Considerations for Endpoint Selection in Rare Disease Trials

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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 greatest unmet medical need

- Even within a domain of interest:
  - Broad range of severity
  - One measure may not work for all patients

- Pilot testing potential measures on a small set of patients is critical to assess feasibility and appropriateness
  - Try different measures to find the right subset
  - Goal is to find 1-2 measures per domain that most patients can do reliably without floor and ceiling effects
  - Use data to support your choice at regulatory meetings

- Perform battery of tests at Screening to identify the best one(s) for each patient
  - Avoid missing and uninterpretable data
  - Each patient may need their own endpoint

- Minimum requirement even when natural history data is available to confirm assumptions for your study

Novel Disease-Specific Measure vs. Existing Validated Measure

- Regulatory support exists for creation of novel disease-specific measures to disease 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

Bayley Scales of Infant and Toddler Development (Bayley-4)

- Include tests to evaluate developmental areas:
  - Cognition
  - Communication (Receptive and Expressive)
  - Motor Function (Gross and Fine)
- Validated for neurotypical children from 2 weeks to 42 months of age
- Can be used for assessment of children with disabilities beyond 42 months until the ceiling of a scale is reached
- Can use individual tests or full battery depending on need
- 60-90 minutes for full battery administration
- Administered by a licensed and trained therapist
- Training on Bayley-4 is available through Pearson
- Impression of Test Performance by caregiver should be assessed and recorded after each administration

Vineland Adaptive Behavior Scales – 3rd Edition (VABS-3)

- Administered by interview with caregiver
- Validated for use in all ages
- Used extensively for evaluation of adults and children with disabilities
- Behavior score in context – when needed or appropriate
  - 2 = usually performs it without help or prompting
  - 1 = sometimes performs it without help or prompting
  - 0 = never performs or never performs without help or prompting
- Therapy (physical, occupational, speech/language) may be needed to support skill acquisition
  - Better suited for long-term evaluation of functional independence resulting from treatment augmented by therapy

