Overcoming Challenges in Outcome Measurement in Rare Diseases and Pediatric Populations

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Patient-Reported Outcome Consortium Workshop

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Session Outline and Objectives



- Introduction
- Overcoming challenges in rare disease and pediatric populations
 - Understanding the challenges of developing PRO measures for rare diseases
 - Considering an example of utilizing a PRO measure developed for another disease in the rare disease setting
 - Assessing functioning in pediatric populations
 - Using activity trackers for health research
- Providing a regulatory perspective on advancing the science of study endpoints and clinical outcome assessments
- Examining associations between activity data and patient-reported outcome data in pediatric populations
- Panel Discussion and Q&A

Session Participants



Moderator

Michelle Campbell, PhD – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Presenters

- Nerissa Kreher, MD, MBA Chief Medical Officer, AVROBIO
- Bryce B. Reeve, PhD Professor and Director of Center for Health Measurement, Duke University
 School of Medicine
- Ebony Dashiell-Aje, PhD Reviewer, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Panelists

 Ronald J. Bartek, MA, BS — Co-Founder/Founding President, Friedreich's Ataxia Research Alliance (FARA)



Overcoming challenges in outcome measurement in rare diseases

Nerissa C. Kreher, MD, MBA Chief Medical Officer, AVROBIO

Outline and Objectives



 Objectives: Understand the challenges of developing patient reported outcome (PRO) measures for rare diseases and consider an example of utilizing a PRO measure developed for another disease in the rare disease setting

• Outline:

- Rare Diseases: What is a rare disease
- Challenges of developing PRO measures in rare diseases:
 - Lack of/Limited natural history data
 - Heterogeneity within the disease
 - Patient perspective and health care provider (HCP) perspective
- Fabry Disease: PRO measure development

What is a rare disease?



- In the United States: < 200,000 affected with disease/disorder
- •In Europe: < 1 in 2000 affected
- •80% of rare diseases have identified genetic origins
- 50% of rare diseases affect children
- Over 6,000 rare diseases exist



Natural History Data:



- Lack of/Limited natural history data
 - Limited availability of prospective natural history data
 - Small number of patients
 - Cohorts of patients followed at certain HCP clinics in varying geographies OR no central HCP following patients
 - Large registry/databases lacking or limited accessibility

Phenotypic Variability:



- Variability in phenotype throughout course of disease
 - Phenotypic expression can range from mild to severe
 - Symptoms in childhood vs. adulthood differ
 - Gender influences on phenotypic expression
 - Time to disease signs/symptoms varies considerably

Importance of HCP and Patient Input:



- Difference in focus on important disease manifestations from HCPs and patients
 - Requires significant patient input
 - Depending on disease, may require caregiver input as well

Efficacy Endpoints for Fabry Disease Trials:



- Recent interest in gastrointestinal (GI) symptoms as an efficacy endpoint in clinical trials for Fabry disease:
 - Suggested utilization of FDA irritable bowel syndrome (IBS) guidance to guide endpoint selection:

We are actively participating with the PRO Consortium and others in the consultation and advice stage of qualification for the development of PRO measures of the signs and symptoms of IBS-C and IBS-D. Once qualified, these IBS subtype-specific PRO measures will replace the provisional endpoints described in this guidance as the FDA's recommended measures of treatment benefit for use in IBS-C and IBS-D clinical trials.

Irritable Bowel Syndrome Guidance:



Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment

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

> May 2012 Clinical/Medical

Fabry Disease:



- X-linked inheritance; however, females exhibit disease signs/symptoms
- Mutation in the gene that encodes for alpha-galactosidase A (AGA); enzyme that breaks down glycosphingolipids that when accumulated in lysosomes leads to disease
- Premature morbidity and mortality
 - Males with classic Fabry disease have life expectancy shortened by ~20 years, on average
 - Progressive renal failure, cardiac arrhythmia, myocardial infarction, stroke, GI distress, anhidrosis, pain, fatigue
- 1 in 40,000 live births (classic males)

