Introduction: Why ISPOR has a Rare Disease SIG

- Attention on rare diseases is increasing as policy incentives for R&D are working.
- Rare disease treatment costs are increasing rapidly.
- Unmet needs, and therefore, opportunities for advancements in care are great, with ~75% of currently recognized rare diseases with no effective treatment.
- Numerous challenges make research and HTA in rare diseases especially difficult.
- Comprehensively understanding these challenges is the first step in addressing them.
Our Work Will Be Valuable to:

Stakeholders…

- Regulators
- Life sciences industry
- HTA authorities
- Public and private payers
- Physicians and other healthcare providers
- Rare disease organizations
- Patient advocacy organizations
- Patients and their families
- Researchers

Rare Disease Special Interest Group Overview

Started 3 years ago with a meeting at ISPOR 15th Annual European Congress in Berlin 2012.

Topics defined. Two working groups formed.

- Rare Disease Terminology & Definitions Working Group
- Rare Disease Challenges In Assessment and Appraisal of Diagnostics & Treatments Working Group
Rare Disease Special Interest Group Overview


- Rare Disease Challenges In Assessment and Appraisal of Diagnostics & Treatments – presenting final report / will submit to *Value in Health* December 2015

NEW SIG Working Group
- HTA of Rare Disease Treatments – Open Meeting

Speaker: Terms & Definitions Working Group Publication

Sandra Nestler-Parr, PhD, MPhil
Head of Rare Diseases
Roboleo & Co
London, England, UK
Terms and Definitions Working Group

Co-Chairs:
Dyfrig Hughes, PhD, MSc, Professor, Centre for Health Economics and Medicines Evaluation, Bangor University, Wales, UK
Zeba M. Khan, PhD, Vice President, Strategic Market Access & Policy, Celgene Corporation, Summit, New Jersey, USA

Article Available
Via Value in Health or RD SIG webpage
Rare Disease Terminology & Definitions: A Systematic Global Review

- Many different concepts and terms exist to describe rare diseases, their treatments and related health technologies.
- Growing global connectivity of health care and the rise of targeted medicines for small, well-defined, patient groups has intensified the need for a better understanding of the definitions related to rare diseases.
- The working group conducted primary research in 32 jurisdictions representing the six major geographic regions of the world: Europe, North America, South America, Asia, Africa, and Oceania.
- Terms & definitions were found to differ:
  - Within and across geographic boundaries and jurisdictions
  - Across stakeholder types
- The similarities and differences in definitions used by various stakeholder groups across different jurisdictions were discussed.

Key Findings

- >1,000 stakeholder organizations (HTA agencies, private and public payers, regulators, research organizations, umbrella patient organizations) from 32 jurisdictions
- 296 definitions identified, frequently combining descriptive terms and/or prevalence thresholds
- Descriptive terms, relating to:
  - Type of disease, e.g., “rare”, “orphan”, “neglected”
  - Condition, e.g., “disease”, “condition”, “syndrome”
  - “Rare disease” most commonly used (38%)
- Explicit prevalence thresholds used in 58% of definitions
  - Wide range: 5 - 76 cases/100,000 people
  - Average threshold: 40 – 50 cases/100,000 people
Summary and Conclusions

- Despite variations, there is global consistency in the preference for terms “rare disease” and “orphan drugs”.
- <30% of definitions included other qualifiers.
- 58% of definitions included prevalence threshold.
- Patient organizations have the highest, most liberal, average threshold, whereas private payers have the lowest, most conservative, average threshold.
- Further research necessary to better understand extent of existing diversity of definitions and roots of these variations between stakeholder groups within and across jurisdictions.
- Attempts to harmonize rare disease definitions should focus on standardized, objective criteria, such as prevalence thresholds, and should avoid qualitative descriptors.

Speaker: Rare Disease Challenges in Assessment and Appraisal of Diagnostics & Treatments Working Group

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Stakeholder Challenges

- Stakeholders dealing with rare diseases are confronted with special challenges.
  - Some are unique to rare diseases.
  - Some are more severe in rare diseases.
- Too often, stakeholders perceive challenges solely from their perspective.

