

## **Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes**

### **Process for the evaluation of highly specialised technologies**

1. The approach to the evaluation of highly specialised technologies (HST) is based on NICE's Guide to the Process and Methods of Technology Appraisal with variations required to evaluate technologies for very rare conditions, as described in this document.
2. The core evidence submission is provided by the company developing the technology.
3. A review of the company submission is undertaken by an evidence review group (ERG). The ERG remit is to critically evaluate the submission, identify its strengths and weaknesses, clarify where necessary and supplement it with further analysis as required. On occasion, the NICE Decision Support Unit will be asked to provide advice or further analyses on specific aspects of the case made by the company.
4. The ERG contribute to the scoping phase, provide technical input into interactions that NICE may have with the company and provide other information and evidence when necessary.
5. The Evaluation Committee is an independent advisory body. Members include people who work in the NHS, patient and carer organisations, relevant academic disciplines, and people from pharmaceutical and medical devices industries. The Evaluation Committee makes recommendations to the Institute regarding the benefits and costs of highly specialised technologies for national commissioning by NHS England. It is also the role of the Evaluation Committee to recommend against the use of a technology if the benefits to patients are unproven or costs of technology are unreasonable. NICE is responsible for the dissemination of the final guidance to the NHS.
6. Consultee and commentator organisations will be identified for each evaluation. These are the patient, professional and commercial organisations that have an interest in the technology, in addition to NHS England, other relevant NHS organisations, and the Department of Health.
7. Statements from patient/carer groups and professional organisations on current management of the disease and patient experience will be sought, and nominated experts (clinical, patient, NHS) will be invited to attend the evaluation committee meeting(s).

8. If needed, formal clarification of aspects of the evidence submissions from the company, ERG or occasionally other consultees, will be sought by the NICE team in advance of the meeting of the full Evaluation Committee.
9. A report for the Committee will be developed by NICE with input from the Chair and the Lead Team, based on the evidence submission by the company, submissions by other consultees and review by the ERG.
10. NICE advisory committee meetings are open in part to members of the public and press. Arrangements for attendance at public meetings are similar to those used for those for Technology Appraisals.
11. Clinical experts, NHS commissioning experts, and patient experts are invited to the meeting and respond to questions from the Committee and provide clarification. They contribute to the discussion with the Committee but do not make a formal presentation to the Committee. Two company representatives will be invited to attend evaluation committee meetings. Arrangements for selection of specialists and experts follow those set out for Technology Appraisals at NICE.
12. There may be occasions when a meeting will be entirely closed because it is not possible to conduct any discussion without referring to confidential information.
13. Committee decisions are normally based on consensus. If a vote is taken, it will be noted in the minutes.
14. Formal consultation will only take place if the recommendations emerging from the Committee are substantively restrictive. A substantively restrictive recommendation will be one that is more limited than the terms of regulatory approval (or, in the absence of a regulatory approval process, the claims of the sponsor for how the technology should be used), to an extent judged to be significant in clinical practice.
15. When required, the consultation phase will be similar to the technology appraisal consultation process: a request for feedback on the preliminary recommendations from consultees and commentators plus the opportunity for feedback from members of the public via our website. Consultees and commentators will be supplied with committee papers at this point, containing all the evidence seen by the Committee, including any economic models developed by the company or used to inform exploratory analyses by the review group. Information designated as commercial or academic-in-confidence will be redacted.
16. The purpose of the consultation is to seek views on the Committee's provisional recommendations and to determine whether they are an

appropriate interpretation of the evidence considered. NICE invites comments on whether:

- all the evidence available to the Evaluation Committee has been appropriately taken into account
- the summaries for benefits and costs are reasonable interpretations of the evidence
- the provisional recommendations are sound and constitute a suitable basis for guidance on national specialised commissioning
- there are any equalities-related issues that need special consideration that are not covered in the consultation document.

