

# **Public Stakeholder Meeting on Prescription Drug User Fee Act (PDUFA) Reauthorization**

January 15, 2021

## **Dr. Theresa Mullin**

Associate Director for Strategic Initiatives  
Center for Drug Evaluation and Research  
Food and Drug Administration

# Outline for this meeting

- Welcome and Roll Call
- Presentation Topics:
  - Enhancing Diversity in Clinical Trials
  - Digital Health Technology and Decentralized Clinical Trials
  - Strength and reach of patient and rare disease programs in patient engagement and encourage greater data sharing
- Topics for upcoming meetings
- Recap and Closing

# Enhancing Diversity in Clinical Trials

Jamie Gamerman  
Office of Medical Policy  
Center for Drug Evaluation and Research

**January 15, 2021**

# Background

- FDA Reauthorization Act of 2017 required a public meeting and publication of a draft and final guidance on improving clinical trial diversity
- Public Meeting held April 16, 2018
- Draft Guidance *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* published June 2019.
  - FDA received approximately 90 public comments in response to the guidance.
- [Final Guidance \*Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Design\*](#) published November 2020

# Recommendations- Inclusive Trial Practices

- Develop new eligibility criteria for each trial- avoid templates
- Ensure representative eligibility criterion when developing clinical trial protocols
- Eliminate restrictive criteria from phase II trials when moving into phase III trials

# Recommendations- Inclusive Trial Practices (Continued)

- Enroll participants from clinically relevant populations
  - Include both sexes in clinical trials to allow detection of clinically significant sex-related differences
  - Include pediatric patients (when appropriate)
  - Include race and ethnic minorities in trials and analysis to identify population-specific signals; include a plan for inclusion of relevant populations by end of Phase 2 meeting

# Recommendations- Trial Designs

- Use adaptive clinical trial designs (e.g. start with a narrow population and later expand to a broader population)
- In early clinical development, characterize drug metabolism and clearance across populations that may metabolize or clear the drug differently
- Consider a broader pediatric development program early- justify age-based enrollment staggering

# Recommendations- Trial Designs (Continued)

- Consider including pharmacokinetic sampling to establish dosing in women who become pregnant during a trial
- Consider including a broader participant group even in enriched clinical trials
- Expanded access regulations provide patients with a serious or immediately life-threatening disease or condition with a pathway to treatment with an investigational drug, provided certain criteria are met



# Recommendations- Study Conduct

- Make trials less burdensome:
  - Reduce the frequency of in-person visits and consider electronic communication (e.g. email, social media, telephone)
  - Consider digital health technology tools
  - Use mobile medical professionals (e.g. nurses and phlebotomists)
- Make participants aware of financial reimbursements

# Recommendations- Recruitment

- Hold recruitment events on nights and weekends and in non-clinical locations (e.g. places of worship, social commercial venues, public events)
- Recruit using real-world data (e.g. claims data, electronic health records) and social media
- More inclusive strategies for public outreach and education (Patient-focused research)
  - Consult patient advocacy groups and medical associations to educate patients about potential trials
  - Engage communities through focus groups, medical societies, and disease registries

# Recommendations- Retention

- Provide trial documents in multiple languages
- Design clinical trial protocols along with patients, patient advocates, and caregivers
- Hold clinical trials in locations with higher concentrations of racial and ethnic minorities
- Use electronic informed consent, while considering the needs of patients without internet access
- Explore agreements to facilitate the exchange of medical records between clinical trial sites

# Recommendations- Rare Diseases

- Engage with rare disease patients and their advocates early in the trial design process
- Re-enroll patients from early-phase trials into later-phase trials
- Use open-label extension studies

**Questions?**



# Digital Health Technology and Decentralized Clinical Trials

Leonard Sacks MD  
Office of Medical Policy  
Center for Drug Evaluation and Research  
US Food and Drug Administration

