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IMPACT-HTA: Special processes to appraise rare disease treatments – Developing feasible, consistent approaches

Moderator: Sheela Upadhyaya, NICE Consultant

November 4th 2020

IMPACT-HTA: Special processes to appraise rare disease treatments – Developing feasible, consistent approaches

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Do we need special processes to appraise medicines for rare diseases?

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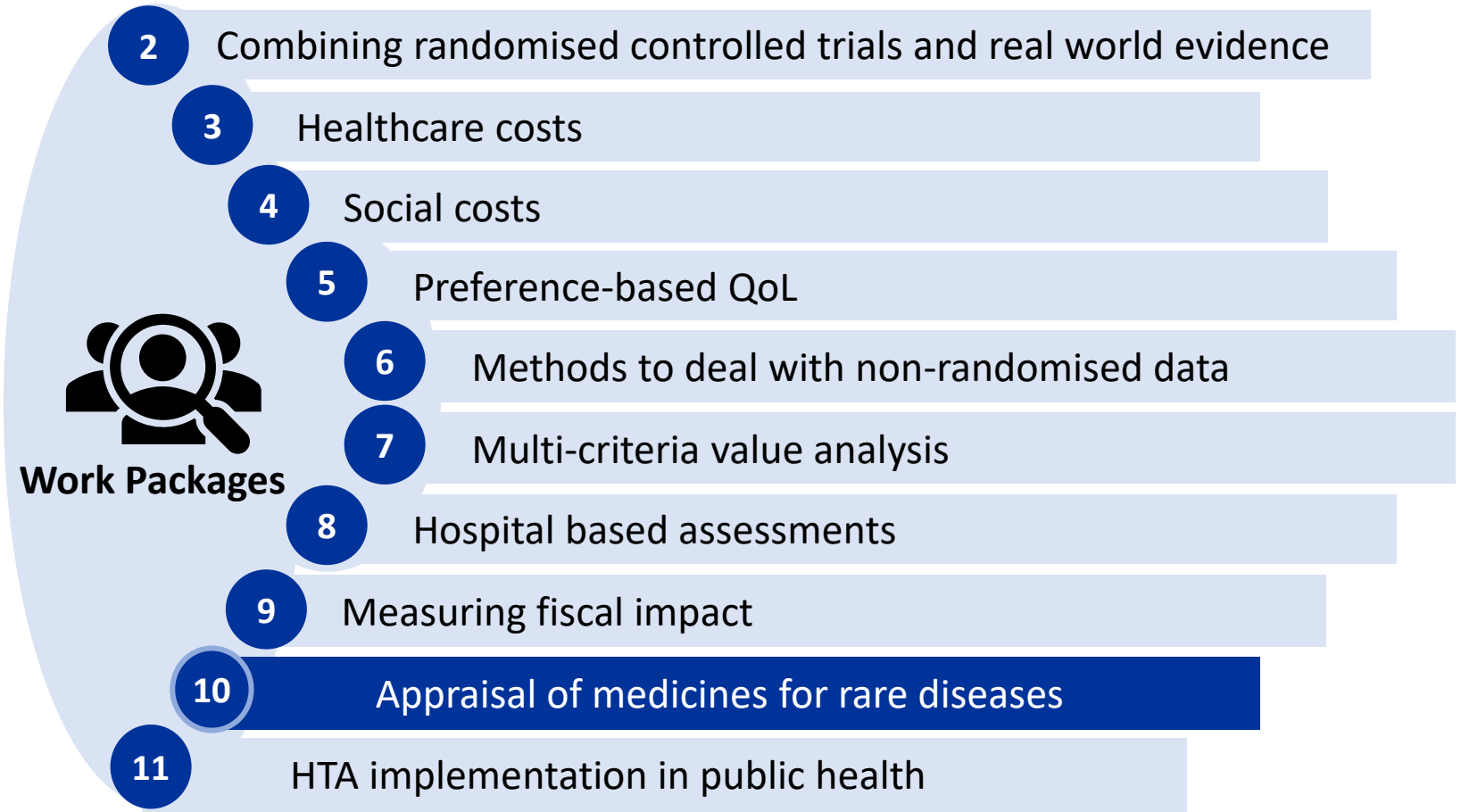
Outline of presentation

