RARE DISEASES: TERMS, DEFINITIONS, AND CHALLENGES IN ASSESSING AND APPRAISING DIAGNOSTICS AND TREATMENTS

Tuesday, 5 November 2013

Moderator

Chris Pashos, PhD
Vice President, United BioSource Corporation, Lexington, MA, USA
ISPOR RARE DISEASES SPECIAL INTEREST GROUP

FORUM

SPEAKERS

Mondher Toumi, MD, MSc, PhD
Professor & Chair of Decision Sciences, Department of Public Health and Market Access, University Claude Bernard Lyon I, Lyon, France

Dyfrig Hughes, PhD, MSc
Professor, Centre for Health Economics and Medicines Evaluation, Bangor University, Wales, UK

Zeba M. Khan, RPh, PhD
Vice President, Strategic Market Access & Policy, Celgene Corporation, Summit, NJ, USA

ISPOR RARE DISEASES SPECIAL INTEREST GROUP

FORUM

WHY IS ISPOR DOING THIS NOW?

• Attention to rare diseases is increasing as policy incentives for R&D are working.

• Rare disease treatment costs are increasing rapidly.

• Opportunities for continued advancements in care are great, especially with ~75% of currently recognized rare diseases having no effective treatment.

• Numerous challenges make research and HTA in rare diseases more difficult.

• Various healthcare stakeholders need to comprehensively understand these challenges, so that they can be addressed.
ISPOR RARE DISEASES SPECIAL INTEREST GROUP

OUR WORK WILL BE VALUABLE FOR:

• Governments
• Life sciences industry
• Physicians and other healthcare providers
• HTA authorities and payers
• Rare disease organizations
• Patient advocacy organizations
• Patients and their families
• Researchers

ISPOR RARE DISEASES SPECIAL INTEREST GROUP

OUR WORK WILL BE GOVERNED BY CERTAIN CONSIDERATIONS. Specifically, we will:

• Be mindful of the needs of the multiple stakeholders.
• Begin by bringing together various definitions for rare disease terms.
• Describe a challenge, discuss its consequences and the way(s) that it is being addressed.
• Challenges to be included will be those that are:
  • Unique to rare diseases, or
  • More difficult or extreme in rare diseases.
• Published examples will be referenced.
RARE DISEASE TERMINOLOGY & DEFINITIONS USED IN OUTCOMES RESEARCH WORKING GROUP

FORUM

Co-Chairs

Dyfrig Hughes, PhD, MSc
Professor, Centre for Health Economics and Medicines Evaluation, Bangor University Wales, UK

Zeba M. Khan, RPh, PhD
Vice President Strategic Market Access & Policy Celgene Corporation Summit, New Jersey, USA

GOAL

To bring together the various definitions for rare disease terms (regulatory, HTA, and rare disease organizations) from a select group of countries representing Europe, North America, Asia-Pacific and Latin America.
<table>
<thead>
<tr>
<th>FORUM</th>
<th>RARE DISEASE TERMINOLOGY &amp; DEFINITIONS USED IN OUTCOMES RESEARCH WORKING GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEADERSHIP GROUP:</strong></td>
<td></td>
</tr>
<tr>
<td>Ruzan Avetisyan, PhD, MD, Global Evidence and Value Development Department, Genzyme / Sanofi, Belmont, MA, USA</td>
<td></td>
</tr>
<tr>
<td>Robert Babela, PhD, MSc, Head of Department of Public Health / HM St. Elizabeth University, Bratislava, Slovakia</td>
<td></td>
</tr>
<tr>
<td>Bryan Bennett, PhD, BSc, Senior Outcomes Researcher, Oxford Outcomes, Oxford, UK</td>
<td></td>
</tr>
<tr>
<td>Jacqueline Bowman-Busato, Executive Director, EPPOSI, Brussels, Belgium</td>
<td></td>
</tr>
<tr>
<td>Annie Chicoye, PhD, Development Vice-President, Health Management Institute, ESSEC Business School, Paris, France</td>
<td></td>
</tr>
<tr>
<td>Melike Deger, MSc, Senior Manager, Fresenius Biotech GmbH, Munich, Germany</td>
<td></td>
</tr>
<tr>
<td>Meg Franklin, PharmD, PhD, Associate Professor of Pharmacy Administration, Department of Pharmaceutical and Administrative Sciences, Presbyterian College School of Pharmacy, Clinton, SC, USA</td>
<td></td>
</tr>
<tr>
<td>Vivian Herrera, Director, Global Evidence and Value Development, Rare Diseases &amp; MS, Sanofi US, Bridgewater, NJ, USA</td>
<td></td>
</tr>
<tr>
<td>Zoltán Kaló, PhD, MD, MSc, Director, Health Economics Research Centre, Faculty of Social Sciences, Eötvös Loránd University (ELTE), Budapest, Hungary</td>
<td></td>
</tr>
<tr>
<td>Katarzyna Kolasa, MSc, Market Access Associate Director, Biogen Idec, Zug, Switzerland</td>
<td></td>
</tr>
<tr>
<td>Yasufumi Kuroda, PhD, Manager, Daiichi Sankyo Pharma Development, Edison, NJ, USA</td>
<td></td>
</tr>
<tr>
<td>Zhimei (Jamae) Liu, PhD, Director, Oncology US Health Economics &amp; Outcomes Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA</td>
<td></td>
</tr>
<tr>
<td>Sandra Milev, MSc, Health Economist, Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, Canada</td>
<td></td>
</tr>
<tr>
<td>Sandra Nestler-Parr, PhD, Mphil, Director, Market Access &amp; Reimbursement, Advocate Consulting, London, UK</td>
<td></td>
</tr>
<tr>
<td>Chris Pashos, PhD, Vice President, United BioSource, Lexington, MA, USA</td>
<td></td>
</tr>
<tr>
<td>Trevor Richter PhD, MSc, BSc, Research Manager, Health Economics, Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, ON, Canada</td>
<td></td>
</tr>
<tr>
<td>Phil Ruff PhD, BSc, Director, Global Market Access, Shire HGT, Lexington, MA, USA</td>
<td></td>
</tr>
<tr>
<td>Ruth Suter MBA, RD, Market Access - Pt S, BioMarin, Novato, CA, USA</td>
<td></td>
</tr>
<tr>
<td>Vlad Zah PhD, BSc, Health Economist, ZRx Outcomes Research Inc., Belgrade, Serbia</td>
<td></td>
</tr>
</tbody>
</table>
**BACKGROUND**

