BIA response to consultation on NICE processes of health technology evaluation

April 2021

UK BioIndustry Association

The below sets out the BIA's responses to the proposals in NICE's consultation on processes of health technology evaluation.

The four themes consulted on are:

- Alignment of current processes
- Opportunities for new process improvements and ways of working (adapting to the changing healthcare environment and addressing key challenges)
- Commercial & Managed Access processes
- Objectives & vision of the Highly Specialised Technologies (HST) programme

Alignment of current processes

General comments

We are broadly supportive of NICE's proposals to streamline and align NICE's processes along a single simplified pathway with simplified terminology. We are particularly supportive of proposals to enhance engagement with stakeholders, and in particular, patient groups. However, we have some concerns around reducing the extent of the topic selection and scoping process – in particular consultation and stakeholder engagement elements being eliminated from 'simple' topics. In addition, we have major concerns with regard to proposals to use Multiple Technology Appraisals (MTAs) in HST.

Specific comments

– Develop a simplified singular process for all Centre for Health Technology Evaluation (CHTE) programmes

Agree

We can see the significant benefits of a simpler process for Health Technology Appraisals (HTAs). However, we would caution that where differences between different processes exist, that they are effectively signposted.

– Align terminology used across all CHTE programmes

Agree

– Terminating, discontinuing and suspending guidance

Agree

We would like to see further detail on the pathway, timeline and appeal process before they are finalized.

– Scoping consultation length will be flexible from 5-20 days dependent on the needs of the topics

Disagree

The final scope for a technology appraisal or guidance development is a fundamental cornerstone of NICE procedures. We believe that the proposal to introduce a consultation length of 5 working days for some topics would not allow the necessary time for all stakeholders to respond. However, we acknowledge that NICE wishes to find efficiencies at the scoping stage. Therefore, a flexible consultation period of between 10 and 20 working days would allow for some efficiencies to be found while still allowing adequate time for stakeholders to respond. We also suggest that NICE agrees the length of consultation period, and the date the draft scope will be issued, with the submitting company before the scoping stage commences in order to set the appropriate consultation length and to give notice of when the consultation period would begin.

– Scoping workshops will take place virtually

Agree

We believe this is one positive that has come out of the experience of COVID-19 and working from home, which will help to provide greater flexibility and opportunities for engagement. This change could provide an important opportunity for those living with rare and ultra-rare diseases and their carers. In the context of ultra-rare diseases, NICE should consider permitting patient representatives from outside England to join committee meetings to enable an improved understanding of the patient perspective, this is particularly important in cases where patient numbers are limited in England.

– Some topics will not be consulted on and NICE will issue a final scope

Disagree

Scopes for previous products may not always work well copied and pasted across to a new entrant and even in established disease areas companies may lose out on insights into appropriate comparators where other new products may also be in the appraisal pipeline.

It is unclear why accelerated regulatory processes remove the need for scoping. We recognise the need to shorten appraisal timelines, but ensuring a fit for purpose decision problem based on scoping with relevant stakeholders will be important for a successful appraisal.

There is also some ambiguity in para 49, introducing the possibility of a scoping workshop without a consultation, which requires clarification.

It would be helpful for companies to have a routine, formal touch point with NICE ahead of the scoping process to ensure that any unforeseen circumstances that may affect the scoping approach, possibly in light of confidential data, are not missed.

– Companies will provide a 'Summary of Information for Patients' with their evidence submission

Agree

We very much welcome this proposal and believe it will be a useful and beneficial addition to the process. Further clarity around whether it would be expected that further submissions would be needed at technical engagement stage and response to appraisal consultation documents (ACDs) would be welcome to ensure they fit with timelines. We would also welcome clarity on how patient group representatives will be further

supported when participating in other parts of the process and how the impact of patient engagement will be demonstrated.

– Patient and carer organisations can provide written submissions to all guidance programme

Agree

We strongly agree with this proposal and believe it will be a significant beneficial addition to the programme. Patient and carers have unique insight into the conditions they live with and their input will certainly help to provide a useful understanding of the lived experience of having a disease and consequently the impact of any treatment. However, NICE must consider the resource challenges for smaller patient groups which already have limited resources and continue to experience increased demand as a result of the pandemic. It will be important to ensure that smaller patient groups are not disadvantaged and are supported to provide submissions which can provide a greater understanding of the lived experience of patients. NICE should also consider those patients with ultra-rare conditions who do not have an advocacy group to support them and ensure that support is given to enable all relevant patients and caregivers can participate appropriately in the process.