# History of our efforts to support technology in clinical trials

- Some in the audience will remember when all clinical trials relied on paper records and face-to-face encounters.
- That made sense; Internet was rudimentary, some dialup, big home desktops, big clunky cellphones, no smartphones.
- In the next few years, electronic data capture and management was becoming the norm in many sectors (banking, business, income tax)
- Clinical trials were being left behind

# Technological revolution

- Electronic data
  - easily analyzed, stored, transferred
  - capacity for management of large datasets
- Electronic communication
  - Remote transfer of audio, video and other signals, regardless of distance
  - Instantaneous transfer between one or more parties
  - Communication between devices
- Sensors
  - Miniaturized technologies that make physical measurements
  - Can be placed in environment, worn, implanted or ingested
- Computing Platforms
  - Portable and powerful- cellphones, smartwatches, tablets
  - Support integration of many electronic activities



# Why bother?

- Burden of travelling to trial site
- Disease is rare
- Patients are widespread
- Measurement of response to drugs is clumsy
- Intermittent assessments are unreliable
- Long term follow up is needed
- Local healthcare providers are underutilized in clinical research



# Duchenne's drug evaluation-6MWD

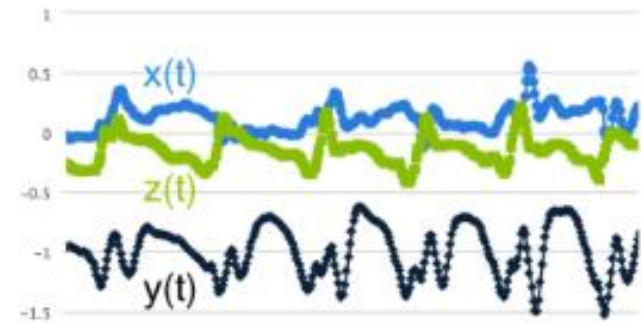


# Accelerometer



**total acceleration**  
measured by the phone

(  $x(t)$ ,  $y(t)$ ,  $z(t)$  )



# Accelerometers-

- ▶ present in cellphones, smart watches, fit bits.
- ▶ 3 dimensional picture of movement.
- ▶ helpful in measuring steps or other activities
- ▶ no need to depend on snapshot measurements and clumsy tests
- ▶ measurements can be recorded over long periods of time
- ▶ baseline comparisons can be made

# Measuring functionality

- ▶ They capture objective data on **functionality** which has traditionally been challenging in clinical trials
- ▶ Potentially useful in neuromuscular and cardiorespiratory diseases, muscular dystrophy, Parkinson's, heart failure, COPD, pulmonary hypertension
- ▶ Potential role in neuropsychiatric diseases, depression, ADHD, schizophrenia



# What are digital health technologies?

## Biosensors

Continuous  
glucose  
monitor



Continuous  
ECG monitor



Continuous  
blood pressure  
monitor



Fall  
detector



Smart pills



Actigraphy

Patient  
reported  
outcome

## Interactive mobile applications



Cellphone  
camera



Coordination  
test in  
Parkinson's



# Digital health technologies

- Digital health technologies (DHTs) are technologies that use computing platforms, connectivity, software, and/or hardware, including sensors, for health care and related uses
- Uses in clinical trials
  - Enrollment, screening and enrichment
    - Help us quantify disease severity, functional status at enrollment
  - Safety monitoring
    - Identification of rare AEs, real time access to safety data
  - Dose effect
    - Visualize response over dosing interval
  - Endpoints
    - Most compelling in superiority studies. Non-inferiority studies may be challenging to interpret

# Novel types of data that continuous recording by biosensors can provide

Opportunities	Examples
Richer data instead of snapshots	average steps per day v.s. 6MWD, continuous glucose monitoring v.s. HBA1C
Ability to detect rare events	arrhythmias, seizures, apneic spells
Data from patients who cannot report	scratching in infants with atopic dermatitis, sleep in patients with dementia
Dose response information	on/off effects in Parkinson's
New types of measurement	Accelerometer measurements of gait stability that may predict falls Measurements of coughing, sneezing, tremor Behavior patterns in dementia or depression