GI PROM Development for Fabry Disease PRO



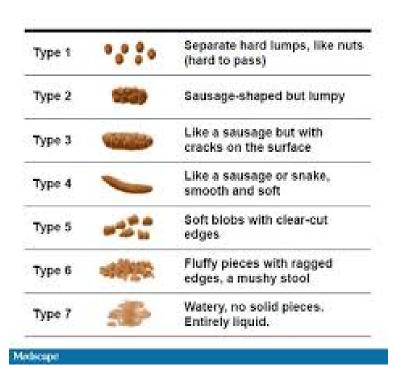
• FDA PRO Guidance (2009)*: PRO measure used to support labeling must be supported with extensive input from individuals drawn from the target population

- 3 PRO measures corresponding to three types of IBS developed by C-Path Institute PRO Consortium (Fehnel et al., 2017)
 - IBS-Constipation Predominant
 - IBS-Diarrhea Predominant
 - IBS-Mixed (encompasses both diarrhea and constipation sub-types)

Diary of Irritable Bowel Syndrome Symptoms – Mixed (DIBSS-M)

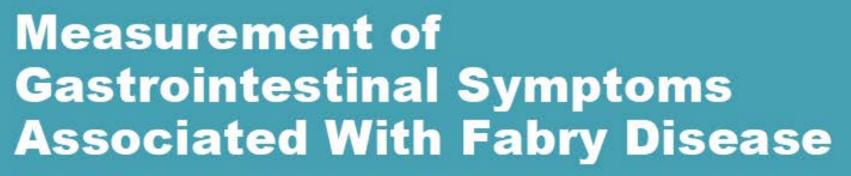


- Ten-item measure
- Each toilet visit is evaluated via the items
- One item includes the Bristol Stool Form Scale (BSFS) with images
- Items include the following response types:
 - Yes/no
 - Rating scales



GI PROM Development for Fabry Disease





Final Report

RTI (h)(s)Health Solutions

GI PRO Measure Development for Fabry Disease



- Objective of Research Study:
 - Identify most important and relevant GI symptoms experienced by patients with Fabry disease
 - Identify the best way to measure these GI symptoms in clinical trials

- Possibilities for PRO measure development:
 - Use or modification of existing scale (such as *DIBSS-M*)
 - Development of new measure

GI PROM Development for Fabry Disease



- Study Population:
 - Closely mirrored the clinical trial population:
 - Patients with Fabry disease:
 - Males > females (~75% males)
 - > 16 years of age
 - Treatment naïve (or >7 years since treatment)
 - Ongoing GI symptoms
 - Patients were identified with the cooperation of two U.S. patient organizations:
 - Fabry Support & Information Group (FSIG)
 - National Fabry Disease Foundation (NFDF)
 - IRB approval obtained prior to study initiation and informed consent obtained prior to each interview

GI PROM Development for Fabry Disease



- •Methods:
 - •2 pronged approach:
 - Targeted literature review
 - Patient Interviews

Targeted Literature Review:



• Targeted **literature review** to evaluate pertinent GI symptoms in patients with Fabry disease and understand any impact of demographics on these GI symptoms (i.e., sex, age)

• Results:

- High variability of GI symptoms by sex and age, and potentially for a given patient over time
- Especially for males with classic Fabry disease, abdominal pain and diarrhea identified as the most common symptoms and important treatment targets
- Supported use of *DIBSS-Diarrhea* predominant

GI Symptoms Identified From Literature Review*:



Table 3. Prevalence of Gastrointestinal Symptoms Among Adults With FD

Source	n	Adults, %	Males, %	Females, %
Pensabene et al., 2016	35	71	_	_
Fabry Outcomes Survey, Mehta et al., 2004	201	_	55	_
Fabry Outcomes Survey, Mehta et al., 2004	165	_	_	50
Fabry Registry, Hoffmann et al., 2007 ^a	271	50	_	_
Miners et al., 2002	38	_	53	_
UK Registry, MacDermot et al., 2001a	70		69 ^b	_
UK Registry, MacDermot et al., 2001b	60	_		58

⁻ indicates that data was not reported; FD = Fabry disease; UK = United Kingdom.

^a Total sample with GI symptoms N = 342, including 271 adults.

^b Sample included 16 children.

