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IMPACT HTA

Improved methods and actionable tools for enhancing HTA

Appraisal Framework suitable for Rare Disease Treatments

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28 June 2021 – Basler Biometrics Section and EFSPI
Precision and Innovative Medicine and HTA

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The results presented here reflect the authors' views and not the views of the EC.
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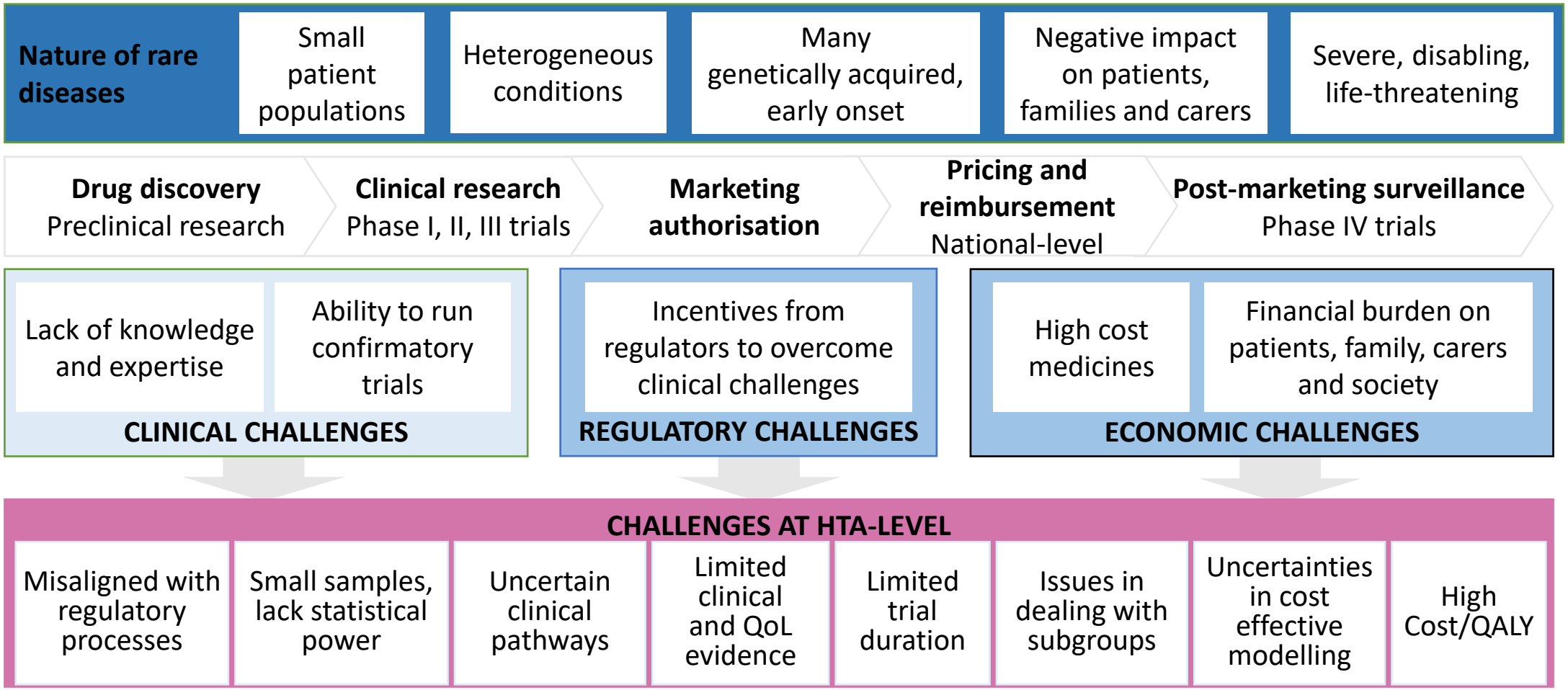
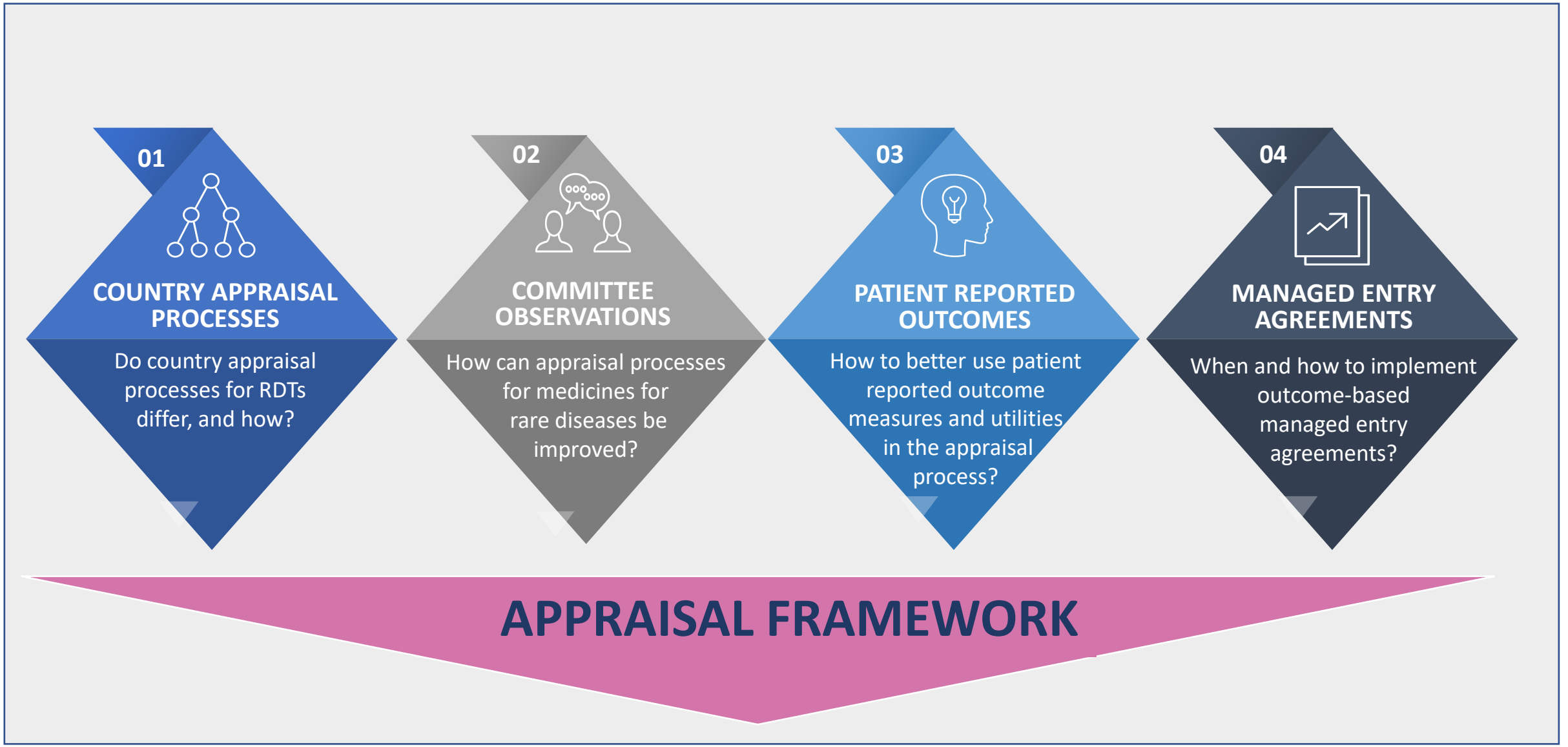
IMPACT HTA

