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RARE DISEASE WORKSHOP SERIES
Improving the *Clinical Development Process*

Development of Rare Disease Evaluation Tools

Alison Skrinar
Senior Director, Clinical Research & Regulatory Affairs
Enobia Pharma



Presentation Overview

- Define burden of illness
- Outline potential uses for this data
- Provide rationale for instrument development in rare diseases
- Review development/validation process for PROs
- Present challenges to development, validation and interpretation of data
- Provide examples of instruments developed for rare disease
- Discuss path forward



What is Burden of Illness?

- The **PERSONAL** cost of acute or chronic disease
- May be an economic, social, or psychological cost or personal loss to self, family, or immediate community
 - Absenteeism
 - Loss of productivity
 - Caregiver dependence
 - Quality of life
 - Disability
 - Pain



Why Collect Burden of Illness Data?

- Increase disease awareness
- Facilitate diagnosis earlier in disease course
- Identify patient for clinical trials
- Inform trial design and endpoint selection
- Assist in interpretation of clinical trial results
- Promote multidisciplinary management in a post-marketing setting
- Support reimbursement



How Do You Establish Burden of Illness?

- Quality of life
 - Physical health scores may show significant limitations
 - Mental health scores may not be abnormal if clinical course is slowly progressive
- Resource utilization
 - Many disease-related complications require surgical intervention and the use of medical devices
 - Overall consumption may be low when progression is slow, no treatment options exist and/or care is palliative
- Disability
 - Impact of disease on FUNCTION as described by the PATIENT



What Type of Instrument Do You Need?

Patient-Reported Outcomes

– Advantages:

- Most reliable source of information about the clinical symptoms of a rare disease and the impact of these symptoms on daily function
- Best means of putting a “face to a name”

– Disadvantages:

- Scores affected by compensatory behaviors
- May not be sensitive enough to detect small changes in function in a clinical trial setting
- Long and arduous development and validation process



What Type of Instrument Do You Need?

Performance Measure

– Advantages:

- Better reflection of the physical capabilities of patient
- Increased ability to detect small changes in function in a clinical trial setting
- Easier to interpret findings and put into context for various audiences

– Disadvantages:

- Limits ability to identify the source of the change
- Limited ability to characterize the value of a new therapy for rare disease



Why Not Use Existing Instruments?

- Rare diseases are not well characterized in the literature from a functional perspective
- Clinical manifestations of rare diseases are often unique and multi-systemic
- Substantial inter-relationships among clinical symptoms that can't be captured with a single instrument
 - What CAN'T the patient do?
 - Why CAN'T they do it?
 - Are the reasons the same for different diseases?



How Do You Develop a New Instrument?

- **START EARLY AND START WITH THE PATIENTS!**
 - Natural history studies are critical to establishing the burden of disease
 - Best source of information on diagnosis, clinical presentation, disease progression and disability
 - Heart of clinical trial design
- **FDA Guidance for Industry: PROs**
 - Endpoint model
 - Choice of PRO instrument
 - Conceptual framework
 - Content validity
 - Reliability, other validity and sensitivity to change
 - Instrument modification



Why Aren't More PRO Instruments and Performance Measures used in the Rare Disease Drug Development Process?

- Natural history studies and instrument development are started too late
- FDA Industry Guidance for PROs is difficult to implement in rare disease
 - Small, multinational, clinically heterogeneous patient populations complicate validation process
 - Need for statistical power in clinical trials limits patient selection process
- Is there a way to adjust this process to accommodate rare diseases?