Manuscript Goal

- Comprehensively catalogue and explain challenges associated with rare diseases so that relevant stakeholders can start with a common shared understanding of the obstacles faced.
- Leading to collaboration and consensus on the means to address these challenges and ultimately, promote more effective treatments. Reflects the needs of multiple stakeholders.
- Describes challenges, discusses their consequences, and identifies way(s) they are being addressed.
- Published examples are referenced.
RESEARCH RELATED CHALLENGES

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Challenges in Assessment and Appraisal of Rare Disease Diagnostics & Treatments
### Disease-related Challenges

1. Rarity of disease may make it more difficult to identify patients for research
2. Heterogeneity of a disease and its course
3. Geographic dispersal of population reduces the ability to understand the disease
4. Lack of diagnostic capability/modalities increases the time to diagnosis and treatment
5. Severity challenges associated with including very impaired or minimally impaired patients in research
6. Lack of effective treatments reduces the willingness to diagnose and the ability to learn more about the disease

### Treatment Related Challenges

1. Rapidly evolving science causes difficulty in understanding the natural history of a disease
2. Difficulty in evaluating average treatment effect and how treatment effect may change over time
3. Heterogeneity of treatment effect Outcomes measurement – use of patient-relevant health outcomes
4. Legal and ethical hurdles to obtain sufficient sample size for prospective research and maintaining differentiation from marketing/promotion activities
5. Lack of guidance related to rare disease-specific research methodologies
HTA & Appraisal Related Challenges

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HTA related challenges

**Limited evidence:**
- No control arm
- Small study population
- No validated outcome
- Disease heterogeneity
- No long-term data

Uncertainty

Transferability  Generability  Benefit estimation
HTA related challenges

**Limited background data:**
- Clinical burden of disease
- Epidemiology
- Current management
- Unmet needs

Uncertainty

- Added value
- Targeted population
- Place in treatment strategy

HTA related challenges

- Poor data on economic burden and current management
- Rapidly growing expenditures on OD
- High ICER of ODs

Uncertainty

Quantify healthcare costs, utilization and possible savings over the lifetime of the disease or treatment
Most countries do not have HTA and/or pricing and reimbursement-specific orphan drug (OD) decision framework.

However, applying existing decision framework will be either a facilitator or a major hurdle.

- **Facilitator**
  - When effect size and rarity are valued

- **Major hurdle**
  - When incremental cost-effectiveness is used

Informal HTA assessment

Under usual circumstances, orphan drugs (OD)s are not cost-effective.

Two approaches can be used to make it possible for orphan drugs to be considered cost-effective:
- Set higher ICER for ODs
- Apply weighted ICER criteria

There is a variation in terms of the criteria that are considered by HTA agencies.

Evidence requirements differ between HTA agencies.
Finding the Right Balance

- Wide patient access to OD is a legitimate objective, but affordability is a major obstacle.
- OD prices are commonly associated with
  - Hidden payback
  - Coverage with evidence development
  - Market access agreement
  - Etc.
Global & Equity Considerations

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Director Healthcare Policy and External Affairs
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Regulatory Acts

- **USA**
  - 1983: Orphan Drug Act
- **EU**
  - 2000: Regulation (EC) No 141/2000 (the Orphan Regulation)
- **Japan**
  - 1993: Orphan drug regulation
- **Singapore**
  - 1991: Medicine Order ‘Orphan Drug Exemption’
- **Australia**
  - 1997: Orphan Drug Policy
- **Taiwan**
  - 2000: Rare Disease and Orphan Drug Act
Incentives

- The primary objectives of the established incentives are to encourage research & development (R&D) and to ensure a return on investment (ROI) for pharmaceutical manufacturers.

**Research**
- Grants
- Founding registries

**Market authorisation**
- Accelerated centralised procedure
- Fee reduction
- Market exclusivity
- Protocol assistance

**Market Access**
- Special criteria
- No cost-effectiveness threshold (in some countries)
- Automatically assumed additional benefit status (in some countries)

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**New drugs with Orphan Status in the European Union**

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Source: vfa (Verband Forshenden Arzneimittelherstellern) the Association of German Innovator / Research Pharmaceutical Companies, 2015
Access level: Dramatically Different From Country To Country…

Leading to high inequality

Source: Inventory of Access and Prices of Orphan Drugs across Europe: A Collaborative Work between National Alliances on Rare Diseases & Eurordis, Eurordis 2011

