How strongly do you agree or disagree with the proposals related to:	
A modifier for severity of disease. Please share comments.	Agree. The BIA agrees in principle with the proposal to replace the current end-of-life modifier with a severity modifier that quantifies severity of disease using both absolute and proportional QALY shortfall and implicitly encompasses concepts such as burden of illness and unmet need. This proposal will benefit indications across a wider range of diseases than the end-of-life modifier, which typically only benefits oncology treatments. Rare and ultra-rare diseases face a high degree of unmet need and are some of the most severely burdensome for patients and their families. A severity modifier therefore has the potential to benefit more rare disease medicines than currently benefit from the end-of-life criteria. Despite this, it is disappointing that NICE has taken an 'opportunity cost neutral' approach by reallocating the average weight that is currently invested in end-of-life treatments. While a broader range of conditions will be captured by a severity modifier, the currently proposed cost-neutral approach will have very little impact on the prospects of success for rare and ultra-rare disease medicines routed to STA, despite NICE's attestation otherwise. Whilst we agree in principle that a severity modifier is preferable to the current end-of-life modifier, we do not agree that the current proposals are sufficient. Though the BIA acknowledges that NICE is operating within an environment of financial limitations imposed by system partners, the cost-neutral approach to the proposal is inconsistent with other government initiatives. For example, the Innovative Medicines Fund (IMF) will receive £340m on top of the sum currently ringfenced for the Cancer Drugs Fund (CDF). This additional funding will benefit innovative treatments including for severe and rare diseases. It is therefore unclear why, when additional funding has been found for the IMF, NICE must implement a severity modifier within the existing envelope, particularly given that many of the same treatments will be affected. NICE's planned research to determine the magnitude of the societal value for health benefits in severe diseases is welcome and we believe that the findings of such research will inform the need to expand the magnitude of the proposed severity modifier. It is crucial that when determining societal value, NICE considers the differences between the value for the patient, the value for the carer and the value for society. These need to be addressed holistically in order to truly capture the value society places on treatments for severe conditions.

	The BIA urges NICE to engage with industry in shaping the approach to this research and consult stakeholders on the scope and methodology. We strongly recommend that NICE expands the planned research to reassess the societal value for health benefits in rare diseases and identify the extent to which severity and rarity overlap. We also urge NICE to communicate a clear plan and timeline to deliver this research so that they can be accountable. The BIA recently conducted an opinion survey to understand how people feel about rare diseases and access to medicine. The findings, presented in the BIA's report *Public attitudes to rare diseases: the case for equal access*, indicate that there is public appetite for specific measures that would support access to rare disease medicines, even if it would mean a higher cost to the NHS. In response to concerns highlighted by stakeholder about rare disease topics routed to the STA programme, NICE contends that the Methods Review has taken steps, including the introduction of a severity modifier, to address the needs of rare disease technologies in the technology appraisals programme. The proposed severity modifier does not mitigate the unsuitability of the STA programme to assess rare disease and should not be considered a proxy for a rarity modifier. NICE's own research shows that most medicines would only qualify for a medium severity weight. Further, it shows that a host of orphan medicines previous appraised would not even qualify for a severity modifier, including some that would have previously received an end-of-life modifier. The proposals will therefore have minimal effect on the prospects of orphan or ultra-orphan medicines securing positive reimbursement decisions in the TA programme. To make a real difference for rare and ultra-rare diseases, what is needed is a modifier that bridges the gap between the £30,000/QALY STA threshold and baseline HST threshold of 100,000/QALY. Even the maximum QALY weight of 1.7 (proposed by option 1) will not sufficiently bridge this gap. To bridge the gap, a severity modifier with higher QALY weight multipliers (up to 3.5x the current threshold) or an additional rarity modifier, that would provide an additive modifier, is required. The BIA is deeply concerned that the current proposals for a severity modifier do not deliver on the promise of a highly ambitious methods review set out in the Life Sciences Vision, nor meet the level of ambition set out at the start of the review. We urge system partners to work collaboratively to enable NICE to deliver on the ambition of the Life Sciences Vision and develop proposals that will enable rapid and equitable access to treatments for all conditions including rare and ultra-rare diseases.

