MDRI as an Endpoint Strategy for Rare Neurodevelopmental Disorders

Alison Skrinar, PhD
Vice President
Endpoint Development and Strategy
Ultragenyx

Disclosure

- Alison Skrinar is a full-time employee of Ultragenyx and an Ultragenyx stockholder

Endpoint Selection Challenges in Rare Disease

- Most rare diseases are complex and multisystemic with a heterogeneous clinical presentation
- Clinical trials for rare diseases are typically powered for a single primary endpoint
- There is no “one-size-fits-all” solution for the selection of efficacy endpoints in a rare disease trial
- Limited numbers of patients lead to broad eligibility criteria to achieve adequate sample size
- Alternatives methods are needed to evaluate the efficacy of investigational products for rare diseases

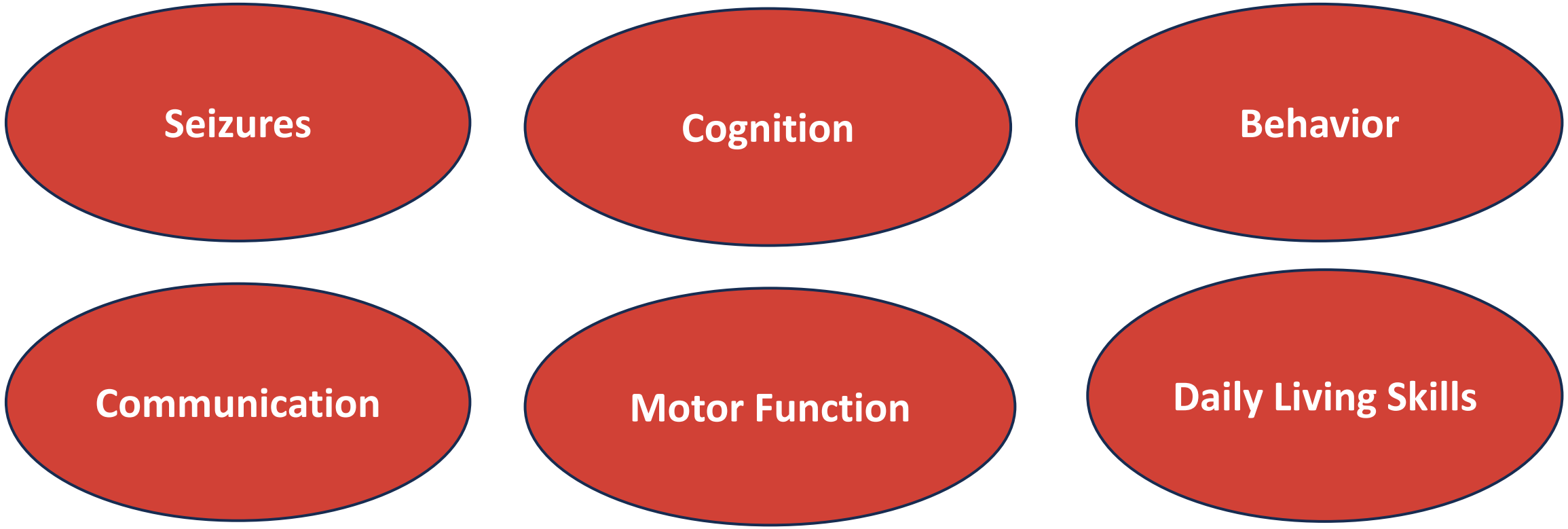
Multi-Domain Responder Index (MDRI)[1] Rationale

- Several clinical domains can be evaluated as a single endpoint without compromising statistical power or rigor
- Reduced risk of diluting efficacy effect for secondary endpoints due to clinical heterogeneity and small sample size
- Full impact of treatment on safety and efficacy outcomes can be assessed in a broad range of patients
- Methodology first applied as a post-hoc analysis of data from a Phase 3 study of laronidase for MPS I
- To date, the MDRI has not been accepted for use a primary endpoint in a registration study by regulatory authorities

