing the UK life science sector.

Consultation response

The BIA welcomes the opportunity to provide feedback on these proposals. Please see below our response to the specific questions of the proposals.

Do you have any comments related to routing criterion 1?

Routing criterion 1: The disease is ultra-rare and debilitating, that is, it:

- *is defined as having a point prevalence of 1:50,000 or less in England*
- *is lifelong after diagnosis with current treatment, and*
- *has an exceptional negative impact and burden on people with the disease.*

The BIA welcomes NICE's stated aim in the HST vision to encourage research on, and innovation for, ultra-rare diseases and it is positive that NICE have recognised the difficulties associated with research and generating robust evidence bases in this space. Routing criterion 1 refers to the requirement to demonstrate the prevalence and debilitating nature and impact of the ultra-rare disease under consideration. Although we understand the purpose of this criterion, we are concerned about some of the proposed definitions that go alongside it.

'Disease does not refer to subgroups based on age, sex, severity or genetic subtype when these are not clinically meaningful.'

We are concerned about the proposed definition of a disease which explicitly excludes genetic subtypes when these are not deemed 'clinically meaningful'. It is unclear the circumstances under which genetic subgroups would not be considered to be 'clinically meaningful', as if a treatment is proven to be only effective in a genetic subgroup of a disease, then this indicates that the underlying basis of the disease is different, and it is therefore clinically distinct from the whole disease population and should be considered as clinically meaningful under this definition.

NICE should further clarify the circumstances under which genetic subgroups would suffice as satisfying this criterion and confirm that if a treatment is effective only in a particular genetic subtype, it is indeed clinically meaningful. Further, advancements in science are moving in the direction of a more precise understanding of diseases, enabling greater development of targeted treatments to tackle the root causes of a wide range of diseases, including rare genetic diseases and cancers. These innovative medicines can treat patients with debilitating symptoms, creating savings in ongoing healthcare costs and enabling patients and families to enter or return to the workforce and remain economically active. Targeted therapies can also avoid exposing patients unlikely to benefit from a specific treatment to any potential adverse events, which also have personal and economic impacts.

The UK is a leader in genomic science and has made significant advances into the development of genetically targeted precision therapies and the Government has set ambitions to harness these strengths, including to create the most advanced genomic healthcare system in the world.

In order for the UK to retain its global leadership as a location to invest in the research, development and manufacture of these medicines, and for citizens to benefit from it, these strengths must be translated into patient access. We are highly concerned that the uncertainty around demonstrating clinical distinction within genetic subtypes could have implications on patients access to life changing medicines and risks undermining the UK's ability to deliver genetically targeted therapies as part of its ambition to create the most advanced genomic healthcare system. NICE should consider the wider societal and economic value of encouraging research into targeted therapies for ultra-rare conditions when developing its criteria for HST. We recommend that the definition of disease should be clarified to reduce ambiguities in assessing product eligibility, enable greater acceptance of innovative medicines for genetically defined populations and foster research and development in ultra-rare diseases.

The disease is lifelong and has an exceptional negative impact

The BIA welcomes the greater focus and emphasis on the link between rare diseases and the lifelong and debilitating impacts of these conditions. We recognise the need for subjective judgement to assess whether a condition has an 'exceptional negative impact' on people living with the disease and the relevant quality of life (QoL) threshold needed to satisfy this criterion. Whilst the BIA understands the challenges in further clarifying this element, it is important to recognise that this ambiguity and subjectivity could risk impacting the predictability and transparency of how new products will be assessed and routed by NICE, which is a key intent of this consultation.

Further, it is notable that the wider impacts on families, carers, and society are not considered in the assessment of negative impact and burden as this has been limited to 'people with the disease'. The BIA believes that the assessment of a disease's negative impact should consider beyond the individual patient, since ultra-rare, debilitating diseases often have significant and lifelong impacts on patients as well as families, carers and the wider society and economy. Further, NICE should recognise the socioeconomic value of health interventions in treating and preventing further decline in diseases within its HST routing criteria and wider methods to facilitate government ambitions around prevention and increasing the number of people that are economically active.

NICE should also clarify the role of patients and clinical evidence from experts in the decision-making process to determine the degree of impaired quality of life. We recommend that the patient voice and clinical input should be fully incorporated during the decision-making process as clinical distinctions in ultra-rare diseases can be nuanced.

