Appraisal Framework suitable for Rare Disease Treatments

Karen Facey PhD CStat
Evidence Based Health Policy Consultant

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

**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

**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

**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

**DRUG DISCOVERY**
- Preclinical research

**CLINICAL RESEARCH**
- Phase I, II, III trials

**MARKETING AUTHORISATION**
- National-level

**PRICING AND REIMBURSEMENT**
- Phase IV trials

**POST-MARKETING SURVEILLANCE**
- Phase IV trials

Do country appraisal processes for RDTs differ, and how?

How can appraisal processes for medicines for rare diseases be improved?

How to better use patient reported outcome measures and utilities in the appraisal process?

When and how to implement outcome-based managed entry agreements?

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

<table>
<thead>
<tr>
<th>Categories of EVIDENCE submissions</th>
<th>ASSESSMENT of the evidence</th>
<th>APPRAISAL/deliberative process decision-making</th>
<th>PRICING, REIMBURSEMENT of the RDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different requirements for clinical submission</td>
<td>Disease-specific input to inform appraisal</td>
<td>Earlier start</td>
<td>Conditional approval</td>
</tr>
<tr>
<td>Different requirements for economic submission</td>
<td>Different (appraisal) committees</td>
<td>Broader consideration of value</td>
<td>Different formulary listing</td>
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<tr>
<td></td>
<td>More leniency around quality of evidence</td>
<td>More flexibility in economic modelling</td>
<td>Different budget</td>
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<tr>
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<td>More flexibility in economic modelling</td>
<td>Decision modifiers</td>
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<tr>
<td></td>
<td>Different WTP</td>
<td>Alternative reimbursement rules</td>
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Available at: impact-hta.eu/work-package-10
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)

**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

**INTERVIEWS**

30 interviews of individuals involved throughout the Appraisal process of those observed
Table 4.1.1 continued  Voretigene neprevovec for inherited retinal dystrophy, **One-off gene therapy**: HST

<table>
<thead>
<tr>
<th>Issue discussed by committee</th>
<th>Assessment Group</th>
<th>Patient input</th>
<th>Clinical input (MAH)</th>
<th>Committee conclusion</th>
</tr>
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<tr>
<td>Mortality</td>
<td>No deaths in the clinical study</td>
<td>Loss of functional vision could increase mortality in older people but this was not reflective of the people that would be treated</td>
<td>HRs for mortality highly uncertain – exclude additional mortality.</td>
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<tr>
<td>Transitions to death not captured in MSM – but based on life tables. Mortality multipliers based on an old study from a much older population.</td>
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<tr>
<td>Resource Use</td>
<td>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.</td>
<td>Patient expert disagreed with exclusion of depression costs given the considerable impacts of vision loss on mental health.</td>
<td>Health state adjustments should be removed but additional depression costs should be included.</td>
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<tr>
<td>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]</td>
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<td>Discount Rate</td>
<td>Base case of 3.5% with alternative of 1.5% presented.</td>
<td></td>
<td>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.</td>
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<td>Nature of condition</td>
<td>Clinical effectiveness</td>
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<td>Patient, carer, family impacts</td>
<td>Ethical issues</td>
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<td>Cost-effectiveness, budget impact</td>
<td>Organisational issues</td>
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Principles – equality, encouraging innovation

- Severe
- Rapid Progression
- Unmet Need
- Premature death
- Rare
- Ultra
- Non-cancer
- Children
## 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.

### 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.

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

## Expanded Evidence Submissions and Critical Assessment

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**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

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

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
Evidence Submission and Critical Assessment

Appraisal Deliberation considers all dimensions of value

Iterative Clinical and Patient Input

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

- 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