Consideration of uncertainty within decision-making Please share comments.	Strongly Agree. The BIA is supportive of the proposals to enable Committees to accept a higher degree of uncertainty where evidence is difficult to obtain. We also welcome the commitment by NICE that Committees will be mindful that there are circumstances where generating evidence is complex and where further data collection to resolve uncertainty is not realistic or feasible. These proposals are important in the context of innovative therapies such as ATMPs where securing patient access can be challenging due to the inherent uncertainty around long term outcomes. Generating robust data is particularly difficult for treatments for rare diseases where small populations make it difficult to conduct randomised controlled trials with appropriate comparators. The BIA is encouraged by NICE's plans to further explore how different types of uncertainty are addressed and to implement a visualisation framework. The BIA recognises the positive work carried out by the Task and Finish Group on uncertainty around how to visualise and communicate uncertainty and it is important that the progress made here is not lost. To ensure that Committees and ERGs develop a different approach to uncertainty in practice, it is crucial that NICE implement a training programme as well as a review mechanism. Committees should also document and publish how uncertainty has been considered and fed into decisions. The BIA welcome the opportunity to further engage with NICE on the development of a visualisation framework and recommend that NICE seek consultation with stakeholders through forthcoming modular updates.
Health inequalities Please share comments.	Agree. The BIA is supportive of the case for the introduction of a formal health inequalities modifier designed to tackle issues of health inequality arising during an evaluation. It is also positive that the first 'NICE listens' topic will be on health inequalities. It is crucial that a health inequalities modifier considers the potential health inequality implications arising from, as well as during, health technology evaluations. People with rare diseases face several obstacles that have led to inequalities in access to medicine and quality of care between them and the rest of society. A health inequality modifier should recognise the inequity in gaining consistent access to treatments for rare disease patients and account for this during the evaluation process. Where

	treatments qualify for a severity modifier, there may be additional health inequality implications that need to be considered, and treatments may require a higher cumlative threshold to account for this. The BIA request further clarification from NICE on when challenges surrounding health inequalities will be resolved and the progress that has been made to date.
Aligning modifiers across programmes Please share comments.	Agree.
Discounting Please share comments.	Strongly Disagree It is positive that NICE has maintained its view that there remains an evidence-based case for reducing the discount rate 1.5%. We are also encouraged by the recognition that doing so could make a particularly big difference to some treatments, like gene therapies. Nevertheless, it is very disappointing that discounting will not remain within the scope of the review. NICE has stated that one of the objectives of the Methods Review was to 'support the attractiveness of the UK as a first-launch country for important and promising new health technologies.' Discounting is an area of the Review that has the potential to meet this objective. The current discounting approach values outcomes accrued today more than outcomes accrued in the future. This disadvantages medicines such as potentially one-time cures and those that deliver benefits far in the future. A lower reference case discount rate for future health gains would better recognise the value of treatments that considerably extend life, by attributing greater value to predicted future health outcomes. Advanced Therapy Medicinal Products (ATMPs) such as cell and gene therapies are some of the most innovative treatments being developed by the life sciences sector and have the potential to be transformative for patients suffering from a range of diseases. This includes rare and genetic diseases where there is a high level of unmet need. ATMPs tend to incur a high up-front cost while the benefits are seen over a long-time frame and may occur far in the future. The current discount does not adequately value therapies in a way that appropriately accounts for the long-term health benefits that they can provide. Reducing the discounting rate for health outcomes to 1.5% in line with the Treasury Green Book would ensure that the benefits of these treatments are appropriately evaluated based on the value they bring in the long term. With a

	growing pipeline of innovative treatments, discounting is an issue that cannot wait to be addressed until the next VPAS negotiations. NICE is an independent body responsible for its own methods and processes and therefore should not be constrained from progressing proposals on discounting by system partners; doing so risks compromising the attractiveness of the UK market and undermining the overall impact of the Review. Industry was encouraged by the Government's recognition of the potential of innovative treatments evidenced through the aspiration set out in the Life Sciences Vision for the UK to be the world leader for development, testing, access, and uptake of new and innovative treatments and technologies. Excluding discounting from the scope of the review seriously impedes efforts to position the UK as a first-launch country and risks companies choosing to launch these technologies in the UK later in their lifecycle, or not at all. Priority 4 of The Rare Disease Framework states that *'it is essential that the UK can offer an environment that will attract substantial investment in high value life science products of the future'*. Exclusion of the discounting rate from the scope of this review completely undermines the UK's ability to offer this environment and threatens the Government's ability to deliver on the Rare Disease Framework and the Life Sciences Vision. The BIA urges DHSC, NHSE&I and other government departments to work constructively with industry under the guarantees afforded by the Voluntary Scheme for Branded Medicines Pricing and Access to enable NICE to change the discount rate within the scope of the Methods Review.
Of the 2 alternative options presented in proposal g and h (and appendix 1 paragraphs 1.18 and 1.19), which do you prefer? Please share comments.	Option 1. The BIA believes that both severity modifier options proposed by NICE are unsatisfactory. Neither option will address the needs of rare disease technologies in the STA programme, as NICE claims, and both will have a very limited impact on the prospects of success for securing positive reimbursement recommendations for these treatments. What is needed to address the challenges for rare disease treatments in the STA programme is a modifier that bridges the gap between the upper STA threshold (£30,000/QALY) and the baseline HST threshold (£100,000/QALY). This cannot be achieved with the current cost-neutral approach taken by NICE. The BIA welcome NICE's planned research to determine the magnitude of the societal value for health benefits in severe diseases and believes this will inform the need to expand the magnitude of the proposed severity modifier. We urge that NICE

