

# ***Leveraging Information that Can Inform the Evaluation of Clinical Benefit in Rare Diseases***

***Tenth Annual  
Patient-Reported Outcome Consortium Workshop***

**April 24 – 25, 2019 ■ Silver Spring, MD**



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# What we Know



- It is estimated to be as many as 7,000 rare diseases<sup>1</sup>
- 25-30 million Americans living with a rare disease<sup>2</sup>
- Orphan Drug Act defines a rare disease “one affecting fewer than 200,000 people in the US”

1- <https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases> Accessed April 1,2019

2- <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm> Accessed April 1, 2019

# Rare Disease Development Challenges



- Heterogeneity
  - Maybe unclear on what to measure and how to measure relevant concepts
- Small Sample Size
- Wide Age Range
- Limited Number of Trials
- Known Natural History and/or Disease Progression may be limited

# Session Objectives



- To learn about FDA current thinking in Rare Disease Drug Development
- To identify approaches industry is taking to address these challenges
- To understand how novel COAs can be utilized using the real world setting

# Session Participants



## Moderator

- *Michelle Campbell, PhD* – Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, DNP, OND, CDER, FDA

## Presenters

- *Lucas Kempf, MD* – Associate Director Rare Diseases Program (acting), OND, CDER, FDA
- *Dylan Trundell, MSc* – Senior Outcomes Research Scientist, Patient-Centered Outcomes Research, Roche
- *Mindy Leffler, MEd* – President, Casimir

## Panelists

- *Billy Dunn, MD* – Director, Division of Neurology Products, OND, CDER, FDA
- *Lili Garrard, PhD* – Senior Statistical Reviewer, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences, CDER, FDA
- *Montserrat Vera-Llonch, MD, MPH, MSc* – Senior Director, Global Outcomes Research and Epidemiology, Takeda

# COA Challenges in Rare Diseases

**It is more than just a numbers game**

**Lucas Kempf, MD**

**Rare Diseases Program**

Mission: to facilitate, support, and accelerate the development of drug and biologic products for the benefit of patients with rare disorders.

**2019 PRO Consortium Workshop**

**Leveraging Information that Can Inform the  
Evaluation of Clinical Benefit in Rare Diseases**

**April 24, 2019**

# The public health impact of rare diseases



Katherine: Complex 1, NUBPL

- **1 in 10 Americans have a rare disease** (~30 million)
  - over 7,000 identified rare diseases
  - impact often overlooked due to small numbers of patients per disease
- Most rare diseases are **serious and progressive**, many fatal, and **few have FDA approved treatment**
- 85% are genetic and 50% affect **children** - severe impact on patients and their families



# The 1983 Orphan Drug Act (ODA)

Enacted to stimulate product development for rare disease/condition diagnosis, prevention or treatment



Max and Austin

Duchenne Muscular dystrophy

- Prior to the ODA fewer than 1 drug a year approved for rare diseases in the US.
- Now, over 500 diseases with at least one treatment