- **Overview of IMPACT-HTA and Work Package 10**
- **What are the common challenges encountered when appraising medicines for rare diseases?**
- **How are countries dealing with these challenges?**
- **What are the key considerations to ensure appraisal processes allow Committees to make the best well-informed decisions?**

1 Overview of IMPACT-HTA and Work Package 10

Improved methods and actionable tools for enhancing HTA

- EC funded H2020 project under the call for improved methods for economic evaluation
- Developing ***methods, tools and guidance*** for decision-makers in the context of HTA and health system performance



WP10 team and collaborators

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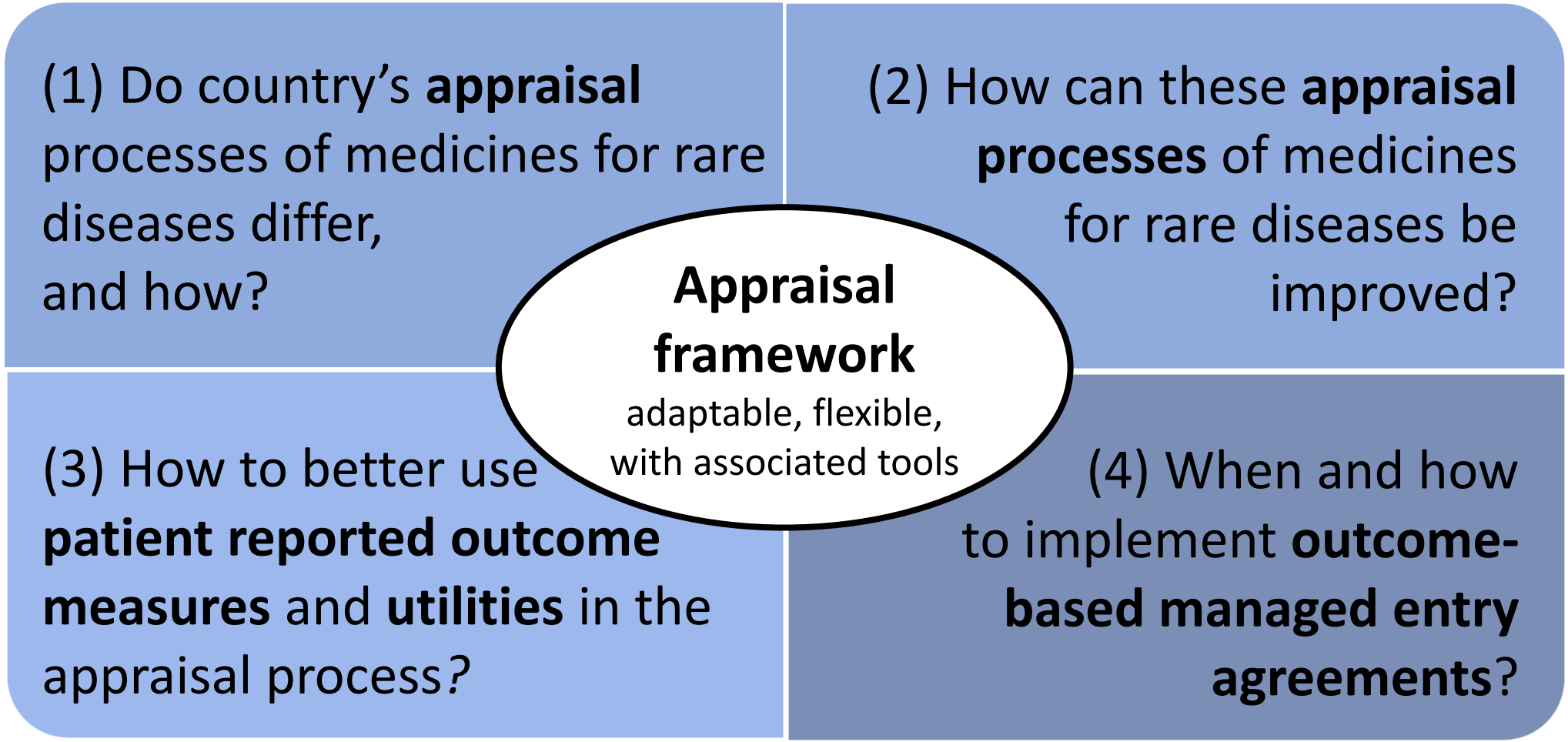
IMPACT HTA