	plan and undertake this research as a matter of urgency and engage with industry in shaping the scope and approach to this research. In the meantime, the BIA would prefer Option 1 to be adopted. Option 1 has a higher maximum QALY weighting than Option 2 and will therefore do slightly more to bridge the gap between the upper STA threshold and baseline HST threshold. We emphasise the point that even the with the maximum QALY weighting of 1.7 offered by Option 1, the impact on many rare and ultra-rare disease medicines is likely to be minimal. To level the playing field for rare and ultra-rare diseases, a severity modifier with higher QALY weight multipliers (up to 3.5x the current threshold) or an additional rarity modifier that would provide an additive modifier is required.
How strongly do you agree or disagree that you support the proposals related to:	
Implementing the proposed cases for change for sourcing, synthesising and presenting evidence, and considering health-related quality of life Please share comments.	Agree. The BIA welcomes NICE's recognition that there are some cases where EQ-5D may not be appropriate. It is also positive that NICE has provided further clarity about the evidence that is required for the use of alternative health related quality of life measures. For many rare diseases, disease specific quality of life measures are better able to capture the experiences of specific patient populations and can provide a clearer picture of the effect a treatment will have on patients and their families and carers. These measures should not be less preferable to EQ-5D. The draft manual stipulates that in order to use alternative health related quality of life measures, companies will need to provide substantial evidence that EQ-5D is not appropriate or cannot capture disease specific changes. This evidence is unlikely to exist for rare and ultra-rare diseases. We call for NICE to recognise the challenges of rare/ ultra-rare diseases and permit the use of disease-specific measures in indications without this evidence. The BIA requests that when companies are required to provide evidence that shows that EQ-5D performs poorly, NICE accepts evidence on discriminant validity as well as on responsiveness in a particular patient population. Though the draft manual stipulates a requirement for literature-derived evidence on responsiveness, most measures in the literature do not provide this and often data on discriminant validity is the best evidence available. We ask that NICE includes data on discriminant validity as an alternative option to responsiveness where this evidence cannot be provided.
Considering Real-World-Evidence	Agree.

Please share comments.	The BIA welcomes the proposals to consider a comprehensive evidence base including non-randomised controlled trials (RCTs) and real-world evidence. This will have positive implications for orphan and ultra-orphan treatments, for which randomised clinical trial (RCT) data are often difficult to obtain. In particular, the option to use registries and other observational sources for resolving uncertainty around treatment effects will allow for a much clearer understanding of a treatment's likely impact on the population under consideration. The BIA is supportive of the commitment not to place any restrictions on the types of evidence and the recognition of the usefulness of qualitative research in informing many elements of the decision problem. For conditions where the clinical effects can be hard to measure, qualitative evidence can play an important role in providing Committees with a better understanding of what patients value in a treatment, as well as their treatment preferences. The BIA is particularly supportive of the recognition that qualitative research can be a useful way to assess the views of carers. As many patients with rare diseases are children, the burden of care on their families is often great. Consideration of the health benefits that a treatment can provide to carers is something that is particularly important when assessing the potential quality-of-life implications of an orphan or ultra-orphan treatment and is something that the rare disease community feels has not been adequately considered. While it is positive that NICE will accept greater consideration of RWE during appraisals, the manual needs to do more to recognise that for many technologies designed to treat rare and genetic diseases only single armed trials may be feasible. NICE has also maintained a general preference for RCTs where feasible. It is important that this general preference does not disadvantage treatments where RCTs have not been used such as for ultra-rare conditions. The BIA recommends that NICE Committee's undergo training to avoid general bias towards RCTs, which could impact patient access to treatments in therapy areas for which this is not possible and could ultimately exacerbate existing health inequalities.
Calculating the costs of introducing health technologies Please share comments.	Disagree. It is positive that NICE have taken a positive step forward by allowing apportionment of certain costs in the non-reference case. This could be particularly important for rare disease technologies with a companion diagnostic or where there is an established plan to change practice or service delivery in the NHS. The BIA urges