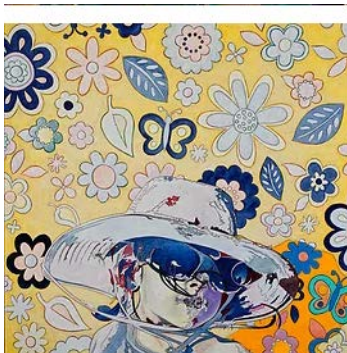
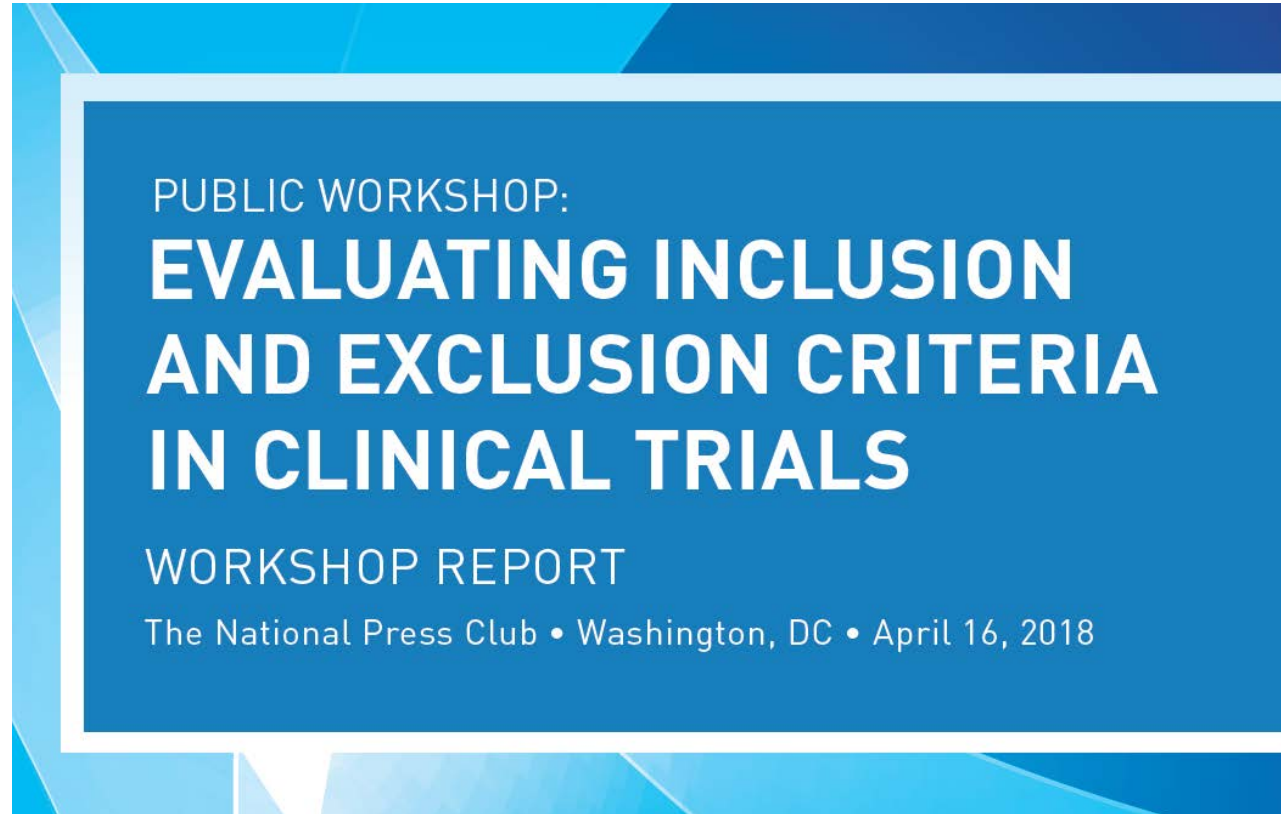
# What do ‘rare’ and ‘orphan’ mean?

- A **rare disease** is defined in the **Orphan Drug Act** as a disease/condition that affects <200,000 people in the US  
note: prevalence can be >200,000 people if there is “no reasonable expectation” of recovering development and marketing costs
- An **orphan drug** is a designation for a drug or biological product used for the prevention, diagnosis, or treatment of a rare disease in the US



Allie:  
Paternal Uniparental Isodisomy Chromosome 4

# Inclusion Criteria vs Enrichment



Eliza:  
Sanfilippo Syndrome



# Early Advice is Critical

## Rare Diseases: Common Issues in Drug Development Guidance for Industry

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

February 2019  
Rare Diseases  
Revision 1

## Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings Guidance for Industry

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

October 2018  
Rare Diseases

## Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Office of Orphan Products Development (OOPD)

March 2019  
Rare Diseases

# Clinically Relevant Endpoints Require Good Natural History Studies and Patient Input



## PFDD Meetings

### Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

#### DRAFT GUIDANCE

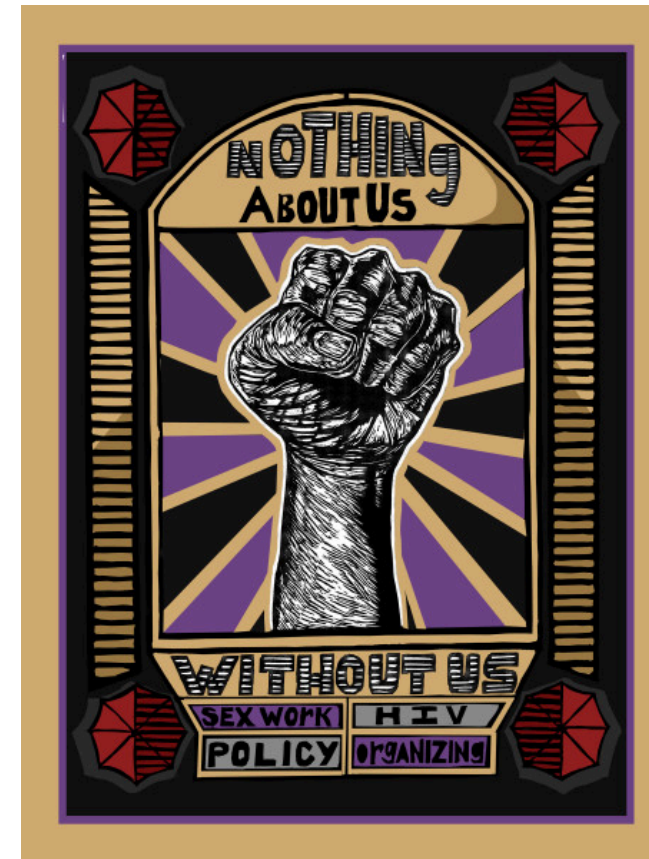
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March 2019  
Rare Diseases