Global & Equity Challenges

- Economic pressure on healthcare budgets
- Growing investors expectations
- Demographic pressure
- High unmet medical need
- Equity in health
- Societal value
Equity challenges

- Limited tools to measure utilization of RD technologies
- Limited interest to conduct research on patient access to RD technologies in countries with smaller market potential
- Inequitable access to rare diseases technologies across geographic regions
- Global policy tools in rare diseases are mainly based on experiences in higher income countries.
- Limited information on the magnitude of inequity across countries with different economic status

Further public policy interventions

- Research programs
  - Public-Private Partnerships
- International regulatory collaboration (FDA – EMA)
  - Common guidelines
- Collaboration between regulators and payers (EMA & HTA)
  - Parallel Scientific Advice
- Cooperation between national payers
  - EU HTA assessment
- Progressive Patient Access / Adaptive Licensing
Potential Solutions

- Special HTA criteria for technologies in rare diseases?
- Supranational collaboration (coordinated purchasing)?
- MCDA tool for orphan drugs?
- Managed Entry Agreements / Coverage with evidence development?
- Exclusion from external price referencing / Differential Pricing?

Need for improvement

- Secure evidence generation of technologies as a continuum
- Enhance encompassing stakeholder dialogue across the entire value chain of technologies
- Increase flexible regulatory policies
- Emphasis on value and effectiveness of technologies (together with Quality, Safety and Efficacy)
- Overcome gap between international regulatory and national pricing & reimbursement decisions
Conclusion

- Agreeing on common definition is already problematic.
- Identifying and listing in a structured way the challenges is difficult.
- The manuscript's goal is to set the foundations for further research addressing the orphan drug HTA-related and research-related challenges.

Access to Forum Slides

Via Released Presentations Green Pull-down Menu on ISPOR Milan homepage or RD SIG webpage
Open Meeting

Health Technology Assessment (HTA) of Rare Disease Treatments Working Group

Health Technology Assessment (HTA) of Rare Disease Treatments Working Group

Co-Chairs:

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  Professor & Chair of Disease Economics
  Department of Public Health and Market Access
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  Lyon, France

- Sandra Nester-Parr, PhD, Mphil
  Head of Rare Diseases
  Robelco & Co
  London, England, UK

Leadership Group: TBD
Research Questions

- To systematically review the HTA landscape for the adoption of specific orphan drug HTA pathways.
- To analyze which criteria drive HTA decisions of orphan drugs.
- To identify current best practice and trends in orphan drug HTA.

Background and Rationale

- Orphan drug legislation was introduced in many global regions and has contributed to a continuous increase in:
  - Number of market authorizations for orphan drugs
  - Therapeutic options for patients suffering from rare conditions
- Many jurisdictions globally have not adopted formal HTA policies.
- Most HTA agencies do not currently employ specific, well-defined appraisal policies for rare disease therapies.
- Not all HTA agencies publish their recommendations or details of the rationale for appraisal decisions.
Proposed Scope

- Geographical scope includes jurisdictions globally that:
  - Conduct formal HTAs, and
  - Publish HTA recommendations and/or the details relating to criteria that contributed to the final appraisal decisions

- Review HTA decisions for all orphan products that:
  - Received EMA and FDA marketing authorization from 2009 to 2013
  - Have undergone a formal HTA in at least two jurisdictions that meet the selection criteria for the geographical scope

Proposed Methods

- Identify drug-indication pairs and jurisdictions within the scope
- Analyse and compare HTA decisions, according to different parameters:
  - HTA process, incl. type, origin and quality of data considered for appraisal (e.g. clinical; economic; prospective RCTs; observational studies)
  - Decision criteria (e.g. cost-effectiveness; level of unmet need; therapeutic alternatives; disease severity)
  - Reimbursement recommendations
  - Potential restrictions (e.g. inclusion, exclusion and stop criteria; requirement for ongoing RWE generation)
- Derive good practice recommendations and trends for orphan drug HTA
Work Product and Process

- A manuscript for publication in *Value in Health*.
- *Leadership Group*: TBD
- *Activities and Timelines*: TBD

**How to get involved**: Go to [www.ispor.org](http://www.ispor.org)

- Click on the **GREEN Interest Groups menu** at the TOP of the homepage
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Q & A