MEASURING PATIENT AND OBSERVER-REPORTED OUTCOMES (PROS AND OBSROS) IN RARE DISEASE CLINICAL TRIALS - EMERGING GOOD PRACTICES TASK FORCE

Outline

I. Introduction: Current environment of clinical research for RD and the role of PRO and ObsRO endpoints in rare disease populations

II. Challenges to PRO/ObsRO research in rare disease populations, e.g.,
   A. Small populations that may limit the opportunity for study and replication
      1. May not allow for subgroup analysis in clinical trials
   B. Patients dispersed among many different geographical and multinational areas
   C. Poorly or incompletely understood conditions (e.g., major or important morbidities associated with condition; time course of clinical manifestations, including mortality; phenotype/genotype considerations, age range, full spectrum of disease description); difficulty with and/or delayed diagnosis,
   D. Highly diverse collection of disorders; clinical heterogeneity within individual disorders
   E. Vulnerable populations (children, cognitively impaired, physical disability)
   F. Lack of established, fit-for-purpose endpoints, outcome measures, tools, instruments, biomarkers to evaluate RD treatment efficacy
   G. Lack of RD knowledge and limited number of clinicians and clinical centers with expertise in the individual disorders
   H. Unmet medical needs; lack of targeted treatments; lack of standard of care/best practices for individual disorders
   I. Ability to meet regulatory standards for evidence of validity, reliability, ability to detect change, and levels of clinically meaningful response given the limitations and differences in RD patient populations and treatment patterns.

While there are considerable challenges to implementing PROs and other COAs in clinical trials for rare disease indications, there are suggested solutions and
methodological innovations that could be used to frame the task force recommendations (Leidy 2011; Benjamin 2013). See, for example, Tables 1 - 3.

III. Methods of choosing or developing a PRO or ObsRO measure for RD clinical trials
   A. There are established guidances and methods for selecting or developing a PRO or ObsRO measures (see Figures 1 and 2 for specification of these processes).
      1. May not have sufficient information to enable comprehensive definition of population, context or use or conceptual framework, as per Challenges (section II).
   B. Defining clinical trial context of use in RD populations
      1. Disease definition
         a. Many RDs not recognized by community practitioners due to rarity; patients may be misdiagnosed and treated.
         b. Need to define disease characteristics, especially variations in:
            i. Within and between - patient severity of disease
            ii. Disease presentation
            iii. Disease duration
            iv. Clinical course over time
            v. Clinical (treatment) History
         c. Disease subtype(s)
            i. May not be completely known or described in RDs
            ii. Variations due to other factors (comorbidities, iatrogenic conditions, cultural and country-specific differences in treatment or access to care) may not be clearly differentiated from RD subtypes
   C. Patient subpopulations
      1. Clinical characteristics
      2. May be difficult to distinguish between RD specific clinical signs and symptoms and iatrogenic clinical characteristics due to inaccurate diagnosis and inappropriate treatments.
      3. May vary between regions due to lack of gold standard therapies for many RDs and country- or region-specific variations in market approval and reimbursement for RD treatments. Treatments may also vary based
upon local practice patterns, regional access to clinical experts, as well as cultural variations in the understanding and management of disease.

D. Patient demographics (e.g., age groups)
   1. Different demographic groups may have different disease risk and clinical course or symptoms due to genetic subtypes (see, for example, Giraldo et al. 2012)

E. Culture and language
   1. Small patient populations and lack of RD experts and treatment centers in all countries frequently necessitates inclusion of patients from several regions or countries.
   2. Variations in access to treatments and patterns of medical care may exist for different countries or regions
   3. Meaning and awareness of specific RDs not always well-understood across all regions; cultural validation and equivalence evaluation of PROs will often be needed.
   4. Many patients may travel to other regions for treatment due to the dearth of clinical experts and dedicated treatment facilities for their condition in their country of origin. This may affect the timing as well as the linguistic and cultural validity of PRO endpoints.

IV. Clinical trial designs and objectives for RD outcomes research
   A. Many RD drugs fast-tracked due to severity of indication and lack of good treatment options.
   B. Traditional clinical trials program with separate (and large) patient populations for each study phase not feasible for most RDs.
   C. Increased regulatory emphasis on alternative approaches to studying drugs with RD indications, including consideration of non-traditional clinical development programs, study designs, endpoints, and statistical analysis (Hamburg 2011).

V. Study design
   A. Need to modify PRO development, validation, data collection methods for:
      1. Use in innovative study designs (e.g., adaptive trials, cross over trials, seamless adaptive trials, sample size re-estimation studies) (Orloff et al. 2009).
2. Challenges due to small populations plus disease heterogeneity

B. Successful endpoints evidence of efficacy in RD clinical trials must demonstrate that they are reliable, meaningful, well-defined and “fit for purpose” (Lesko 2011).
   1. Assess most proximal outcomes possible to ensure optimal interpretation of PRO endpoint results.
   2. Efficacy of treatment for progressive diseases may be difficult to assess without thorough understanding of natural history

C. Use as much information as is available – results from simulation and modeling studies to understand disease processes and pathways, time to and duration of response, proof of concept studies; dose-finding and safety evaluations.