# COA Development Public vs Private

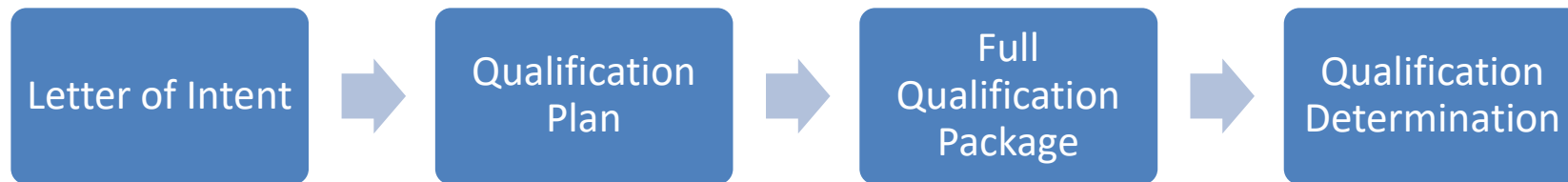
- Individual Development Programs
  - Endpoint may be unique to the mechanism of action of the drug
  - Disadvantages
    - Multiple competing programs may silo data and slow enrollment
  
- Public efforts
  - CPIM meetings
  - Support group or government supported development
  - COA Qualification program



Ava:  
Achondroplasia Dwarfism

# CDER's COA Qualification Program

- Provides a framework for interactions between the FDA and requestors to guide the collection of data to support a COA's prospectively specified context of use.



Chagtaa:  
Waardenburg Syndrome

# OOPD and CDER Grant Programs

GRANT PROGRAMS	
1	<p>Clinical Trials Grant Program (more than \$15M)</p> <ul style="list-style-type: none"> <li>Supports the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the proposed product will be superior to the existing therapy</li> </ul>
2	<p>Pediatric Device Consortia Grant Program (\$6M)</p> <ul style="list-style-type: none"> <li>Supports the development of nonprofit consortia designed to stimulate projects which will promote pediatric device development</li> </ul>
3	<p>Natural History Grant Program (\$2M)</p> <ul style="list-style-type: none"> <li>Supports studies that advance rare disease medical product development through characterization of the natural history of rare diseases, identification of genotypic and phenotypic subpopulations, and development or validation of clinical outcome measures, biomarkers or companion diagnostics</li> </ul>
4	<p>COA/Endpoints Grants Development of Standard Core Clinical Outcomes Assessments (COAs) and Endpoints (UG3/UH3 Clinical Trial Optional)</p> <ul style="list-style-type: none"> <li>FDA <b>soliciting applications</b> to support the development of a publicly available standard core set(s) of COAs and their related endpoints for specific disease indications</li> </ul>





# Standard Core Clinical Outcome Assessments (COAs) and Related Endpoints Grant Program - Deadline May 31, 2019

- **FDA [soliciting applications](#) to support the development of a publicly available standard core set(s) of COAs and their related endpoints for specific disease indications**
  - Minimum list of impacts that matter most to patients and are likely to demonstrate change relating to disease burden and treatment burden
  - Link: <https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-006.html>
- **Conduct well-managed, transparent, and methodologically-sound process following a development protocol that provides for:**
  - Consistent application of appropriate methods (e.g., new guidance)
  - Consideration and use of vetted publicly available measures
  - Milestones workshops engaging key stakeholders (e.g., patients, FDA and other regulators, HCPs, industry, HTA, payers, researchers)
  - Milestone work products made publicly available

## Disease areas or disease impacts of interest

- COAs and endpoints for use in trials in **gastrointestinal diseases/conditions**, specifically for use across gastrointestinal diseases/conditions with overlapping signs and symptoms
- COAs and endpoints to assess **physical/functional status** including, but not limited to, standardized assessment of activities of daily living dependent on gross and fine motor function (including upper and lower limb function) across a range of diseases and populations
- COAs and endpoints for use in **migraine** trials, including functional impact or disability from migraine
- COAs and endpoints for use in trials of **opioid sparing drugs** intended to treat acute pain
- COAs and endpoints for use in **schizophrenia** trials, including but not limited to, shortened versions of current instruments, as appropriate