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



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

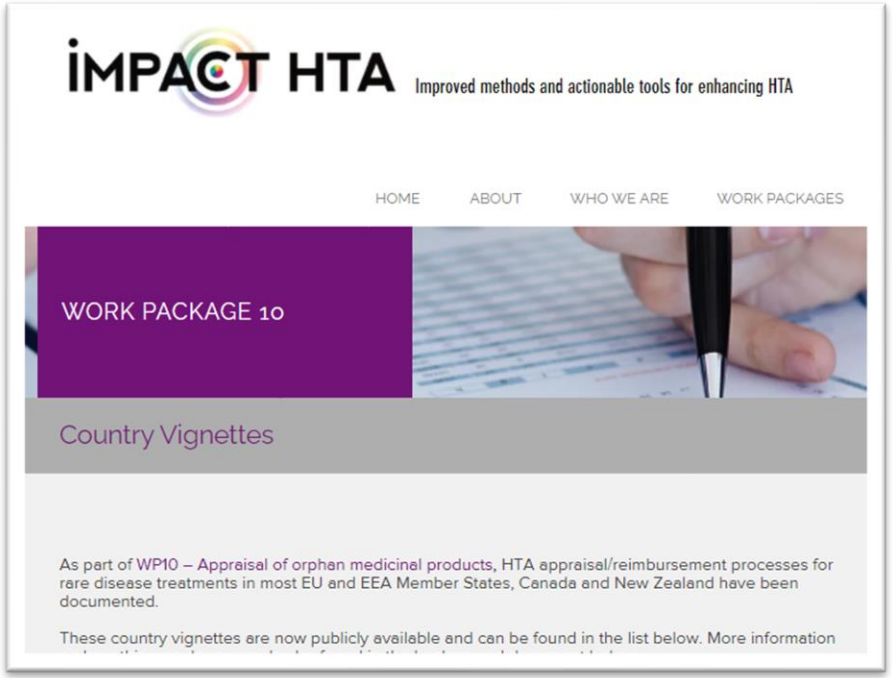
IMPACT-HTA WP 10: Appraisal of Rare Disease Treatments (RDTs)



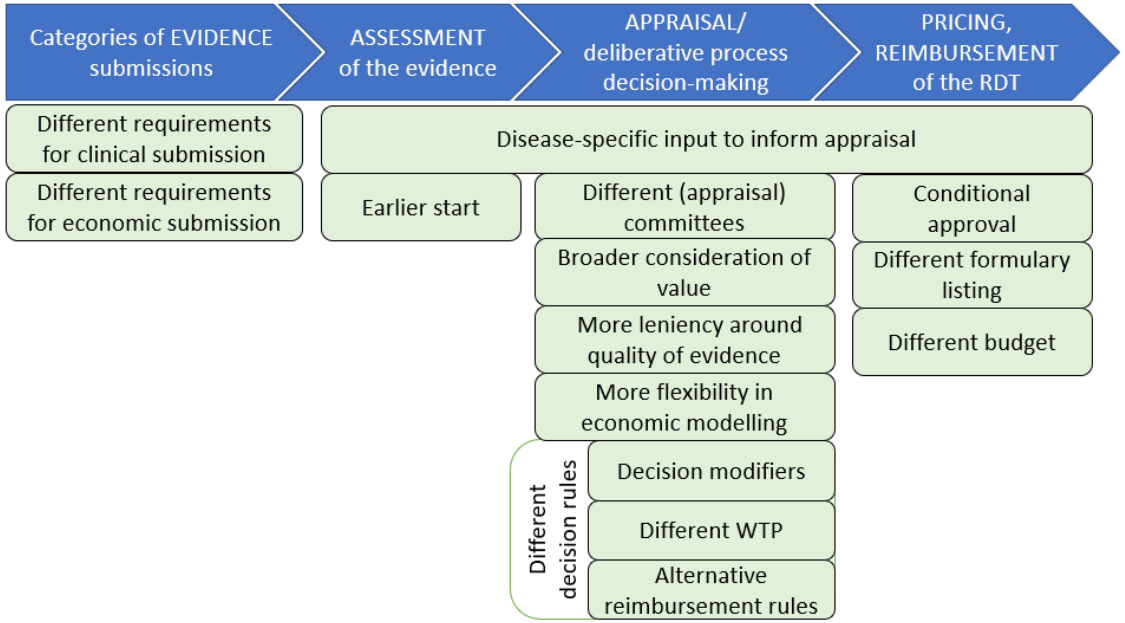
*More information can be found at: https://www.impact-hta.eu/work-package-10

1 Overview of appraisal processes for RDTs

IMPACT-HTA WP10 country vignettes of appraisal processes for RDTs (n=36)



Overview of countries with supplemental process for RDTs and process characteristics



Nicod et al. 2020. Are supplemental/appraisal reimbursement processes suitable for rare disease treatments? An international comparison of country approaches. Orphanet Journal of Rare Diseases

Available at: impact-hta.eu/work-package-10

iMPACT HTA

2 Ethnographic observation and interviews of Appraisal Committees

OBSERVATIONS

SMC (Scotland)