– NICE provide dedicated stakeholder relationship managers for patient and carer organisations

Agree

This is another useful addition. We would welcome clarity on whether this will apply to only patient groups, clinical experts and/or to a wider range of stakeholders – there is some uncertainty in the document as to which it refers to. If separate stakeholder relationship managers are designated, it would be useful to have clarity on their roles and responsibilities. Some ultra-rare disease patients do not have a patient organisation representing them. We would therefore welcome clarity on how these stakeholder relationship managers would interact with ultra-rare patients and/or their caregivers.

– Committees will make recommendations on different types of guidance (TA, MTG, HST, DG)

Agree

With regards to the HST committee reviewing HTA topics, is unclear what ‘when required means’. Is there an intention to route HST-like topics to this committee? This is perhaps where there will be most value in making the most of the experience of this committee rather than routinely.

– Committee meetings will be held virtually

Agree

We believe this is one positive that has come out of the experience of COVID-19 and working from home, which will help to provide greater flexibility and opportunities for engagement.

– A shorter (less than 20 working days) consultation length can be used for some topics

Disagree

The current consultation length (at 20 working days) is already challenging for many stakeholders to respond to a highly technical and lengthy document. The consultation on draft guidance is often a crucial stage in a technology appraisal, seeking views on draft negative or optimised guidance to understand if there is additional evidence that can be provided to support turning the decision into a positive or broader

patient coverage recommendation. There is also a risk otherwise that the number of appeals will increase if stakeholders have not felt sufficiently consulted.

– Option of MTAs for HST

Strongly disagree

It is unclear how MTAs for HSTs will achieve the aims of increased flexibility, maximizing resource, or providing timely guidance for the NHS, and this option should not be included for HST simply to align across programmes. In fact, MTAs take longer and this may be unacceptable in the context of high unmet need.

Very small patient populations, high levels of investment and uncertain data will present unique challenges for this approach. For example, the nature of clinical trials may vary more noticeably for ultra-rare treatments which could present challenges for MTAs as part of the HST programme.

It is imperative that company submissions underpin the HST process, and contextualise any novel endpoints, sparse data and uncertainties based on their extensive experience in under recognized and under researched areas.

– Routing topics to clinical guidelines.

Strongly disagree

We have significant concerns regarding the proposal to use guidance as an alternative to technology appraisal and believe it goes against the spirit of the agreement between industry and the Government to assess all active substances in their first indication or new significant therapeutic indication. We believe this risks creating an unnecessary and potentially harmful two-tier system for medicines.

Opportunities for new process improvements and ways of working

General comments

We generally welcome alignment with the regulatory process and MHRA and would like to understand in particular how this maps onto the Innovative Licensing Access Pathway (ILAP). We are also supportive of experts being used from scoping and nominated experts from related topics. We have, however, major concerns regarding to changes to technical engagement as an option in TAs where we believe the benefits to be significant.

For medicines for rare diseases and Advanced Therapy Medicinal Products (ATMPs) in particular, a greater degree of discussion is likely to be required given expected challenges around data collection in the context of small patient populations. NICE should seek to ensure that processes include enough flexibility to 'work' for rare disease medicines.

A focus on the reduction of health inequalities is welcome, particularly in the area of rare diseases where there is so often a challenge in this regard.

It would be useful to understand how NICE plans to implement the changes resulting from the methods and process review and whether it would consider establishing an implementation group, with representative

from all relevant stakeholders to work through appropriate and effective implementation and transition plans.

It is critical that the changes arising from this significant review and implemented consistently across the NICE work programme. We would therefore welcome further information on how NICE plans monitor and assess the change management required internally to achieve the aims of the review.

Specific comments

– DHTs developed as medical technologies and diagnostics guidance

Agree

We broadly agree with this proposal. Requirements in terms of methods and process for Digital Health Technologies (DHTs) are currently available in a number of different documents and there is a need to consolidate this in the process guide.

– Use experts from scoping in guidance development

Agree

We agree with the proposal to start the expert nomination process earlier in the guidance development process and to use the same experts to contribute to scoping and the development of the guidance where possible. This will help ensure a good understanding of the topic and continuity of input throughout the appraisal process.