(1) Do country's **appraisal** processes of medicines for rare diseases differ, and how?
(2) How can these **appraisal processes** of medicines for rare diseases be improved?
Appraisal framework
adaptable, flexible, with associated tools
(3) How to better use **patient reported outcome measures** and **utilities** in the appraisal process?
(4) When and how to implement **outcome-based managed entry agreements**?

2 Challenges in appraising medicines for rare diseases

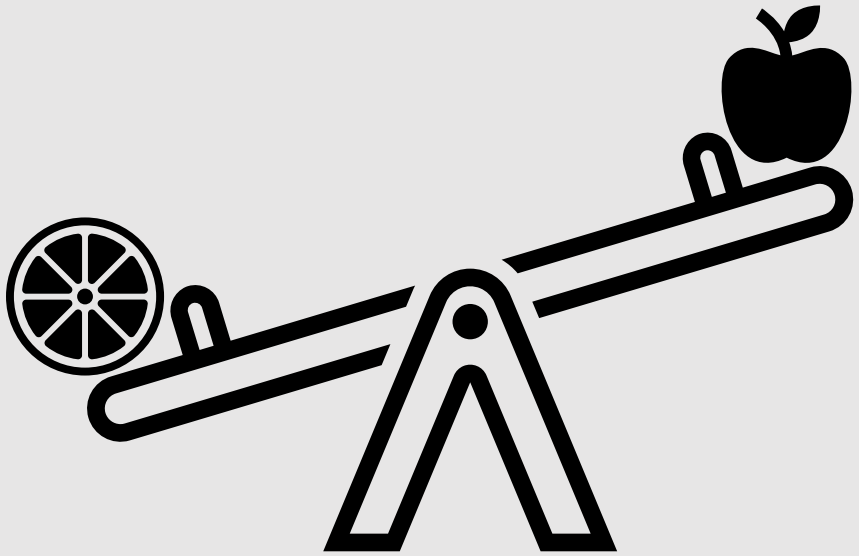
Health Technology Assessment is a multidisciplinary process* that uses explicit methods to determine the **value** of using a *health technology* at different points in its lifecycle

The purpose is to inform health policy and decision-making *(pricing and reimbursement)* to promote an equitable, efficient and high-quality health system

*The process is formal, systematic, and transparent, and uses state-of-the-art methods to consider the best available evidence

"Value for money"

When resources are limited and choices have to be made



HTA compares benefits (and sometimes also costs) of a new versus a comparator treatment

O'Rourke B, Oortwijn W, Schuller T, the International Joint Task Group (2020). The new definition of health technology assessment: A milestone in international collaboration. International Journal of Technology Assessment in Health Care 1–4.