17. Responses to consultation will be considered by the Evaluation Committee at a second meeting and final recommendations will be prepared.
18. At the consultation stage, the Centre or Programme Director must approve the request for submission of new evidence before it is submitted. New evidence will only be accepted if it is likely to affect the provisional recommendations. The new evidence must be presented as a separate appendix to the general comments to be submitted in response to consultation. NICE may need to extend timelines to allow for new evidence to be considered.
19. If the recommendations emerging from the first meeting of the Evaluation Committee support use consistent with the approved indications of the technology in whole or part, a Final evaluation document (FED) will be prepared.
20. The NICE project team undertakes a review of the final recommendations, signs them off, and submits a report to NICE's Guidance Executive. The Guidance Executive verifies that the Committee has appraised the technology in accordance with the terms of the Secretary of State for Health's referral, the scope and the methods and processes. If satisfied, the Guidance Executive approves the final recommendations for publication on behalf of the NICE Board. Consultees and commentators will be also supplied with committee papers at this point, comprising all the evidence seen by the evaluation committee, except that which is designated commercial-in-confidence or academic-in-confidence by the company.
21. Appeals can be lodged against the final recommendations by consultees engaged in the evaluation. The appeals guide can be found here [Appeals Guide](#).
22. The core process requires approximately 17 weeks from receipt of submissions from stakeholders. In the event that a public consultation is necessary, the process is extended to 27 weeks.

23. A reconsideration step is available at specific points in the HST evaluation process.

24. A reconsideration step provides the opportunity, if required, to develop new, or enhance existing Managed Access proposals and for NICE to discuss with the company, and NHS England one or more of a number of elements, for example

- identification of sub-group(s)
- clinical tests
- starting and stopping criteria
- Patient Access Schemes
- conditions for collection of data
- commercial agreements between the company and NHS England

25. The HST Evaluation Process is shown below.

Action	By	Duration (weeks)	Time from submission (weeks)
<b>Core process</b>			
Consultation on the scope	Company, patient groups and other consultees	4	n/a.
Preparation evidence submission	Company, patient groups and other consultees	8	0
Evidence review, critical appraisal and exploratory modelling	Review group	8	8
Report for Committee	NICE on behalf of Chair and Lead Team	2	10
Committee meeting and drafting of consultation document*	Evaluation Committee, NICE	3	13
Public consultation**	Consultees	4	17
Consideration of comments received	Chair, lead team and NICE	3	20
Committee meeting and drafting of final recommendations	Evaluation Committee, NICE	4	24 or 14***
Appeal consideration	Consultees	3	27 or 17***
<b>Additional process</b>			
Formal clarification of evidence submission(s)	Chair, Lead team, Review group, NICE, Company (occasionally other consultees)	3 (2 for company, 1 for NICE review)	
Reconsideration	Company, NICE, NHS England, Review	4-12	

	group		
Appeal Hearing Held	Consultee(s), NICE	10 weeks	

\* Positive opinion from the relevant regulatory body must have been received

\*\* Marketing Authorisation must have been granted.

\*\*\* Without public consultation.

### **Selection and referral of topics**

26. As far as possible, topics will be scheduled so that the Committee first considers a topic as soon as possible after a positive opinion has been given by the Committee for Medicinal Products for Human Use or the equivalent committee at MHRA. Draft recommendations cannot be published without receipt of marketing authorisation for the technology, and are anticipated to be issued within 4 months of confirmation from the European Commission that a marketing authorisation has been granted.

27. The process for selection of HST topics is similar to that of the current process for the selection of technology appraisals. The topic selection process has five distinct decision points, involving input from expert clinicians and NICE at the filtering stages, and from consultees and commentators during the scoping stage (including at scoping workshops). Decisions on progression of a topic to scoping and subsequently to recommendation for referral are made by representatives from NICE, the Department of Health and the NHS England. More information on the process of topic selection is available [here](#).

28. Topics evaluated through the HST programme will be formally referred to NICE by Ministers. HSTs are selected using the following criteria, **all** of which have to apply:

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
- The target patient group is distinct for clinical reasons;
- The condition is chronic and severely disabling;
- The technology is expected to be used exclusively in the context of a highly specialised service;
- The technology is likely to have a very high acquisition cost;
- The technology has the potential for life long use;
- The need for national commissioning of the technology is significant.

29. Referrals to the programme will be phrased as follows:

*'To evaluate the benefits and costs of <technology x> within its licensed indication for the treatment of <disease y> for national commissioning by the NHS England'.*

30. Guidance published by the programme will be phrased as follows:

*'<Technology x> is recommended as an option for the treatment of <disease y> in the context of national highly specialised commissioning by NHS England'*

31. Regulations laid before parliament indicate that the guidance will refer to NHS England providing funding within a specified period to ensure that the highly specialised health technology can be made available for the purpose of treatment of patients.