Patient Interviews:



- Objective:
 - Evaluate applicability of *DIBSS-M* in Fabry disease:
 - Identify additional items and/or modifications to yield appropriate version for use in Fabry disease
- Methods:
 - Open-ended questions:
 - To elicit GI symptoms associated with Fabry disease
 - To identify GI-related benefits of treatment most important to patients
 - Patients asked:
 - Describe GI symptoms, frequency, and severity
 - What improvements they would need to experience
 - Cognitive debriefing interviews:
 - Describe thought processes as they interpreted and responded to items in the DIBSS-M
 - 2 rounds of interviews:
 - 1st round to identify any additions/modifications that should be tested
 - 2nd round to test any additions/modifications

Example Interview Probes:



Table 1. Example of Scripted Probes

		•
Tested DIBSS-M Item #5	Scripted Probes	Goals
How much did you strain during your bowel movement?	• In your own words, what is this question asking?	 To evaluate respondents' interpretation of the item
	 You said [answer selected]. Tell me what [answer selected] means to you. What were you thinking about when you chose [answer selected]? 	 To obtain information about how participants interpreted and selected their response
	• What do you think about the answer choices? What is the difference between [answer selected] and [another response option]?	 To gain patient feedback on the response options
	• How relevant is this question to you? How bothersome is this to you?	 To understand if this question applies to the individual with FD and if it is an important concept for FD patients

Research Study Results and Recommendations:



Table 10. DIBSS-Mixed and DIBSS-Diarrhea Concept Comparison

	•	•
GI Symptom Concept	DIBSS-Mixed Items	DIBSS-Diarrhea Items
BM-related Symptoms		
Stool frequency	✓	✓
Recurrent BMs	✓	✓
Stool consistency	✓	✓
Urgency	✓	✓
Straining	✓	_
Incomplete BMs	✓	_
Abdominal Symptoms		
Abdominal bloating	✓	✓
Abdominal discomfort	✓	✓
Abdominal pain	✓	✓
Abdominal cramping	✓	✓

^{— =} not included.

BM = bowel movement; DIBSS = Diary of Irritable Bowel Syndrome Symptoms; GI = gastrointestinal.

Assessing how a child feels and functions using patient-reported and activity data



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How does the child feel and function in daily life?

Clinical Outcome Assessments (COAs)



- Patient-reported outcome (PRO) measures
- Clinician-reported outcome (ClinRO) measures
- Observer-reported outcome (ObsRO) measures
- Performance outcome (PerfO) measures



What we observe is not nature itself but nature exposed to our method of questioning.

Werner Heisenberg, 1958

Assessing feeling and functioning in pediatric populations



We are designing better PRO measures to capture the child's voice.







- 7-17 years of age
- 62 Symptom AEs



- 8-17 years of age
- > 20 PRO domains₄

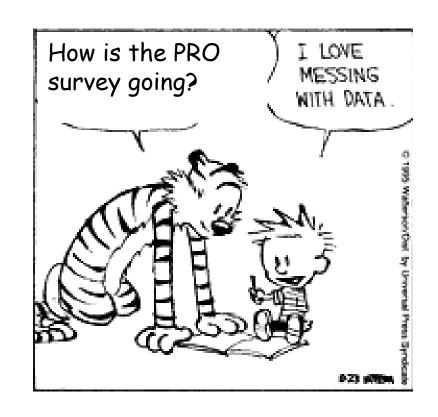
Challenges for Assessing PROs in Children and Adolescents

- Children go through developmental stages of life (different cognitive abilities).
- Disease and/or treatments may delay or stunt their learning.



PRO measures may be limited or not an option....

- Too ill
- Low literacy
- Unable to communicate
- Too young
- Too much of a burden



How well do activity trackers inform our understanding of how a patient is feeling and functioning?



Activity Trackers for Health Research



Benefits

- Passive data collection.
 - Wear the device throughout day.
 - Not dependent on a patient's cognition, literacy, language or health status.
- Provide long term, continuous, and real time monitoring of activity.
- Capture a range of activity.
 - Steps taken, floors climbed, distance, minutes of activity, calories burned, sleep time, heart rate.

