Rare Disease Research, Health Technology Assessment and Evidence for Reimbursement

FORUM

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Introduction

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Rare Access, UK
Alpha-1 UK Support Group
Why ISPOR has a Rare Disease SIG

- High unmet need, with ~75% of currently recognized rare diseases with no effective treatment → offering significant opportunities for advancements in care
- Policy incentives for R&D in rare diseases have been effective, and focus on rare diseases continues to increase
- Total budget impact of rare disease treatments is steadily rising, whilst pressure on health care budget also increases
- Numerous challenges make research and HTA in rare diseases especially difficult
- Comprehensively understanding these challenges is the first step towards addressing them

ISPOR Rare Disease SIG - Projects


- Rare Disease Challenges In Assessment and Appraisal of Diagnostics and Treatments – in progress
Rare diseases and their treatments face inter-related challenges

- Stakeholders dealing with rare diseases and their treatments are confronted with special challenges relating to:
  - Understanding the disease
  - Developing effective treatments
  - Demonstrating value-for-money and achieving reimbursement and patient access
  - Equity and societal value consideration

- Some challenges are unique to rare diseases, some are more pronounced in rare diseases

- Too often, stakeholders perceive challenges solely from their perspective

Collaboration across broad range of stakeholders required to address challenges

- Researchers
- Life sciences industry
- Regulators
- HTA agencies
- Public and private payers
- Physicians and other healthcare providers
- Patients and their families
- Patient advocacy organizations
Multi-stakeholder discussion panel

- Christopher Blanchette, PhD  MBA
  Associate Professor, University of North Carolina, Charlotte, NC, USA &
  VP, Precision Health Economics, Charlotte, NC, USA

- Ken Redekop, PhD
  Associate Professor, Institute for Medical Technology Assessment, Erasmus
  University Rotterdam, Rotterdam, Netherlands

- Sheela Upadhyaya, Dip
  Associate Director, Highly Specialised Technologies, NICE, UK

- Janis Clayton, BSc
  VP and General Manager UK & Ireland, PTC Therapeutics Ltd., UK

- Moderator: Sandra Nestler-Parr, PhD  MSc  MPhil
  Managing Director, Rare Access, London, UK &
  Trustee, Alpha-1 UK Support Group, UK

Challenges

Christopher Blanchette
University of North Carolina, USA
Precision Health Economics, USA
Research-related challenges

Rarity - Low disease frequency

<table>
<thead>
<tr>
<th>Disease recognition and diagnosis</th>
<th>Evaluation of treatment effect</th>
<th>Patient recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Lack of familiarity with RDs</td>
<td>❖ Heterogeneity of disease prognosis and treatment effect</td>
<td>❖ Geographic limitations in patient recruitment</td>
</tr>
<tr>
<td>❖ Disease heterogeneity</td>
<td>❖ Selection bias</td>
<td>❖ Insufficient coding systems</td>
</tr>
<tr>
<td>❖ Lack of established diagnostic criteria</td>
<td>❖ Uncertainties related to validated trial outcomes</td>
<td>❖ Ethical and legal hurdles</td>
</tr>
<tr>
<td>❖ Misdiagnosis</td>
<td></td>
<td></td>
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<tr>
<td>❖ Geographic variation</td>
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HTA, reimbursement & access challenges

No tailored HTA method for orphan drugs

❖ Lack of sufficient clinical data
❖ No established standard of care
❖ Insufficient knowledge of the natural history of the disease
❖ Lack of validated instruments to assess relevant endpoints
❖ Application of incremental cost-effectiveness ratio (ICER) thresholds

Uncertainty for healthcare payers

Equity of access as a result of HTA outcomes
Observations

- Multiple challenges may increase the size of the overall challenge.
  - So: \( c + c = C \), and \( C + c = C \)

- It’s not about the challenges per se, but rather about the ultimate goals, which are to:
  - Improve (normalize) the lives of patients with rare diseases in a sustainable manner.
  - Assess the “value” of a RD treatment and make a reimbursement decision…
Overall challenge:
Uncertainty about treatment effectiveness

- One overarching challenge is the difficulty in determining if the effectiveness of a treatment is clinically important and statistically significant.
- Various challenges described earlier contribute to this challenge.
- Illustrated by examining the formula to calculate the statistical power of a clinical trial to assess the effectiveness of an RD treatment:

\[ t' = \frac{\mu_1 - \mu_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \]

- Components:
  - sample size (n)
  - variation in prognosis between patients within a study arm (s)
  - size of the average treatment effect (\(\mu_1 - \mu_2\))
- These components are affected by the challenges presented earlier.