	NICE to extend this into the reference case to ensure that interventions entering new disease areas or novel mechanisms actually benefit from this change and do not continue to be penalised in the appraisal process. In order to ensure the programme manual meets its ultimate goal of improving the health of those using the NHS, NICE must correct the issues that arise from the inclusion of healthcare costs incurred during extra years of survival for therapies that extend life to ensure decisions aren't inherently disadvantaging those with chronic conditions. The consultation document states that NICE's appraisals will seek to consider prices that are reflective of the real price paid by the NHS for any medicine. Modelling of longer-term time horizons should consider known pricing dynamics, notably where prices decline upon patent expiry.
Analysing uncertainty Please share comments.	Strongly Disagree. The BIA is concerned with the proposal to utilise probabilistic analysis in sensitivity and threshold analysis. We believe this will be unfeasible from a practical perspective and medicines with greater uncertainty are more likely to be those with higher probabilistic ICERs than deterministic ICERs, which contradicts the proposal of more flexibility around uncertainty. Therefore, we recommend that deterministic analysis should remain the Committee preferred ICER for decision making. We strongly disagree with the scenarios around duration of treatment effects suggested in 4.5.17, which are contrary to one of the main steps forward in the proposals of the committee taking a more pragmatic and risk-neutral approach to uncertainty. This will lead to more unrealistic scenarios being implemented for committee deliberation. Whilst they may be appropriate in some circumstances, they should not be considered a standard approach to deal with uncertainty in the treatment effect. Formalising this within the manual risk giving rationale to the committee to utilise these scenarios within their preferred base-case analysis, despite there being no clear evidence for such a pessimistic scenario.
Please share any comments on whether the proposed methods will help to achieve the aim of promoting equality of opportunity, or if the proposals raise	The BIA remains concerned about the potential equality implications an opportunity cost-neutral severity modifier might have. Though it is positive that the proposed modifier will use both absolute and proportional shortfall, the cut off scores for proportional shortfall are very high. As proportional shortfall is most relevant for elderly populations, the current scores risk creating a bias against the elderly. We call on NICE to re-assess the

any concerns with regards to equalities.	proportional shortfall cut off scores to avoid creating a bias against elderly populations. The BIA is concerned about the equality implications of the proposal to deny treatment to a particular subgroup where a technology is deemed not to be cost-effective, even when it is found to be clinically and cost-effective for the whole population. It is inequitable to deny these patients access to cost-effective treatment from which they would benefit and where the medicine is cost-effective for the total population.
Please share any other comments.	**Rarity** The Methods Review presents a unique opportunity to reform the current HTE process to ensure that it is equipped to evaluate all treatments fairly and robustly, including those for rare and ultra-rare diseases. Industry and patients had been hopeful that a highly ambitious Methods Review would be the means to level the playing field for the evaluation of orphan and ultra-orphan treatments. The BIA welcomes the proposal to introduce a severity modifier in place of that for end-of-life and the proposal to allow greater flexibility when dealing with uncertainty. Both proposals have the potential to mitigate some of the challenges faced by rare disease medicines during the evaluation process. Despite these positive changes, rarity in and of itself is a specific challenge that is not wholly or satisfactorily resolved by the current proposals. Though the BIA warmly welcomes a severity modifier which will benefit many treatments for rare diseases, a severity modifier doesn't specifically target orphan medicines, nor does it address the unique challenges associated with rarity. Small patient populations and lack of current treatment alternatives make it particularly challenging for orphan treatments to demonstrate their clinical effectiveness. Coupled with high development costs, orphan treatments often struggle to meet the cost-effectiveness threshold required in the STA pathway. Though a severity modifier will add a QALY weight to the most severe treatments in this pathway, the QALY weight proposed for the highest severity category does not adequately bridge the gap between the STA pathway and the HST pathway. This means that, as before, many orphan and ultra-orphan treatments will continue to fall in the gap between the two. Additionally, not all rare diseases are considered severe and many rare disease treatments routed down the STA pathway will not receive any QALY weight associated with a severity modifier. In such cases, it remains completely inappropriate for these medicines to be assessed against a £30k cost-effectiveness threshold.

	The BIA supports the introduction of a rarity modifier and believe that this is crucial to addressing the unique challenges faced by medicines for rare and ultra-rare diseases that don't meet the strict HST criteria. The BIA strongly recommends that NICE introduces a rarity modifier to the STA process to help bridge the gap between the STA and HST pathway and level the playing field for treatments for rare diseases. In October 2020, NICE's Modifiers Task and Finish Group concluded that though there may be a moral case for the use of a rarity modifier, '*evidence strongly suggests that the public do not regard rarity on its own as an important modifier*'. It was on these grounds that NICE discounted the need for a rarity modifier. The BIA recently published a report - *Public attitudes to rare diseases: the case for equal access* – which presents the findings of a public attitudes survey commissioned to understand whether people would be open to specific measures to support access to medicines for people with rare diseases. The survey found support for the idea that patients living with rare diseases should be able to access medicines on the basis of clinical need even if this would be more costly to the NHS because of a disease's rarity. The BIA recommends that NICE revisits its position on the public's appetite for targeted measures to support improved access to medicines for people with rare diseases and considers the value of a rarity modifier to people with rare diseases and to the public. We call on NICE to extend existing research plans to include assessment of public appetite for a rarity modifier and request that NICE publish a detailed plan and timelines to conduct the research as well as the full results. **Subgroups** The BIA strongly disagree with the proposal to allow Committees *'not to recommend a technology for a particular subgroup for which the technology is not cost-effective even when the technology is found to be clinically and cost-effective for the whole population.'* This proposal is incongruent with the need for HTE methods to support rapid patient access to clinically and cost-effective health technologies. If a technology is deemed cost effective in the total population under consideration, it does not seem equitable to deny access to this technology to a particular subgroup of patients who would benefit from it on the grounds that it is less cost-effective for these patients. We also suggest that this proposal goes against the spirit of NICE's ethical and legal duty to support fairness and equality. **Data extrapolation**