- New Drugs Committee (NDC)
- Patient & Clinician Engagement (PACE)
- SMC Appraisal Committee (orphan, ultra-orphan framework/pathway)

NICE (England)

- HST and TA Appraisal Committee

CADTH (Canada)

- Canadian Drug Expert Committee (CDEC)

INTERVIEWS

30 interviews of individuals involved throughout the Appraisal process of those observed

TREATMENTS OBSERVED

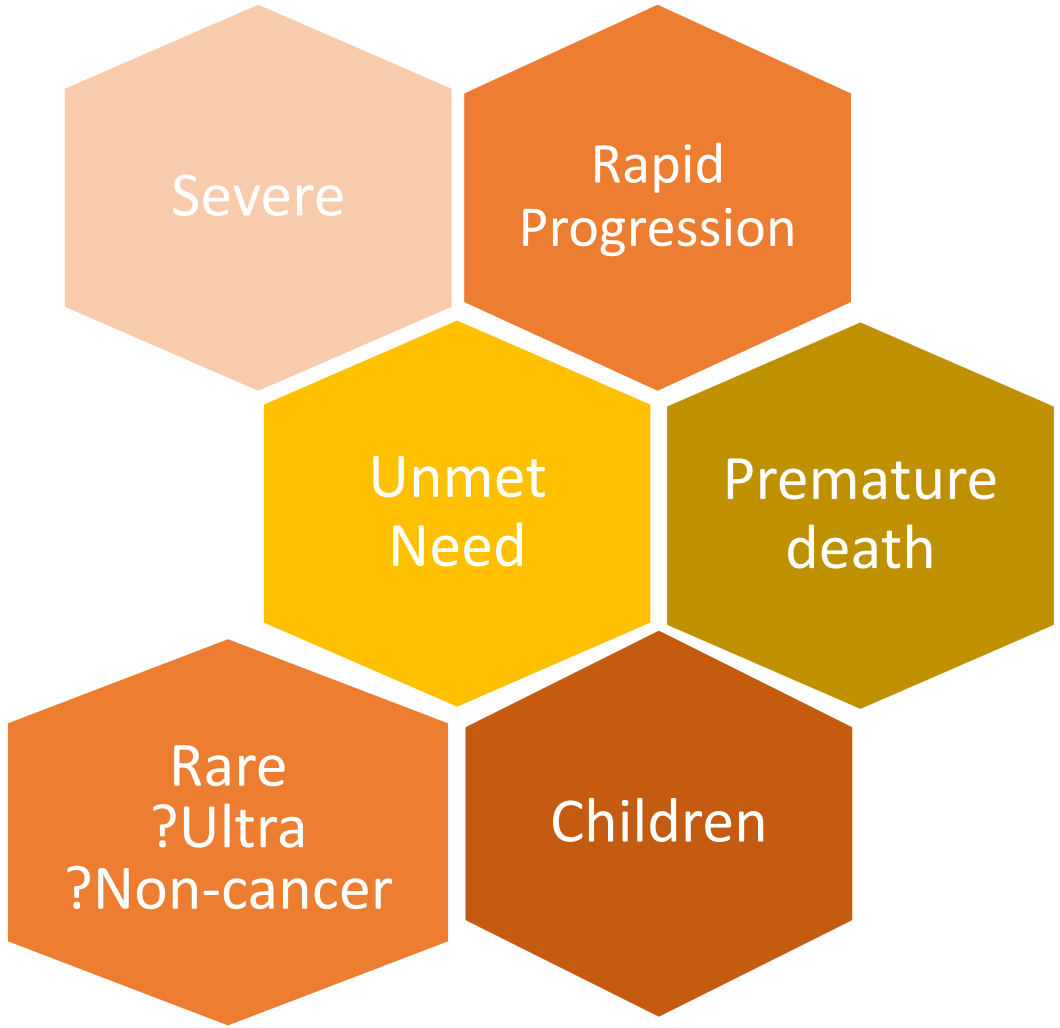
Tisagenlecleucel	B-cell acute lymphocytic leukaemia
Patisiran	Amyloidosis
Lumacaftor/Ivacaftor & Tezacaftor/Ivacaftor	Cystic Fibrosis
Voretigene Neparvovec	Inherited Retinal Disorder
Onasemnogene Abeparvovec	Spinal Muscular Atrophy
Volanesorsen	Familial chylomicronaemia
Emapalumab	Primary paediatric haemophagocytic lymphohistiocytosis