We would welcome clarity from NICE on the process for nominating and selecting experts and how NICE will ensure they have the right expertise to fully contribute to the guidance being developed. We would welcome consideration of a pool of clinical experts is which ensure the right clinical experts are present, representing the right clinical community.

It is important that clinical experts who have been involved in clinical trials or who have worked with companies, are not automatically excluded. Often, they are the experts in treating the condition for rare diseases they are often the only clinicians with sufficient or relevant expertise to support the guidance development. Companies would welcome being informed who the selected clinical experts for the appraisal are at the start of the appraisal. The process as it currently stands is very opaque.

– Professional, patient and carer organisations to nominate for all guidance topics

Agree

We believe that involving patient and carer representatives at all stages is vital to ensure that guidance and HTA process reflects the priorities of patients and those living with the diseases being discussed.

– Use experts nominated for related topics and guidelines

Agree

We welcome this and other proposals to expand the pool of experts who are able to input into the guidance development process. Including experts who have worked on related technology areas therefore appears sensible. It will be important to consider the implications of this proposal with respect to rare or ultra-rare conditions, where they may be only limited experts with relevant knowledge in the disease area.

– Working in parallel with the regulatory process

Neither agree nor disagree

While in principle we agree that NICE should seek to work in parallel with the regulatory process, there are areas of clarification that would be useful to understand.

We would welcome further work towards greater alignment across the various stages of the market access pathway, and particular consideration should be given to the impact of the implementation of this proposal on ATMPs, which often bring complex challenges around uncertainty.

However, it would be useful to understand how "an expedited variation to the standard evaluation process to facilitate alignment with accelerated UK regulatory processes" would function. The processes must take into consideration the feasibility of providing full evidence submissions and economic models within expedited timeframes. It is crucial that additional flexibilities in the process are implemented to ensure the system works in an aligned and collaborative way. NICE needs to work closely and flexibly with companies to ensure that the ultimate outcome – access for patients – is positive.

– Managing company submissions; relates to not asking committees to make decisions where ICERs are v high e.g. >£200k)

Disagree

We believe this approach will significantly and disproportionately disadvantage rare disease medicines and ATMPs. All opportunities should be explored with the company to bring the value proposition into an acceptable range. It will be important that NICE processes ensure flexibility in what constitutes an acceptable range, with respect to the evolving area of innovative technologies such as ATMPs. There continues to be particular challenges in meeting the ICER threshold for innovative treatments like ATMPs for ultra-rare conditions, where the patient population is particularly small. A pathway within the process is needed to ensure appropriate opportunities for input from the company and transparency around who will decide.

It is essential that detailed and collaborative discussions and consultation takes place with the submitting company before any decision is made. Any potential termination or rejection should only be undertaken following thorough discussions with companies and considerable advance notice.

Furthermore, early engagement with NHS England is critical, but these discussions are often contingent on the appraisal committee's most plausible assumptions. Considering the company's base case for these initial discussions is pragmatic starting point, with opportunity for further refinement if the appraisal committee's conclusions vary.

– Technical engagement (TE) shall become an option

Strongly disagree

It is important to retain the option for early engagement in the updated processes for all topics, even if technical engagement is not a mandatory part of the process. As an example, an additional information request following the Evidence Review Group (ERG) report for an Fast Track Appraisal (FTA) topic resulted in a revised ERG base case for the committee meeting, which may otherwise have resulted in lengthy committee discussions and consultation. This opportunity for more straightforward topics should not be lost.

The technical engagement step is of particular importance for treatments for rare diseases and innovative technologies such as ATMPs, which often involve challenges around uncertainty around the long-term impact.

The bigger issue appears to be a disconnect between the ambition of the TE step to address and eliminate uncertainties in advance to increase 'straight to FAD' decisions versus the expectation of the appraisal committees to discuss and conclude on all issues independently. Similarly, because appraisal committees may take different views to the NICE team and the ERG, it is challenging for companies to alter value propositions ahead of the committee discussions. Working towards creating synergies between TE and committee discussions would go a long way in achieving the aim of TE.

Additionally, when an "issues-based" technical report is issued, the questions being asked of stakeholders should be made clear and should be within the scope of the appraisal. Particularly with regards to ensuring appropriate participation from patient groups, there may be a role for the stakeholder manager to ensure that the ask is clear.