**FDA is also interested in applications for disease areas or disease impacts that are not represented on this list.**

**Questions? Please email [CDER\\_StandardCoreCOAs@fda.hhs.gov](mailto:CDER_StandardCoreCOAs@fda.hhs.gov).**

Thank you



# Malia and Callie: Undiagnosed

Portraits used with permission from *Beyond the Diagnosis*



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ADMINISTRATION

# Leveraging Information that Can Inform the Evaluation of Clinical Benefit in Rare Diseases

## *A Sponsor Perspective*

Dylan Trundell, MSc, Senior Outcomes Research Scientist, Patient Centered  
Outcomes Research, Roche

# Disclaimer and Acknowledgement



## Disclaimer

Any opinions or information given by me are based on general industry standards and not the opinions of Roche. Any information given at the presentation should be used and disseminated by attendees at their discretion and Roche shall not be liable for any information relied upon by you or the attendees as a result of the presentation.

## Acknowledgement

Dr. Tom Willgoss and the Roche/Genentech PCOR team contributed to the preparation of this presentation.

Key challenges  
and industry  
factors

Potential  
solutions (focus  
on measurement)

# Overview of challenges

- There are numerous challenges when developing new therapies in rare and orphan diseases.

Population

Trial Design

Measurement

- There are factors within industry that interact with the above challenges.

Time

Risk

Measurement  
understanding/  
focus



- Trial design
  - Heterogeneity (which population to study)
  - Lack of natural history data (power/sample size calculation)
  - Pediatric and/or cognitively-impaired populations
  - Ethical concerns
    - Justification for placebo arm
    - Pressure to expedite development
    - Shorter trials and/or accelerated pathways
    - Ability to consent in cognitively-impaired populations
- Recruitment challenges
  - Small populations
  - Geographically diverse
  - Many do not attend specialist centres

# Challenges (2)

- COA selection
  - Heterogeneity of disease
    - Symptom manifestation and progression
  - Complexity of disease
    - Often multidimensional – challenging to isolate individual symptoms
  - Lack of suitable COAs/established endpoints
    - No precedence to guide sponsors, need for new COAs
  - Pediatric and/or cognitively-impaired populations
    - Limits use of PRO measures
    - Higher reliance on ObsRO measures (often limited options/proxy-report rather than observable signs)
    - Scaled-back schedule of assessments
  - Pre-symptomatic subpopulations
    - Could be a long period (e.g., Huntington’s disease) without clear functional impairment yet could have strong rationale for delaying functional impairment with a disease-modifying treatment
    - 20 year clinical trials are not feasible
    - Reliance on surrogate biomarkers

# Industry factors



- Time – expedited clinical development
  - Leads to challenges in novel scale development or modification of existing scales
  - Partnership with small biotechs following positive Phase 1 results
- Risk – better the devil you know
  - Desire to go with sub-optimal but adequate measures where longitudinal performance is known
- Measurement – understanding/focus
  - Clinical community sometimes focus on sensitive measures of disease progression and/or widely used legacy COAs that may not meet regulatory standards
  - Decision-makers unfamiliar with guidance documents (e.g., PFDD)
  - Strive for balance between regulator and clinical community needs

# Potential solution - MDRI

- Multi-domain responder index (MDRI)
  - Useful in heterogeneous populations where benefit could be experienced either in different domains of health, or at different levels within a domain (where a single measure has inadequate range)
  - Uses multiple assessments, each one requiring a definition of response/progression, from which a single metric can be calculated
  - Can be used to identify responders/progressors in one or more domain in diseases with multi-domain symptom manifestation

Cognition

Motor Function

Behaviour

- Can be used to identify responders/progressors in one or more aspect of a domain in diseases where there is a wide range of within-domain impairment