D. Take advantage of available registries, early clinical studies and natural history studies to develop PRO concepts, measures and strategies.

E. Consider use of non-equivalent or non-concurrent control or comparison groups

F. Small size of patient population may necessitate inclusion of range of age groups in single study.

G. Methods for interpretation of study results: Where possible, evaluate response and MID using changes in biomarkers where proof of concept efficacy is established.
   1. Surrogate endpoints frequently used in RD studies due to lack of clear clinical indicators of efficacy (Bruzzi 2009). Their relationship to COAs may not be well understood, making interpretation difficult.

VI. Choosing or adapting an existing PRO measure, by context of use

A. Use already-developed and validated measures where possible.

B. Follow recommendations of the ISPOR Patient-Reported Outcomes (PRO) Task Force on Use of Existing Instruments and their Modification (Rothman et al., 2009) for adapting existing measures.

C. Consider signs, symptoms and common impacts on daily activities to support evaluation of treatment benefit.
   1. Focus on core symptoms and impacts of the RD that can be measured across a range of ages and severities of disease (Papadopoulos 2012).

D. May need to adapt measures of treatment benefit to different age groups and severities of illness due to small size of patient population that necessitates
enrolling a wider range of patients than is standard in trials of non-rate
conditions.

E. May need to develop or adapt measures for completion by different respondents
   in same study, e.g.,
   1. PRO format for adults/those with milder disease who able to respond
      independently, ObsRO format for young children, those with more
      severe/progressive disease.
   2. In longitudinal studies, it may be necessary to administer measures in
      different formats as patients with progressive disease worsen over time,
      or as children age and become able to independently complete a PRO.

F. Refer to the Report of the ISPOR PRO Good Research Practices for the
   Assessment of Children and Adolescents Task Force report on Pediatric Patient-
   Reported Outcome Instruments for Research to Support Medical Product
   Labeling for guidance on measuring PROs and ObsROs in pediatric patients
   (Matza et al. 2013). These methods may also be helpful in framing
   recommendations for use of these measures in disabled or cognitively impaired
   patients.

G. Developing a new PRO Measure for use in RD Clinical Trials [Figure 2]
   Alternative study designs for validating PRO measures in small patient
   populations
   1. Insufficient patient population to allow for separate instrument
      validation study sample.
   2. If appropriate, consider validating on patients with similar conditions or
      clinical characteristics to those evaluated in the clinical trial (e.g.,
      including patients with both Fabry’s Disease and Gaucher’s disease in
      instrument validation study, or patients with condition of interest who
      are ineligible or don’t wish to participate in the clinical trial for reasons
      unrelated to clinical characteristics)

H. Evaluation of instrument validity and reliability in small, geographically and
   clinically diverse samples
   1. There may be few publications in the scientific literature to assist in
      identification of important concepts.
   2. Few clinical experts in many RDs to provide clinician perspective.
3. Standard statistical tests may be underpowered; work with regulators to achieve optimal SAP given constraints

I. Work with patient advocacy organizations to identify appropriate representatives who can provide direct experiences regarding RD symptoms and impacts – may include caregivers, family members, etc. as well as (or instead of) patients and clinicians. May need to go through sponsor patient liaison to successfully contact patient advocacy organizations.

J. In addition to the challenges to evaluating statistical associations in small populations, there are concerns regarding the assumptions driving the hypothesized associations. For example, the heterogeneity of many RDs may confound the association between age and functional status if patient subgroups have not been completely defined.

K. Test-retest reliability
   1. Estimation of appropriate time intervals between tests may be challenging due to external factors such as long duration between visits to far away clinics or variations in availability of treatments for acute symptom exacerbations

L. Inter-rater reliability
   1. May be especially challenging when validating ClinROs due to scarcity of clinical experts.
   2. Dispersion of patients over wide geographic area may make training and standardization of observation for more than one caregiver or other non-clinical observer difficult.

M. Longitudinal psychometric analysis
   1. Stable disease difficult to recognize in some RDs due to lack of well-defined natural history and incomplete understanding of rate of progression of the condition.
   2. Ability to detect change may be compromised due to heterogeneity of the disorder, small sample sizes.

VII. Presenting the results in a format useful for the decision maker
   A. Work with stakeholders to identify different information needs.
   B. Variety of levels of experience, knowledge and comprehension both within and between different stakeholder groups.
C. Patients and patient advocacy groups key to acceptance of measures and outcomes.

VIII. Conclusion