ISPOR TASK FORCES

Clinical Outcomes Assessment Measurement in Rare Disease Clinical Trials – Emerging Good Practices Task Force

Speaker

Katy Benjamin, PhD
Director, Patient Reported Outcomes
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Task Force Leadership Group

- **Katy Benjamin, PhD, SM**, Director, Patient-Reported Outcomes, **ICON Commercialisation and Outcomes** Bethesda MD USA **(Co-chair)**
- **Margaret K. Vernon, PhD**, EU Director and Senior Research Scientist, Evidera London, England UK **(Co-chair)**
- **Laurie Burke, RPh, MPH,** Founder, LORA Group LLC Royal Oak MD USA
- **Eleanor Perfetto, PhD, MS,** Professor, Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore MD USA
- **Donald L Patrick, PhD, MSPH,** Professor and Director, Seattle Quality of Life Group University of Washington Seattle WA USA

Task Force Leadership Group

- **Anne Pariser, MD,** Associate Director for Rare Diseases, Office of New Drugs, CDER, Food & Drug Administration (FDA),
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- **Luis Rajmil, MD, PhD, MPH**, Senior Researcher, Catalan Agency for Health Technology Assessment & Research (CAHTA), & Collaborator, Health Services Research Unit, Municipal Institute of Medical Research (IMIM-Hospital del Mar) and CIBER en Epidemiologia y Salud Pública, (CIBERESP), Barcelona, Spain

Rare Diseases: An Introduction

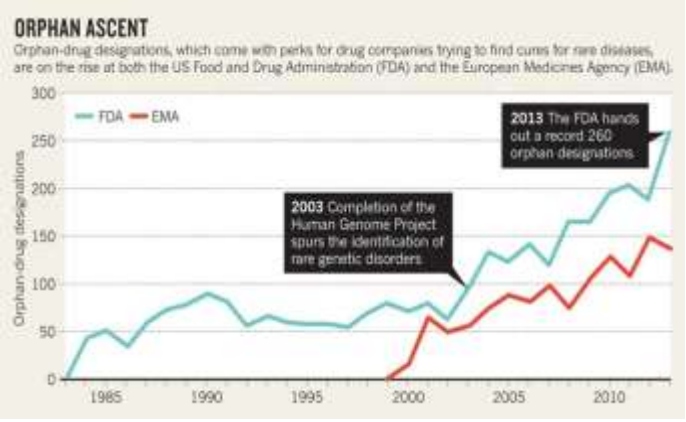
- About 7,000 distinct rare diseases recognized today
- The majority (about 80%) have a genetic etiology
- Approximately 50% affect children
- Most are chronic, many are progressive
- 30% of patients die before their 5th birthday
- About 4000 with known molecular diagnosis
- BUT ~ 350 have identified treatments

Rare disease treatment development landscape

❖ **A "deluge" of new discoveries for potential targets**

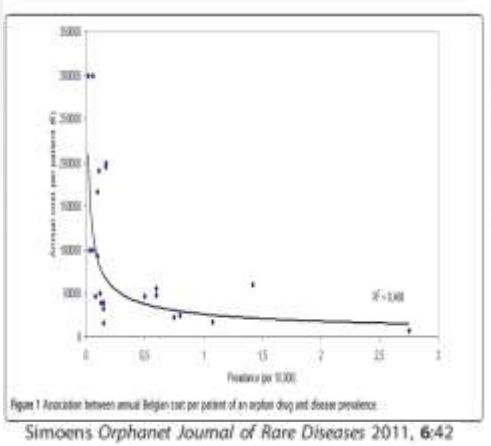
- Advances in genomic science
- Increasing by ~100 new diseases/year
- Common diseases being divided into medically plausible subsets
- As of 2011, approximately 460 products in development or submitted for approval
- An average of 5 new rare conditions described in the literature per week
- Orphan drug market estimated at $50m USD in 2011, a 25% increase in past decade
- Increasing number of major pharmaceutical companies developing drugs for orphan conditions