Fine Motor

Proximal and Axial Motor

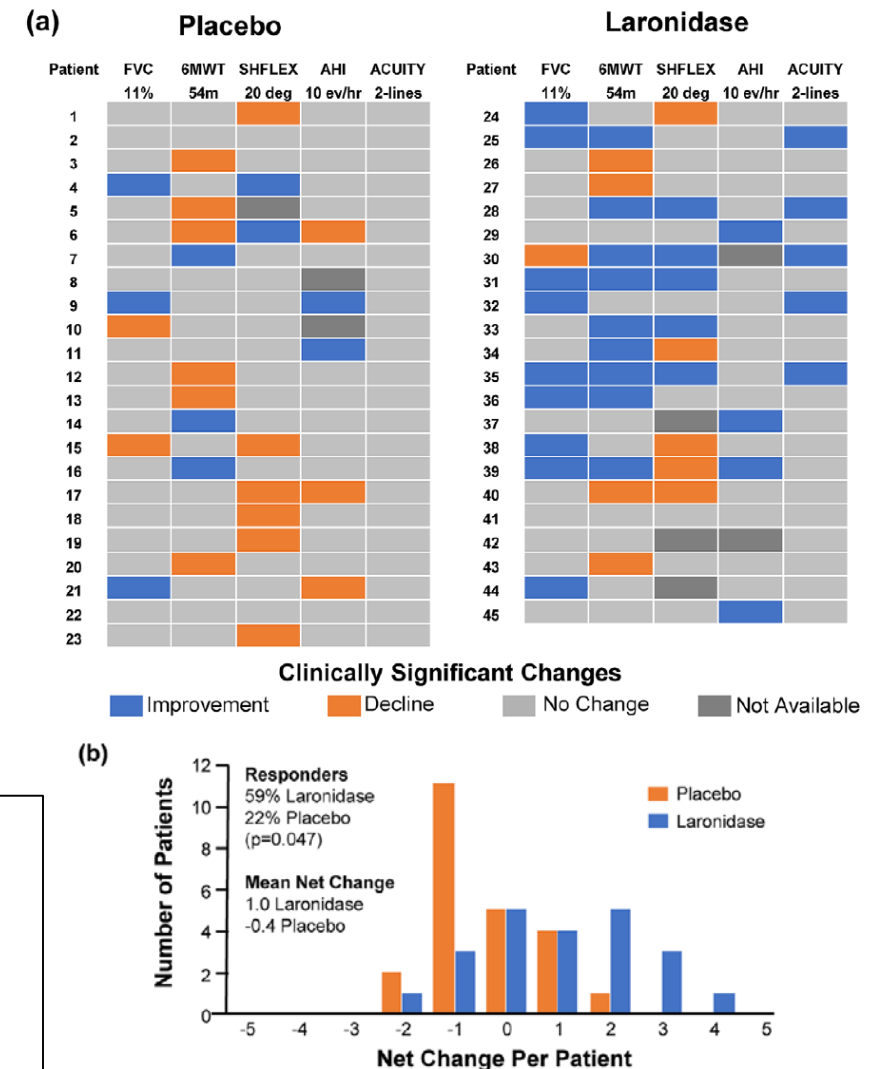
Transfers & Ambulation

# Potential solution – MDRI (2)

- Spinal muscular atrophy (SMA) example: motor milestones in SMA Type 1 infants
  - Assign +1 for improvement, 0 for no change, -1 for decline
  - Milestones include sitting, crawling, standing, walking etc.
  - Clearly clinically meaningful within context of disease
  - ‘Established’ measure used to define level of function

- Mucopolysaccharidosis 1 (MPS 1)
  - Assign +1 for improvement, 0 for no change, -1 for decline
  - Mixture of respiratory function, walking capacity, shoulder flexion, sleep apnea-hypopnea, and visual acuity
  - Appropriate definition of response for each scale is challenging to establish
  - Relative importance of each domain is challenging to establish

- Inherent challenges in selecting multiple measures, defining response/progression for each measure, and defining the overall metric of response/progression (weighting of domains, how many individual scales you need to meet)
- Can be driven by a single domain



# Potential solution – Global scores



- Global impression of severity/change
    - An overall rating based on all available information across multiple domains
    - Angelman syndrome example: a global impression scale is planned to be used to combine multidimensional features into a single overall rating
- <https://www.globenewswire.com/news-release/2018/12/06/1663049/0/en/Ovid-Therapeutics-Announces-Plans-to-Move-into-a-Phase-3-Trial-in-Pediatric-Patients-Based-on-End-of-Phase-2-Meeting-for-OV101-in-Angelman-Syndrome.html>
- Still requires establishing a method for adequately assessing the multiple domains (often reliance on existing measures)

# Potential solution – CAT

- Computer Adaptive Testing

- Utilises Rasch/IRT
- Items selected based on responses to earlier items
  - Identify an individual's location on the spectrum of a specific construct
  - Focus on the construct and not on specific items



- Can address issue of heterogeneity within a domain
- Requires a measure with good coverage across the spectrum