MPS HAQ: Health Assessment Questionnaire

- **10-point Likert Scale**
 - 0 to 10 with higher scores representing greater difficulty performing the basic activities of daily living
- **Self Care Domain and Proficiency Scores**
 - Eating/Drinking
 - Dressing
 - Bathing
 - Grooming
 - Toileting
- **Mobility Domain and Proficiency Scores**
 - Transfers
 - Walking
 - Stairs
- **Caregiver Assistance Domain Score**

n = 17 patient interviews



MPS PPM: Physical Performance Measure

- **Arm function**
 - Simulated eating
 - Fine grasp
 - Instrument use
 - Hand raise
 - Pullover shirt
 - Donning backpack
 - Rolling with arm clearance
 - **Total Arm Performance Score**
- **Leg function**
 - Come to sit
 - Sit to stand
 - Putting on pants
 - Floor to stand
 - Stand to squat
 - **Total Leg Performance Score**
- **Functional endurance/walking efficiency**
 - 3MWT fast pace
 - 3MWT comfortable pace

n = 10 test administrations



MPS PPM References

- Dumas HM, Fragala MA, Haley SM, Skrinar AM, Wraith JE, Cox GF. Physical Performance Testing in Mucopolysaccharidosis I: A Pilot Study. *Pediatric Rehabilitation*, 7(2): 125-131, 2004.
- Haley SM, Fragala-Pinkham MA, Dumas HM, Ni P, Skrinar, AM, Cox GF. A Physical Performance Measure for Individuals with Mucopolysaccharidosis Type I. *Developmental Medicine & Child Neurology*. 48(7):576-81, 2006 Jul.



Pompe PEDI: Pediatric Evaluation of Disability Inventory

- Disease-specific modification of existing questionnaire for the evaluation of pediatric disability
- Items were added to the original PEDI to:
 - Raise the ceiling
 - Lower the floor
 - Add assistive technology items
 - Create smaller skill increments between items to improve scoring precision and potential sensitivity to change
- New items added to mobility and self-care domains
- Reliability and validity testing performed and instrument re-normed

n = 30 telephone surveys



Pompe PEDI

- **Functional Skills Self-Care**
 - Eating/drinking/self-feeding
 - Dressing
 - Bathing/Brushing
 - Nose care
 - Bowel/Bladder and Toileting
 - **Play**
- **Functional Skills Mobility**
 - **Head control**
 - **Prone activities**
 - Sitting skills
 - Floor mobility
 - Transfers
 - Standing/walking/stairs
 - **Gross motor skills**
 - **Device use**
- **Functional Skills Social Function**
 - Language comprehension
 - Expressive communication
 - Problem resolution
 - Social interaction with adults/peers
 - Play
 - Self-identification
 - Time orientation
 - Household chores
 - Self-protection
 - Communication
- **Caregiver Assistance**



Pompe PEDI References

- Haley SM, Fragala MA, Asetine R, Ni P, Skrinar AM. Development of a Disease-specific Disability Instrument for Glycogen Storage Disease II (GSD-II). *Pediatric Rehabilitation* 6(2):77-84, 2003.
- Haley SM, Fragala MA, Skrinar AM. Pompe Disease and Physical Disability. *Developmental Medicine & Child Neurology*, 45:618-623, 2003.
- Haley SM, Fragala MA, Ni P, Skrinar AM, Kaye EM. Pediatric Physical Functioning Reference Curves. *Pediatric Neurology*, 31(5):333-341, 2004.
- Haley SM, Ni P, Fragala MA, Skrinar AM, Corzo D. A Computer Adaptive Testing Approach for Assessing Physical Functioning in Children and Adolescents. *Developmental Medicine & Child Neurology*. 47:113-120, 2005.



HIPS:

Hypophosphatasia Impact Patient Survey

- **Disease history**
 - Presenting symptom
 - Path to diagnosis
 - Progression
- **Medical history**
 - Development
 - Bone/joint
 - Pulmonary
 - Dental/oral
 - Muscle
 - Renal
- **Fracture**
 - Number
 - Timing
 - Location
 - Cause
 - Healing time
- **Surgical history**
 - Hardware placement
- **Medication**
 - Pain management
- **Mobility**
 - Device use

n = 82 online surveys



Discussion