The difficulties to develop medicines for rare diseases lead to HTA challenges

Nature of rare diseases

- Small patient populations
- Heterogeneous conditions
- Many genetically acquired, early onset
- Negative impact on patients, families and carers
- Severe, disabling, life-threatening

Drug discovery Preclinical research → **Clinical research** Phase I, II, III trials → **Marketing authorisation** → **Pricing and reimbursement** National-level → **Post-marketing surveillance** Phase IV trials

CLINICAL CHALLENGES
- Lack of knowledge and expertise
- Ability to run confirmatory trials

REGULATORY CHALLENGES
- Incentives from regulators to overcome clinical challenges

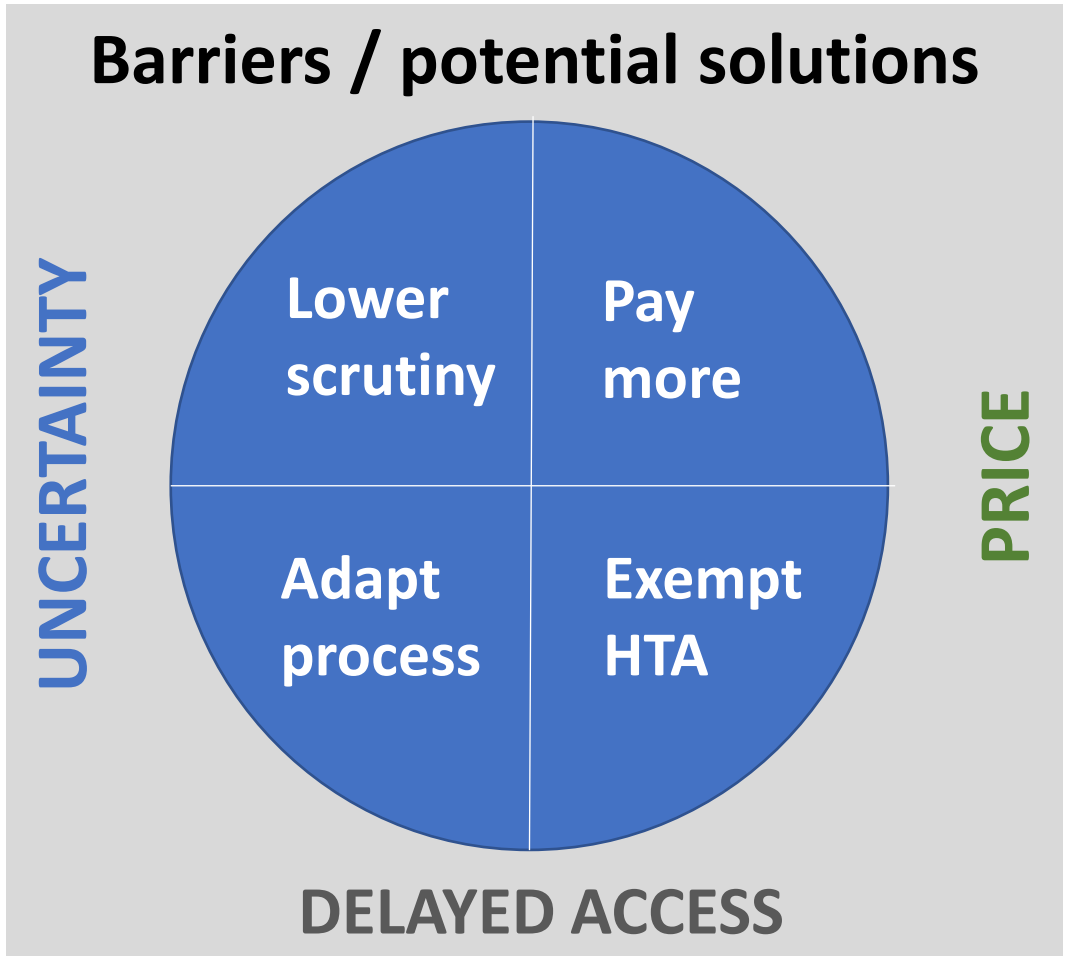
ECONOMIC CHALLENGES
- High cost medicines
- Financial burden on patients, family, carers and society

CHALLENGES AT HTA-LEVEL
- Misaligned with regulatory processes
- Small samples, lack statistical power
- Uncertain clinical pathways
- Limited clinical and QoL evidence
- Limited trial duration
- Issues in dealing with subgroups
- Uncertainties in cost effective modelling
- High Cost/QALY

Source: Nicod E, Annemans L, Bucsics A, Lee A, Upadhyaya S, Facey K. HTA programme response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European Countries. Health Policy, 2019

Conventional HTA appraisal processes may not be suitable to appraise medicines for rare diseases

Often high cost, no/few alternative treatments	High	Higher WTP? Societal preferences
Cost (A) – Cost (B) / Effect (A) – Effect (B)	= ICER	≤ WTP
Higher uncertainty because of issues around trial design and conduct	Uncertain	Willing to accept greater uncertainty?