Activity Trackers for Health Research



Limitations

- Wearing device may be an inconvenience.
- Data may need to be synched....device needs to be charged.
- Variation in performance among different devices.
- Variation in where the child wears the device.
- Algorithms for summarizing "activity" can be device-specific (and sometimes proprietary).
- Large amounts of data require increased level of expertise and labor needed to analyze actigraphy data.
 - What are best practices for statistically analyzing the data?
 - How to handle missing data?
 - What is a meaningful metric to summarize the data?

Using Activity Trackers in Health Research



39 clinical trials listed in ClinicalTrials.gov are using Fitbit activity trackers.

- Applications
 - Intervention for weight loss or weight maintenance.
 - Intervention to improve physical fitness.
 - Intervention to prevent disease, worsening of disease, or comorbidity
 - Outcome for an exercise intervention or treatment (e.g., steroid injection for lower back patients).
 - Predict poor outcomes (e.g., post treatment)
 - Bayer ran study to look at Fitbit as alternative to 6MWD test.
- Used in Diverse Populations
 - Young and old
 - Cystic fibrosis, obese patients, COPD, diabetes, cancer, asthma, osteoarthritis, heart disease, kidney disease, lupus, caregivers

√/ mobi health news April, 2016

Jonah Comstock: http://www.mobihealthnews.com/content/18-more-clinical-trials-using-fitbit-activity-trackers-right-now-40

We are interested in how activity data can be used to <u>complement</u> <u>PRO data</u> or <u>used as a substitute</u>, when patient-reporting is not feasible, to capture how patients function in their daily lives.







Advancing the Science of Pediatric Patient Reported Outcomes for Children with Chronic Diseases

Children's Hospital of Philadelphia

- Crohn's Disease
- Chronic Kidney Disease
- Cancer (survivors)

Duke University / UNC

- Inflammatory Bowel Disease
- Cancer (active)
- Lupus
- Juvenile Idiopathic Arthritis



Medical College of Wisconsin

- Asthma
- Sickle Cell
- Type I Diabetes

Northwestern University

- Atopic Dermatitis
- Asthma

Funded by the National Institutes of Health. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Grant # U19-AR065922

Duke / UNC PEPR Study Aims



- Examine the association between activity and PRO data in pediatric populations under conditions of changing health states:
 - Children undergoing active treatment for cancer
 - Children with juvenile idiopathic arthritis (JIA) or systemic lupus erythematosus (SLE)
 - Children with "not well controlled" asthma

Sample Sizes



	8 to 12 year olds	13 to 17 year olds
Cancer	50*	75
JIA or SLE	50*	75
Asthma	50*	50*

^{*}supported through supplemental funding by PEPR.

Study Design



- Participants wear a Garmin VivoFit 3 Activity Monitor
 - Step count turned off during study.
- Wear tracker for 7 days and complete PRO measures on day 7

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
← Wear Activity Monitor →						
						Complete PRO
						Measures

 Two 7-day window "assessments" representing different health states of child/adolescent

Assessment Schedule: Children with Cancer



Baseline (T1)	Treatment	Follow-up (T2)	Expected Change
Routine clinic visit before treatment begins*		,	Decrease in health status

Study Measures



- PROMIS Pediatric measures (via computerized-adaptive testing):
 - Physical Activity, Physical Function-Mobility, Pain Interference, Fatigue, Depression, Anxiety, Psychological stress
- Pediatric PRO-CTCAE measures
 - Core symptomatic adverse events (e.g., pain, nausea, diarrhea)
- Clinical Data
 - Treatment initiation, Performance status, Disease activity markers
- Ecological Survey
 - Participation in organized sports, other circumstances affecting activity (e.g., weather, safe area), and days/times in which the device was not worn (and why)