32. Arrangements have been put in place for circumstances when NHS England requests a variation to the timescales to the mandatory funding - see procedure for assessing the budget impact and varying funding [here](#).

33. NICE guides the company in preparing their evidence submission for the Committee. NICE's technical leads do not validate the submission but they help to clarify substantive issues. If, after all reasonable requests for clarification, NICE is not satisfied that the evidence submission is adequate for the Committee to make a decision or no evidence submission has been received, the Centre Director will recommend to NICE's Guidance Executive that the highly specialised technology evaluation should be terminated. NICE will return an inadequate evidence submission to the company. NICE will subsequently advise the NHS that the evaluation has been terminated and that NICE is unable to make a recommendation about the use in the NHS of the technology because no evidence submission was received from the company. NICE will also provide an explanation to help the NHS make local decisions on making the technology available. A terminated evaluation can be re-initiated if the company indicates that they wish to make a full evidence submission.

34. Information submitted to NICE will be handled in line with obligations, processes and procedures in place for the Technology Appraisals programme. NICE publishes unconfirmed minutes of the Committee meeting on its website within 15 working days of the meeting. When the Committee has approved them, NICE publishes the confirmed minutes on its website normally within 6 weeks of the meeting. The minutes of a Committee meeting provide a record of the proceedings and a list of the issues discussed.

## Methods for the evaluation of highly specialised technologies

35. The methodological approach to the evaluation of highly specialised technologies (HST) is based on the NICE Guide to the Methods of Technology Appraisal with variations required to evaluate technologies for very rare conditions, as described in this document. The following sections should be read in conjunction with that Guide.
36. As described in the Guide to the Methods of Technology Appraisal, when formulating its recommendations to the Institute, the Evaluation Committee has discretion to consider those factors it believes are most appropriate to each evaluation. In doing so, the Evaluation Committee has regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE, and NICE's legal obligations on equality and human rights. The Act expects NICE, in undertaking its general duties, to have regard to:
- The broad balance between the benefits and costs of providing health services or social care in England.
  - The degree of need of people in England for health services or social care.
  - The desirability of promoting innovation in providing health services or social care in England
37. The Evaluation Committee takes into account advice from NICE on the appropriate approach to making scientific and social value judgements. Advice on social value judgements is informed by the work of the Citizens Council, NICE advisory bodies, and NICE's Board, as well as legislation on human rights, discrimination and equality as reflected in NICE's equality scheme. Principles that describe the social value judgements that should, generally, be considered by the Evaluation Committee have been provided in the Institute's document, 'Social value judgements: principles for development of NICE guidance, second edition'.
38. A lead team consisting of the Chair and other members of the Committee meets in advance of the full Committee to review aspects the evidence submissions received from the company, other consultees, and the review group.
39. Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for companies in making a reasonable return on their research and development investment because of the very small populations treated. Nevertheless, as part of its consideration of the value

for money of the technology, the committee must give consideration to the balance between the costs and the benefits.

40. In reaching its decision, the Committee bases its recommendations on the evidence presented, including statements from consultees and commentators and the views expressed by clinical experts, commissioning experts and patient experts at the Committee meeting.
41. The Evaluation Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Evaluation Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts who have used the technology being evaluated or are familiar with the relevant condition. In evaluating the evidence base, the Evaluation Committee will exercise its judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.
42. The importance given to these various kinds of evidence depends on both the overall balance and quality of the evidence from different sources, and the suitability of a particular type of evidence to address issues under consideration. In general, greater importance is given to evidence derived from high-quality studies with methodology designed to minimise bias.
43. In order to form the guidance, the Committee will take account of the following factors in its deliberations:
  - **Nature of the condition**
    - Extent of disease morbidity and patient clinical disability with current standard of care
    - Impact of the disease on carers' quality of life
    - Extent and nature of current treatment options
  - **Clinical Effectiveness**
    - Overall magnitude of health benefits to patients and, when relevant, carers
    - Heterogeneity of health benefits within the population
    - Robustness of the current evidence and the contribution the guidance might make to strengthen it
    - Treatment continuation rules
  - **Value for money**
    - Incremental cost effectiveness using cost per QALY adjusted life year
    - Patient access schemes and other commercial agreements