[1]Tandon & Kakkis, 2016

Broad Set of Common Symptoms Across Neurodevelopmental Disorders

- Areas of impairment for affected individuals may be similar across disorders although impact on the individual and caregivers may differ



MDRI Development Process

- Set of 4-6 clinically important domains identified that cover the clinical spectrum of a disease
- A single outcome measure is selected to represent each domains
- Outcome measure for each domain should be relatively independent of the others
- Not necessary for all patients to produce a score for each domain
- Expected effects of treatment should be factored into choice of domains and measures

MDRI Scoring and Interpretation

- The MDRI encompasses multiple endpoints with pre-specified responder thresholds
- Scores assigned based on the outcome in each domain, then summed across domains.
  - A score of + 1, 0, or −1 may be assigned to an individual's outcome in each domain to indicate clinically significant improvement, no significant change, or clinically significant worsening
- The total score summed across all domains represents the net number of domains improved vs. worsened for an individual
- Total score can then be averaged and compared across treatment groups
- By design, MDRIs are sensitive to treatment effects that lead to improvement and/or the prevention of worsening across domains
- The clinical meaningfulness of the responder threshold (MID) must be established for each domain

Process of Identifying Domains and Measures

Identify domains based on high impact areas and expected treatment effect:

- Patients/
- Caregivers
- Disease Experts
- Physicians
- Clinicians

- Seizures
- Cognition
- Behavior
- Communication
- Motor Function
- Daily Living Skills

Identify Domain Measures based on:

- Appropriateness for population
- Use in clinical practice
- Published literature
- Regulatory precedent

Administer domain measures to target study population to ensure feasibility for use in a multi-site, global clinical trial

Determine smallest change in measure score associated with meaningful treatment effect

- Prior studies
- Advisory boards
- In-trial interviews

Example of MDRI for Neurodevelopmental Disorders

Domain	Assessment	Endpoint	MID
Seizures	At-Home Diary	Seizure frequency	+/- 50%
Cognition	Bayley-4	Cognitive GSV score	+/- 5 points
Behavior	ABC-C	Irritability score	+/- 5 points
Communication	ORCA	Total raw score	+/- 5 points
Motor Function	Activity Monitor	Fall frequency	+/- 50%
Daily Living Skills	Vineland	Personal GSV score	+/- 5 points

Sample MDRI Response for Neurodevelopmental Disorder

	Seizure +/- 50% frequency	Cognition +/- 5 Bayley-4 Cognitive GSV	Behavior +/-5 ABC-C Irritability	Communication +/-5 ORCA Total Score	Motor Function +/- 50% Fall frequency	Daily Living Skills +/- 5 VABS-3 Personal GSV	Total
Patient 1	-60	+3	-7	-7	+30	+6	+2
	+1	0	+1	-1	0	+1	
Patient 2	+20	+7	+10	+8	-75	-7	+1
	0	+1	-1	+1	+1	-1	
Patient 3	+55	+10	-13	+11	-30	+8	+3
	-1	+1	+1	+1	0	+1	
Patient 4	-30	-8	+12	+8	+55	-10	-3
	0	-1	-1	+1	-1	-1	
Patient 5	-70	+2	-3	-6	-20	+4	0
	+1	0	0	-1	0	0	

MDRI Statistical Considerations

- All domains are expected to benefit from treatment, although the magnitude of the effect could be variable
- No domain considered more clinically important or more likely to show benefit resulting in equal weighting
- No adjustment required to overall type-one error
- Individual domain data can be presented descriptively
- Power may be affected if some domains are not sensitive to treatment, although analysis is still valid

MDRI Challenges

- What is the best process for establishing the MIDs?
- Can domains be weighted based on impact?
- How is missing data accounted for?
- Is there a way to add more granularity to the scores for each domain?
- What sensitivity analyses could be performed to evaluate efficacy at the individual domain level?
- What are some options for presentation of MDRI data in the label for an approved product?
- How would unexpected decline in a domain be handled?

Thank You

Alison Skrinar, PhD
Vice President
Endpoint Development and Strategy
Ultragenyx
Novato CA

askrinar@ultragenyx.com