- There are many different concepts and terms that describe rare diseases, their treatments and other related health technologies.
- There are national and international differences.
- Definitions themselves vary according to factors besides disease prevalence / incidence.
- Terms & definitions differ according to context:
  - among jurisdictions
  - stakeholders
  - rare disease organizations
  - HTA
  - payers

**METHODOLOGY**

- Select world regions and countries

**COUNTRIES**

- **NORTH AMERICA:** USA & Canada
- **LATIN AMERICA:** Mexico, Brazil, Argentina
- **EUROPE:** UK, France, Sweden, Poland, Hungary, Slovakia, Italy, Germany, the Netherlands
- **ASIA–PACIFIC:** Australia, China, South Korea, Japan
FORUM METHODOLOGY

- Identify agencies / organizations where terms are used

AGENCIES

- Payer - private
- Payer - public
- HTA
- Regulatory - national or regional
- Policy groups focused on rare diseases
- Advocacy (patient) groups for rare diseases
- Specialist RD group(s) or societies of specialist physicians that engage in RD research, develop treatment guidelines
- Other – does not fit into the above categories

RARE DISEASE TERMINOLOGY & DEFINITIONS USED IN OUTCOMES RESEARCH WORKING GROUP

METHODOLOGY

Conduct systematic review of terms

TERMS RELATED TO RARE DISEASE
17 terms that we identified for research

- Rare disease(s)
- Rare disorder(s)
- Rare condition(s)
- Neglected disease(s)
- Orphan disease(s)
- Orphan subset
- Syndrome(s) without a name
- Rare and neglected disease(s)
- Undiagnosed disease(s)
- Ultra-orphan disease(s)
- Ultra-rare disease(s)/disorder(s)
- Very rare disease
- Rare disease therapy(ies)
- Orphan drug(s)
- Orphan medicinal product(s)
- Orphan product(s)
- Ultra-orphan drug(s)
- Other
FORUM

RARE DISEASE TERMINOLOGY & DEFINITIONS USED IN OUTCOMES RESEARCH WORKING GROUP

METHODOLOGY

- Share learning, synthesize information, and develop full dataset
- Analyze data
- Develop manuscript and submit to *Value In Health*

INITIAL FINDINGS

22 definitions for 6 terms from 13 countries (regions)

- Orphan disease(s)
- Orphan drug(s)
- Rare disease(s)
- Highly specialised technologies
- Ultra-orphan drug(s)
- Orphan medicinal product(s)
FORUM

EXAMPLES

EUROPEAN MEDICINES AGENCY (EMA)
“ORPHAN MEDICINAL PRODUCT”

Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 thousand persons

Without incentives it is unlikely that the marketing would generate sufficient return to justify the necessary investment.

No satisfactory alternative has been authorised or, that the medicinal product will be of significant benefit to those affected by that condition.