# Potential solution - Digital



- Leveraging new technologies
  - A platform...
  - Broad range of possibilities from those that assist with measurement of daily function to those sensitively targeting underlying phenomena
  - Broad range of modalities
    - Video assessments (e.g., DMD)
    - Sleep monitoring (potential use in Angelman)
    - Digital suites (many companies investing in suites of cognitive and motor app-based assessments, and passive monitoring)
  - Guidance needed to direct efforts



# Potential solution – Qualitative data



- Leveraging qualitative data
  - Embed qualitative research into clinical studies
  - Use of exit interviews increasing but limited use of longitudinal qualitative research (LQR)
    - ISOQOL Mixed Methods Special Interest Group have a dedicated LQR sub-team looking to summarise current evidence and advise on standards
    - Challenging to create standards for analysis and presentation of data
    - Quantitative metrics easier to aggregate (potential to score qualitative data to create quantitative metric).

# Summary



- There are multiple challenges for measuring clinical benefit in rare diseases
- Even potential solutions have limitations
- As sponsors, we are looking to innovate but flexibility and pragmatism are still needed to be successful

# Quality of Movement in Duchenne Muscular Dystrophy

Mindy Leffler, President, Casimir

# Duchenne Muscular Dystrophy



Genetic disorder characterized by progressive muscle degeneration:

- Wheelchair-bound by late childhood/early teens
- Progressive loss of upper limb function
- Death in late teens to early twenties due to heart or respiratory failure



# Conversations with Duchenne Parents



- How the children test in the clinic isn't always reflective of how they're doing at home:
  - Travel fatigue
  - Clinic fatigue
  - Medical anxiety
  - Unfamiliar people
  - Vacation mode

# Conversations with Duchenne Parents



- Sometimes, you can't predict how treatment benefit will show up
- Parents can tell you one task for their child that's sensitive to disease progression over the short term
- For parents, it's about how easy it is to move, not about how fast they can move

# Caregiver Observation





# Caregiver Observation



# Duchenne Video Assessments (DVA)



## Quantification Goals:

- Meet each patient where he's at and quantify the trajectory of the individual patient
- Quantify ease of movement not speed of movement by counting compensatory movement
  - Instinctive adaptations to healthy movement patterns adopted to work around progressive weakness
- Capture all nuanced and significant compensations
- Allow for different compensatory strategies

# Duchenne Video Assessments (DVA)



## Clinician-Reported Outcome (ClinRO) Measure:

1. Sponsor selects from a menu of daily tasks based on trial inclusion criteria
2. Caregivers watch training videos that standardize video capture procedures
3. Caregivers record their children performing those tasks in the home environment using a mobile app
4. Trained physical therapists serving as central raters count the compensations present on each activity with a validated scorecard
5. The change over time is calculated for individual patients

## Additional video captures:

- “Caregiver Choice” – can more fully characterize the individual patients’ trajectories
- New Ability – can generate hypotheses about potential future standardized tasks

# Mobile App



- 21 Part 11 and HIPAA-compliant
- Multi-platform support
- Full audit trail
- Built in training capability
- Configurable and automated data capture window

# DVA Qualification



Validation required before capture in clinical trials commences:

- Task Selection
- Capture Procedures
- Mobile App Usage

Validation required before scoring commences:

- Scorecard
- Scoring Methodology

DVA's acceptance into FDA's Clinical Outcome Assessment (COA) Qualification Program will provide a mechanism for more systemic feedback from FDA during the qualification process.

# Validation – Task Selection and Capture Procedures



1. Task selection: done with input from clinicians, parents and physical therapists.
2. Capture procedures: developed and produced into a training manual and videos
3. Training materials: sent to group of five families; resulting videos evaluated by PTs for scorability
4. Training materials sent to second group of families; resulting videos also evaluated and cognitive debriefing interviews completed on task selection, instruction clarity and app usage
5. Training materials sent to group of North American and European physicians who evaluated task selection and procedure clarity

# Validation - Quantification



1. Compensatory criteria list for each task
2. Consensus list of criteria with PT expert panel
3. Score card formulation
  1. Distinguishes between non-Duchenne and Duchenne, early Duchenne and later Duchenne
  2. Each criteria needed to be distinct and of equal weight
4. Delphi panel for scorecard consensus
5. Source Material Study
6. Reliability testing and known groups analysis