The growth of orphan drugs



Source: *Nature* Volume: 508, Pages: 16–17 03 April 2014

Rare Disease Treatment Costs



Simoens *Orphanet Journal of Rare Diseases* 2011, **6**:42

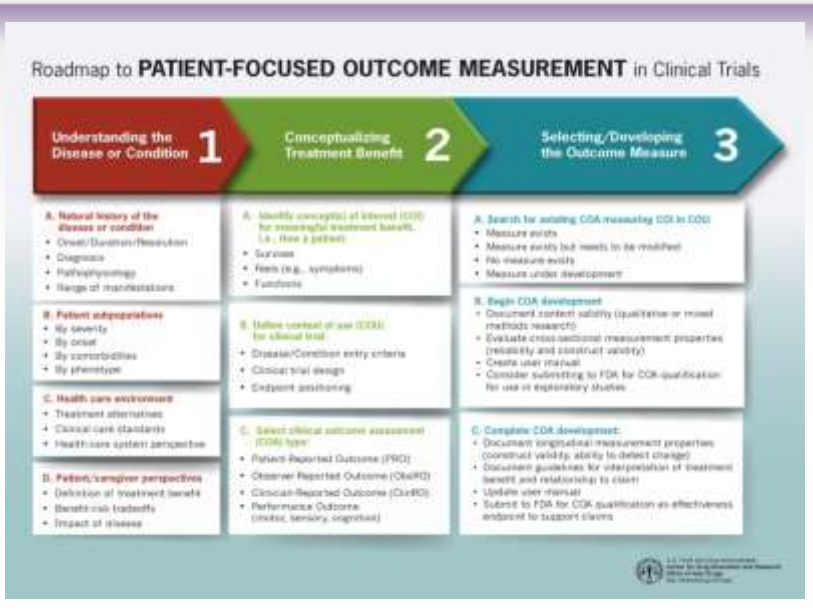
- Average US pp/py drug cost, orphan drugs: $137,782 (€127,974)[a]
- Average US annual pp/py drug cost, non-orphan drugs: $20,875 (€ 19,392)[a]
- 44% of orphan drugs cost an average of
- € 200,000 pp/py[b]
- Expected to be approximately16% of all Rx drug sales by 2018[c]

Sources: a. Picavet et al. Orphanet J Rare Dis.2014;9:62. b. Rollett et al. Orphanet J Rare Dis.2013;8:109 c. EvaluatePharma Orphan Drug Report 2014

Task Force Objective

To develop emerging good practices for outcomes research on measuring COAs in rare disease clinical trials

Organization of Report



Please Note!

- Each RD drug-development program presents different challenges for selecting, developing and implementing COAs.
- No one solution can address diverse challenges in implementing COAs and developing evidence to support their use for clinical trial COUs.
- The report outlines recommendations for *possible* solutions to address common obstacles.

Please Note!

- These same challenges may also be present for non-rare conditions, BUT…
  - They tend to be magnified in RDs due to the small size of patient populations.
  - Rare diseases frequently have highly heterogeneous populations.

Speaker

Eleanor Perfetto, PhD, MS
Professor, Pharmaceutical Health Services Research
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COLUMN 1: CHALLENGES AND SOLUTIONS IN UNDERSTANDING THE DISEASE OR CONDITION

Challenge 1: Incomplete Understanding of the Rare Disease

- Generally, the natural history is poorly or incompletely understood.
- Treatment benefit is not readily defined.

Suggested Solutions:

- Use all available sources of data - will likely need non-traditional approaches.
- Engage the rare-disease community – Partner with patients, patient advocacy groups, to obtain information, design studies, recruit patients, etc.
- Engage the experts.

Challenge 2: Difficulty Distinguishing Rare Disease Signs and Symptoms

- Difficult to distinguish between RD-specific clinical signs and symptoms from iatrogenic clinical characteristics:
  - Early misdiagnosis
  - Consequences from inappropriate (or appropriate) treatments.

Suggested Solutions:

- Focus on core symptoms and impacts.
- Select well-defined signs and symptoms based upon the product' s expected treatment effect in the context of use (COU).

Challenge 3: Difficulties in Diagnosis

- Often delayed, diagnostic testing not always available.
- Often enter treatment at different stages in the trajectory.
- RD-specific versus iatrogenic issues

Suggested Solutions:

- Collect data on treatment history
- Focus on core symptoms and impacts
- Consider a treatment's (hypothesized) effects per the context of use (COU).
- Conduct concept-elicitation interviews with patients/caregivers/clinicians to understand disease experience over time
- Understand timeframe from first disease symptoms to diagnosis

Challenge 4: Diversity in Disease Presentation and Patient Experience

- Heterogeneity (e.g., phenotypic diversity)
- Time to diagnosis, diagnosis at specific points in progression
- Symptom and clinical presentation diversity due to other factors

Suggested Solutions:

- Identify the common outcomes associated across phenotypes/diversity of disease presentation
  - Definitive, prevalent characteristics and concepts expected to change with treatment
- Engage clinical experts to understand geographic differences in patient and treatment characteristics

Challenge 5: Variation in Access to Appropriate Medical Care

- Access issues magnified (e.g., regional differences in clinical expertise, public health policies, variations in care, and regulatory and reimbursement processes)

Suggested Solutions:

- Understand variations in local practice
- Work with local patients and patient-advocacy organizations to identify treatment patterns
- Define the patient experience throughout the trajectory

Challenge 6: Complexity in Capturing Perspectives

- Delay in diagnosis or misdiagnosis; subsequent lack of care; restricted/limited access to treatments
- Erosion of patient/caregiver confidence in care
- Lack of educational resources for patients/caregivers
- Inability to accurately assess treatment benefits/risks

Suggested Solutions:

- Conduct concept elicitation interviews in a range of patients/caregivers/clinicians
- Identify common themes as a basis for the PRO strategy

Possible Information Sources

- *Patient/ Caregiver Interview*
- *Patient Advocacy Groups*
- *Expert Clinician Interviews*
- *Claims Data*
- *Medical records*
- *Clinical Trial Data*
- *Post- hoc Analysis of RCT Data*
- *Observational Studies*
- *Registries*
- *Local Policies & Regulations*
- *Simulations & modeling*