FORUM

EXAMPLES

FOOD AND DRUG ADMINISTRATION (FDA)
“ORPHAN DRUGS”

To treat any rare disease or condition which:

Affects less than 200,000 persons in the United States,

or

Affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug.
IMPLICATIONS

DIFFERENCES IN LEGAL FRAMEWORK AND INCENTIVES
- Market exclusivity
- Protocol assistance (scientific advice for orphan products)
- Fee reductions (fee waivers for orphan designation and reduced fees)
- Funded research (programs)

IMPACT ON PATIENTS
- Could impede development, or preferentially make treatments (un)available in one country sooner than in another

NEXT STEPS

COMPLETE THE REVIEW

DRAFT MANUSCRIPT FOR VALUE IN HEALTH WHICH WILL:
- Identify the terms that are commonly accepted versus those that are considered contentious
- Identify where there is consensus and where there is not
- Explore issues around the similarities and differences in stakeholder definitions
- Draft recommendations that might include best approaches to international harmonisation
RARE DISEASE TERMINOLOGY & DEFINITIONS USED IN OUTCOMES RESEARCH WORKING GROUP

FORUM TIMELINE

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare Disease Meeting in Berlin</td>
<td>November 2012</td>
</tr>
<tr>
<td>RD SIG meeting 18th Annual ISPOR International Meeting New Orleans</td>
<td>May 21, 2013</td>
</tr>
<tr>
<td>T &amp; D Kick Off TC</td>
<td>July 29, 2013</td>
</tr>
<tr>
<td>Gather sources, develop research methodology, select countries</td>
<td>August – October 2013</td>
</tr>
<tr>
<td>RD SIG Forum ISPOR 16th Annual European Congress Dublin</td>
<td>November 5, 2013</td>
</tr>
<tr>
<td>Country research completed</td>
<td>December 2013</td>
</tr>
<tr>
<td>TC to discuss findings and plan manuscript development</td>
<td>December 2013</td>
</tr>
<tr>
<td>Development of the draft manuscript</td>
<td>January – February 2014</td>
</tr>
<tr>
<td>Draft circulated to RD SIG Review Group</td>
<td>March 2014</td>
</tr>
<tr>
<td>Finalize manuscript</td>
<td>April 2014</td>
</tr>
<tr>
<td>Final review by RD SIG Review Group</td>
<td>May 5-14, 2014</td>
</tr>
<tr>
<td>RD SIG Forum presentation of draft manuscript at ISPOR Montreal</td>
<td>June 2 or 3, 2014</td>
</tr>
<tr>
<td>Final paper submitted to <em>Value in Health</em></td>
<td>July 2014</td>
</tr>
</tbody>
</table>

CHALLENGES IN ASSESSING AND APPRAISING RARE DISEASE DIAGNOSTICS & TREATMENTS WORKING GROUP

CO-CHAIRS

Mondher Toumi, MD, MSc, PhD
Professor & Chair of Decision Sciences, Department of Public Health and Market Access, University Claude Bernard Lyon I, Lyon, France

Chris Pashos, PhD
Vice President, United BioSource Corporation, Lexington, MA, USA
GOAL

To catalogue key challenges confronted while evaluating diagnostic and therapeutic modalities for rare diseases.

LEADERSHIP GROUP:

Joe Biskupiak, PhD, MBA, Professor, College of Pharmacy, University of Utah, SLC, UT, USA
Christopher Blanchette, PhD, MS, MA, Research Associate Professor, Department of Public Health Sciences, University of North Carolina – Charlotte, Charlotte, NC, USA
Jacqueline Bowman-Busato, Executive Director, EPPOSI, Brussels, Belgium
Ruediger Gatermann, MA, MBA, Director Public Affairs Europe, CSL Behring, Biotherapies for Life, Marburg, Germany
Dyfrig Hughes, PhD, MSc, Professor, Centre for Health Economics and Medicines Evaluation, Bangor University, Wales, UK
Mohit Jain, MBA, PhD, Market Access & Public Policy, BioMarin, London, UK
Zoltán Kaló, PhD, MD, MSc, Director, Health Economics Research Centre, Faculty of Social Sciences, Eötvös Loránd University (ELTE), Budapest, Hungary
Katarzyna Kolasa, MSc, Health Economics Manager, Biogen Idec, Zug, Switzerland
Zhimei (Jamae) Liu, PhD, Director, Oncology, US Health Economics & Outcomes Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
Matthew Magestro, Global Rare Diseases Health Economics & Market Access Team Leader, Novartis Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
Rare Diseases: Challenges in Assessment and Appraisal of Diagnostics & Treatments