Under the definition of a 'lifelong' condition in the consultation paper, NICE has explicitly excluded relapsing-remitting conditions. We disagree with this proposal, since relapse-remitting conditions can place exceptional negative impacts and burden on patients, families and caregivers and often require a need for lifelong clinical management. Excluding treatments for these conditions from HST risks unfairly limiting access to treatments for some ultra-rare disease patients with high unmet need. This would make the criteria more restrictive than the existing criterion, which does not rule relapse-remitting conditions as ineligible.

The disease has a point prevalence of 1:50,000 or less

We understand the challenges associated with collecting data around populations and disease prevalence, particularly for rare and ultra-rare conditions. To support companies' in assessing the suitability of potential products eligible for HST routing, the BIA would also welcome further information around whether NICE will exercise flexibility in instances where there is uncertainty around the prevalence of the disease or where the disease marginally exceeds the 1:50,000 prevalence threshold but effectively satisfies the other routing criteria.

Further, it is important to note that the treatment window for some ultra-rare diseases can be critically narrow, sometimes limited to early symptomatic or pre-symptomatic stages. The exclusive focus on point prevalence in this criterion could overestimate the number of patients that can be treated and unfairly disadvantage medicines that target rapidly deteriorating rare diseases, where only a proportion of affected patients can be treated due to disease progression.

Do you have any comments related to routing criterion 2?

Routing Criterion 2: The technology is an innovation for the ultra-rare disease.

As highlighted above, the BIA supports NICE's aim to encourage innovation and research in ultra-rare and debilitating diseases, and we believe that appropriate incentivisation of innovation in the HST programme to address high unmet need is critically needed. Criterion

2 is a new addition to the routing criterion which outlines the requirements to demonstrate that the technology under consideration is an innovation for the ultra-rare disease.

We welcome the definition of an innovative treatment in the consultation paper which includes 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 disease.

However, the requirements listed to demonstrate the technology is an innovation for the ultra-rare disease also include a number of products that will be excluded under this criterion, including repurposed technologies, technologies that are a significant extension of an indication from another population or disease and technologies that are currently being explored in clinical trials for other indications. These criteria are unrelated to the degree of innovation of the products, we are concerned that this will significantly reduce the number of eligible medicines for HST routing, which is at odds with the consultations proposed intention to clarify the criteria and to neither increase nor decrease the number of medicines routed to the HST programme. The BIA believes this criterion should be removed.

We are particularly concerned that these proposed changes would exclude multi-indication products from entering the HST programme, which is more restrictive than the existing guidance. Exploring the potential of medicines with multiple indications in other populations or in new indications can play an important role in addressing unmet needs in rare diseases and companies will often seek to identify various indications and expand into new indications to bring greater benefits to the health system. These proposed exclusions are at odds with the approach to how medicines are typically researched and developed and risks discouraging research and innovation in ultra-rare diseases. We believe that a medicine that is proven in other indications should still be considered an innovation for the ultra-rare disease under consideration.

Further, BIA believes that people living with rare conditions with no existing treatment options available should not be disadvantaged based on launch sequencing. The requirement to demonstrate that the technology is only indicated for one indication, with no clinical trials in other indications, prevents the HST criteria from being applied consistently and could lead to a number of ultra-rare indications being deprioritised or withdrawn from HST routing. We are concerned this could limit both the potential of innovation and the potential benefits to other patient groups. We are also concerned that the proposals contradict NICE's own approach to evaluating each indication independently on its own merits to ascertain the level of value of a technology within a single indication.

Excluding treatments with clinical trials in other indications may also unfairly impact a number of single indication products as it does not take into account the highly variable nature of investigations in clinical trials in which many rare and ultra-rare disease trials are not successful and do not result in a commercial launch. The BIA therefore strongly recommends that this criterion is removed. We are concerned that in its existing form it directly conflicts with the HST vision to encourage research and innovation in ultra-rare diseases, as well as contradicting principle 8 of NICE's own principles. This criterion could act as a significant barrier to patients accessing promising therapies as well as risk positioning the UK as an unattractive market for launching rare disease medicines. NICE should recognise that the innovative nature of the technology under consideration should not be based on launch sequencing, whether other patients are benefiting from the product or if a subsequent indication is introduced.