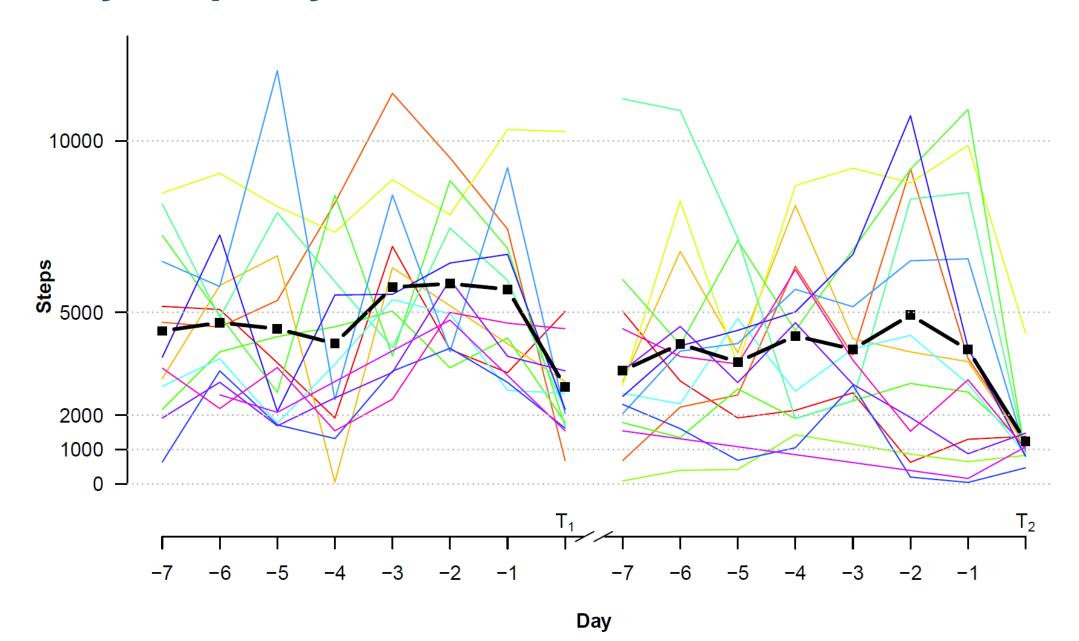
Preliminary Findings

Preliminary sample of 15 children/adolescents



- 10 Hodgkin's Lymphoma; 5 Acute Lymphocytic Leukemia (ALL)
- 8 Female
- 6 African American; 1 Asian
- Ages 8 to 17 years, average 13.7 years

Daily steps by week



Association between PROMIS Pediatric measures and daily steps at T2*

Patient-Reported Outcome	Pearson Correlation
Physical Activity	.51
Fatigue	48
Physical Function – Mobility	.28
Pain Interference	27
Psychological Stress	27
Anxiety	11
Depressive Symptoms	06

Association between Pediatric PRO-CTCAE symptomatic adverse events and daily steps at T2*

Symptomatic AE	Spearman Correlation
Vomiting	-0.47
Cough	0.31
Abdominal Pain	-0.28
Anorexia	0.28
Headache	-0.28
Nausea	-0.26
Pain	-0.25
Fatigue	-0.22
Insomnia	-0.22
Anxiety	0.13
Diarrhea	-0.11
Depression	0.11
Neuropathy	0.09
Mucositis Oral	0.08
Constipation	0.07



Final Thoughts

In relation to Activity data...



- A. How do we determine a "meaningful" change in activity data?
- B. How may we represent <u>quantity</u> and <u>quality</u> of activity into a metric?
- C. How to handle missing data?

Potential options to deal with missing data from activity trackers*



- Examine the # of days with either no or very low # of recorded steps.
- Examine the intra-day data which shows activity in approximately 15 minute increments, to develop algorithms which can indicate if the activity tracker was worn either all day or for at least the large majority of day.
- Consider adjustments to total data estimated data based on % worn during day (not sleeping).
 - 80% wear time with 900 observed steps: 900 / .80 = 1000 estimated steps
- Ecological survey will ask participants if they wore the tracker all the time every day (yes/no) and if no, why not.

In relation to Activity and PRO data...



- A. To what extent can activity data be used as a substitute measure for kids who cannot (or do not) self-report?
- B. To what extent can we create a composite endpoint of activity and patient-reported data to assess how a child functions?
- C. What would be the supportive evidence needed to consider activity data alone or as a composite measure (activity and patient-reported data) as an indicator of treatment benefit?