OUTLINE

I. Introduction and background: what, why, for whom
II. Overview of challenges to be addressed
III. Research-related challenges
IV. HTA / Appraisal-related challenges
V. Global overarching challenges
VI. Conclusions
RESEARCH-RELATED CHALLENGES

- Special difficulties in rare disease research-related research and development – beginning early in the process with candidate selection – to show the burden of disease, and the safety and efficacy of new diagnostic tests and treatments

- Challenges in developing new diagnostics and treatment, generating appropriate evidence for assessing their value, and making the evidence available for HTA and payer review

- Identifying patients for study – rarity-related challenges
- Heterogeneity of both disease and disease course
- Lack of diagnostic capability
- Severity of disease
- Legal and ethical challenges
- Geographic dispersal of population
- Lack of guidance related to RD-specific research methods
- Lack of treatment options and treatment guidelines
- Challenge of rapidly evolving knowledge base
- Difficulty of evaluating treatment effect
- Obstacles in evaluating patient-relevant outcomes
- Others?
HTA / APPRAISAL-RELATED CHALLENGES

- 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
- As a consequence, inequity across and within region affects access to OR.

HTA BENEFIT ASSESSMENT CHALLENGES

- Some studies suggest that society preference does not support funding of rare disease.
- However, policies clearly support the society willingness to make available to patients treatment for rare diseases.
- Although, clear incentives are available, as well as some regulatory guidelines, very little does exist for OD-specific HTA decision framework.
- HTA of OD does face multiple challenges, which are undertaken on a case-by-case basis with no systematic process leading to heterogeneous decisions.
PRICING AND REIMBURSEMENT CHALLENGES

• Valuing benefit for OD through HTA is already a challenge.
• However, moving from benefit to price is even more complex and a controversial matter.
• External reference pricing and heterogeneity in rewarding benefit lead to multiple distortions in OD prices.
• OD prices are commonly associated with:
  - hidden payback
  - coverage with evidence development
  - market access agreement
  - other

WIDE PATIENT ACCESS TO OD IS A LEGITIMATE OBJECTIVE

• While affordability is a major obstacle, two major challenges to overcome before being able to achieve patient access:
  - appreciating the benefit and
  - setting a fair price

IDENTIFYING THOSE CHALLENGES IS A CRITICAL ISSUE.
CONCLUSION

- Major project potentially impacting a very large group of patients poorly or not serviced today
- Before addressing the challenges:
  - Agreeing on common vocabulary
  - Identifying, understanding and putting in perspective the challenges are key steps for success

Thanks to the Leadership Group for contributing and to the exceptional support of the ISPOR Staff Liaisons, we are moving in the right direction.

TIMELINE

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare Disease Meeting in Berlin</td>
<td>November 2012</td>
</tr>
<tr>
<td>RD SIG meeting 18th Annual ISPOR International Meeting New Orleans</td>
<td>May 21, 2013</td>
</tr>
<tr>
<td>Challenges Kick Off TC</td>
<td>July 29, 2013</td>
</tr>
<tr>
<td>Challenges identified, outline developed</td>
<td>August - September 2013</td>
</tr>
<tr>
<td>RD SIG Forum at ISPOR 16th Annual European Congress in Dublin</td>
<td>November 5, 2013</td>
</tr>
<tr>
<td>Development of sections into the draft manuscript</td>
<td>November 2013-January 2014</td>
</tr>
<tr>
<td>Draft Paper sent to RD SIG Review Group</td>
<td>February 2014</td>
</tr>
<tr>
<td>Revision of manuscript based on comments</td>
<td>March 2014</td>
</tr>
<tr>
<td>Final review by RD SIG Review Group</td>
<td>April 2014</td>
</tr>
<tr>
<td>Finalize manuscript for submission</td>
<td>April 2013</td>
</tr>
<tr>
<td>Final paper submitted to Value in Health</td>
<td>May 2014</td>
</tr>
<tr>
<td>RD SIG Forum presentation of draft manuscript ISPOR Montreal</td>
<td>June 2 or 3, 2014</td>
</tr>
</tbody>
</table>
If you would like to join the Rare Disease SIG, either email Theresa (ttesoro@ispor.org) or go to www.ispor.org and click on the GREEN Interest Group menu at top of the homepage. Select “JOIN” on pull-down menu.

Q & A
QUESTIONS FOR DISCUSSION

- Given the global nature of our work, how have you addressed the definition of rare diseases globally?
- What are other research-related challenges?
- What are some obstacles that you have faced in the rare disease area?
- How have you dealt with patient recruitment in rare disease clinical trials?
- How did you evaluate patient-relevant outcomes?
- What are some lessons you have learned regarding pricing and reimbursement in rare diseases?
- How have you leveraged patient advocacy organizations to support rare disease initiatives, research, development, and patient access?