This is especially important as companies are finding it increasingly difficult to make the case for the UK, in comparison to global competitors, as a launch market for new medicines, and there is a risk of the UK becoming further deprioritised as a launch market for rare disease treatments. Recent European Federation of Pharmaceutical Industries and Associations (EFPIA) Patients W.A.I.T (Waiting to Access Innovative Therapies) data demonstrates that the UK lags behind countries, including France, Germany and Spain, on the degree of availability of rare disease treatments. The data shows that 47% of rare disease drugs approved by the EMA were reimbursed in England between 2019-2022 and 40% in Scotland compared to 85% in Germany, 68% in France and 51% in Spain. Further, a 2023 BIA/ABPI survey of members engaged in the discovery, development, and commercialisation of treatments for rare diseases found that approximately half of approved rare disease medicines are not being reimbursed for patients in England. It is therefore crucial that the UK provides an attractive commercial environment to support improved access to these treatments.

Do you have any comments related to routing criterion 3?

Routing Criterion 3: No more than 300 people in England are eligible for the technology for its licensed indication, and the technology is not an individualised medicine.

Despite the focus on population size in the proposed changes for criterion 3, there is substantial overlap in the definitions and sub-criterion between proposals for criterion 3 and criterion 2, particularly on the new requirements for a technology to demonstrate it is an innovation for the ultra-rare disease under consideration. We disagree with the new

requirement in criterion 3 that 'to promote innovation, the technology should only be developed for the ultra-rare disease, so the eligible population is small' as this may further discourage innovation and research into ultra-rare diseases. The overlaps of definitions and concepts across criteria is confusing, and NICE should ensure that each criterion is distinct from one another to ensure consistency and predictability in NICE's decision making when routing new products.

Eligible population limit

The proposed criteria 3 retains the requirement of the eligible population for the technology in its licenced indication to be 300 or fewer patients in England. Despite the additional information provided in the consultations supporting documentation, it remains unclear as to why 300 was, and still is, the target population chosen to determine appropriate eligibility for an ultra-rare technology. We believe that the prevalence limit in criterion 1 is the only criterion needed to establish that the disease is 'ultra-rare', and a limit on population numbers is not required. NICE should provide additional information as to the rationale behind the 300 patient limit to ensure transparency and accuracy of its methods to assess and determine population limit.

A notable difference between the existing and proposed criteria is the omission of the allowance of up to 500 eligible patients across all possible indications. Further, both the exclusions detailed in criterion 2 and the requirement for the technology to be the first treatment for the licensed indication under consideration, implies that multi-indication products will not be eligible for HST routing. These requirements impose further limitations to the application of the HST criteria and reduce the number of eligible products for HST routing which will continue to drive inequitable access to treatments for ultra-rare conditions in the NHS, particularly since exploring the potential of therapies in other populations or new indications can support addressing high unmet need in rare and ultra-rare diseases, especially those without any treatment options.

In the definitions under this criterion, the technology must also be unlikely to be suitable for other subgroups of the population with the ultra-rare disease in the future that are outside of its first indication, or other populations with other diseases. It is unclear how NICE will seek to evaluate whether a company is able to conduct clinical trials for other indications in the future and provides no clarity as to how NICE will determine this. As addressed in previous answers, this requirement appears to impose further limitations to the routing criteria and is at odds with the way medicines are researched and developed.

'Individualised medicine refers to a medicine that is developed based on a person's unique genetic profile (n of 1).'

Criterion 3 also excludes individualised medicines as a suitable technology for HST routing, however we believe that based on the definition provided under the proposals, individualised medicine is not clearly defined. Further, the consultations supporting documentation notes that NICE does not believe HST is the right approach to evaluating individualised medicine. It would be useful to understand the proposed approach to evaluating individualised medicines in the future to ensure patients can benefit from these treatments and support the development and delivery of individualised medicine in the UK.

NHS medicines budget

In terms of the challenges NICE presents in the HST vision, and in the background of this criterion proposal, around balancing access to treatments for ultra-rare diseases against the potential impact on health gains in other areas of the NHS, the BIA believes there should be greater consideration of existing budget control mechanisms, including the cap on NHS spending on branded medicines through the Voluntary Pricing Access and Growth scheme (VPAG), and the Budget Impact Threshold (BIT), which are designed to facilitate patient access to cost-effective medicines in a sustainable way that does not inflate the NHS budget. It is also important to highlight in this context that the intention of this consultation is to provide additional clarity on the application of the routing criteria, and not to change the essence of the criteria or the number of products being routed through the programme.