Component 1: Sample size

- A small source population makes it difficult to find sufficient patients.
- The obvious solution is to increase the sample size.
  - BUT: The source population is small!
  - AND: Difficulty in diagnosis (including lack of familiarity with RD, etc.) means false-positive and false-negative results.
    - False-positive results lead to inclusion of patients in the study who do not have the disease → this will likely reduce the treatment effect.
    - False-negative results will limit the pool of patients for inclusion.
Component 2: Variation in prognosis between patients

- Large disease prognosis heterogeneity means variation in outcome
- Solutions:
  - Include patients with a poorer prognosis (higher chance of the outcome of interest) using prognostic tests
    → BUT:
      - a prognostic test may not exist or not be widely available
      - this selection will reduce the size of the source population
  - Increase the follow-up duration of the trial
    → BUT: This will increase study costs and delay market access

Component 3: Size of the average treatment effect

- Large variation in treatment effect due to heterogeneity of study population means a smaller average treatment effect if wide spectrum of patients are included in a study
- Solution (to improving the statistical power) is to include patients with a greater chance of treatment response, e.g. use “predictive tests” to identify patients who are likely to respond better
  → BUT:
    - no such test may be available
    - this selection will reduce the size of the source population
The different challenges need to be considered collectively.

They can create a ‘perfect storm’ making it very difficult to obtain a precise estimate of the effectiveness (and cost-effectiveness) of a treatment.

Challenges are only important if they prevent us from achieving our goals.
- Adopt a more goal-oriented approach (not all challenges are equally relevant)
- Primarily consider the criteria that policymakers use in reimbursement decision-making

Multicriteria decision analysis (MCDA) has been suggested by many in the RD literature.

Case study:
Ataluren for Duchenne Muscular Dystrophy

Janis Clayton
PTC Therapeutics, UK

Sheela Upadhyaya
NICE, UK
Ataluren for Duchenne Muscular Dystrophy - Challenges and Solutions

Manufacturer vs. HTA perspective

- **Challenges:**
  - Disease-related
  - Evidence-related
  - Process-related

- **Solutions:**
  - Short-term
  - Mid-term
  - Long-term

Conclusions and generalizable considerations

- Real-world evidence generation
- Holistic approaches to understanding RDs, drug development and evaluation
- Harmonisation of solutions across jurisdictions
- Limitations
- Etc.

Questions & Answers

- For more information on SIGs, visit [www.ispor.org](http://www.ispor.org)
- To join a SIG, click the green Special Interest Group menu and select “JOIN” on the pull-down menu.
Thank you

Evaluation criteria, proposed by Hughes-Wilson et al., 2012

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Price Differential</th>
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<tbody>
<tr>
<td>Rarity</td>
<td>Lower</td>
</tr>
<tr>
<td>1:2,000 - 1:20,000 or COMP figures &gt; 3 in 10,000</td>
<td>1:20,000 - 1:20,000 or COMP figures 1:3 in 10,000 (5%)</td>
</tr>
<tr>
<td>Level of research undertaken</td>
<td>Literature review</td>
</tr>
<tr>
<td>Level of uncertainty of effectiveness</td>
<td>Immature, but promising data</td>
</tr>
<tr>
<td>Manufacturing complexity</td>
<td>Not complex – small molecule / classic galenic form</td>
</tr>
<tr>
<td>Follow up measures (additional benefits and associated costs)</td>
<td>Moderate to none</td>
</tr>
<tr>
<td>Characteristics without direct cost impact</td>
<td></td>
</tr>
<tr>
<td>Disease severity</td>
<td>Morbidity</td>
</tr>
<tr>
<td>Available alternatives / unmet medical need</td>
<td>Alternatives with similar characteristics</td>
</tr>
<tr>
<td>Level of impact on condition / disease modification</td>
<td>Low</td>
</tr>
<tr>
<td>Use in unique indication or not</td>
<td>Existing orphan or non-orphan indicators for the same molecule*</td>
</tr>
</tbody>
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*N.B. Another element could be the total revenues in the context of multiple indications for the same molecule owned by the same company.