Can we design a standardized approach to assessing HRQOL across the life span? Physical Health **HRQOL** Social Well-Being Mental Health Life **Older Adult Baby Toddler Child** Adolescent **Young Adult** Adult Span 100+ Clinician-reported outcome (ClinRO) Measures Observer-reported outcome (ObsRO) Measures Data Sources Performance outcome (PerfO) Measures Patient-reported outcome (PRO) Measures



Advancing the Science of Study Endpoints and Clinical Outcome Assessments in Rare Disease and Pediatric Trials:

A Regulatory Perspective

Ebony Dashiell-Aje, PhD

Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration





- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.
- I have no actual or potential conflict of interest in relation to this activity.

Objectives



• To Discuss:

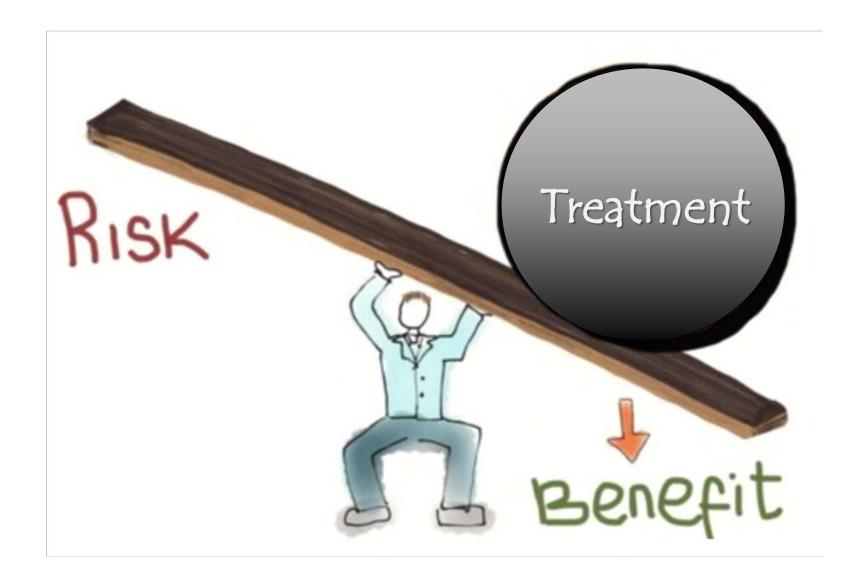
- The importance of measuring clinical benefit
- Clinical Outcome Assessments (COAs) as measures of clinical benefit
- Regulatory considerations for endpoint selection and the use of COAs in rare disease and pediatric trials: challenges and opportunities



Measuring Clinical Benefit

Taking a Step Back: Clinical Benefit





Taking a Step Back: Clinical Benefit



- Clinical benefit is demonstrated through evidence showing that the treatment has a positive impact on:
 - How a patient feels or functions in daily life
 - How long a patient lives (survival)



Clinical Outcome Assessments: Measures of Clinical Benefit

Why Clinical Outcome Assessments (COAs)?



- Measure or reflect a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions
- May be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of clinical benefit



Evidentiary Standards and Regulatory Guidance: Selection, Development and Implementation of COAs in Clinical Trials

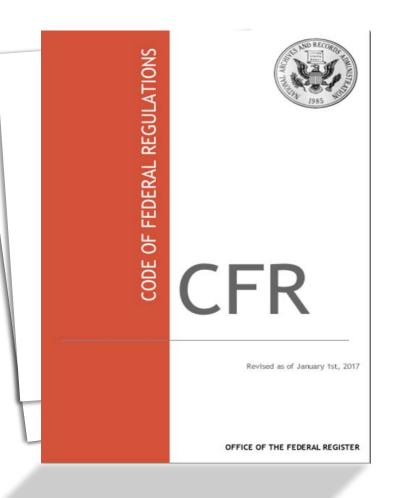


Evidentiary Standards

FDA's Regulatory Standards (21 CFR 314.126)

COAs need to be well-defined and reliable

- There is sufficient empirical evidence to support its use in the target patient population
- Evidence suggests that the tool is measuring:
 - The right thing (concept)
 - In the right way
 - In a defined patient population
 - A score that accurately and reliably reflects the concept of interest.