	The proposals seem to permit consideration of unrealistic clinical eventualities e.g. a rapid waning in treatment effect even where existing evidence suggests this is not realistic. The BIA ask NICE to only request extrapolations that are truly clinically plausible. In addition, proposals to wait for 'long term' data to substantiate assumptions about curative effect could restrict and delay access to first in class, potentially curative, ATMPs and go against efforts to manage uncertainty and use real world evidence.

Processes

Have the processes been aligned appropriately? Please share comments.	Agree. The BIA remains concerned about the inclusion of an M-HST process in the draft manual. Though NICE believe it is likely to be used rarely, an M-HST could increase the time of an evaluation resulting in further delays to patient access. The MTA process is a slow and complex process for non-rare treatments and we are concerned about the capability of such a process to deal with the additional complexities of the treatments that go through the HST pathway. This could ultimately delay access to patients who already face a high level of unmet need. We are also concerned about the possibility of NICE using the M-HST process to revisit historic reimbursement decisions. This should not be within the remit of NICE and would be unacceptable given that NICE is already struggling to find resources to meet its existing obligation of reviewing all new medicines in a timely manner. The BIA also concerned about the option to route technologies to the clinical guideline programme. While it is encouraging that NICE will provide stakeholders with clear and transparent rationale when this does occur, it is important that NICE consults stakeholders if this takes place, rather than just inform them. The BIA recommends that NICE also provides clarity on the appeal routes that will be available to companies whose technologies are routed straight to clinical guidelines.
Are there any remaining unwarranted differences in the processes of guidance development different programmes? Please share comments.	No.
How strongly do you agree or disagree that you support the proposals related to:	
Technical Engagement	Disagree.

Please share comments.	Though it is positive that technical engagement will remain part of the standard NICE process, it is disappointing that it will not remain an option which companies can request (and within the current fee). 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 about the long-term impact. It is currently unclear who will determine whether Technical Engagement will 'unlock key challenges' and thus be deemed useful. We request further clarity on which stakeholders will be engaged and what say the company will have over this decision. The decision on the need for Technical Engagement should not be made unilaterally by NICE. The BIA supports the proposal to include clinical experts in the technical engagement process, but we are concerned that these proposals don't go far enough to achieve what NICE and stakeholders need it to. To optimise the quality of the engagement, we recommend that all stakeholders are involved in this process including patient experts, EAG, NICE technical team and the company.
Rapid review of guidance for biosimilars Please share comments.	Disagree. The proposals suggest rapid review will be conducted where the original economic model can be used; pharmaceutical companies who made original submissions and developed the original models should retain 'ownership' of those models and NICE should not have any right to repurpose/reuse those models without the express permission of the company. The proposals also indicate that NICE will review biosimilars to coincide with CMU tenders. NICE's work timelines should not be determined by NHS England's commercial agenda but by NICE's obligations to appraise new medicines in a timely manner. By prioritising work on biosimilars to coincide with CMU tenders, there is a risk that other appraisals will be deprioritised, particularly as NICE is struggling with resourcing constraints that do not look like they will be easily/rapidly resolved.
Treatment eligibility criteria Please share comments.	Strongly Disagree. The BIA strongly disagrees that NHS England should be able to impose further treatment eligibility criteria following the NICE process. Defining the treatment criteria is a fundamental part of the NICE scope and should be defined at that stage and properly consulted upon with all stakeholders. Once the treatment eligibility criteria are defined, we don't believe that NHS England should be free to limit the eligible patient population beyond the NICE recommendation. We ask that NICE includes a transparent process

	with clear timelines that NHS England will follow should they wish to apply further treatment eligibility criteria beyond the criteria defined in the appraisal scope. This process should include the provision of a clear rationale explaining the need for additional criteria and a requirement to publish this rationale alongside the new criteria and NICE draft guidance. Though the BIA welcome's the attempt to clarify treatment eligibility criteria, the proposals need to go further to avoid restricting access to eligible populations. We are concerned about the lack of any clear process to resolve issues arising with the wording of the Blueteq form. To prevent restricting access to medicines that NICE has deemed cost-effective, clear measures need to be put in place to ensure that the exact wording on the Blueteq form is in line with NICE's recommendation. NICE should develop a clear process with a point of contact to resolve any issues.
Managing high company base-case ICERs Please share comments.	Disagree. It is welcome that rather than terminating guidance development, NICE will meet with the company to discuss how to progress the individual evaluation in cases where a company submission is putting forward a base-case ICER significantly higher than the standard threshold. We disagree that NICE should remain able to make a final decision on whether the evaluation can continue. This proposal will disproportionately impact rare disease treatments and ATMPs where there remain particular challenges in meeting the ICER threshold. The BIA maintain that all opportunities should be explored with the company to bring the value proposition into an acceptable range. Any potential termination or rejection should only be undertaken following thorough discussions with companies and considerable advance notice. This proposal will also further compromise the attractiveness of the UK as a first-launch country.
Alternative draft scope consultation timings Please share comments.	Disagree. The BIA disagrees with the proposals for introducing draft scoping consultations as short as 7 days. Whilst we appreciate the attempt to provide flexibility, 7 days for a short consultation response time is too short to allow patient groups and other stakeholders to participate and develop responses. Without meaningful engagement from all stakeholders, the scoping process would become tokenistic only. The BIA recommends that NICE reconsider this approach and implement a short consultation response time of 14 days.