There is merit to the suggestion to offer TE to topics with where additional support is needed. However, there needs to be a clear framework to identify these topics, and clear aims for the engagement.

– The low ICER fast-track appraisal option will be removed

Neither agree nor disagree

While we have no particular comments on this proposal, we would welcome information on how NICE hopes to continue to expedite the process should technologies with a low ICER do come to them for appraisal.

– A simpler approach to evaluations of technologies with multiple indications

Neither agree nor disagree

While supportive of the proposal that a process which allows the appraisal of a technology for multiple indications would be desirable, we are concerned that the mechanism may limit access to medicines for some patients. We would seek reassurance from NICE that this mechanism would not be used to recommend a sub-group of a cost-effective population and thereby limit patient access to cost-effective medicines.

We welcome NICE taking a more pragmatic approach in these scenarios and considering what is the optimal use of NICE, company and other stakeholder resources.

– Developing guidance on combination treatments

Agree

While we agree with the principles of this proposal, support to find solutions to enable companies to engage with one another during the evaluation of combination therapies which will otherwise not be recommended by NICE, we would appreciate further detail on how this would function – for example what would be the forum for cross-company discussion? Would these be facilitated by NICE? How would value be apportioned to each element of the combination?

– NHS Treatment eligibility criteria

Strongly agree

This proposal is welcomed and will help to facilitate earlier engagement with NHS England on the criteria as part of the evaluation process. It will be important for NICE to provide further guidance on the process for this to ensure stakeholders will be able to contribute effectively. If implemented sufficiently early and transparently this could help to bridge an existing gap in the processes.

While we welcome the proposal, it will be important that there is dialogue on potential eligibility criteria ahead of the appraisal so that cost-effectiveness evaluations in relevant subgroups can be considered, rather than the eligibility criteria being implemented subsequent to the NICE appraisal and resulting in further restrictions within what NICE have deemed cost-effective populations.

– What changes can we make to our processes to help reduce health inequalities in the way we develop our guidance, stakeholders participate and how health inequalities are identified and considered in making recommendations?

The case for change consultation acknowledged that further work would be needed to define health inequalities – this seems like a necessary first step (e.g. is it purely based on socio-economic factors, or also encompass rarity of condition and / or geographical variations in care?).

Ensuring that processes include enough flexibility to 'work' for rare disease medicines and ATMPs is important in reducing health inequalities. There is a clear tilt in favour of treatments that have robust, large, randomised control trial datasets within NICE processes. There should be in-built caveats to ensure that less common and/or highly innovative medicines , which by their very nature cannot rely on large clinical trials, can still be appropriately managed.

In order to build on the positive proposals made through this consultation, we suggest NICE also introduces a meeting for patient and carer organisations representing patients with rare conditions that would take place prior to the committee meeting and gather further evidence of the lived experience of patients with rare conditions.

Other changes to process are required to more fully address the inequality between rare and common conditions, and we call on NICE to consider the need for an alternative assessment process for treatments for rare conditions in order to close the gap between STA and HST. We support proposals to introduce a single assessment pathway for medicines that treat both rare and ultra-rare diseases. This would be a more appropriate system to recognise the challenges that face those with rare and ultra-rare conditions alike, such as those stated in the recently published rare disease framework, including limited and uncertain data.

Commercial and Managed Access processes

General comments

Commercial and managed access processes have broad support among industry and are recognised for their ability to address uncertainties, provide life-changing treatments for patients and value to the wider system. We are therefore supportive of the below proposals, but would add that they should be flexible enough to reflect the unique needs of treatments for rare and ultra-rare conditions, including ATMPs. Any clarity on associated criteria and processes is helpful, particularly in relation to approaches that will and

will not be considered. Proposals should be developed in consultation with industry partners as any options must be feasible for both the NHS and industry to implement.

Specific comments

– Commercial and managed access proposals

Agree

In principle, we fully agree that a process or framework is needed for commercial managed access proposals because within the current process there is a lack of transparency and significant delays – which is why the BIA has selected agree to this question. However, this proposal contains no details about the process proposed and there are concerns around some wording included.

It is imperative that the new process is co-developed closely with stakeholders and consulted on before it is finalised. The process should clarify the role of NICE and NHS England and set out timelines for engagement and who is point of first contact for industry. NHS England has a key role in these early discussions and there needs to be a strong commitment and buy in to support productive early discussions. Currently, discussions are often slow because committee's views on the most plausible assumptions and key uncertainties are awaited by both NHS England and companies to progress commercial discussions. For it to be successful, any new process should pragmatically outline how this challenge may be overcome.

