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. General tax revenue (includes employment-related insurance contributions). Decisions on providing medicines for routine use can undergo several pathways: - NICE: All drugs will undergo appraisal by NICE (HST or STA programmes) - NHS England commission: services people with a range of rare and complex conditions. They often involve treatments provided to patients with rare cancers, genetic disorders or complex medical or surgical conditions NHS England and Improvement commission offer 146 such services and NICE is responsible for appraising all new treatments that have been given a marketing authorisation. NHS England and Improvement are mandated legally to fund new medicines and some devices recommended by the National Institute for Health and Care Excellence (NICE) 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. RDTs currently: can go through two potential routes: 1. NICE --> HST or TA - based on topic selection criteria 2. Can be recommended by clinical reference groups to be prioritized by NHS England. Currently most go through HST or TA, although it's being challenged because of the gap between TA and HST (different threshold; TA doesn't enable RDTs to get fair trial). Theoretically, methods of HST and TA are similar except for WTP threshold. Challenge with RDTs is 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.	

England	Single technology appraisal (STA)	Highly specialised technology program (HST)
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	• 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?

Process	Process based on NICE's Guide to the Process and Methods of Technology Appraisal with variations required to evaluate technologies for very rare conditions. Submission is made by the company. The company submission is reviewed by the Evidence Review Group (ERG), and supplemented with further analyses when needed. 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.	• 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. • Consultees identified • Scope prepared and consulted on • 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 • 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 • 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 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.

Disease specific expert input (e.g. clinicians or patients in any stage of the process)	The Evaluation 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.	- 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). - Clinical experts, NHS commissioning experts, and patient experts are invited to the meeting and respond to questions from the Committee and provide clarification [1] - No disease experts on the committee, but are invited to the committee
Key domains in assessment	- Clinical effectiveness - Cost-effectiveness HTA 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.	More proxy/surrogates to show that 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.
PROMs	EQ5D, caregiver QoL Disease specific measures are considered, but must be validated.	EQ5D, caregiver QoL, disease specific measures considered - want validated measures. May require large investment and technical challenges from manufacturers to do in time, and the ability to map those measure to EQ5D.

Appraisal framework	- Clinical effectiveness - Cost-effectiveness (WTP threshold) 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 system would probably also be for Managed Access Agreement - WTP may also change	- Nature of condition - Impact of the technology - cost to the NHS and Personal services - Value for money (adjusted WTP threshold) - 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
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.
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. HST may be much further. Companies may give small discount of 10-15%, which are often not cost effective so more negotiations required (e.g. uncertainties that committee feels are unresolved --> discussion about MAA or other PAS). Actual price negotiation happens at NHS England - BI and patient access schemes can be negotiated In new voluntary scheme new options will be available (not established yet). Agreement will be kept confidential. Generally done after NICE assessment (so NHS England knows value of product).	
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)
Impact of special processes	HST: fragmentation between OMPs and UOMPs - created a difficult situation for stakeholders to deal with. Mixed messages from industry because they want to go thru 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	PPRS discussions may have some impact on this but difficult to tell at this point. Changes in the way NICE appraises in the STA program. New system planned: RDTs new (~next few months). 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 due to capacity 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

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Do not hesitate to contact the Impact-HTA team if you have any comments or updates about the information provided in this vignette at the following email addresses:

- Elena Nicod at elena.nicod@unibocconi.it
- Amanda Whittal at amanda.whittal@unibocconi.it