FDA PRO Guidance (2009)



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

> 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) Center for Devices and Radiological Health (CDRH)

> > December 2009 Clinical/Medical

- Defines good measurement principles to consider for "well-defined and reliable" (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit
- All clinical outcome assessments can benefit from the good measurement principles described within the guidance
- Provides optimal approach to COA development; flexibility and judgment needed to meet practical demands

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



Understanding the Disease or Condition

Conceptualizing Treatment Benefit

Selecting/Developing the Outcome Measure

3

A. Natural history of the disease or condition

- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- · Range of manifestations

B. Patient subpopulations

- By severity
- By onset
- · By comorbidities
- · By phenotype

C. Health care environment

- · Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives

- · Definition of treatment benefit
- · Benefit-risk tradeoffs
- Impact of disease

A. Identify concept(s) of interest for meaningful treatment benefit. i.e., How a patient:

- Survives
- · Feels (e.g., symptoms)
- Functions

B. Define context of use for clinical trial:

- · Disease/Condition entry criteria
- · Clinical trial design
- Endpoint positioning

C. Select clinical outcome assessment (COA) type:

- · Patient-Reported Outcome (PRO)
- · Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- · Performance Outcome (motor, sensory, cognition)

A. Search for existing COA measuring concept of interest in the context of use:

- Measure exists
- · Measure exists but needs to be modified
- No measure exists
- · Measure under development

B. Begin COA development

- Document content validity (qualitative or mixed) methods research)
- · Evaluate cross-sectional measurement properties (reliability and construct validity)
- · Create user manual
- · Consider submitting to FDA for COA qualification for use in exploratory studies

C. Complete COA development:

- · Document longitudinal measurement properties (construct validity, ability to detect change)
- · Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- · Submit to FDA for COA qualification as effectiveness endpoint to support claims

Link to detailed version of Roadmap diagram:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProg ram/UCM370174.pdf



U.S. Food and Drug Administration Center for Drug Evaluation and Research http://www.fda.gov/Drugs



Key Regulatory Considerations for use of COAs to Support Clinical Trial Endpoints

Key Considerations When Evaluating a COA Measurement Strategy







Regulatory Challenges: Endpoint Selection and Use of COA Endpoints in Rare Disease Clinical Trials





- Absence of natural history data
- Limited knowledge related to the likelihood, range, and course of clinical manifestations associated with the disease
- Uncertainty regarding clinical characteristics (manifestations and timing)
- Heterogeneity in clinical manifestations and rate of change



Treatment Target and Measurement Concepts

 Uncertainty about aspects of the disease that are meaningful to the patient and might also be affected by the treatment



Endpoint Derivation & Positioning

- Issues surrounding:
 - What constitutes a meaningful endpoint
 - How to derive a meaningful endpoint
 - Determining COA endpoint positioning



Adequacy of COAs

- Limited availability of existing COAs that might be adopted or modified to support COA endpoints
 - Lack of or very limited evidence generated to support reliability and validity in the target patient population





- Issues surrounding:
 - Whether the COA score reliably and accurately reflects the concept of interest
 - How to derive a meaningful score
 - Reliability, validity and ability to detect change
 - Interpretation of clinically meaningful within-patient change
 - Impact of small sample sizes

Challenge Overview



1. UNDERSTANDING THE DISEASE OR CONDITION

2. CONCEPTUALIZING TREATMENT BENEFIT

3. SELECTING/DEVELOPING OUTCOME MEASURE

What is known about the condition?

- · Natural history data may be limited
- Heterogeneity in clinical manifestations over time and by disease subtype

What constitutes meaningful treatment be nefit?

- ID of a single concept of interest (COI) may be difficult due to heterogeneity of RD sub-populations
- A responder to treatment may be defined differently across subgroups
- Direct measures of treatment benefit (how patients feel and function) may not be possible

Are there any extant COAs that are appropriate?

- The answer is usually "no"
- Modification of extant COAs is still time-consuming, but usually quicker than development of a new COA
- Time and resources may not be available for modification or development of a new COA

How is it treated?