How are countries dealing with these challenges?

41% (13/32) with special HTA processes informing routine use of medicines for rare diseases

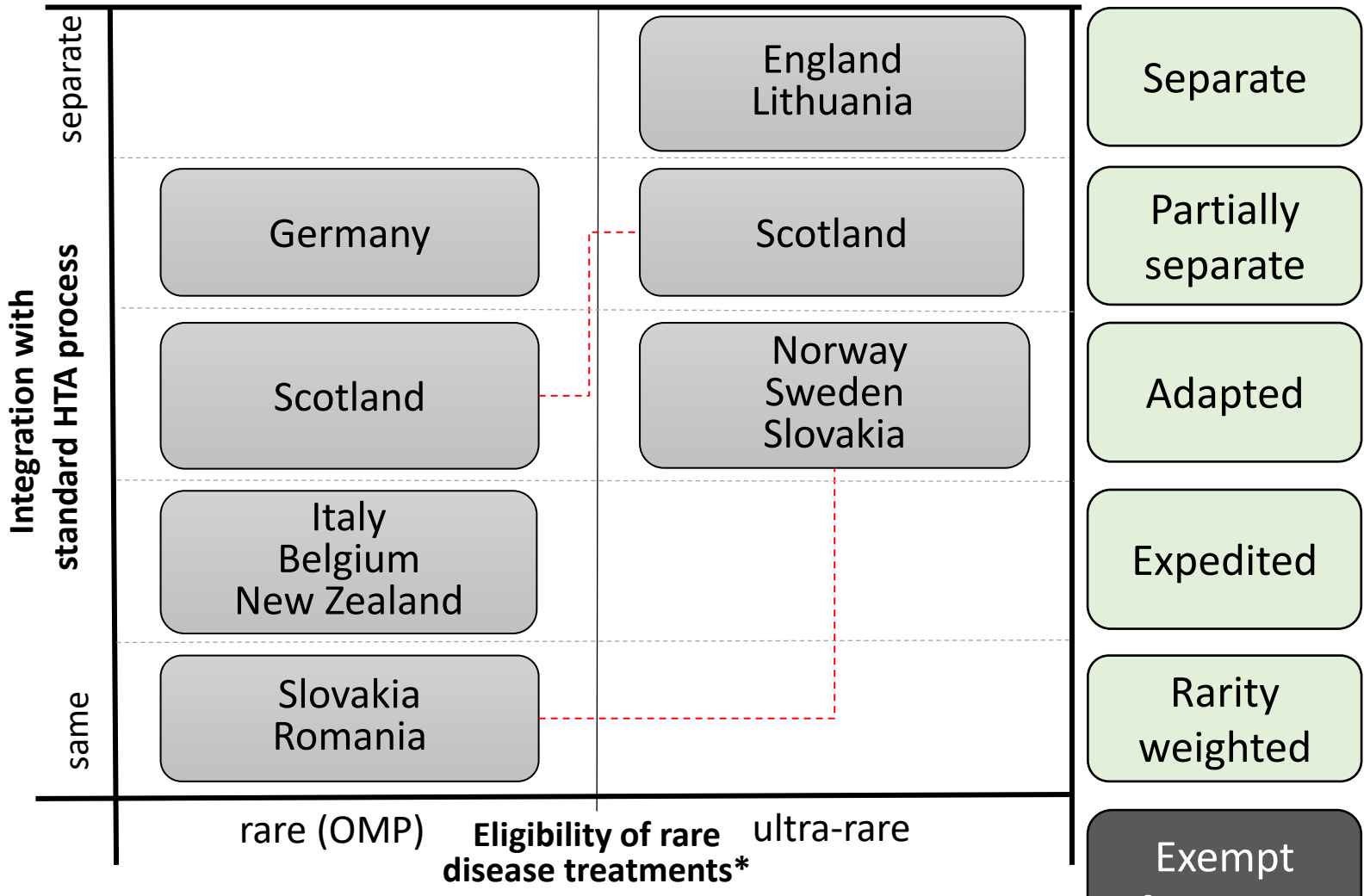
37 countries invited

- EU + EAA, New Zealand, Canada, Australia