We strongly support the proposal to provide greater opportunity after the first committee meeting to allow commercial discussions to take place once the committee's preferred assumptions for the economic modelling are known. The process needs to tie this in with expectations from early engagement so that early dialogue is productive.

Specific challenges are set out below:

- Para 140: Suggests that Patient Access Schemes (PAS) will form the core of all submissions to NICE. However, there will be topics where no PAS is required. With regards to always including a simple PAS within a commercial proposal, it is not always possible for companies to submit a simple patient access scheme that might involve risk-sharing challenges, due to the nature of more innovative treatments. There may be cases where a complex PAS is the best route for patient access and is associated with manageable administrative burden and monitoring costs. The language should be amended to retain flexibility.
- Para 141: Further detail is required here. Importantly, there will need to be some timelines around this step, otherwise once a topic goes "off process" there can be significant delays. The process should outline how experts will be involved in the discussion around gaps identified by companies.
- Para 143: The development of a criteria to assess the exceptional needs which warrant commercial and managed access options should be carefully considered with a view to ensure flexibility and future-proof NICE's processes for innovative medicines, in recognition of the growing pipeline of these types of treatment that may not be adequately covered under strict criteria. To date there has been too much emphasis on being close to or likely to deliver on standard cost-effectiveness thresholds to open up commercial discussion.

– The Budget impact test

Disagree

We welcome the acknowledgement that there are opportunities for further refinement in the phasing of the Budget Impact Test (BIT) and we would welcome further transparency around what these learnings are.

However, we have selected disagree to reflect some of the significant concerns we have around the proposed time limits. The proposal to reconsider timelines after the appraisal committee meeting where a FAD has been agreed in exceptional cases is a positive step to enable faster patient access. The commitment from NICE to keep stakeholders fully informed is also positive. However, we are not supportive of NICE's proposal to allow a time limited period for negotiations following a significant breach of budget impact threshold. This is because the limited time has not been defined. Further, commercial negotiations may be complex, and an arbitrary cut-off will not benefit patients, industry or the NHS. There is therefore a significant risk that by placing a considerable time limit on this could result in significant barriers for companies in challenging commercial negotiations.

Importantly for this proposal, it is unclear when BIT breach is 'significant' and who will assess this? There also remain issues around BIT methodology and forecast methodology, which have not been addressed in this document which would need further clarification on.

– Clarifying the status of a recommendation for managed access

Agree

The recognition that the status of a recommendation for managed access for highly specialised technologies is unclear is encouraging. The proposal to work with stakeholders across the system to confirm this will be a step in the right direction. Para 150 is unclear about what status is being recommended and what impact this will have.

– Managed access entry

Agree

We are encouraged that NICE recognises that it may be valuable to explore opportunities to develop a more streamlined market access entry process aligned with the MHRA's ILAP. Closer alignment between HTA and regulatory parts of the system is welcome.

Exploring opportunities to route promising technologies directly into managed access without requiring a full health technology evaluation is positive, this could significantly speed up patient access and would be particularly beneficial for medicines for rare conditions and ATMPs, where longer term data can often be uncertain. However:

- the details around this process must be co-developed with stakeholders and consulted on. For example, how would a plausible cost-effective price to enter the Managed Access Agreement (MAA) be determined?
- what are the criteria for topics that will not have a full appraisal compared with topics that are likely to have a MAA but after committee consideration?
- guidance via MAA must remain timely in relation to marketing authorisations

- this route should only be used if a full appraisal will not result in routine commissioning. The standard TA/HST process should have the flexibility to consider uncertainties and base decisions on surrogate outcomes, expert elicitation wherever appropriate

Flexibility is welcome, but consideration of potential burden this may place on stakeholders would be warranted.

For very rare conditions, it is unlikely that data collection will fully resolve uncertainties due to small sample sizes. The re-evaluation process will therefore still need flexibility

– Data collection agreement development and oversight

Agree

The proposal to develop a process for the establishment and oversight of data collection agreements could be a positive step in terms of ensuring consistency between programmes and provide clarity to companies. However, we would welcome further detail on the process, role and remit of the Oversight group.