We understand that bringing treatments for ultra-rare diseases to market can result in higher upfront costs for the NHS, however we believe that greater understanding is needed across the system of the socioeconomic value and long-term benefits of rare disease treatments to patients, families and carers that can provide significant benefits and long-term savings for the NHS, society and economy. This is consistent with the Government's ambition to embed a greater focus on prevention in healthcare and meet economic growth missions, including through increasing the number of people in the workforce. We also understand through engagement with Government on the development of the Life Science Sector Plan and 10-Year Health Plan that there is a recognition of this insufficient focus on assessing the holistic value of innovative medicines in the UK and the need to recognise long-term value for money.

UK BioIndustry Association

Do you have any comments related to routing criterion 4?

Routing Criteria 4: The technology is likely to offer substantial additional benefit for people over existing established clinical management, and the existing established clinical management is considered inadequate.

There are approximately over 7,000 recognised rare diseases of which 95% do not have any licensed treatment. The BIA therefore agrees that Criterion 4 should be designed to address the significant lack of effective treatment options for ultra-rare diseases in the NHS and alleviate high levels of unmet need for people living with these conditions.

We welcome the additional clarity provided around the definition of 'substantial additional benefit' to mean extension of life or improved quality of life. However, we are concerned that demonstrating the technology offers 'substantial additional benefit' over existing established clinical management will remain challenging, due to the requirement to demonstrate this through long-term evidence and data on patient-reported outcome measures (PROMs), as stated in the proposed definition. Collecting robust data and QoL assessments on this element can be highly challenging due to the inherent uncertainties associated with very small patient populations in ultra-rare diseases as well as the high prevalence of rare diseases in children. This data on the additional benefit a technology can offer is also unlikely to be available at the routing stage.

Additional clarity is needed on whether clinical outcome measures and validated surrogate endpoints will also be considered when evaluating a treatment's impact on patient's impaired quality of life since capturing PROMs can be especially challenging for ultra-rare diseases. NICE should clearly outline the types of data and evidence that will be considered when determining 'substantial additional benefit'. It should also be clarified how evidence presented by patient and clinical experts during the scoping session would be considered by the NICE prioritisation board and the rationale behind determining the degree of benefit at routing stage rather than during evaluation by the HST.

The proposed evidence requirements needed to meet this criterion is inconsistent with the recognition in the HST vision of the challenges associated with rare disease research and generating robust evidence. We recommend that the patient and clinician voice and expert input should be highly valued and formally incorporated when determining the additional benefits of a treatment and reflected within the prioritisation board's disclosure on routing decisions.

Furthermore, we understand through engagement with NICE that the definition of 'existing established clinical management' in this criterion includes off-label treatments, though this is not clearly stated under the criterion's definitions. We 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 access to innovative, licensed treatment options.

The proposed changes to routing criteria 4 also include new wording which mandates both the inadequacy of existing clinical management and that the technology offers substantial additional benefit compared to the existing criteria which only requires there to be either no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. This indicates that the proposals impose a higher threshold for the criteria to be met since both elements must now be proven, which is at odds with the consultations intention to clarify the criteria and not impose further restrictions to HST routing. Further information is also required around the definition of 'inadequate clinical management' as the evidence thresholds needed to demonstrate inadequacy remains unclear.

The BIA disagrees with the requirement to demonstrate that there is no other disease-modifying treatment (DMT) available in the NHS for the same ultra-rare disease or that there is no other treatment available in the NHS for the same symptom for which the technology is indicated at the time of routing decision. Under this criterion, we believe that NICE should consider a treatment if it is the second DMT or technology to treat a symptom and offers substantially greater benefit compared to the first treatment. It is important to understand that research and innovation can occur between DMTs being developed as understanding about ultra-rare diseases grows, and patients should benefit from these advancements and innovation in treatment options.

Do you have any comments on the overall proposal for the refinement of the existing HST routing decision criteria?

