Individualized Endpoints in Pediatric Rare Disease Trials: a clinical perspective

Patroula Smpokou, MD, FACMG
Lead Medical Officer/Team Leader
Division of Gastroenterology and Inborn Errors Products (DGIEP)
Office of New Drugs
CDER/ FDA

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Overview

- Defining clinical benefit
- Assessing clinical benefit
- Traditional efficacy endpoints
- Endpoint challenges in pediatric rare disease trials
- Individualized (novel) endpoints
- Example of the use of an individualized endpoint in a pediatric rare disease trial

Defining and Assessing "clinical benefit"

- Clinical benefit = a positive effect on how an individual **feels, functions, or survives ("clinically meaningful")**

- Measured through clinical outcome assessments (COAs):
  - Patient reported outcomes (PROs)
  - Clinician reported outcomes (ClinROs)
  - Observer reported outcomes (ObsROs)
  - Performance outcomes (PerfOs)

- Biomarker assessments do not directly measure clinical benefit and are not generally sufficient for demonstration of effectiveness (clinical benefit)

  Except: surrogate endpoints

  "validated" surrogates for traditional approval vs "reasonably likely" surrogates for accelerated approval

“Traditional” Endpoints

- Symptom(s) or burden(s) specific to the disease and to the population studied
- Evaluated in all patients with the same frequency and using the same COA tool(s) in the trial
- Individual data aggregated to generate group statistics
- Aggregate (group) data compared statistically to comparator group data
- Endpoint hierarchy (order of statistical testing) and additional statistical considerations
- Clinical interpretation of treatment effect(s)
  - clinically meaningful differences vs not
  - based on patient/caregiver input/perspectives
  - Using evidence-based approach

Endpoint Challenges in Pediatric Rare Disease Trials

- Multisystemic, chronic diseases
  - Heterogeneity in the presence, baseline severity, and rate of progression of different symptoms among pediatric patients with the same rare disease
- Children with a rare disease often have the most severe, early-onset manifestations within the disease spectrum
- Insufficient natural history information to guide appropriate endpoint selection and prioritization in a trial
- Pediatric patients may have completely different manifestations of the disease or different severities of the same manifestation at baseline, e.g. primary mitochondrial diseases

“Individualized” (Novel) Endpoints

- Specific to each patient or to group of patients
  - Specific concept or symptom
  - Specific domain of function
- Pre-selected for each patient or set of patients prior to trial initiation
- Most bothersome disease manifestation(s) for individual patient
- Clinical interpretation of changes in this endpoint (definition of clinical “response”) is difficult and should be guided by patient/caregiver input

Defining Clinical "Response"

- Clinical response thresholds/limits
  - Responder definitions
- Lack of strong evidence to support response thresholds in rare diseases
  - Not systematically studied in the disease of interest
  - Too few patients to study (rare disease)
  - "response" may be defined differently by different patients/caregivers
- Does it truly reflect how an individual patient perceives "benefit" from the drug?
- Responder thresholds for COAs vs for domains of function
  - Clinical response in a PerfO: 6MWD
  - Clinical response in a functional domain: muscle weakness

Case example: MPS type VII

- Autosomal recessive disease
  - *GUSB* gene on chromosome 7
- 1 in 345,000-5 million
- Non-immune hydrops fetalis
- Short stature
- Skeletal dysplasia
- Low muscle tone
- Hernias
- Liver and spleen enlargement
- Cognitive disability
- Corneal clouding
- Cardiac valvular disease

Type	Name of the syndrome	Gag accumulated
MPS Type I	Hurler's syndrome/scheie syndrome	Dermatan, heparan sulfate
MPS Type II	Hunter's syndrome	Dermatan, heparan sulfate
MPS Type III	Sanfilippo syndrome	Heparan sulfate
MPS TYPE IV	morquio syndrome	Keratan sulfate, chondriotin sulfate
MPS Type VI	Maroteaux lamy syndrome	Dermatan, chondriotin sulfate
MPS Type VII	Sly syndrome	Dermatan/heparan/ chondriotin sulfate
MPS Type IX	Natowicz syndrome	Hyaluronan

Source: National Organization for Rare Disorders (NORD).[4]
MPS: Mucopolysaccharidosis

Mepsevii for MPS type VII

- Enzyme replacement therapy approved for MPS VII

- Multi-Domain Responder Index (MDRI) used as efficacy endpoint (6 domains):
  - 6-minute walk test (distance walked in meters in 6 minutes)
  - Shoulder flexion as a measure of joint range of motion
  - Forced Vital Capacity (FVC) from pulmonary function testing
  - Visual acuity
  - Fine motor testing
  - Gross motor testing

Mepsevii for MPS type VII

- Domains and COAs assessing each domain not sufficiently explored prior to trial initiation
  - COAs sensitive to change over trial duration?
  - COAs measuring concepts of interest/ major disease burdens?
    - Shoulder flexion was not restricted in MPS VII
- Patients unable to understand and complete many efficacy assessments (FVC, fine and gross motor testing)
  - baseline cognitive disability compromised ability to collect informative data
  - large amount of missing data
- Selected domain response thresholds not based on natural history data in the patient population
- <u>Eventual efficacy evaluation mainly based on single functional domain (6MWD) and not on MDRI</u>

Summary

- Drug approval in pediatric rare disease trials is based on demonstration that a drug impacts how patients feel or function (clinical benefit), assessed through different COAs
- Special endpoint considerations in pediatric rare disease trials
  - Heterogeneous manifestations and severity of symptoms at baseline
  - Insufficient natural history of untreated disease to inform endpoint selection, COA selection
- Use of responder thresholds to define clinical benefit in individual patients should be based on solid evidence within the population of interest
- Defining clinical "response" in pediatric rare disease trials is challenging and should be guided by patient/caregiver input and solid knowledge of the disease natural history
- Mepsevii program for MPS VII (pediatric rare disease)
  - MDRI composed of 6 different functional domains
  - Large amount of missing data compromised data interpretation for all domains assessed: poor selection of certain COA instruments, population's inability to understand instructions to perform COAs
  - Regulatory decision ultimately based on a "traditional endpoint" (walking ability; 6MWD) and not on a proposed "novel" endpoint (MDRI), which had several limitations


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