Considerations for Endpoint Selection in Rare Disease Trials

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Endpoint Development and Strategy

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Special Challenges in the Study of Rare Diseases

- Multiple domains affected in a rare disease

- May not be a single domain that has biggest impact for all patients/caregivers
  - Interviews with clinicians and patients/caregivers essential to identify the unmet medical need

- Even within a domain of interest, one measure may not work for all patients

- Pilot testing potential measures on a small set of patients is critical to assess feasibility
  - Try different measures to find the right subset
  - Goal is to find 1-2 measures per domain that most patients can do reliably
  - Use data to support your choice at regulatory meetings

- For ultra-rare, it may be necessary to try several tests to identify the best one(s) for each patient
  - Important to avoid missing and uninterpretable data
  - Each patient may need their own control
  - Medical records documenting developmental and/or disease progression are critical

Clinical Outcomes Assessments (COAs)

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment.

There are four types of COAs

Clinician-reported outcome (Global Impression of Severity)	Observer-reported outcome (Caregiver report Vineland, ABC-C)	Patient-reported outcome (Pain, Fatigue)	Performance outcome (6-Minute Walk Test)

Novel Disease-Specific Measure vs. Existing Validated Measure

- Regulatory support exists for development of novel disease-specific measures of impact, progression and post-treatment change
    - FDA guidance document outlines steps required for development and validation of novel measure
        - Significant cost and time required to follow guidance
        - External expertise typically needed to perform qualitative and psychometric work
    - COA Qualification Process available to provide guidance to academic, research and patient groups
        - Turnaround time for feedback is slow
        - No specific accommodations made for rare disease given the challenges of finding patients and caregivers to assist with measure development and validation
- Using a gold-standard measure or performing a disease-specific validation of an existing measure with established measurement properties is likely the best option until there is a guidance for rare disease
    - Subscale and even select items from a subscale(s) of an existing measure is acceptable
    - Consider assembling a group of patients or caregivers to identify the most relevant items

COA Selection & Development

What types of initiatives help identify the best clinical endpoint and interpret the results?

Prior to Trial

- Burden of Disease Surveys
- Patient Advisory Boards/ Focus Groups
- 1:1 Interviews with Patients/ Caregivers
- Pilot studies to test clinical efficacy measures

Determine if you can use an existing measure or need to develop a disease-specific measure

During Trial

- 1:1 Interviews with Patient/Caregiver
- Observed changes in symptoms/function
- Benefit/ Risk Assessment
- Treatment expectations/satisfaction

Get a better understanding of the patient experience to assist with interpretation of data

Use of Technology to Quantify Efficacy

- Interest in measures to quantify concepts, such as sleep and activity has led to many technological advances in COAs
  - Goal to have a measure with increased sensitivity to detect small changes and minimize noise

- To date, limited regulatory support for use of wearables
  - Endorsement by EMA for use of stride velocity by actigraphy as label-enabling endpoint for DMD
  - Currently no labels for approved products that include data from wearables
  - Clinical significance of observed changes has not been established
  - Sensory deficits can impact compliance with wearables
  - Lack of natural history data

- E-diaries are more generally accepted, particularly for the assessment of seizures
  - Need for careful consideration of patient/caregiver burden
    - Limit the required number of consecutive days
    - Limit the amount of data collected for each required entry
    - Allow for flexibility in time of entry
    - Provide adequate training and support – invest in EASY!

Videos

- Great way to translate quantitative changes into home and community setting
- Consider optional video assessment with pre-selected list of ADLs in the protocol
- Consent must be obtained to allow for sharing of videos
- Blurring of faces is not ideal but may be required by some IRBs/ethics committees
- Caregiver training can be conducted at the time of enrollment
- Phone app allows for video capture and has secure portal used to upload pre- and post-treatment videos
- Can't "unsee" changes

- Consider the information needed by stakeholders other than regulators:
  - Physicians - to determine if a treatment makes sense for their patient(s)
  - Patients and/or caregivers - to make informed decisions about treatment options
  - Payers - to determine reimbursement that defines patient access

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Example of Disease-Specific Modification of Existing COA

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Neuromuscular Gross Motor Outcome (GRO)

- The GRO is a measure of gross motor function based on clinical observation developed to evaluate patients with a broad range of ages and abilities
    - Measure has been validated for use in SMA

- Ultragenyx is collaborating with Nationwide Children's Hospital and the developers of the GRO to perform a disease-specific validation for DMD
    - There is currently no single measure of gross motor function that covers all patients with DMD and allows them to be monitored over time
    - Validated clinical outcome assessments (COA) in DMD typically focus on a portion of the total cohort based on age (i.e. infants & toddlers) or function (i.e. ambulatory)
        - NSAA to assess lower extremity function in ambulatory patients
        - PUL to assess upper extremity function in non-ambulatory patients
    - The DMD community has expressed a need for a single measure to monitor disease progression and response to treatment over time

Neuromuscular Gross Motor Outcome (GRO)

- AIM 1: Establish the content validity and feasibility of use of the Neuromuscular Gross Motor Outcome (GRO) to quantify gross motor abilities in persons with Duchenne muscular dystrophy

- AIM 2: Establish the minimal detectable change, convergent and divergent validity of the Neuromuscular GRO in a cross-sectional sample compared to other validated outcomes in persons with DMD

- AIM 3: Establish the sensitivity to change and minimal clinically important difference of the Neuromuscular GRO longitudinally compared to other validated outcomes in persons with DMD

- AIM 4: Evaluate the test-retest reliability of the Neuromuscular GRO

Neuromuscular GRO Validation Project

- Where are we now?
  - 100 participants have been enrolled to date
  - Recent presentation at the Muscular Dystrophy Association Meeting in March, 2024
    - Results:
      - Unlike many of the traditional COAs, GRO was:
        - Completed in ALL patients
        - Correlated highly across all functional outcomes, including patient-reported mobility
        - Correlated moderately with spirometry and upper extremity function
        - Safely completed in all patients enrolled without obvious floor or ceiling effects
        - Able to quantify function in pre-ambulatory, ambulatory and non-ambulatory phases of disease progression

Neuromuscular GRO Validation Project

What does this mean and what is next?

- Development and validation of an assessment that quantifies functional ability across a wide age range and range of functional abilities has the potential to:
  - Enable expanded clinical trial enrollment criteria
  - Reduce the battery of testing completed as part of standard clinical practice
  - Evaluate disease progression and response to treatment over time

- Future research includes:
  - Longitudinal follow up to understand sensitivity to change and identify thresholds that may inform proactive clinical care recommendations
  - Rasch analysis to understand the psychometrics of the Neuromuscular GRO
  - Collection of normative performance data by age to serve as a reference group for DMD patients

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Questions

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