Scope of vignette:
- authorised products (with marketing authorisation)
- decision process about routine use (and not individual requests for reimbursement)
- submissions for P&R made by manufacturers

Green = related to/any special considerations for rare disease and ultra-rare disease treatments

England	**Single technology appraisal (STA)**	**Highly specialised technology program (HST)**
Overview of health system and P&R/HTA process	National Health Service (NHS England) manages the NHS budget, oversees 209 local clinical commissioning groups (CCGs), and ensures that the objectives set out in an annual mandate by the Secretary of State for Health are met. NHS England Specialised services support people with a range of rare and complex conditions. They involve treatments provided to patients with rare cancers, genetic disorders or complex medical or surgical conditions. In total, there are 146 specialised services directly commissioned by NHS England. A proportion of these are highly specialized services. General tax revenue (includes employment-related insurance contributions). Decisions on providing medicines for routine use can undergo several pathways: - *NICE*: All drugs, including RDTs, will undergo appraisal by NICE (HST or STA programmes); eligibility is based on topic selection criteria and a scoping workshop or consultation . - *Cancer drug fund*: eligible are cancer drugs undergoing the STA process and recommended "for routine use within the CDF". These are drugs for which there is a plausible potential for a drug to satisfy the criteria for routine commissioning, but where there is significant remaining clinical uncertainty [3] All drugs within the CDF have a managed access agreement aiming to resolve significant clinical uncertainty. At the end of the MAA period, NICE re-evaluates the drug and determines whether it should be provided for routine use. Methods of HST is similar to STA, except for the following: a different WTP threshold, consideration of evidence and the types of evidence taken into account to inform the decision in a more holistic way, and applicability of HST modifiers, if appropriate. Challenge with RDTs is the magnitude of uncertainty: less known, less understanding, no natural history, no possibility to test long term patient outcomes. This is not as big of an issue with cancer.	
Yes it is Differentiation of rare disease treatments in the P&R system	No recognition of EMA's OMP designation. Distinction relating to ultra-rare disease eligible for the HST programme based on whether they are very rare diseases with specific characteristics (see below).	
Eligible medicines	Selection of topics by a committee according to pre-defined criteria [6, 7]:	For a topic to be selected, all prioritisation criteria need to be met [6, 7]:

England	Single technology appraisal (STA)	Highly specialised technology program (HST)
	• Is the technology likely to results in significant benefit, if given to all patients for whom it is indicated? • Is the technology likely to result in a significant impact on other health-related Government policies? • Is the technology likely to have a significant impact on NHS resources if given to all patients for whom it is indicated? • Is there significant inappropriate variation in the use of the technology across the country? • Is NICE likely to be able to add value by issuing national guidance?	• 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.
Process	• NICE produces provisional list of topics • Decisions on which topics to route to which program are undertaken with NHS England, NICE, Department of Health and Social Care colleagues (see eligibility criteria described above [6,7]). • Stakeholders identified • Scope prepared and consulted on • Scope updated to reflect any inaccuracies or new information • Topics referred by Minister to NICE • Evidence submitted by manufacturer and other consultees, comments invited on potential clinical effectiveness and value • Evidence review group (ERG) report independently commissioned and prepared • Papers sent to consultees and commentators for comment within 30 calendar days of NICE receiving the ERG report. Technical engagement undertaken with relevant stakeholders to answer and address as many issues before the committee meeting. Such as standard of care questions, pathway questions, outcomes as well as any other issues that arise. The technical engagement is an opportunity to resolve	The HST process is similar to the TA process, with the main difference that the HST has its own committee made up of slightly different members with some background in providing and commissioning RDT services: e.g. clinicians who provide RDT services to NHS (not necessarily the same condition but would understand the complexities), ethicist. HST currently does not have the technical engagement step, but it is due to be implemented soon.

England	Single technology appraisal (STA)	Highly specialised technology program (HST)
	as many issues before the committee meeting as possible. • Committee papers prepared: Evidence submissions from manufacturer, patients, clinical specialists and NHS England, ERG report, pre-meeting briefing • Evaluation committee considers all evidence, who make recommendation to institute • There can be several committee meetings and company may be asked to produce additional analyses that helps to answer any remaining questions posed by the committee • Evaluation committee document (ECD) produced only if recommendations are more restrictive than license; public consultation for 4 weeks • Evaluation committee considers responses to public consultation [8]	
Disease specific expert input (e.g. clinicians or patients in any stage of the process)	- The Appraisal Committee is an independent advisory committee that makes recommendations to NICE regarding the benefits and costs of these technologies for national commissioning by NHS England. NICE is responsible for the dissemination of the final guidance to the NHS. - Consultee and commentator organisations will be identified for each evaluation. These are the patient, professional and commercial organisations	- The Evaluation committee consists of people who work in the NHS, patient and carer organisations, relevant academic disciplines and people from pharma and medical device industries - Consultee and commentator organisations will be identified for each evaluation. These are the patient, professional and commercial organisations - 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). - disease clinical experts, NHS commissioning experts, and patient experts are invited to the meeting and respond to questions from the Committee and provide clarification [1]
Key domains in assessment	- Clinical effectiveness - Cost-effectiveness	