Table 4.1.1 *continued* Voretigene neparvovec for inherited retinal dystrophy, One-off gene therapy: HST

Issue discussed by committee	Assessment Group	Patient input	Clinical input (MAH)	Committee conclusion
Mortality				
Transitions to dead not captured in MSM – but based on life tables. Mortality multipliers based on an old study from a much older population.	No deaths in the clinical study		Loss of functional vision could increase mortality in older people but this was not reflective of the people that would be treated	HRs for mortality highly uncertain – exclude additional mortality.
Resource Use				
Costs in 2 phases 1-off in year 1 Longer-term resource use for managing severe visual impairment and blindness with health state adjustments. [*details not presented here]*	ERG corrected some costs and noted many estimates based on assumptions and removed costs associated with depression as they were due to loss of vision in later life, not lifelong vision loss.	Patient expert disagreed with exclusion of depression costs given the considerable impacts of vision loss on mental health.		Health state adjustments should be removed but additional depression costs should be included.
Discount Rate				
Base case of 3.5% with alternative of 1.5% presented. Non-reference rate of 1.5% may be used when treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives, if it is highly likely that there will be long-term benefits and if treatment does not commit NHS to significant irrecoverable costs.				Technology could be transformative for people who without treatment would lose their ability to see, but recalled clinical expert's explanation that people may not regain full vision if photoreceptor cells have already been damaged and if treatment is not applied to all photoreceptor cells. Committee was highly uncertain about whether people would have "normal or near-normal health" and large uncertainties about long-term benefit. Will consider both discount rates in decision-making, but prefers 3.5% because uncertain whether Voretigene fully meets criteria for 1.5% discount rate.

Nature of condition	Clinical effectiveness
Patient, carer, family impacts	Ethical issues
Cost-effectiveness, budget impact	Organisational issues

Principles – equality, encouraging innovation



Recommendations for an appraisal framework that enables consistent flexibility to ensure fairness for RDTs

Expanded Evidence Submissions and Critical Assessment

1. The entire HTA process is shaped around clearly defined decision-making domains and modifiers
2. All relevant evidence is obtained for each domain of decision-making and all modifiers
3. Critical assessment of clinical evidence explicitly considers what evidence could have been generated in the rare condition
4. Critical assessment of economic models takes account of paucity of knowledge in RDs and judges whether the model is sufficient for decision-making

Structured Appraisal Deliberation

5. Appraisal committees are bespoke for RDTs, or general appraisal committees include several RD specialists
6. The deliberative appraisal discussion is driven by the domains of decision-making and use of modifiers is clearly understood
7. Uncertainties are characterized in terms of form, extent and implications for decision-making
8. Outcomes-Based Managed Entry Agreements may be used to resolve decision-relevant uncertainties, if collection of sufficient data is feasible

Iterative Clinical and Patient Input

Clinical and patient experts are involved throughout appraisal process to explain context of condition, existing care pathway and help resolve uncertainties related to determination of treatment value

Source: Facey K, Whittal A, Drummond M, Upadhyaya S, Junghans T, Nicod E. IMPACT HTA WP10 HTA Appraisal Framework Suitable for Rare Disease Treatments. 12 May 2021. [Online]. Available from: Impact HTA | Health Technology Assessment | Work Package 10 (impact-hta.eu)

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2. All relevant evidence is obtained for each domain of decision-making and all decision modifiers

Submissions from Industry

- The best possible clinical evidence - RCTs, Novel trial designs, use of pre-authorisation RWD
- Reduce bias - Blinded assessment of important outcomes, avoidance of missing data

- Economic models not overly complex
- Consistent assumptions and realistic scenario analyses

- Nature of condition, patient-based evidence, organisational issues

Evidence from other sources

Stakeholder submissions (including audits, surveys etc), literature reviews, expert meetings, interviews, consensus surveys, questionnaires

3. Critical assessment of clinical evidence explicitly considers what evidence could have been generated in the rare condition