- 5/37 non-responders excluded

32 countries included

www.impact-hta.eu/country-vignettes

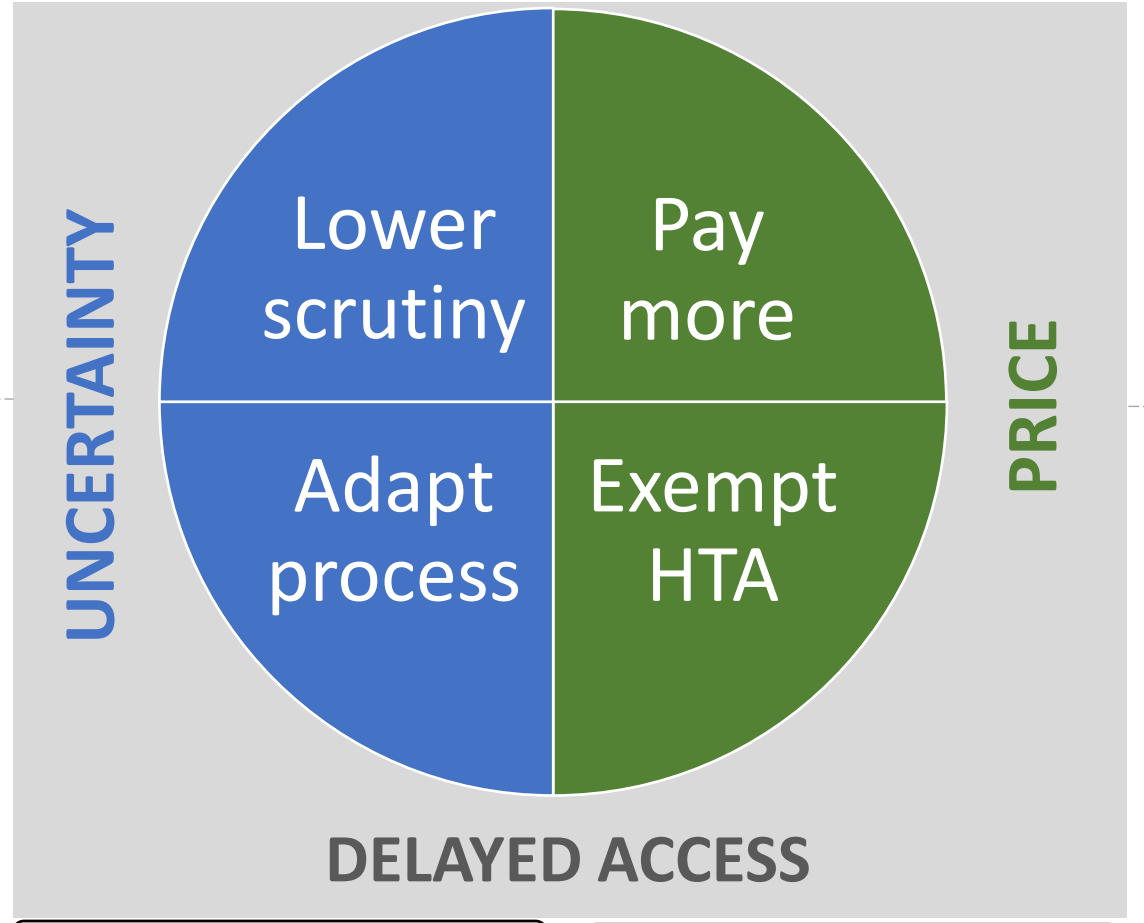
- 41% special process
- 53% standard process
- 6% other programmes applicable to rare disease treatments