- Disease-specific treatments may not
- · Treatment variation across regions, age, groups, payers, subgroups

How will the clinical study be designed,

- Difficulty with patient recruitment results in less restrictive entry criteria to achieve maximum sample size possible
- Need for creative study design and analysis

i.e., the context of use (COU)?

How does condition impact patients and caregivers?

- · May differ by disease stage, subtype, age, region
- · Little data may exist

Which COA types are needed?

- PRO measure often unfeasible
- ClinRO measure may need to be general in nature
- ObsRO measure must be based on observations-not proxy measures
- PerfO measure development standards are not established

How to develop or adapt the COA for context of use?

- Traditional methods may not be feasible
- No one size fits all solution exists
- · Difficulty with recruitment for patient engagement and qualitative research
- Need for creativity in COA development methods

Fig. 1 - Challenges for Implementing COA Endpoints in Rare Disease Clinical Trials. *Adapted from Food and Drug Administration [28]. https://www.ispor.org/Patient-Reported-Outcome-Observer-Assessment-Rare-disease-trials-guidelines.pdf



Regulatory Challenges: Endpoint Selection and Use of COA Endpoints in Pediatric Clinical Trials





- Cognitive and linguistic developmental differences
- Potential differences in disease manifestations by age subgroups





- Uncertainty about aspects of the disease that are meaningful to the patient and caregivers and that might also be affected by the treatment
- The complexity of the measurement concept and the assessment methods used to measure these concepts



Adequacy of COAs

- Determining what type of COA is the most appropriate
 - PRO, ObsRO, ClinRO, or PerfO instrument?
 - Willingness and ability to self-report (e.g., determining the age of valid and reliable self-report and other age-specific considerations; how to measure symptoms and functioning among patients that cannot self-report)
 - Motivation to comply with study assessments



Adequacy of COAs

- Availability of existing COAs that might be adopted or modified to support COA endpoints
 - There may be limited evidence generated to support reliability and validity in the target patient population



Surmounting Challenges: Regulatory Flexibility and Successful Engagement



Regulatory Flexibility

- Consideration of supportive evidence from multiple sources (COAs and other endpoint measures)
- Encouraging leveraging of existing COAs and data where feasible and appropriate

Pathways for FDA Clinical Outcome Assessment Review & Advice



1

IND/NDA/BLA Pathway

Within an individual drug development program

Potential to result in *labeling* claims

2

DDT COA Qualification Pathway

Outside of an individual drug development program

Development of novel COAs for use in multiple drug development programs addressing unmet measurement needs

Potential to result in *qualification* of COA

Meetings Pathway (e.g., CPIM)

Outside of an individual drug development program

Potential for *general CDER* advice on specific methodology or technology in its early stages of development

DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome IND = Investigational New Drug; NDA = New Drug Application; BLA = Biologics Licensing Application COA DDT Qualification Program Submissions:

Summary



• **Key to overcoming regulatory challenges -** Early planning and discussion with FDA to ensure COAs are fit-for-purpose and measure what is most important to patients and caregivers; advice should be sought early and often.

 There are evidentiary standards that are used to determine whether a COA is adequate for use in clinical trials.
 However, FDA maintains flexibility in our evaluation of evidence, taking into account feasibility and practicality within special patient populations.

Helpful links



- FDA COA Staff Website:
 - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- PRO Guidance:
 - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- DDT COA Qualification Guidance: <u>http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/</u> Guidances/UCM230597.pdf
- COA DDT Qualification Website: <u>http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm</u>
- Critical Path Innovation Meeting Website & Guidance: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm3958 88.htm
- CDER COA Compendium: <u>https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentApprovalPro</u>







Panel Discussion and Q & A



Moderator

Michelle Campbell, PhD – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Presenters

- Nerissa Kreher, MD, MBA Chief Medical Officer, AVROBIO
- Bryce B. Reeve, PhD Professor and Director of Center for Health Measurement, Duke University
 School of Medicine
- Ebony Dashiell-Aje, PhD Reviewer, COA Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Panelists

 Ronald J. Bartek, MA, BS — Co-Founder/Founding President, Friedreich's Ataxia Research Alliance (FARA)