# Types of measurements where Mobile Technology Tools may play a role

- ▶ Clinical laboratory measurements
  - Continuous glucose monitoring, pulse oximetry
- ▶ Physiological measurements
  - Heart rate and rhythm, breathing and lung function, seizures, syncope, temperature, weight
- ▶ Performance assays
  - Activity, stamina, strength, coordination, abnormal movements, sleep, cognition

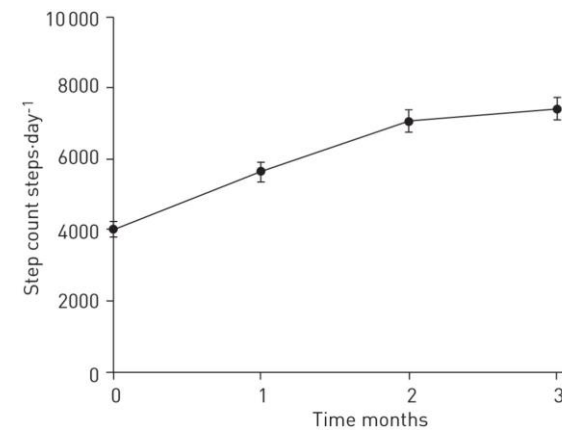
# What does the DHT look like and how does it work?

## **Description** of the DHT

- ▶ relevant physical characteristics of the DHT
- ▶ information on the fundamental physical principles employed by the DHT
- ▶ data output
- ▶ how the DHT is worn, operated, charged

# Can we rely on the DHT?

- **Verification** in the laboratory
  - Accuracy and precision to measure acceleration, temperature, pressure etc?
  - Reliability in different environments- temperature, humidity
  - Does the algorithm used to interpret the raw signal reliably represent the clinical characteristic or event we are trying to capture (e.g. steps, breaths)?

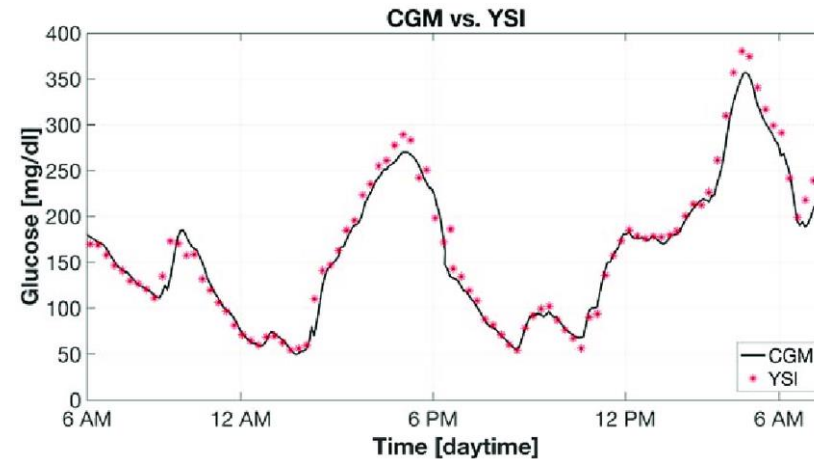


# Discrete events versus continuous measurements

Discrete events



Continuous measurements



# Can we rely on the DHT?

- **Validation** in the field
  - Is the data recorded by the DHT in patients the same as the data we would report if we were looking at the patient? (steps in a patient with Duchenne's, Parkinson's disease,)
  - Is the result affected by how the patient wears or uses the DHT?
  - Are there things that a patient might do that would be misinterpreted by the DHT? (e.g. tapping a foot, riding a bike)



# Is the DHT suitable for use in the trial?

(Operational issues)

- **Usability** determination
  - Ugly or elegant?
  - Easy to put on?
  - Easy to operate?
  - Comfortable to wear for the required time period?
  - Battery life?
  - Syncing data?
  - “Bring your own” devices?