	We also disagree with the proposal that indicates NICE can unilaterally decide on the duration of the scoping consultation. The BIA suggests that NICE propose a length of consultation to stakeholders but if any objects to the proposal for a short consultation, then the standard 28-day approach should be adopted.
How clear were the proposals relating to commercial activity? Please share comments.	Clear
How clear were the proposals relating to managed access activity? Please share comments.	Unclear. It is disappointing that NICE has not taken this opportunity to adopt the excellent, well thought through and detailed proposals for MAA developed by the IMPACT HTA team. NICE itself was involved in this research and has first-hand knowledge and understanding of its outputs so it is very disappointing that it is not adopting 'best practice' proposals that it had a hand in developing. It is unclear whether MAAs will be possible in the future outside of the Cancer Drugs Fund (CDF) or Innovative Medicines Fund (IMF) if the IMF is the only possible route for MAA for rare and ultra-rare non-cancer drugs in the future. With no information on entry and exit criteria, timelines for funding, funding/resource mandates for data collection, etc. within the IMF (as the IMF consultation hasn't even been issued as yet), then there is no clarity whatsoever on the proposals for MAA via the IMF at present. The BIA is also concerned that the requirement to submit a managed access proposal comprised of both data collection and commercial access proposals in advance of Committee meeting, is a particularly onerous requirement. For smaller companies with limited resources, to develop such submissions which may not even be required, is particularly challenging. We would suggest instead that, as with the CDF, there is a checkbox in the NICE submission template that a company can tick to advise the Committee whether it would be prepared to consider MAA in the event the Committee is unable to recommend routine commissioning. It is encouraging that all HTE Committees will be able to recommend managed access where there remain uncertainties. This will be crucial for orphan treatments for which uncertainty may be inherent to the evidence base.
NICE is committed to promoting equality of	

opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please share any comments on whether the proposed processes will help to achieve this aim, or if the proposals raise any concerns with regard to equality. Please share any other comments.	The BIA is disappointed with the extent to which the package of proposals when taken together create an HTE process that works for rare and ultra-rare disease treatments. Though NICE has made clear that the HST programme is designed to evaluate treatments for very rare diseases, the narrow entry criteria proposed mean that most orphan treatments and even some ultra-orphan treatments will be routed for evaluation via the STA pathway. The BIA recognises that some of the proposed changes to NICE's methods, including the introduction of a severity modifier and plans to accept greater flexibility when dealing with uncertainty, will benefit a range of treatments including for rare diseases. Nevertheless, this is not the wholesale radical reform that industry and patients had hoped would be achieved and does not meet the vision of the review (as laid out by NICE themselves) of improving patient access to medicines in the UK. The STA pathway remains entirely inappropriate for the evaluation of rare disease medicines which struggle to demonstrate clinical and cost effectiveness in the same way as medicines designed to treat more common conditions. The BIA anticipates that the 'refined' HST eligibility criteria proposed by NICE will increase the number of orphan and ultra-orphan treatments that get routed down the STA pathway. Many of these treatments, especially those that only narrowly miss the HST entry criteria, will be unable to meet the cost-effectiveness threshold within the STA pathway and will fall down the gap between the two. Even if these treatments receive a severity modifier, a maximum ICER of £50k will do little to bridge the gap to the baseline HST ICER of £100k. This means that HST qualification will continue in many cases to make the difference between a positive and negative recommendation. The BIA recommends creating a single process for the evaluation of orphan and ultra-orphan medicines, separate from the STA process for non-orphan medicines. The introduction of a separate process would negate the need for the controversial criteria that create arbitrary divisions between orphan and ultra-orphan medicines - which both face the same significant challenges related to obtaining evidence and ensure that these medicines are assessed by a process tailored to their specific characteristics. In addition, such a process will prevent HST qualification dictating whether patients are able to benefit from the treatments they need. In the absence of this wholesale change required to level the playing field for rare and ultra-rare disease medicines and other medicines for more common diseases, NICE should reconsider its opportunity cost neutral approach to the severity modifier, implement a rarity modifier, include rare disease inequity in its health inequalities analysis and provide clear guidance to ERGs and Committees on provision of flexibilities related to uncertainties.