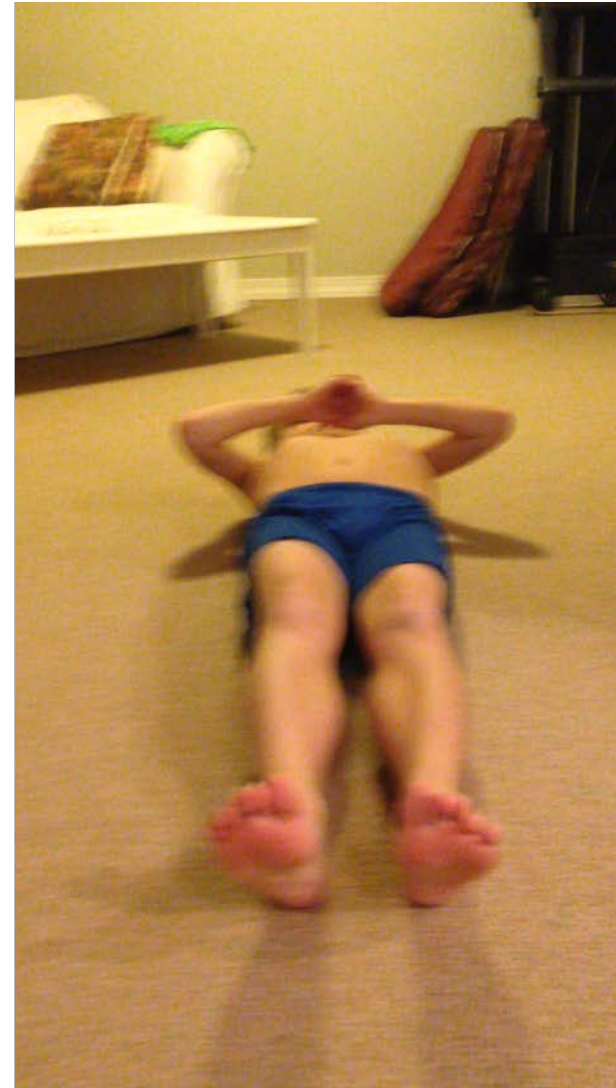
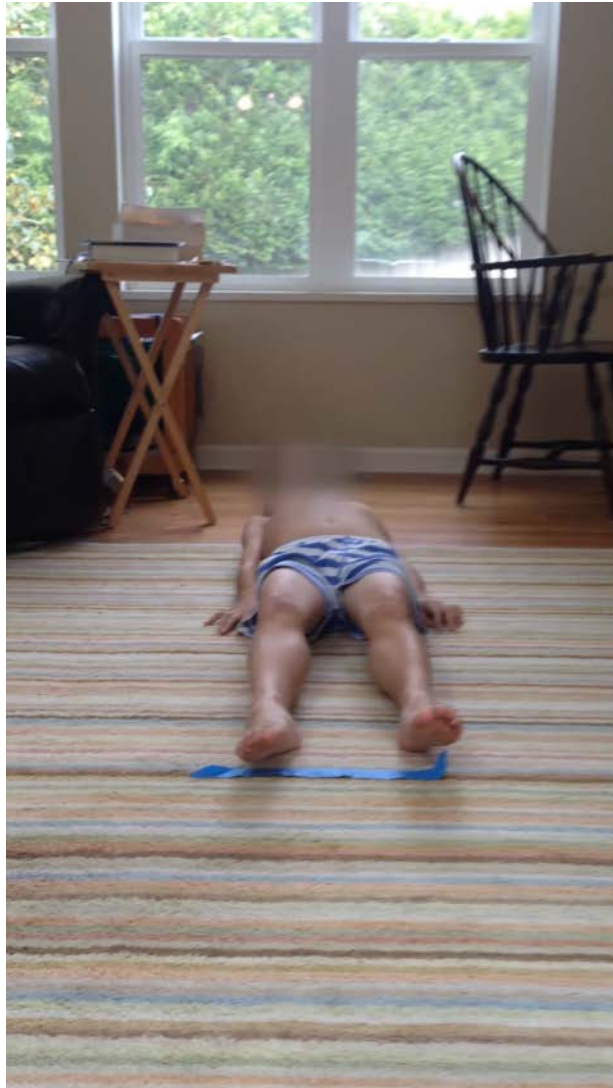
# Stairs