# Bring your own device

## **BYOD**

- allows patients to use their own DHTs e.g., cellphones, smart watches, tablets
- risk of variable data quality
- minimum technical and performance specifications that would allow use of the participant's own DHT
- which commercial DHTs are acceptable

# Endpoints using DHTs

## ► **Defining** the endpoint

What is being measured?	Steps
What is the time window of observation?	4 weeks
What is the formula for the response in each patient?	Change from week 1 to week 4 in average daily step count



# Endpoints using DHTs

## Established endpoints

- ▶ DHTs may serve as new ways to measure clinical characteristics or events that were previously measured in a clinical setting

## Novel endpoints

- ▶ meaningful reflection of how a participant feels, functions, or survives
- ▶ input from stakeholders, such as patients, disease experts, caregivers, clinicians, engineers, and regulators
- ▶ comparison with existing benchmarks of performance- UPDRS, other Patient reported outcomes, 6MWD, hospitalization, mortality

# Regulatory position

- ▶ Regulations do not directly address the use of digital health technologies in clinical trials
- ▶ DHTs used in clinical trials do not need to be approved/cleared by FDA for marketing
- ▶ 1962 FD&C act- the evidence standard: “For drug approval, substantial evidence of effectiveness is **required**, consisting of adequate and well-controlled investigations from which experts could conclude that the drug would have the effect described in labeling”
- ▶ Regulatory implication: Is the quality of the evidence from DHTs adequate for experts to make the right conclusions?

# Other considerations

- Updates and upgrades
- Loss and replacement of DHTs
- Data security and attributability

# Decentralized clinical trials



Source: Duchenne Foundation Australia

# Why the interest in DCTs?

- Patient convenience
- Improved recruitment of patients with limited mobility
- Ability to study patients in widespread locations
- “Real world” data
- Ability to study diseases in new ways
- Continuous data rather than snapshots
- Objective measurements
- Reduced missing data
- Capturing rare events

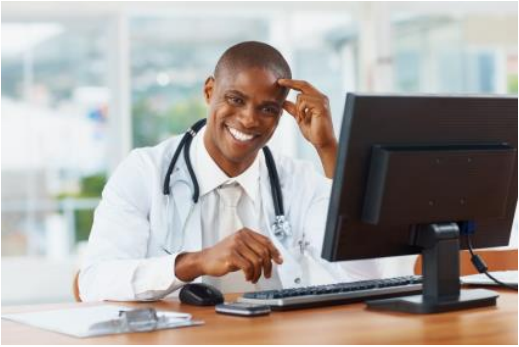


# Decentralized clinical trials

- Clinical investigations where some or all trial-related activities take place at locations remote from the investigator.
- May involve a mix of site-based and decentralized activities
- When are they appropriate?
  - Stable medical conditions, no need for specialized nursing and complicated trial-related procedures
  - Investigational products that are easy to administer, with low risk safety profiles

# DCT setup

Network of locations where delegated personnel and HCPs provide trial-related health care services (e.g., imaging and laboratory services) are provided, all under the oversight of the investigator



Clinical  
investigator



Trial participant

# Remote study visit



- Conducted using telehealth -video or telephone based communication
- Visiting healthcare providers/study nurses may assist with study-related activities at patients' homes
- Accessible local health services for adverse events or other emergencies





# Oversight\*



- Investigator
- Sub-investigator

FDA form 1572

- Local health care providers, radiologists, phlebotomists, visiting nurses
  - Qualified by experience and training
  - Documentation of decentralized activities

Responsibility log

- Local emergency room
- Neighborhood clinic
- Pharmacy

Not part of study staff

\*Guidance for industry-Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009

# Safety



- High risk products and severe diseases may not be suitable for DCTs
- Patients should be able to contact study staff
- Local medical facilities should be available for urgent care