Speaker

Laurie Burke
Founder, LORA Group, LLC, and
Affiliate Associate Professor,
University of Maryland School of Pharmacy

Column 2: Conceptualizing Treatment Benefit

Define the Future Study Context

Taking all data gathered in preparation for study planning (Column 1):

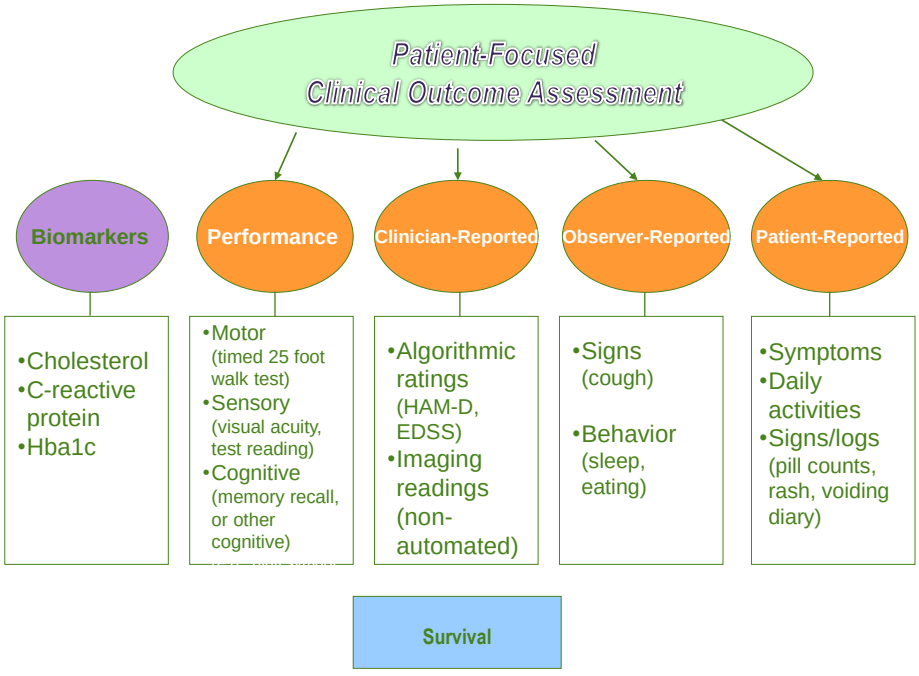
- Start with a well-characterized, specific disease definition
  - Based on the natural history of the disease
- Define enrollment population
  - Identify the optimal balance between population representativeness and homogeneity to support interpretation of results
- Identify the geographical regions, languages, and cultures to be studied
  - Group patients by similar treatment patterns across regions

Identify the Concept(s) of Interest for Meaningful Treatment Benefit

- Focus on measureable core signs, symptoms, and impacts on daily activities
  - Identify additional measures that support interpretability of results
  - Modify concept(s) of interest with initial qualitative research
- Compare study context with concept(s) of interest and make adjustments to each
  - What is meaningful treatment benefit for each targeted patient subgroup?
  - Define patient selection criteria to exclude diseases with overlapping signs, symptoms, and daily activity impacts, if possible

Finalize the study plan

- Determine hierarchy of study objectives
  - Primary concept of interest
  - Secondary concept of interest
  - Exploratory concept of interest
- Define the endpoints
  - How will the scores representing each concept of interest be analyzed statistically?
- Identify the appropriate measure type



Speaker

Donald L Patrick, PhD, MSPH
Professor and Director, Seattle Quality of Life Group
University of Washington

Roadmap Column 3: Challenges & Solutions
Selecting or Developing Outcome Measure

- Selecting an Existing Measure
  - Use as existing or modify?
- Developing a new measure
  - Cultural adaptation and translation
  - Qualitative Research –concept elicitation
  - Validity testing
  - Psychometric evaluation including test-retest, inter-rater reliability and longitudinal assessment\interpretation
- Heterogeneity impacts ability to measure across disease spectrum with small samples

Selecting or Modifying Existing Measure

- Use previously-validated measures when possible--
  - Easy to say, hard to do
  - Keep columns 1 and 2 (COU) in mind
- Adapt measure from similar rare disease using qualitative and quantitative methods
- Risk of not conducting full assessment of concepts and measurement properties
- Consider including generic or domain-specific instruments if sensitive enough to treatment

Heterogeneity impacting ability to measure across disease spectrum

- Consider use of multi-concept instrument or battery customized to symptom profile with skip patterns
- Computer adaptive test batteries
- Individualized measures
- Use ObsRO measure and PRO measure in parallel when necessary

Developing a New Measure

- Standard methods may not be feasible because of small sample sizes
- Limited access to patients/caregivers/clinicians for validation and other studies
- Use small samples in concept elicitation
- Use clinic visits if at all possible
- Telephone and internet methods
- Cultural adaptation may need to be examined in smaller samples

Validity and Psychometric Testing

- Use continuous variables
- Use sensitivity analyses
- Non-parametric statistics when sample size and distributions require
- Select criteria for stable patients carefully and confirm with clinicians

Questions?