Criteria – check the box if the criterion is present in the video	Timepoint 1	Timepoint 2	Number of Severity Points
A. Leg clearance (If applicable, select only 1)			
1. Alternating legs every step, but with external hip rotation	<input type="checkbox"/>	<input type="checkbox"/>	1 point
2. Leading with dominant leg at least once	X	<input type="checkbox"/>	2 points
3. Leading with dominant leg majority of steps	<input type="checkbox"/>	X	3 points
B. Use of upper body assistance (thighs, wall, or handrail) (If applicable, select only 1)			
1. Using one arm	X	<input type="checkbox"/>	1 point
2. Using two arms	<input type="checkbox"/>	X	2 points
C. Upper body positioning (If applicable, select only 1)			
1. Dipping trunk toward knee or to the side when stepping up	<input type="checkbox"/>	<input type="checkbox"/>	1 point
2. Leaning torso toward wall or railing while facing upwards; the body forms the hypotenuse of a right triangle with the floor and wall	<input type="checkbox"/>	<input type="checkbox"/>	2 points
3. Turning torso to face wall or railing to side step	<input type="checkbox"/>	<input type="checkbox"/>	3 points
D. Inability to perform task	<input type="checkbox"/>	<input type="checkbox"/>	9 points
Enter total number of severity points	3/ 9	5/ 9	
Calculate severity percentage	33 %	56 %	-23%

# Sit from Supine



Criteria – check the box if the criterion is present in the video	Timepoint 1	Timepoint 2	Number of Severity Points
A. Rolling torso to the side (If applicable, select only 1)			
1. Torso leans to the side or kick to create momentum with legs	<input type="checkbox"/>	<input type="checkbox"/>	1 point
2. Trunk turns to the side	<input type="checkbox"/>	<input type="checkbox"/>	2 points
3. Pelvis turns to the side	X	X	3 points
B. Pushing up with: (If applicable, select only 1)			
1. One hand	<input type="checkbox"/>	<input type="checkbox"/>	1 point
2. Two hands	X	X	2 points
C. Initiate torso lift by clasping hands	<input type="checkbox"/>	X	1 point
D. Walking hands along the ground to lift torso	X	X	1 point
E. Bending leg at knee greater than 30 degrees when lifting torso (If applicable, select only 1)			
1. One leg	<input type="checkbox"/>	<input type="checkbox"/>	1 point
2. Two legs	X	X	2 points
F. Use head and neck momentum to lift torso	X	X	1 point
G. Inability to perform task	<input type="checkbox"/>	<input type="checkbox"/>	11 points
Enter total number of severity points	9/ 11	10/ 11	
Calculate severity percentage	82 %	91 %	-9%

# Eating 10 Bites



Criteria – check the box if the criterion is present in the video	Timepoint 1	Number of Severity Points
A. Lowered head	X	1 point
B. Arm/torso movement (If applicable, select only 1)		
1. Elbow up with lean to side/shoulder hike and/or resting on table or armrest due to fatigue rather than habit; elbow still opens and closes	<input type="checkbox"/>	1 point
2. Torso moves forward; there is still some forearm movement	<input type="checkbox"/>	2 points
3. No arm movement at all; moves hand and torso (forward, side, or both) only	X	3 points
C. Using fork as leverage (If applicable, select only 1)		
1. Wrist extension; pointing fork upward	X	1 point
2. Holding fork at top to increase height (if not for all bites, then at the end out of fatigue)	<input type="checkbox"/>	2 points
D. Moving plate around to get food closer to feeding hand	<input type="checkbox"/>	1 point
E. Utensil grip (If applicable, select only 1)		
1. Low tone/floppy utensil grip	X	1 point
2. Cannot grip utensil	<input type="checkbox"/>	2 points
F. Inability to perform task	<input type="checkbox"/>	10 points
Enter total number of severity points	6/ 10	
Calculate severity percentage	60 %	

# What We've Learned



**Leber's Hereditary Optic Neuropathy (LHON):** "It's not about the trouble following people's facial expressions, it's the choice between pretending to look people in the eye and looking above or below their head to access periphery"

**Sanfilippo:** "When my child gets up at night, I worry he's going to run out the front door into traffic"

**Primary Mitochondrial Myopathy (PMM):** "I can get through a six-minute walk, but what matters is how long it takes me to get off the couch afterward"

Mission: utilize a mixed-methods approach to capture patient and caregiver perception of change with rigor:

- Video capture – demonstrate change from individual patient’s perspective in a real-world environment
- Qualitative work – provides context and captures data that’s not visual in nature or feasible to video
  - Provides a way to capture all of the changes patients and caregivers notice over the course of a clinical trial
  - Results are analyzed across the study population for common themes
  - Results are correlated with data captured in the clinic

# Acknowledgements



# Panel Discussion and Q&A



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- *Montserrat Vera-Llonch, MD, MPH, MSc* – Senior Director, Global Outcomes Research and Epidemiology, Takeda