# Shipment of medical products



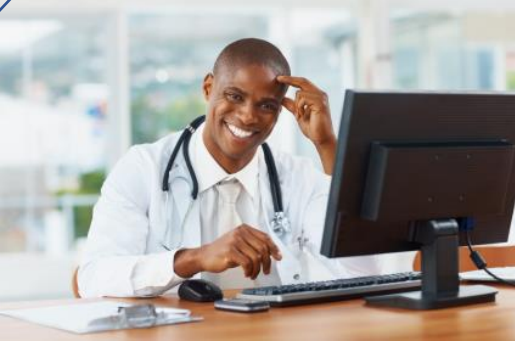
- control the release of the product by the distributor,
- monitor receipt by trial participants
- monitor the return or disposal of any unused product



- Distribution service
- Packaging and shipping



# Inspection



- Investigator
- Sub-investigator

## Site inspection

- where the data are
- where study staff can be interviewed

- Local radiologist
- Local health provider
- Phlebotomist
- Visiting nurse

## Local inspection

- may be necessary if problems are found

- Local emergency room
- Neighborhood clinic
- Pharmacy

# Conclusions

- ▶ Digital trial technologies and new communication technologies may change the way many trials are done
- ▶ As a medical community we cannot ignore the potential advantages of these approaches for patient convenience, inclusivity, continuous monitoring and trial efficiency
- ▶ A thoughtful dialogue with drug developers, patients, disease experts, and regulators is needed to advance these approaches in a judicious way

Questions?



# Office of Orphan Products Development (OOPD): Supporting Rare Disease Product Development

Janet Maynard, MD, MHS  
Director, Office of Orphan Products Development  
PDUFA VII Stakeholder Meeting with FDA  
January 15, 2021

# FDA Rare Disease Product Development

- Many staff throughout FDA collaborate to ensure optimal rare disease product development





# OOPD Core Program Areas



## Designations

1. Orphan Drug Designation (ODD) (and Exclusivity)
2. Rare Pediatric Disease (RPD) Designation
3. Humanitarian Use Device (HUD) Designation

