Rare Disease Challenges in Assessment and Appraisal of Diagnostics & Treatments Working Group
**FORUM**

**Special Interest Groups**

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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.
Currently 2 SIG Working Groups
- Rare Disease Terminology & Definitions Used in Outcomes Research
- Rare Disease Challenges In Assessment and Appraisal of Diagnostics & Treatments

Upcoming 2 More SIG Working Groups
- HTA of Rare Disease Diagnostics & Treatments
- Methodology - Measuring Use, Costs and Effectiveness of Rare Disease Care
Many different concepts and terms are used to describe rare diseases, their treatments and related health technologies.

Terms & definitions differ:
- Nationally and internationally
- Across geographic boundaries and jurisdictions
- Across stakeholders and stakeholder types
The working group conducted primary research in more than 30 countries around the world from Argentina to Sweden, South Africa to South Korea.

The similarities and differences in definitions used by various stakeholders across different countries will be discussed.
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OUR WORK WILL BE VALUABLE FOR:

- 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
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.
OUR 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 will be referenced.
Challenges in Assessment and Appraisal

Rarity

Disease related
- Heterogeneity of the disease
- Geographic dispersal
- Lack of diagnostic modalities
- Severity
- Lack of treatment options

Treatment related
- Rapidly evolving science
- Average treatment effect
- Heterogeneity of treatment effect
- Outcomes measurement
- Sample size
- Lack of guidelines

Uncertainty
- Equity of access
- Value and willingness to pay
- Need for a specific HTA method

Policy harmonization
Accessibility evaluation

Challenges in Assessment and Appraisal
1. Challenge that rapidly evolving science creates for understanding the natural history of the disease (use of genetic testing and the impact on diagnosis patterns, understanding of cell signalling pathways)
2. Lack of treatment options, which in turn leads to absence of treatment guidelines, coding deficiencies, and lack of willingness to issue certain diagnoses
3. Geographic dispersal of population; variation in nation-specific prevalence
4. Heterogeneity of both disease and its course
5. Lack of diagnostic capability/modalities
6. Identifying patients for study
7. Severity - challenges associated with including very impaired or minimally impaired patients in research
8. Legal and ethical hurdles to obtain sufficient sample size for prospective research and maintaining differentiation from marketing/promotion activities
9. Lack of guidance related to rare disease-specific research methodologies
10. Outcomes measurement
11. Heterogeneity of treatment effect - Variation in treatment effect between patients, which introduces new challenges relating to personalized medicine in rare diseases
12. Difficulty in evaluating average treatment effect and how treatment effect may change over time
13. International inconsistencies in definitions differentiating between orphan and ultra-orphan treatments
14. International differences in definitions of rare diseases
15. Policy related challenges
16. Heterogeneity of pricing practices
17. Appropriateness of standard HTA methods
18. Uncertainty challenges to healthcare payers
19. Uncertainty management
20. Equity related challenges
21. Differences between countries in what societies want or value
Ken Redekop, PhD

Associate Professor
Institute of Healthcare Policy and Management
Erasmus University Rotterdam
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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
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
Treatment Challenges

4. Outcomes measurement – use of patient-relevant health outcomes

5. Legal and ethical hurdles to obtain sufficient sample size for prospective research and maintaining differentiation from marketing/promotion activities

6. Lack of guidance related to rare disease-specific research methodologies
Mondher Toumi, MD, MSc, PhD

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**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
- Target population
- Place in therapy
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
NEED FOR A SPECIFIC HTA METHOD

- Under usual circumstances ODs 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.
HTA RELATED CHALLENGES

Equity

Affordability
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.
Ruediger Gatermann, MA, MBA

Director Healthcare Policy and External Affairs
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GLOBAL & EQUITY RELATED CHALLENGES

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
Key objectives of the established incentives are to ensure the return on investment for pharmaceutical manufacturers and to encourage Research & Development.

- **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)
New drugs with orphan status in the European Union

Prior to EU Orphan Drug Legislation

Source: vfa
All diseases are not identical in capturing interest of manufacturers.

**GLOBAL & EQUITY RELATED CHALLENGES**

- **FDA**
  - Oncology: 27%
  - Metabolic disorders: 15%
  - Hematology: 12%
  - Infectious diseases: 12%
  - Neurological disorders: 8%
  - Other*: 26%

- **EMA**
  - Oncology: 45%
  - Metabolic disorders: 35%
  - Hematology: 20%
  - Infectious diseases: 12%
  - Neurological disorders: 12%
  - Other*: 8%

*psychiatric, musculoskeletal, gastrointestinal, dermatologic, respiratory, ophthalmologic, hepatic/biliary, immunologic, cardiovascular, genitourinary, intoxications/envenomation
The access level is dramatically different from country to country leading to a high inequity.

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 RELATED CHALLENGES

- Economic pressure on healthcare budgets
- Growing investors expectations
- Demographic pressure
- High unmet medical need
- Equity in health
- Societal value
GLOBAL & EQUITY RELATED CHALLENGES

- National and regional (EU) policy interventions
- Lower versus higher income countries
- Inequitable access to rare diseases technologies across geographic regions

- Lack of universally agreed public interventions to incentivize RD technologies
- Limited tools to measure utilization of RD technologies
GLOBAL & EQUITY RELATED CHALLENGES

- 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
Special HTA criteria for technologies in rare diseases?

Supranational collaboration (coordinated purchasing)?

Managed Entry Agreements?

External price referencing?

Differential Pricing?
Secure evidence generation of technologies as a continuum

Enhance encompassing stakeholder dialogue across the entire value chain of technologies

Increase flexible regulatory policies

Emphasize on value and effectiveness of technologies (together with Quality, Safety and Efficacy)

Overcome gap between international regulatory and national pricing & reimbursement decisions
Agreeing on common definition is already a challenge

Identifying and listing in a structured way the challenges is also challenging

The aim of this work is to set the foundations for further research aiming to address the OD HTA-related and research-related challenges
1. Go to the ISPOR homepage: www.ispor.org.
2. Click on the GREEN Interest Groups menu at the TOP of the homepage
3. Select JOIN on the pull-down menu OR email Elizabeth (emolsen@ispor.org)
First draft has been sent for review and revisions made based on comments received.

Final draft will be sent out for review in early December. Please comment.

Submission to *Value in Health* expected January 2015
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