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	HST application similar to STA, but more narrative, with evidence to explain disease burden, treatment, why model is a particular way, more information on cost-effectiveness/clinical effectiveness.	
Evidentiary requirements	Evidentiary requirements are the same for rare and the more prevalent conditions. The Appraisal Committee is generally more familiar with the type of evidence for more prevalent conditions and are likely to be less comfortable when faced with uncertainty.	The committee is in some cases more accepting of proxy/surrogates measures which can be utilised to show that the issue being resolved is similar to another condition. Evidence requirements not more lenient for RDTs, but committee is more aware of challenges to make a case. They are more accepting of other types of evidence (e.g. vignettes, expert elicitation, Delphi exercises, etc.), as they can acknowledge that gaps in evidence base are more difficult to fill (e.g. lack/poor quality of life or utility/disutility data, poor understanding of the condition).
PROMs	EQ5D, caregiver QoL Disease specific measures are considered, but must be validated or be able to be mapped to EQ5D	EQ5D, caregiver QoL, disease specific measures considered - want validated measures. This may require large investment and technical challenges from manufacturers to do this in time, and the ability to map those measure to EQ5D.
Appraisal framework	- Clinical effectiveness - Cost-effectiveness (WTP level) Assessment is based on clinical effectiveness and health-related factors, cost-effectiveness and non-health factors Discussion about reforming the system, likely to be a consultation soon: - The new process would probably also be for the instigation of a Managed Access Agreement	- Nature of condition - Impact of the technology - cost to the NHS and Personal services - Value for money (adjusted WTP levels) - Impact beyond direct health benefits - Impact on specialised services - Budget impact test (if treatment > £20 million in first three years of implementation, company and NHS England are asked to engage in a dialogue to help manage implementation (e.g. progressive access based on need, discounts). BI not taken into account in committee's considerations (only value) - Adjusted WTP threshold: If >£100/QALY, magnitude of benefit and QALY weights considered - Managed Access Agreement possible

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Reimbursement decision	Recommended/not recommended, optimized recommendation, for routine use within CDF.	Recommended/not recommended, optimized recommendations (subpopulation), recommended in research (without funding, haven't been used before) - would be reassessed when more data exists, recommended with MAA
Pricing process	NICE is a price taker (not shaper or negotiator) NICE encourages companies to submit patient access schemes (e.g. discounts) from the beginning. Company would give x% discount, then after assessment, they can add % of discount. in HST, companies may give a confidential discount in the form of a patient access scheme agreed by NHS England, which often do not result in a cost effective outcome so more negotiations required (to address e.g. uncertainties that committee feels are unresolved --> discussion about MAA or other PAS). If a MAA is considered then the company and NHS England agree a confidential commercial arrangement that manages the risk to the NHS based on the committee's position . Actual price negotiation happens at NHS England – budget impact and patient access schemes can be negotiated. In new voluntary scheme, new options will be available. This is not established yet, as NHS England are currently consulting on a commercial framework that would enable other commercial options. Agreement will be kept confidential. Generally done after NICE assessment (so NHS England knows value of product in order to undertake constructive discussion)	
Managed entry agreements	- Confidential discount - Budget cap	- Confidential discount - Budget cap - Outcome based scheme to collect additional evidence for later reassessment - Outcome based scheme for individual patients, only paying for certain performance - Other, not specified
Main challenges in appraising medicines for rare diseases (tick all that apply)	X Lack of good quality clinical data ☐ Lack of real world data ☐ Introducing value for money ☐ Monitoring treatment efficacy ☐ Managing budget impact ☐ Lack of criteria/transparency of OMP P&R processes X Making arrangements to work for all stakeholders (including for stakeholders less familiar with how the system works) ☐ Lack of long-term meaningful outcomes X Other (use of qualitative data to try and bridge evidentiary gaps --> hard to translate qualitative data into number; lack of natural history data to know how effective treatment is)	

England	Single technology appraisal (STA)	Highly specialised technology program (HST)
Impact of special processes	Fragmentation between STA and HST, created a difficult situation for stakeholders to deal with. Mixed messages from industry because they want to go through HST process, but when they don't demonstrate sufficient benefit, hard to justify high cost/QALY Has enabled system to be more innovative in their thinking; has made stakeholders more accountable (including patients, clinicians, companies and NHS) for use of high cost medicines.	
Proposed policy change	Changes in the way NICE appraises in the STA program. New system currently being implemented (end of 2019): NICE will appraise all drugs, none will go through NHS England (to be operational around April 2020, replace PPRS). Voluntary scheme - review of STA and HST methods to ensure they are up to date and future proof to address the growing tide of new technologies and address challenges in appraising RDTs. Currently deciding what they will be changing/consulting on. Consultation due in 2020.	
Joint initiatives		
SOURCES		
1	https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf	
2	https://www.nice.org.uk/process/pmg9/chapter/foreword	
3	https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf	
4	https://www.nice.org.uk/about/what-we-do/our-programmes/commissioning-support-programme/policy-working-groups	
5	https://www.england.nhs.uk/wp-content/uploads/2017/09/spec-comm-service-development-policy.pdf	
6	https://www.nice.org.uk/about/what-we-do/our-programmes/topic-selection#ta-selection	
7	https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/topic-selection-flowchart.pdf	
8	https://www.nice.org.uk/process/pmg19/chapter/the-appraisal-process	

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