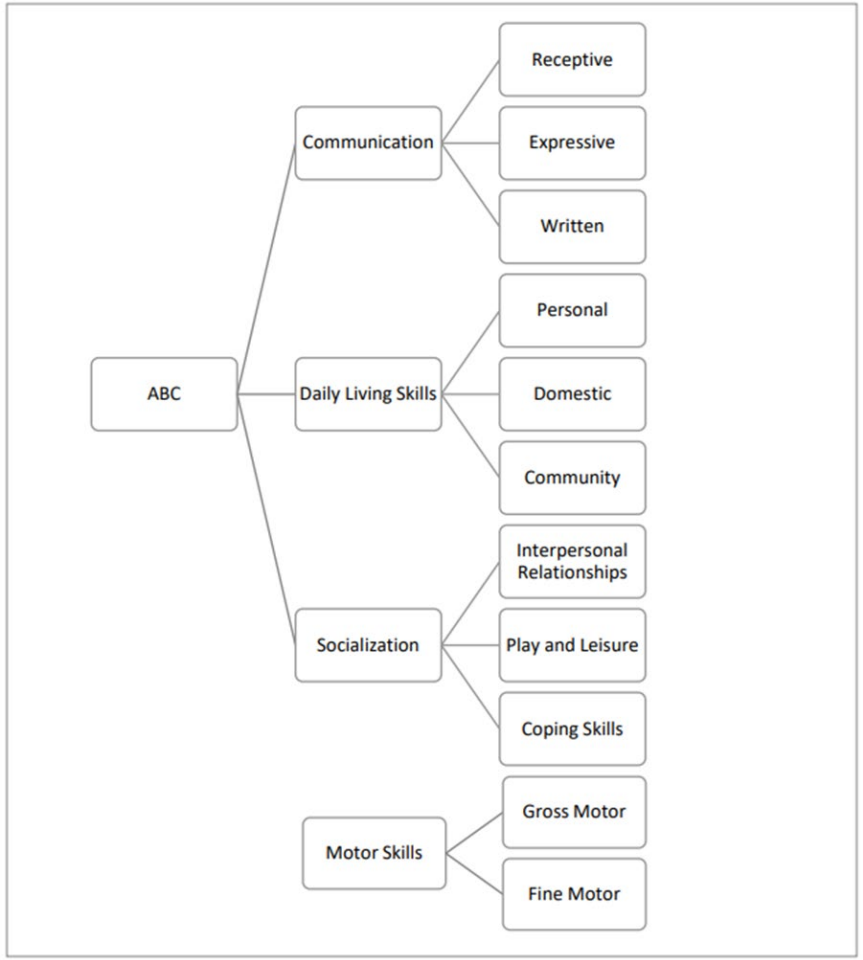

Figure: Structure of the Vineland-3 Comprehensive Interview Form. Adapted from Farmer, Floyd, and McNicholas._2020. https://doi.org/10.1177/1073191120947804
Note: ABC = Adaptive Behavior Composite. The optional Maladaptive Domain is not included in this trial.

Aberrant Behavior Checklist – Community (ABC-C)

Overview

- Caregiver report questionnaire
- Symptom checklist developed to evaluate problem behaviors in children and adults with developmental disorders
- 58 questions divided into 5 subscales
  - Irritability
  - Social Withdrawal
  - Stereotypic Behavior
  - Hyperactivity/Noncompliance
  - Inappropriate Speech

Scoring

- Behavior scored in context
  - 2 = Usually performs it without help or prompting
  - 1 = Sometimes performs it without help or prompting
  - 0 = Never performs or never performs without help or prompting
- Only subscale scores are reported
- Acceptable to use individual domains selected based on the most problematic behaviors

Special Considerations

- 35+ foreign language translations
- Has been used in natural history studies and/or clinical trials for several rare diseases, including Angelman, Fragile X, Rett, Prader-Willi, ASD, etc.
- Appears in USPI for risperidone and aripiprazole for autism spectrum disorders

Videos

- Great way to translate the quantitative changes observed in efficacy measures into functional impact in home and community setting
- Optional video assessment with pre-selected list of ADLs should be included in the protocol
- Consent must be obtained from caregivers to allow for use of videos with regulatory, academic, medical and patient audiences
- 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
- Not every measure needs to be a label-enabling endpoint for regulatory purposes – 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

Use of Technology to Quantify Efficacy

- Interest in highly specific measures to quantify concepts, such as sleep, activity, falls, etc. has led to many technological advances in COAs
  - Goal to have a measure with increased sensitivity to detect small changes and minimize noise
- 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
  - Minimum clinically important difference (MCID) of observed changes has not been established
  - Sensory deficits can impact compliance with wearables designed for use on wrists and/or ankles and increase risk of missing/uninterpretable data
  - Lack of natural history data makes it difficult to assess natural variability within and between patients and creates need for lead-in period
  - May be more suitable to provide supportive 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 (7 days prior to milestone visits may be acceptable)
    - 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!

Recommendations – Increase Disease Awareness

- Request Patient-Focused Listening Session to increase awareness of a rare disease and its impact
  - Start the education process early

What is a Patient-Focused Listening Session?

- Can be requested by FDA if they have a specific set of questions about a disorder or by a patient community who wants to share their perspectives with the FDA
- Helps the FDA better understand what is most important to individuals living with a specific condition
  - What is the unmet medical need?
  - Focus is on patient experiences, perspectives, expectations and preferences
- Small, informal, non-regulatory, non-public teleconference meetings
- All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants
- Only the FDA, patients, caregivers, advocates, and community representatives participate in the session
- Should include multiple patient groups/communities within a disease area

Recommendations – Discuss Clinical Development Opportunities

- Request CPIM (Critical Path Innovation Meeting)
  - Developed by CDER to improve efficiency and success in drug development through communication
  - Forum for FDA and stakeholders to discuss potential scientific advancements in drug development
    - Available to investigators from industry, academia, scientific consortia, patient advocacy groups, and government
  - Not a substitute for other regulatory meetings
  - Not a format for data presentation and review
  - Non-regulatory, drug product-independent and nonbinding for both FDA and CPIM requesters
  - Potential discussion topics:
    - Early-stage biomarkers not ready for review in Biomarker Qualification Program (BQP)
    - Disease-specific COA measures not sufficiently developed for review in COA Qualification Program
    - Natural history study designs and implementation
    - Emerging technologies or new uses of existing technologies
    - Innovative conceptual approaches to clinical trial design and analysis

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Questions

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