- The nature and extent of the resources needed to enable the new technology to be used (including budget impact in the NHS and PSS, including patient access schemes)
- **Impact of the technology beyond direct health benefits**
  - Whether there are significant non-health benefits
  - Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services;
  - The potential for long-term benefits to the NHS of research and innovation;
  - The impact of the technology on the overall delivery of the specialised service
  - Additional staffing and infrastructure requirements, including training and planning for expertise

44. The Evaluation Committee's judgement on clinical effectiveness will be informed by:

- The nature and quality of the evidence derived from:
  - The submission from the company
  - The critique provided by the evidence review group
  - The written submissions of the consultees
  - The views expressed by the clinical experts, particularly their experience of the technology in clinical practice
  - The views of the patient experts and carers on the experiences of patients with the condition and those who have used the technology
- Uncertainty generated by the evidence and differences between the evidence submitted for licensing and that relating to effectiveness in clinical practice.
- The possible differential benefits or adverse outcomes in different groups of patients.
- The impact of benefits and adverse outcomes associated with the technology as seen from the patient's perspective.
- The position of the technology in the overall pathway of care and the alternative treatments that are established in clinical practice.

The extent to which these factors are taken into account when making judgements about the evidence of clinical effectiveness is a matter for the Committee's discretion, which will be exercised in the light of the particular features of the condition and the technology.

45. When considering a treatment continuation rule, the Committee will consider:

- the robustness and plausibility of the end point on which the rule is based;
- whether the 'response' criteria defined in the rule can be reasonably achieved;
- the appropriateness and robustness of the time at which response is measured;
- whether the rule can be incorporated into routine clinical practice;
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective;
- fairness with regard to withdrawal of treatment from people whose condition does not respond to treatment.

46. As part of its consideration of value for money the Committee must give consideration to the balance of the costs associated with the technology relative to the benefits it provides. To do so, the committee will consider the incremental cost-effectiveness ratio (ICER), expressed as an incremental cost per quality-adjusted life year (QALY) gained. The preferred methods for calculating the ICER and the QALYs gained for highly specialised technologies are consistent with those outlined in the reference case for the NICE technology appraisal (see the Guide to the Methods of Technology Appraisal 2013). Similarly, the general principles for applying the reference case and for considering non-reference-case analyses are the same as those in the guide to the methods of technology appraisals. In the reference case, the Committee will regard all QALYs as being of equal weight. However, when considering the overall health benefits, the Evaluation Committee can accept analysis that explores a QALY weighting that is different from that of the reference case in circumstances described in paragraph 53-54 of this document.

47. Of particular note for the evaluation of highly specialised technologies are the considerations for 'discounting'. Discounting ensures that cost-effectiveness analysis reflects the present value of the stream of costs and benefits accruing over the time horizon of the analysis. In cases where treatment restores people to full or near full health when they would otherwise die or have a very severely impaired life, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. It is likely that application of non-reference case discounting will occur more often for highly specialised technologies and analyses that use a non-reference-case discount rate for costs and benefits may be more appropriate. In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly

- likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. .
48. After reviewing the evidence and commentary, the Committee will reach a consensus on whether the highly specialised technology can be recommended for routine commissioning.
49. The Committee's judgements on value for money are influenced by the following factors:
- The strength of the supporting clinical-effectiveness evidence.
  - The robustness and appropriateness of the structure of the economic models. In particular, the Committee considers carefully whether the model reflects the decision problem at hand and the uncertainties around the assumptions on which the model structure is based.
  - The plausibility of the inputs into, and the assumptions made, in the economic models.
  - The Committee's preferred modelling approach, taking into account all of the economic evidence submitted.
  - The range and plausibility of the ICERs generated by the models reviewed.
  - The likelihood of decision error and its consequences.
50. Below a most plausible ICER of £100,000 per QALY gained, the decision to recommend the use of a highly specialised technology is normally based on the cost-effectiveness estimate with respect to the acceptability of a technology as an effective use of NHS resources.
51. When the estimated ICERs presented are less than £100,000 per QALY gained but the Committee judges that particular interventions should not be recommended the guidance will make specific reference to the Committee's view on the plausibility of the inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for example, by sensitivity analysis or limitations to the generalisability of findings regarding effectiveness.
52. Above a most plausible ICER of £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALY's gained. The Committee will consider the size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost-effectiveness of the technology to fall within the HST £100,000 QALY limit.