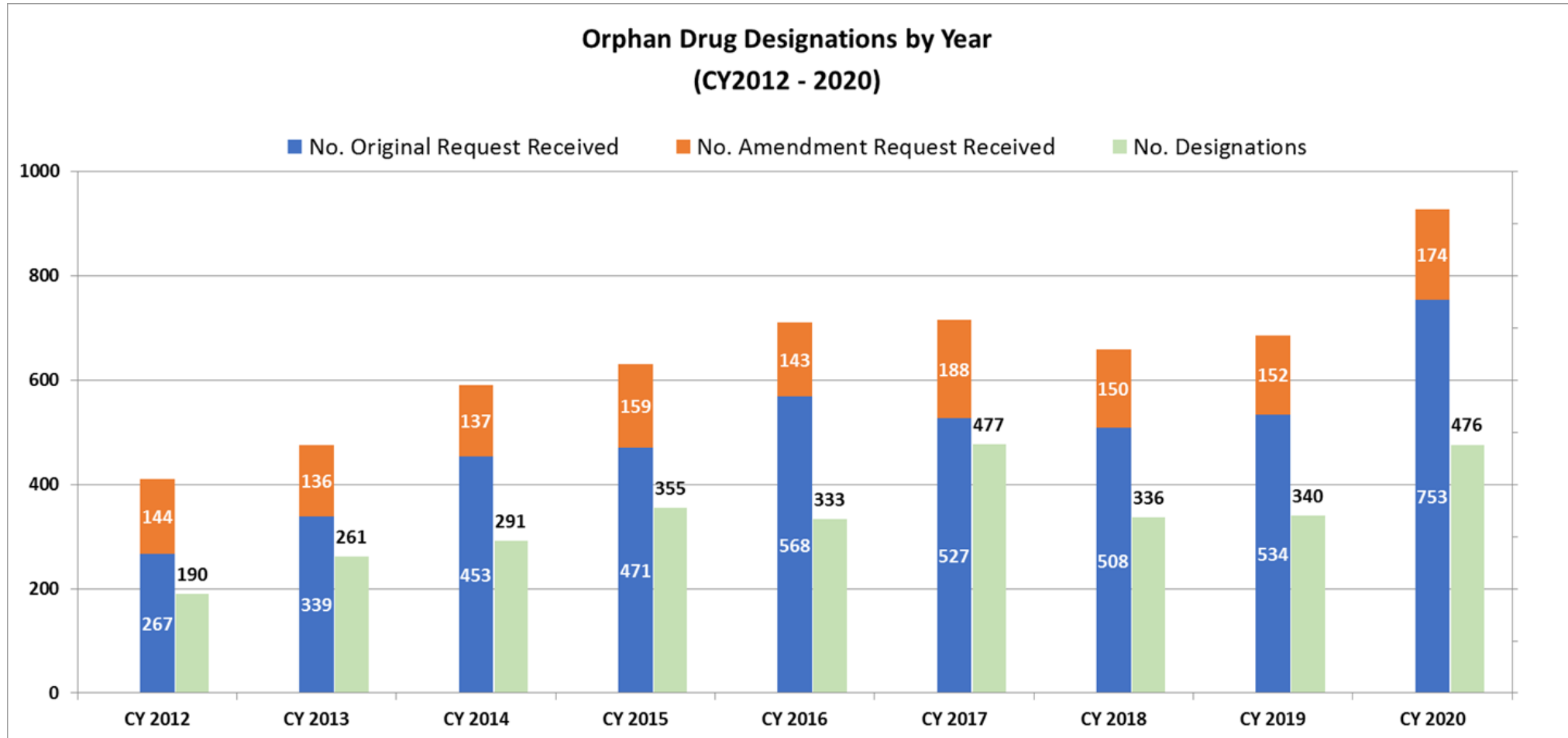
## Outreach

1. Internal Collaborations
2. External Collaborations
3. Public meetings

## Grants

1. Orphan Products Clinical Trials Grant Program
2. Natural History Grant Program
3. Pediatric Device Consortia Grant Program

# Orphan Drug Designation Trends



Note: Designations granted in a given year may include requests received from that year as well as previous years.