* Rare disease treatment with orphan designation from European Medicines Agency ("Orphan Medicinal Product", OMP); ultra-rare disease treatments defined by individual country definitions

Source: Nicod E, Whittal A, Drummond M, Facey K. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. Orphanet Journal of Rare Diseases, 2020; 15:189

Special processes include features – many of which are process adaptations - allowing to better deal with medicines for rare diseases specificities



- More leniency around quality of evidence
- More flexibility in economic modelling
- Decision modifiers

- Different requirements for clinical submission
- Different requirements for economic submission
- Different (appraisal) committees
- Broader consideration of value
- Disease-specific input to inform appraisal
- Conditional approval

- Decision modifiers
- Different willingness to pay
- Alternative reimbursement rules

- Different formulary listing
- Different budget
- Different requirements for clinical submission
- Different requirements for economic submission

- Earlier start
- Alternative reimbursement rules

- Different formulary listing
- Different budget

Features that deal with several issues

3 How are countries dealing with these challenges?

- Revealed preference to treat medicines for rare diseases differently
  - Special processes in 41% (13/32)
  - Standard processes in 59% (19/32), where:
    - ≥ 1 features or appraisal criteria likely favouring medicines for rare disease (12/19)
    - planned changes for 4 of remaining 7
- Not about what an ideal process should look like, but about features better dealing with rare disease treatments in a structured and consistent manner
- All issues not being dealt with via special processes, many are new and continue to be adjusted as experience is gained

3 How are countries dealing with these challenges?

Nicod et al. Orphanet Journal of Rare Diseases (2020) 15:189
https://doi.org/10.1186/s13023-020-01462-0

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches

Elena Nicod[1*], Amanda Whittal[1], Michael Drummond[2] and Karen Facey[3]

Abstract

Background: There is increasing recognition that conventional appraisal approaches may be unsuitable for assessing the value rare disease treatments (RDTs). This research examines what supplemental appraisal/reimbursement processes for RDTs are used internationally and how they can be characterised. A qualitative research design was used that included (1) documentation of country appraisal/reimbursement processes for RDTs via questionnaires, desk research and iterative interactions with country experts to produce country vignettes, and (2) a cross-country analysis of these processes to identify and characterise features in supplemental processes for RDTs, and compare them to countries without supplemental processes.

Results: Thirty-two of the 37 invited countries participated in this research. Forty-one percent (13/32) use supplemental processes for RDTs. Their level of integration within standard processes ranged from low to high, characterised by whether they are separate or partially separate from the standard process, adapted or accelerated standard processes, or standard processes that may be applied to RDTs. They are characterised by features implemented throughout the appraisal process. These features are mechanisms that allow application of different standards to assess the value of the medicine, support to the appraisal/decision-making process, overcome the issues of lack of cost-effectiveness, or exempt from part of/the full appraisal/reimbursement process. They increase the likelihood of reimbursement by adjusting and/or foregoing part of the assessment process, or accepting to pay more for the same added benefit as for common conditions. A large proportion of countries with standard processes include one or more of these features (formally or informally) or are discussing potential changes in their systems.

Conclusions: Results suggest revealed preferences to treat RDTs differently than conventional medicines. Some of the challenges around uncertainty and high price remain, but supplemental process features can support decision-making that is more flexible and consistent. Many of these processes are new and countries continue to adjust as they gain experience.