53. For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained.

54. The weighting would be applied in the following way:

**Weighting of QALYs in HST**

Incremental QALYs gained (per patient, using lifetime horizon)	Weight
Less than or equal to 10	1
11 – 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

## Managed Access Arrangements

55. Above a most plausible ICER of £100,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account the following factors as described in the Guide to the Methods of Technology Appraisal:

- The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.
- Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.
- The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.
- The technology meets the criteria for special consideration in relation to the magnitude of the incremental therapeutic improvement (see paragraph 53 above)
- Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21 of the Guide to the Methods of Technology Appraisal).

56. Recommendations on the use of highly specialised technologies may include a 'managed access arrangement' (MAA). A MAA contains the following elements, as specified by the committee.

- A proposal that addresses a significant uncertainty in the evidence base identified by the evaluation Committee (for example, a plan for generating further evidence for a patient population that is covered by the marketing authorisation but not represented in the clinical trials);
- A duration of the arrangement, with a rationale, that is agreed by the key stakeholders: the company, NHS England and patient groups;
- Clearly defined starting and stopping criteria with identified entry and exit points throughout the treatment pathway;
- Treatment continuation criteria;
- A list of outcomes for which data will be collected;
- How data will be collected and analysed;
- An agreement on how regular the outcomes in the MAA will be reviewed;
- The funding arrangements;
- A statement that describes what will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed following data collection;

- Financial risk management plans agreed between NHS England and the company that undertake risk-sharing for the duration of the agreement;
- An acknowledgement by patient groups of the role and responsibilities they hold within the arrangement.

57. In the context of managed access arrangements, when the evidence of clinical effectiveness or impact of a highly specialised technology on other health outcomes is either absent, weak or uncertain, the Evaluation Committee may recommend that the technology is used only in the context of research or the technology is recommended as an option, but that formal data collection is conducted alongside routine use. Before issuing such recommendations the Committee will consider the following factors:

- the need for and potential value to the NHS of additional evidence that can inform the future development of NICE guidance and clinical practice on the use of the technology;
- the uncertainty in the analysis and what is needed to reconsider the decision in the light of research findings;
- whether the data collection is feasible;
- the extent of irrecoverable costs incurred from introducing the technology and plans to mitigate this risk;
- the likelihood that the research needed will report;
- the time it is likely to take for research findings to be available to inform subsequent NICE guidance and clinical practice;
- other factors that may impact on the data generation, such as other research that is underway or likely to be commissioned and completed.

58. The Evaluation Committee will not normally make recommendations regarding the use of a technology outside of the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics, unless requested to do so by the Secretary of State. Evidence related to the use of a technology under evaluation outside of the terms of the marketing authorisation may be considered during the assessment phase of the evaluation and may inform the Committee's deliberations regarding the licensed use of the technology.

59. The Evaluation Committee can consider as comparator technologies that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established practice for the indication in the NHS. Specifically when considering an 'unlicensed' medicine, the Committee will have due regard for the extent and quality of the evidence, particularly for safety and efficacy, for the unlicensed use.

## Reviews

60. When NICE publishes Highly Specialised Technology guidance, a review date is given. This is the month and year when NICE will consult with relevant organisations on a review proposal to decide whether or not the guidance needs to be updated, and if so, how to update the guidance. The length of time between guidance publication and the review date will vary depending on the available evidence for the technology, knowledge of when ongoing research will be reported and whether Managed Access Arrangements are in place.
61. NICE develops the review proposal after gathering relevant information and undertaking a literature search. NICE identifies new indications for the appraised technology, searches for new related technologies, assesses the progress of ongoing trials, and gathers new available evidence. NICE also asks companies to provide information relating to the marketing authorisations (or equivalent) or any extensions to existing regulatory approvals. NICE's Guidance Executive uses this information to consider the review proposal and to decide if and how the published guidance should be updated.
62. Any update of published Highly Specialised Technology guidance will use the process and methods in place at the time the update is initiated.