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Summary: Approaches to appraising rare disease treatments (RDTs) vary across countries, from the standard processes used for all medicines, to those completely separate from the standard, to adapted standard processes. This study examines the impacts of standard versus supplemental appraisal processes for RDTs in selected countries via case study analyses of country appraisal reports for two RDTs. Results suggest that supplemental processes can consistently manage RDT issues such as evidential uncertainty and higher ICERs than standard processes.

Background and purpose

- Countries appraise treatments to determine their added clinical benefit and/or value for money in their pricing and reimbursement systems that affect the access patients have to medicines. Traditional appraisal and reimbursement approaches may be unsuitable for RDTs
- Often standard appraisal processes are used for RDTs, but this is challenging because RDTs come with a small evidence base and high cost, leading to substantial uncertainties in the determination of value¹
- This raises the question as to whether supplemental processes with specific features as used by some countries¹⁻⁵ are needed. These processes might affect the evidence submissions, critical assessment, wider appraisal and pricing and reimbursement⁶
- The objective of this research is to illustrate the impacts and contrast the influence on decision-making between countries with and without supplemental processes through evaluation of two specific cases

Methodology

- Case studies were chosen that had been appraised in 2018-2019, and had generated substantial discussion in the clinical, patient and payer communities – Spinraza for 5q Spinal Muscular Atrophy (RDT) and Luxturna for Inherited Eye Disorders (ultra-RDT)
- Countries with a variety of RDT appraisal processes were selected
- Public appraisal reports were retrieved from Belgium, England, France, Germany, Netherlands, Norway, Scotland, Sweden, U.S., and BeNeLuXA used (no Luxturna reports for Belgium or BeNeLuXA). Both RDTs were approved in all selected countries
- Information from reports was extracted into pre-designed templates for systematic comparison across countries, following the appraisal process structure (evidence submissions, critical assessment, appraisal, pricing/reimbursement)
- Analysis aimed to identify whether supplemental processes made a difference in the appraisal and decision

- EVIDENCE SUBMISSIONS:** Only countries with supplemental processes allow different clinical or economic submission requirements for RDTs. E.g. Scotland uses a different submission form for ultra RDTs, Germany allows a simplified submission. The same pivotal trials were considered by all countries, and in all except Germany, additional studies (extensions, phase I-II) were considered, but did not have any apparent weight on the final decision. Belgium allowed exemption from submitting an economic model.
- CRITICAL ASSESSMENT:** Stakeholder input had a stronger influence on the decision in countries with supplemental processes. E.g. Scotland engaged with patients and clinicians to discuss benefits beyond that incorporated in the cost effectiveness model. Patient and clinician input was also present in England and Sweden.
- WIDER APPRAISAL:** Similar issues were raised about quality of evidence across countries with and without supplemental processes, and similar considerations beyond clinical/cost-effectiveness were taken into account (Table 1). Countries with supplemental processes had more formal criteria for these considerations, while countries with standard processes did so more informally. E.g. Severity is an explicit part of the criteria in Belgium, Norway, Scotland and Sweden for potentially accepting higher willingness to pay. It is not an explicit part of the criteria in England STA or France, yet was still considered. Additionally, countries with supplemental processes had more explicit criteria for being willing to pay more. E.g. according to the supplemental in process in Sweden, "A higher cost per QALY can usually be accepted when the difficulty is high or if there are few other treatments to choose from." Furthermore, in England, NICE's HST programme has a higher willingness-to-pay threshold than the standard STA approach.
- PRICING AND REIMBURSEMENT:** Countries with both standard and supplemental processes used financial or outcome-based agreements to mitigate risks. Countries with supplementary processes had more formal criteria here as well. E.g. Scotland's process for ultra-rare conditions requires three years of data generation.

SPINRAZA										Other considerations	LUXTURNA							
BENELUXA	ENG (STA)	FR	NL	U.S	BEL	DE	NO	SCO (UOF)	SW		FR	NL	U.S	ENG (HST)	DE	NO	SCO (UOF)	SW
	√		√	√	√	√	√	√	√	Impact on QoL		√	√	√			√	√
	√	√		√				√		Innovation	√		√	√		√	√	
	√									Nature of population			√					
	√	√	√	√	√	√		√	√	Rarity	√	√	√	√		√	√	√
	√	√	√	√	√	√	√	√	√	Severity	√		√		√	√	√	√
√	√	√	√		√	√	√	√	√	Unmet need	√	√		√		√	√	√
	√							√		Financial burden of illness			√					
								√		Substantially improved life expectancy from treatment								
		√						√	√	Impact on specialised services	√		√					√

Figure 1. Broader consideration of value raised for Spinraza and Luxturna

Standard Supplementary

Conclusions and practical application

These case studies enabled illustration of how some features of supplemental processes facilitated the appraisal of RDTs, specifically related to issues around uncertainty and high price. In particular, these features included broader consideration of value, more lenience around interpretation of clinical and economic evidence, more formal criteria for accepting uncertainty, different willingness to pay, and risk sharing to split the risk of high cost medicines. Findings suggest a need for adapted approaches for RDT appraisal, as they facilitate better management of specific challenges associate with RDTs and more consistent decision-making.

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Abbreviations

RDT = rare disease treatment
HST = highly specialised technology
STA = standard technology appraisal
QALY = quality adjusted life year

