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Development of Rare Disease Evaluation Tools

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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


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


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