- Diagram of all data and state of maturity of each study
- What matters (according to clinicians and patients) and is not measured in the clinical trial?
  - impact of disease and treatments on patients' lives
- Limitations of PRO data need to be documented (e.g. use of unvalidated or insensitive instruments, insufficiently powered studies, potential bias in open label studies)
- Use PROs that complement primary clinical outcome (different aspect)
- HTA methods guides and checklists to document leniency allowed for RDTs

4. Critical assessment of economic models takes account of paucity of knowledge in rare diseases and judges whether the model is sufficient for decision-making

- Discuss construct of economic model over entire time horizon with clinicians to ensure it is a sufficiently good representation of the condition and agree best assumptions
- Checklist to scrutinize natural history studies and identify best source
- Extrapolations – see WP6

- Health State Utility Values – challenges!
  - EQ5D may be high at baseline for chronic rare diseases (response shift phenomenon)
  - Disease states described in vignettes need to be verified by unbiased clinicians and patients
  - More work needed on inclusion of carer impacts

3 Better use of PRO data and HSUVs in HTA of rare diseases

What is known in the literature on use of PROs/utilities in rare diseases and implications for HTA

SYSTEMATIC REVIEW

Mapping' Health State Utility Values from Non-preference-Based Measures: A Systematic Literature Review in Rare Diseases

Michela Meregaglia[1] · Amanda Whittal[1] · Elena Nicod[1] · Michael Drummond[2]

International Journal of Technology Assessment in Health Care

The estimation of health state utility values in rare diseases: overview of existing techniques

Michela Meregaglia[1], Elena Nicod[1] and Michael Drummond[2]

[1]Research Centre on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Milan Italy and [2]Centre for Health Economics, University of York, York, UK

There are several techniques for estimating health state utility values, each of which presents pros and cons in the context of rare diseases (RDs). Direct approaches (e.g. standard gamble

https://doi.org/10.1007/s40271-020-00493-w

REVIEW ARTICLE

The Use of Patient-Reported Outcome Measures in Rare Diseases and Implications for Health Technology Assessment

Amanda Whittal[1] · Michela Meregaglia[1] · Elena Nicod[1]

Accepted: 12 December 2020

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Abstract

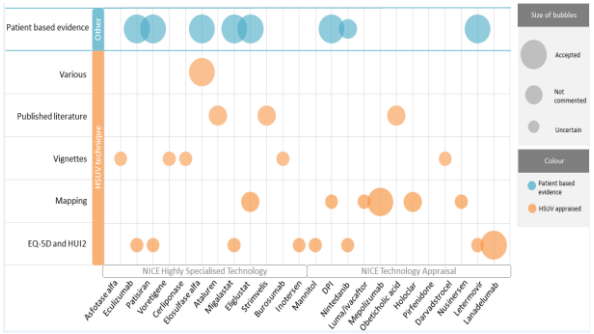
Background Patient-reported outcome measures (PROMs) are used in health technology assessment (HTA) to measur patient experiences with disease and treatment, allowing a deeper understanding of treatment impact beyond clinical end points. Developing and administering PROMs for rare diseases poses unique challenges because of small patient populations disease heterogeneity, lack of natural history knowledge, and short-term studies.

Objective This research aims to identify key factors to consider when using different types of PROMs in HTA for rar disease treatments (RDTs).

Consideration of PROs/utilities for RDTs in practice across 4 countries

PROM/HSUV techniques

- Interpretation
- Influence on decision
- Other evidence to support assessment, interpretation of QoL



Recommendations for improving use of PRO data and utilities in HTA of RDTs

8. Outcomes-Based Managed Entry Agreements may be used to resolve decision-relevant uncertainties, if collection of sufficient data is feasible

Purposeful approach to data collection for decision-relevant uncertainties – agreed by all parties in public document, aligned across health jurisdictions, with ongoing monitoring to ensure data quality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Checklist for a Rare Disease Treatment
Is an Outcomes-Based Managed Entry Agreement Feasible?