Keywords: Rare disease treatment, Orphan medicine, Ultra-orphan medicine, Appraisal, Reimbursement, Access to treatments, Supplemental processes, Health technology assessment

IMPACT HTA

A number of observations on the operationalisation of these process adaptations have arisen from observing HTA appraisal committees

Ethnographic observation, documentation and interviews to explore HTA procedures for medicines for rare diseases (led by Dr Karen Facey, December 2018-February 2021)

- Scottish Medicines Consortium
  - New Drugs Committee
  - Confidential Patient and Clinician Engagement (PACE) Meetings
  - Public SMC Appraisal Committee Meetings
- National Institute for Health and Clinical Excellence
  - TA and HST Appraisal Committee Meetings
- CADTH
  - Confidential appraisal committee meeting

Key considerations to allow for best possible decision-making

*Our reflection has been around what is needed within the appraisal process for rare diseases **to allow Committees to make the best decision possible** given each unique circumstance of a disease*

Understanding circumstances of disease

Adaptable to rare disease specificities

Structured appraisal framework

Need to ensure process allows for a good understanding of the individual circumstances of the disease

Understanding circumstances of disease

>6,000 rare diseases, which are often unique

- Scarcity of knowledge and expertise
- Heterogeneous presentation and progression
- Complex (severity, multi-systemic, disabling, life-threatening, treatment options)

- **Flexibility** is needed in appraisal frameworks, but also consistency ⇒ fairness (Accountability For Reasonableness)
- **Inputs from clinical and patient experts** are more important to explain the evolving understanding of the disease, who would be treated, what outcomes matter, how clinical trial effects can be interpreted in real-life, the impact on quality of life, and advise on treatment stopping protocols

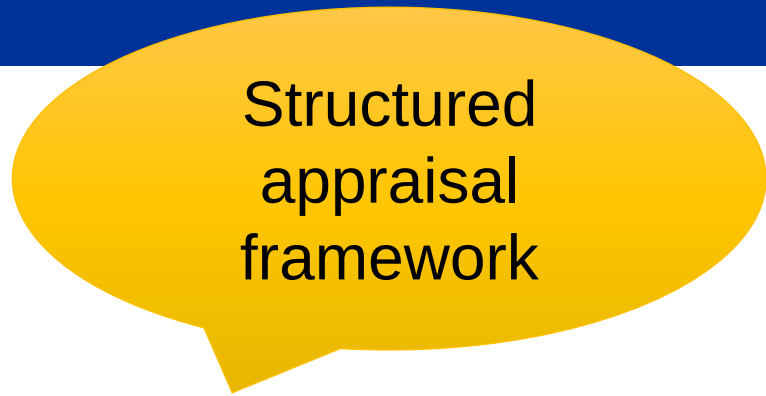
Appraisal processes should ensure that the value of rare disease treatments is being captured appropriately and consistently

Adaptable to rare disease specificities

Different process adaptations may help ensure value is being captured given the specificities of rare diseases relating to high levels of uncertainty and price

- **Additional criteria/alternative processes/modifiers need to be built into the entire HTA process -** evidence submissions for each stakeholder, critical assessment, deliberative discussion (with appropriate frameworks, training and support for all)
- Any **modifiers** to traditional processes should be explicitly **presented for each product** at each meeting so that all understand what flexibility is possible
- Value often discussed in the context of**, e.g. severity, unmet need, existence of treatment alternatives, children, equality, innovative nature of treatment**
- **Stakeholders could help resolve uncertainties if they were notified in advance and able to submit evidence related to specific questions**
- **Guidance is needed on modelling methods that are feasible for rare diseases** – when are models too unstable to be the basis of decision-making?

A structured and flexible appraisal framework is needed to ensure fair decision-making



The Appraisal framework should be sufficiently structured and flexible to allow Committees to make the best decision for each individual case

- **Need to characterise different forms (and levels?) of uncertainty and what this means for decision-making**
- **Need structure for decision-making beyond cost-effectiveness** with clarity about how the decision-making works (stakeholders, invited experts, committee members)
- If clinical uncertainties can be resolved within a reasonable time period, **outcome-based managed entry agreements may be suitable**

Towards a flexible appraisal process better adapted to reflect individual circumstances of rare diseases that allows for fair and consistent decision-making

Thank you for your attention!

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