Presentation of the guidance manual

What are your initial impressions of how the draft guidance manual is presented?	Clear. Delineation between methods and process would be helpful. It would also be helpful to have a timeline flow chart with indicative actions for different stakeholders to increase accessibility.
If you have any comments on the chapters in the guidance manual please provide these here.	**Combination treatments** The process to be followed for combination treatments is not covered in the draft manual. There are a number of areas which need to be further explored in discussions, for example, to deal with cases where two companies both obtain and hold a Marketing Authorisation for the same combination use. Where more than one company holds a marketing authorisation for a combination therapy, each should have equal status within the evaluation. A process question is whether a joint or two separate submissions should be requested (and whether this would indeed be permissible or resource efficient). The relevant references related to the involvement of stakeholders and companies are set out in the draft manual as: - 1.1.18 states that NICE invites the company that holds, or is expected to hold, the regulatory approval for the technology to take part in the evaluation - 1.1.20 lists the company that holds, or is expected to hold, the regulatory approval for the technology(ies) being evaluated as a stakeholder in the evaluation - 1.2.1 submissions are invited from companies (organisations who own or market the technology under licence) of the technology or technologies being evaluated. Further discussions on these are needed given that more and more combination treatments are expected to come to the market in the years ahead.

Topic selection

How clear or unclear is the aim of the HST evaluation programme? Please share comments.	Unclear. It is puzzling that NICE has asked stakeholders to comment on how clear the aim of the HST programme is. The aim of 'encouraging research, facilitating fair and equitable access to treatments for patients with serious and severe very-rare conditions' is clear. What NICE should be asking is whether the proposed criteria will achieve the aim of the HST programme and whether the refined

	criteria deliver on the vision to 'make the outcome clearer, precise, predictable, and efficient for stakeholders and decision makers.' As this is the question that we feel NICE should be consulting on, this is what we have provided comments on. It is unclear how the proposals will deliver on the aims and vision of the HST programme review. Rather than make the outcome clearer and more predictable, we believe the proposals will make the situation more opaque. The proposals seem to now create a 2-step process to entry to HST involving satisfying 4 'qualifying criteria' as laid out on page 11 of the topic selection manual and 4 'routing criteria' as laid out on pages 12 and 13. We have the following comments on the first 4 qualifying criteria: 1. Challenges of securing access relates to the rarity of the disease, which may or may not correlate with severity. 2. It is a given that there are challenges with collecting good quality evidence for very rare conditions and NICE recognises this as one of the underlying reasons for considering them separately in the HST process. It is therefore unclear why there is a need to make this a qualifying criterion. Surely by definition of being an ultra-rare condition, that is qualification enough? 3. This point seems to be referring to the cost of the technology being too high to get through standard processes. NICE has already accepted that the cost of the technology is not normally known at the topic selection stage, so should not be the basis for a topic selection decision 4. On the basis of what evidence would this be determined given this sort of information, particularly with regards ability to recover costs of product development, are certainly not available to NICE and are often not shared with company UK affiliates.
How clear or unclear is the refined routing criteria for HST? Please share comments.	Unclear. Again, it is confusing why NICE has sought comments on the clarity of the refined criteria rather than whether the refined criteria achieve the vision of the HST review and the overall aim of the programme. Though each criterion is, in and of itself, clear and coherent, the BIA is concerned that the criteria only serve to make qualification for

	HST less clear and predictable, contrary to the vision of the HST review. We have the following comments on the refined routing criteria: Criterion 1 is very clear and should be the only criterion needed for routing for HST. Further detail is needed about how a degree of flexibility in applying this criterion will be applied in practice. Criterion 2 appears to contradict and negate criterion 1 by introducing arbitrary patient caps and effectively narrows HST eligibility from around 1,100 patients down to 500. It is unclear why it is deemed necessary for there to be no more than 500 eligible patients across all of a technology's indications when HST is only evaluating a single indication. This contradicts the principle of NICE appraisals which is to assess a single technology (unless an MTA) in a single indication; looking beyond that indication should be outside the scope of any deliberations either at topic selection, routing or technology evaluation stage. This appears to be a mechanism for managing budget impact for the NHS, even though NICE itself recognises is managed via alternative mechanisms such as budget impact test and commercial access agreements. Criterion 3 is duplicative of Criterion 1 in the 'qualification criteria' laid out on page 11 of the topic selection manual. It is unclear how a criterion which NICE cannot define, as 'it requires judgement', is meant to provide clarity and predictability in the routing process. We ask NICE to provide greater clarify on how it will measure the extent to which a condition significantly shortens life or severely impairs its quality. Criterion 4 is clear with regard to the lack of other treatment options, but further clarity could be provided by including further details of unmet need scenarios as provided in paragraph 64 of the topic selection proposal paper.
How clear or unclear is the eligibility criteria (section 4) for devices, diagnostics and digital technologies Please share comments	
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between	**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