The BIA welcomes NICE's intention and efforts to increase the clarity, predictability and transparency of the HST routing criteria to enable fairer decision-making and outcomes for treatments for ultra-rare diseases. We also support the HST programme as representing a pathway that enables greater flexibilities for ultra-rare disease treatments with uncertain evidence bases and welcome the HST's overarching aims to secure more equitable access to treatments in this area of high unmet need and to encourage research and innovation in ultra-rare diseases.

However, we are highly concerned that the proposed changes would make the routing criteria significantly more selective and have a significant impact on the type and number of technologies being routed through HST, which contradicts the intention of the consultation to maintain the number of products being routed through the programme. We have a number of concerns under each specific criterion as addressed in our response above and believe that many of the proposed changes will restrict eligibility to HST and exacerbate inequitable access to medicines for patients with ultra-rare diseases.

We are also concerned that overlapping and combining different issues and concepts across some criteria is confusing for companies assessing the suitability of products, particularly under the definitions of 'innovation' in criterion 2 and criterion 3. NICE should ensure that each criterion is distinct from one another to enhance the transparency and clarity of the routing criteria, otherwise there is a risk that criteria are made less clear, going against the intention of the proposals. There is also a lack of clarification around any mechanisms for appealing or challenging routing decisions. The BIA believes that NICE should ensure consistency with its own principles on operating processes that are transparent and contestable.

These proposals should also be considered in the context of the significant gap between the Single Technology Appraisal (STA) standard cost per QALY thresholds and the HST programmes higher thresholds. Without appropriate application of flexibilities within the STA process and the existing population limits in HST, many treatments for ultra-rare diseases will be routed to STA, where they will be much less likely to receive a positive reimbursement decision and be made available to patients on the NHS. In particular, we disagree with NICE's statement in the HST vision that STA methods "are suitable for most technologies that treat rare conditions and small populations". The cost-effectiveness thresholds, which have remained unchanged for over 20 years, and current flexibilities within STA, do not sufficiently reflect the inherent challenges and uncertainties associated with conducting trials and collecting robust evidence in small populations.

In this context, highly selective routing decisions can be crucially impactful on companies' decisions when considering whether to launch a new medicine in the UK and for patients to benefit from innovative treatments. We are concerned that without addressing this significant gap between STA and HST, the UK will continue to be deprioritised as a launch market for rare disease medicines and fall behind other countries on the availability of these treatments, as demonstrated in the latest EFPIA W.A.I.T data. We encourage alignment between NICE methods and processes and government ambitions to improve the adoption of innovation in the NHS, prevent ill-health and grow the economy.

We are concerned that NICE's emphasis in the proposals on applying a cost-neutral approach to the application of its methods and processes is at odds with the intention to facilitate an environment where patients can access innovative medicines with uncertain evidence bases. There are multiple layers of cost control in the system, including VPAG which limits the total cost of NHS expenditure on branded medicines, BIT, Patient Access Scheme (PAS) discounts and commercial access agreements (CAAs). These mechanisms help to manage the affordability of new medicines in the NHS. NICE's remit should therefore not be to add a further layer of cost containment by ensuring its methods and processes and routing criteria are cost neutral.

We also believe that the retrospective analysis conducted by NICE in the supporting documentation is based on a very limited pool of data and therefore does not provide sufficient evidence that the refined criteria have not been made more restrictive and does not prove that the number of products being routed to HST will be maintained. As addressed in our answers above, a higher threshold for medicines to meet the criteria is being proposed, making it unlikely that the same number of topics would be routed to HST. Also, the refined criterion has been reorganised into different criteria positions from the existing criteria which makes the criteria-based analysis misleading.

The BIA recommends that a more pro-innovation approach should be applied to the HST routing criteria to encourage greater research and innovation in rare diseases and enable global companies to prioritise the UK as a launch market for new medicines. Through the UK Rare Disease Framework, the UK Government has recognised the need to support people living with rare and ultra-rare diseases in the UK, including through facilitating broader and faster access to potential treatment options. It is important that any changes to the HST criteria are aligned with the objectives of the Framework, as well as wider Government ambitions for life sciences.

About the BIA

The BIA is the trade association for innovative life sciences and biotech industry in the UK, counting over 600 companies including start-ups, biotechnology, universities, research centres, investors and lawyers among its members. Our mission is to be the voice of the industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation.

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