Special Interest Groups

Rare Disease Research, Health Technology Assessment and Evidence for Reimbursement

FORUM

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Introduction

Sandra Nestler-Parr
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

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ISPOR Rare Disease SIG - Projects

- Rare Disease Terminology & Definitions: A Systematic Global Review – published report *Value in Health,* Sep/Oct 2015


Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/jval
ELSEVIER
Health Policy Analysis
Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group

- Rare Disease Challenges In Assessment and Appraisal of Diagnostics and Treatments – in progress

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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

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Challenges

Christopher Blanchette
University of North Carolina, USA
Precision Health Economics, USA

Research-related challenges

Rarity - Low disease frequency

Disease recognition and diagnosis	Evaluation of treatment effect	Patient recruitment
❖ Lack of familiarity with RDs ❖ Disease heterogeneity ❖ Lack of established diagnostic criteria ❖ Misdiagnosis ❖ Geographic variation	❖ Heterogeneity of disease prognosis and treatment effect ❖ Selection bias ❖ Uncertainties related to validated trial outcomes	❖ Geographic limitations in patient recruitment ❖ Insufficient coding systems ❖ Ethical and legal hurdles

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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

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Equity of access as a result of HTA outcomes

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Uncertainty about treatment effect and evaluation criteria for orphan drugs

Ken Redekop,
Erasmus University Rotterdam, Netherlands

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 (μ_1-μ_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

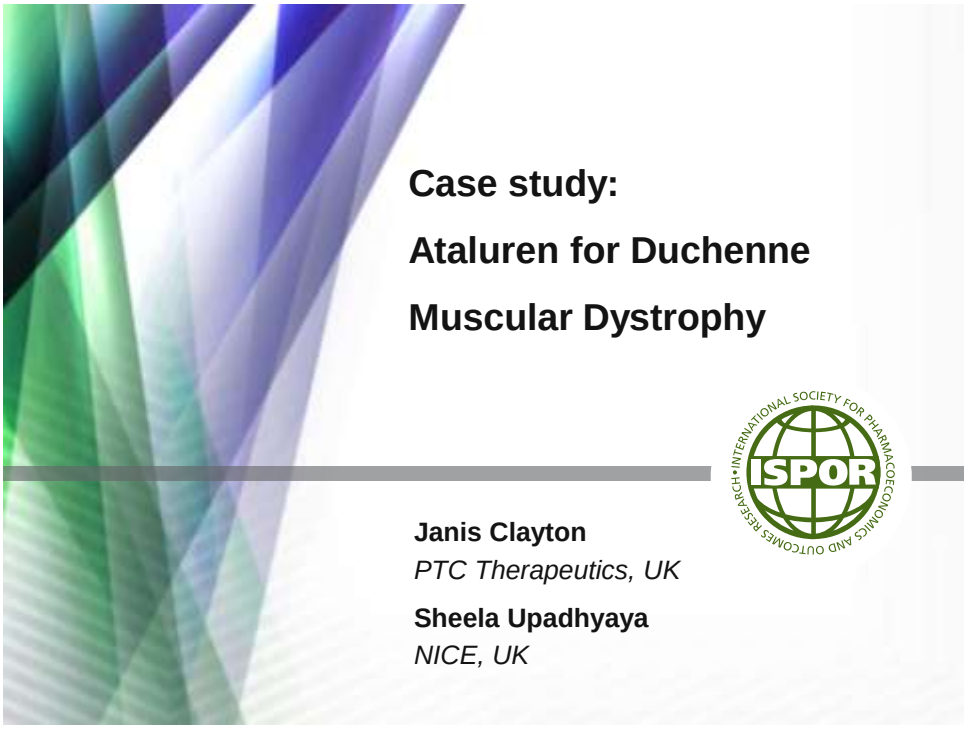
- Large disease prognosis heterogeneity means variation in outcome
- Solutions:
  - Include patients with a poorer prognosis (higher chance of the outcome of interest) using prognostic tests
    - → **BUT**:
      - a prognostic test may not exist or not be widely available
      - this selection will 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

Conclusions and policy consideration

- 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



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.

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Questions & Answers

- **For more information on SIGs, visit 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 1 – Proposed criteria for evaluation of orphan drugs and corresponding potential parameters

Criteria	Price Differential		
	Lower	Medium	Higher
Rarity	1:2,000 - 1:20,000 or COMP figures > 3 in 10,000 (11%)	1:20,000 - 1:200,000 or COMP figures 1–3 in 10,000 (51%)	Less than 1:200,000 or COMP figures less than 1 in 10,000 (38%)
Level of research undertaken	Literature review	Building on previous existing knowledge	"Blue-sky" – starting research & development programme in an unknown area
Level of uncertainty of effectiveness	Immature, but promising data	Appropriate surrogate end-points	Robust clinical end-points
Manufacturing complexity	Not complex – small molecule / classic galenic form	Moderately complex	Highly complex biological and galenic form
Follow up measures (additional benefits and associated costs)	Moderate to none	Designed to answer specific, defined, delineated question	Safety and efficacy studies + size and duration of study
Characteristics without direct cost impact			
Disease severity	Morbidity	Mortality / severe invalidity in adulthood	Mortality / severe invalidity as infant
Available alternatives / unmet medical need	Alternatives with similar characteristics	Alternatives – but offering strong innovation to the disease treatment	No alternative
Level of impact on condition / disease modification	Low	Medium	Strong
Use in unique indication or not	Existing orphan or non-orphan indications for the same molecule*	Potential for multiple indications	Unique indication – no other use possible

*N.B. Another element could be the total revenues in the context of multiple indications for the same molecule owned by the same company.

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