– Managed access exit

Disagree

We believe there are ethical considerations that must be taken into account when examining exit from a programme that facilitates patient access for a finite period. These have not been sufficiently covered in this proposal.

In addition, we do not agree that a full STA is required for all re-assessments. There is a case for an expedited re-assessment that reduces bureaucracy within NICE and seeks to limit the resource requirements on the clinical and patient group community, and companies. We acknowledge that the duration of an MAA period can mean the environment has changed from original scope, but we consider that a blanket full re-assessment for all topics is not in the spirit of flexible, pragmatic engagement and faster patient access.

Finally, a full re-assessment has significant financial costs for companies both in developing dossiers and double the NICE STA fee, which may present an unnecessary chilling factor for companies involved.

Objectives and vision of the Highly Specialised Technologies programme

General comments

The introduction of the Highly Specialised Technologies pathway was, prima facie, a positive step for those with a rare or ultra-rare condition. However, the pathway does not meet the need for a fairer, more flexible appraisal pathway for novel therapies for rare diseases.

Only 14 medicines have been evaluated under the HST process in the eight years since it was created, while the bulk of orphan medicines have historically ended up in a non-HST process, which is not typically suitable for evaluating orphan medicines. We believe should and *can* be done to adapt the value assessment for orphan medicines, ensure fast access without undermining sustainability or value for money. The widespread expectation among many stakeholders, including patient groups, is that HST is the vehicle to achieve that.

One of the key areas of confusion around the HST programme seems to be that NICE narrates it to stakeholders as an appraisal route for treatments for rare conditions, but the criteria for entry impose several other restrictive, and we would suggest unnecessary, considerations.

While the proposals recognise the potential of the HST programme, we are very disappointed that they do not go far enough to ensure that rare disease medicines receive fair and robust appraisals and indeed NICE has explicitly stated that it is not their intention to ensure that they do not fall down the gap between STA and HST.

We hope that NICE will reconsider its approach, as the current proposals do little to tackle the issues that prevented many rare disease medicines from going through the HST process resulting in them failing to achieve a positive recommendation through STA, and in fact may exacerbate some of problems.

In November 2020, the BIA published a report in collaboration with PwC – *A Rare Chance for Reform* – which sets out a revised model for rare disease medicines appraisal and aims to overcome many of the challenges. We commend it to NICE now in the context of this review and hope it will consider its recommendations.

Specific comments

– The vision of the highly specialised technologies programme

Strongly disagree

The 'Vision' is a major missed opportunity to adapt the HST process for rare disease medicines that do not meet the strict HST eligibility criteria and will have a detrimental impact on the whole programme in the context of rare diseases. The 'Vision' does little more than to reassert the initial remit of the programme and its focus on serious and severe ultra-rare conditions. This failure to formally adapt processes for orphan treatments, which are well understood to face significant challenges with small patient populations amongst other issues, is disappointing.

– The key principles for the highly specialised technologies programme

Strongly disagree

The proposed principles of the HST programme do not address many of the challenges that have been encountered in the HST topic selection process to date. This is an area where action from NICE has been anticipated for a long time and we are disappointed that there has been little stakeholder engagement on this important topic. The consultation does not include any concrete, meaningful proposals to enhance patient access to rare disease medicines.

While clarification of the key principles for HST programme eligibility is useful, there remains significant ambiguity in the wording and we would encourage NICE to refine this further together with stakeholders. Furthermore, the 'Key principles' fail to address many of the challenges that have been encountered in the HST topic selection process to date and may, in fact, create more barriers to access.

Out key issues with regard to the proposed principles/criteria include:

- With regard to the proposal in para 186 (a), the manual of prescribed services may not necessarily contain all rare diseases. Exclusion of clinical commissioning group (CCG) commissioning should be approached with caution for disease areas that have had no treatment available to date. Furthermore, there are new structures emerging in the NHS – such as ICSs – which are not taken into account. Rather than focusing on NHS structures, it may be more useful for NICE to focus on the condition itself – particularly in the first criterion listed.
- We are very concerned by the proposal in para 186 (c) that the "HST programme should consider only technologies for which it is biologically plausible that the use will be restricted to an ultra-rare condition – for the duration of the guidance." The statement is unclear with regard to what 'biologically plausible' means and says nothing about how measurement of this might be achieved or what expertise NICE possesses to make that assessment. Our understanding of biology and aetiology is constantly evolving, so how can it be said with any certainty that something is 'biologically plausible'? We also believe it may disincentivise the development of new treatments if developers are not able to conduct research into new therapy areas if it will endanger an HST recommendation. NICE evaluates technologies on an indication-by-indication basis, and it is the ultra-rare indications that are disadvantaged by the standard appraisal process. This principle therefore severely risks disadvantaging patients who have ultra-rare conditions but the treatment for it is (or may be) also clinically effective in other patients. It is patients who will lose out if NICE does not re-think the principles around the use of medicines in different patient groups.
- In para 186 (e), it is suggested that current treatment options should be not very effective in order for a treatment to be considered for HST. Does this mean, for example, that competitors for products that have HST guidance will not be accepted for HST? This would seem to preclude any improvement on a treatment once one indication is approved at HST.
- In para 186 (f), we disagree that this principle is necessary and it assumes motives for medicines pricing that are not recognised by industry. Where there is evidence for a treatment being effective for a larger patient population, it will be assessed through a technology appraisal as such and priced accordingly. The HST programme should be for all indications that are rare or ultra-rare.
- In para 186 (g), the proposal refers to wider research and evidence generation which will not be appropriate, for many companies where they undertake due diligence in research programmes this includes a consideration of possible treatment effects. The translation to full trial data and licensing is far from secure and could disadvantage the primary ultra-orphan indication of a particular treatment. It does not recognise how medicines are researched and developed in relation to the trialling of medicines in different patient populations, high rate of clinical trial failures or science driving areas of new research to improve clinical understanding and disease management. As with the principle in para 186 (c), this may have a significant chilling effect of medicine development.
- In para 186 (h), it would be useful to see additional clarification on how specific characteristics within a disease – i.e. biomarkers and genomic testing – are to be considered in this context. This is increasingly the direction of travel more medicines development and requires clarity at this stage.
- In para 186 (i), in order for a medicine to be put forward for appraisal in any indication – rare or otherwise – it will have to have undergone significant research and development. This is as true for repurposed medicines as it is for entirely novel treatments – efficacy, effectiveness and safety must all still be demonstrated in the new patient population. We therefore question why this principle would exclude a medicine that was repurposed from a larger patient population if new trials demonstrate effectiveness in a new and rare indication. We believe this fails to recognise the value these medicines can bring to patients with rare diseases

- In para 186 (j), we believe this to be contradictory to para 186 (i). Any medicine licensed in another indication that can be re-assessed for a new indication is by definition a repurposed medicine. Clarity is needed on this principle.

The criteria for excluding technologies from HST topic selection

Strongly disagree

The proposed principles set out in c, g, i and j run the significant risk of incentivizing companies *not* to run trials in additional populations, because it could render an existing indication ineligible for HST or prevent future indications from being considered. It also neglects the situation of off-label use, which is largely beyond companies' control. These proposals fundamentally misunderstand how medicines are developed by companies and would likely have a significant chilling effect on the development of new treatments for rare diseases. We would like to draw NICE's attention to the impact of re-purposed medicines in the context of the RECOVERY trials for COVID-19, which have gone a significant way towards alleviating much of the suffering due to the disease.

With regard to the removal of life-long or chronic therapies as an exclusion criterion, the proposal is encouraging; although we note that NICE has already exercised welcome discretion on this point in the context of gene therapies. We hope that the formalisation of this policy will help to ensure that further ATMPs receive positive recommendations.

Other comments

We would like to reiterate our disappointment that NICE has not taken this opportunity to ensure that HST works for rare disease medicines and build in the necessary flexibilities to ensure patient access.

The principles and vision set out above are of major concern as they stand. They will do little to nothing to ensure access to rare- or ultra-rare disease medicines, as was widely hoped, and may in fact do significant harm to access in the UK. We believe that the vision and principles for HST must be revisited to prevent that from occurring. We would encourage NICE to engage with stakeholders from across patient groups, industry and academia, to design a vision and principles for HST that will ensure patient access to medicines for rare diseases.

About the BIA

The BIA is the trade association for innovative life sciences in the UK. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

Our members include: Start-ups, biotechnology and innovative life science companies; universities, research centres, tech transfer offices, incubators and accelerators; and a wide range of life science service providers: investors, lawyers, IP consultants, and IR agencies. We promote an ecosystem that enables innovative life science companies to start and grow successfully and sustainably.