people with particular protected characteristics and others. Please share any comments on whether the proposals for Topic Selection will help to achieve this aim, or if the proposals raise any concerns with regard to equality. Please share any other comments.	fairer, more flexible appraisal pathway for novel therapies for rare diseases. It is disappointing 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 BIA is disappointed that the HST process in the form proposed by NICE will offer no meaningful change for rare disease treatments and has the potential to further limit the number of medicines that qualify for HST. An analysis commissioned by the Association of the British Pharmaceutical Industry (ABPI) applied the proposed criteria to the characteristics of 38 current and in-development HST products to understand whether they would qualify for the HST programme under the proposed criteria. The analysis suggests that the proposed criteria would reduce the number of medicines that have been eligible for HST by approximately one third to a half. By reducing the number of eligible medicines, the criteria will not meet the Review's vision, as laid out by NICE, of improving patient access to medicines in the UK. Rather, it will exacerbate the inequity faced by rare and ultra-rare disease patients. Throughout the review, NICE has consulted on HST topic selection and changes to HTE methods as distinct areas of consideration. In order to understand the impact that the proposals will have on treatments for rare diseases, the revised HST criteria must be viewed alongside the proposals for changes to NICE's methods. NICE has previously acknowledged that a utilitarian approach to the evaluation of health technologies prevents patient access to treatments for rare diseases. The HST programme was introduced as a deliberate departure from the 'level playing field' principle to address this. NICE has also noted that the HST review is taking place against a backdrop of challenges associated with the increase in rare disease technologies being considered for the HST programme. Given that NICE recognises both these issues, it is very disappointing that it is neither proposed to extend the HST programme to accommodate rare disease medicines, nor to introduce any measures to level the playing field for rare disease treatments that are routed down the STA pathway. Though NICE has explicitly stated that it is not the intention that rare disease medicines should fall down the gap between STA and HST, the proposals are likely increase the number of those that do. The Life Sciences Vision set's out the Government's ambition for the UK to be the world leader for access and uptake of new and innovative treatments and technologies. Priority 4 of the Rare Disease Framework is to provide patients with improved access to specialist care, treatments, and drugs. When taken together, the proposed HST criteria and simultaneous cost-neutral changes to NICE's methods fail adequately to tackle the challenges faced by

	rare disease medicines. This will significantly compromise the Government's ability to fully deliver on the Life Sciences Vision or Rare Disease Framework. **Specific comments** The BIA supports the removal of the previously proposed criteria only to only consider technologies for which it is biologically plausible that the use will be restricted to an ultra-rare condition. Similarly, the removal of the proposed requirement for evidence to demonstrate that a technology was only ever intended for us in a very small ultra-rare population with high unmet need is positive. It is positive that the existing criterion requiring that a technology has the potential for lifelong use and that the condition be chronic have been removed. This will enable one-off treatments like cell and gene therapies to be considered in the HST programme. Nevertheless, the sub criterion stipulating that there be a prevalent population of up to 50 and an incidence of no more than 40 patients a year for one-off treatments is arbitrary and overly restrictive. These treatments should not need to satisfy stricter criteria than other treatments for the same patient population. This will disadvantage one-off treatments like cell and gene therapies and will disproportionately affect rare genetic conditions. It is unclear why it is deemed necessary for there to be no more than 500 eligible patients across all of a technology's indications when HST is only evaluating a single indication. This criterion misunderstands the way companies research medicines and could prevent patients with very rare diseases accessing treatments that may also be clinically beneficial to patients with more common conditions. Where there is evidence for a treatment being effective for a larger patient population, it will be assessed through a technology appraisal.
Please provide comments on the following chapters in the topic selection manual:	
Eligibility, selection and routing criteria	
Highly specialised technologies	
Topic Selection Oversight Panel	The BIA is supportive of NICE's efforts to consolidate the different topic selection groups into one panel. We are concerned however that NICE will not include industry in the membership of the panel on the basis of confidentiality and don't believe this position holds up. industry representatives sit on NICE Committees and confidential information is managed in those settings so there is no reason why they shouldn't be manageable in the context of TSOP. While it is understandable that a single company representative

	should not represent industry as this may create a conflict of interest, the BIA supports expanding the membership of the panel to include industry representation from an industry group or association. The BIA is concerned by the option for the TSOP panel to decide not to proceed with an evaluation and to simply inform the stakeholder of this decision and the reasons behind it. The decision not to select a medicine for NICE evaluation should not be made before discussion with the company in question. NICE should also publish TSOP meeting minutes or, at a minimum, share details of the rationale for TSOP routing decisions with the company. This information would be required in order for a company to appeal any topic selection and routing decisions and so must be made available to companies (and other stakeholders) for transparency.