Criteria for use by a Health Technology Assessment (HTA) body or Marketing Authorisation Holder (MAH) to determine whether an Outcomes-Based Managed Entry Agreement (OBMEA) with mandatory data collection for re-appraisal (Coverage with Evidence Development) is feasible for a rare disease treatment (RDT):

Checklist to determine feasibility of an OBMEA


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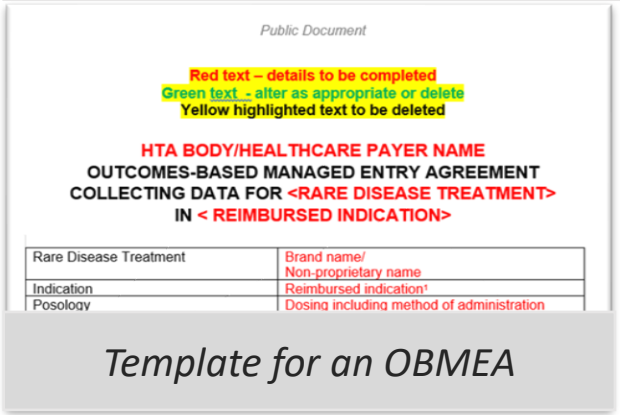
Template for Adaptation by HTA Bodies

Patient Group submission form for re-appraisal after an OBMEA

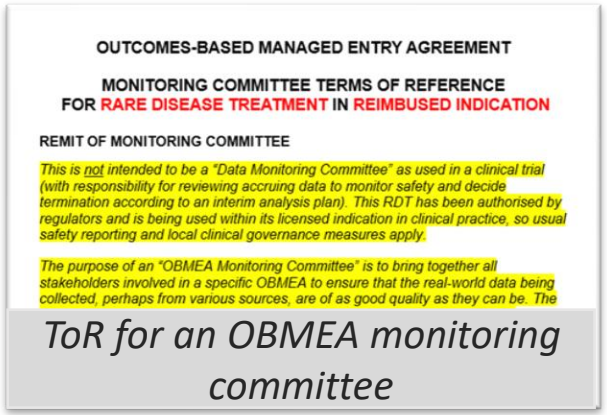

Public Document

Red text – details to be completed
Green text - alter as appropriate or delete
Yellow highlighted text to be deleted

HTA BODY/HEALTHCARE PAYER NAME
OUTCOMES-BASED MANAGED ENTRY AGREEMENT
COLLECTING DATA FOR <RARE DISEASE TREATMENT>
IN < REIMBURSED INDICATION>

Rare Disease Treatment	Brand name/ Non-proprietary name
Indication	Reimbursed indication[1]
Posology	Dosing including method of administration

Template for an OBMEA


OUTCOMES-BASED MANAGED ENTRY AGREEMENT

MONITORING COMMITTEE TERMS OF REFERENCE
FOR RARE DISEASE TREATMENT IN REIMBUSED INDICATION

REMIT OF MONITORING COMMITTEE

This is not intended to be a "Data Monitoring Committee" as used in a clinical trial (with responsibility for reviewing accruing data to monitor safety and decide termination according to an interim analysis plan). This RDT has been authorised by regulators and is being used within its licensed indication in clinical practice, so usual safety reporting and local clinical governance measures apply.

The purpose of an "OBMEA Monitoring Committee" is to bring together all stakeholders involved in a specific OBMEA to ensure that the real-world data being collected, perhaps from various sources, are of as good quality as they can be. The

ToR for an OBMEA monitoring committee

- **Analysis of 283 MEAs initiated in Italy over a 15-year period**
  Xoxi E et al.. 2021; Frontiers in Pharmacology: Drugs Outcomes Research and Policies
- **Documentation of the purpose, form, construct and analysis of OBMEA in countries in EU, Australia and Canada for two case studies** (nusinersen in spinal muscular atrophy and tisagenlecleucel in refractory haematological cancers)
  Facey K et al. 2021; Pharmacoeconomics

Participation Throughout

Scoping - focus on patients to be treated

- nature of condition, care pathway, current management, experience of treatment in clinical trial or early access, important outcomes
- patient and clinician “stories” videoed for reference by all assessors/committee members

Critical assessment of evidence – clinical experts

- Interpretation of effects in clinical studies
- Validity of important modelling assumptions relating to clinical benefit
- Construct of economic model and optimal inputs/assumptions
- Health service impacts in terms of treatment administration and patient monitoring

Appraisal – clinical and patient experts

- Eligible patients, treatment positioning, balancing early access vs clinical trial data, utilities
- Duration of treatment effect, treatment continuation rules
- Infrastructure issues and health service readiness

Thank you!

Karen Facey - k.facey@btinternet.com