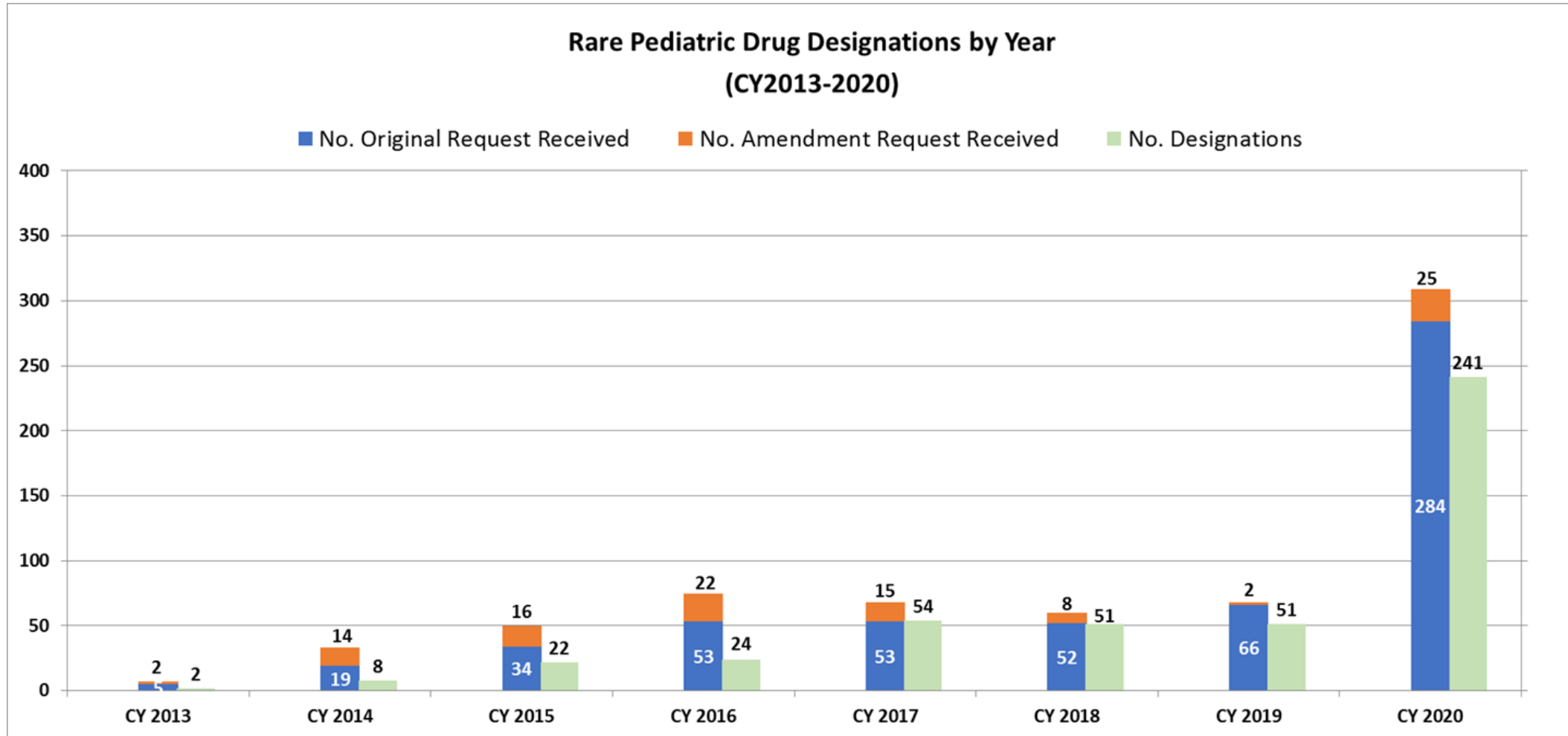
# Orphan Drug Technology Modernization Effort

- **Highlights**

- Move from a paper-based process to a new cloud-based external submission portal
  - Portal for orphan drug designation requests is now available
- Implement a new workflow management tool
- Enhance collaboration, integration, and automation during review and processing of requests



# Rare Pediatric Disease Designation Trends



Note: Designations granted in a given year may include requests received from that year as well as previous years.

# Rare Disease Outreach



[FDA Rare Disease Day 2020: Supporting the Future of Rare Disease Product Development](#)

February 24, 2020

- Some examples
  - Orphan Products Policy Council
  - Rare Disease Council
  - Meetings with Centers
  - Orphan Cluster meetings with European Medicines Agency (EMA)
  - Patient Listening Sessions, led by FDA's Patient Affairs in partnership with the National Organization of Rare Disorders (NORD)

# Orphan Products Grants Program



- **Overall Budget:** \$17.7M
- **Goal:** To advance the development of orphan products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis or treatment of rare diseases or conditions
- **Clinical Trial Grants**
  - Funding ~75 ongoing studies
  - Grants have led to over 70 product approvals, publications, regulatory milestones, impact on field
  - Focus on efficiency, innovative trial designs, and inclusion of patient input
- **Natural History Grants**
  - Currently funding 7 grants
  - Impact in clinical trial development, collaborations with industry and patient groups and publications

# Conclusions

- Vast majority of rare diseases do not have approved treatments
  - Developing rare disease treatments is challenging
- Key to have collaboration and patient involvement

# Strength and Reach of Patient and Rare Disease Programs: Rare Disease Cures Accelerator

Michelle Campbell, PhD  
Office of Neuroscience  
CDER



# Key Activities presenting areas of challenge

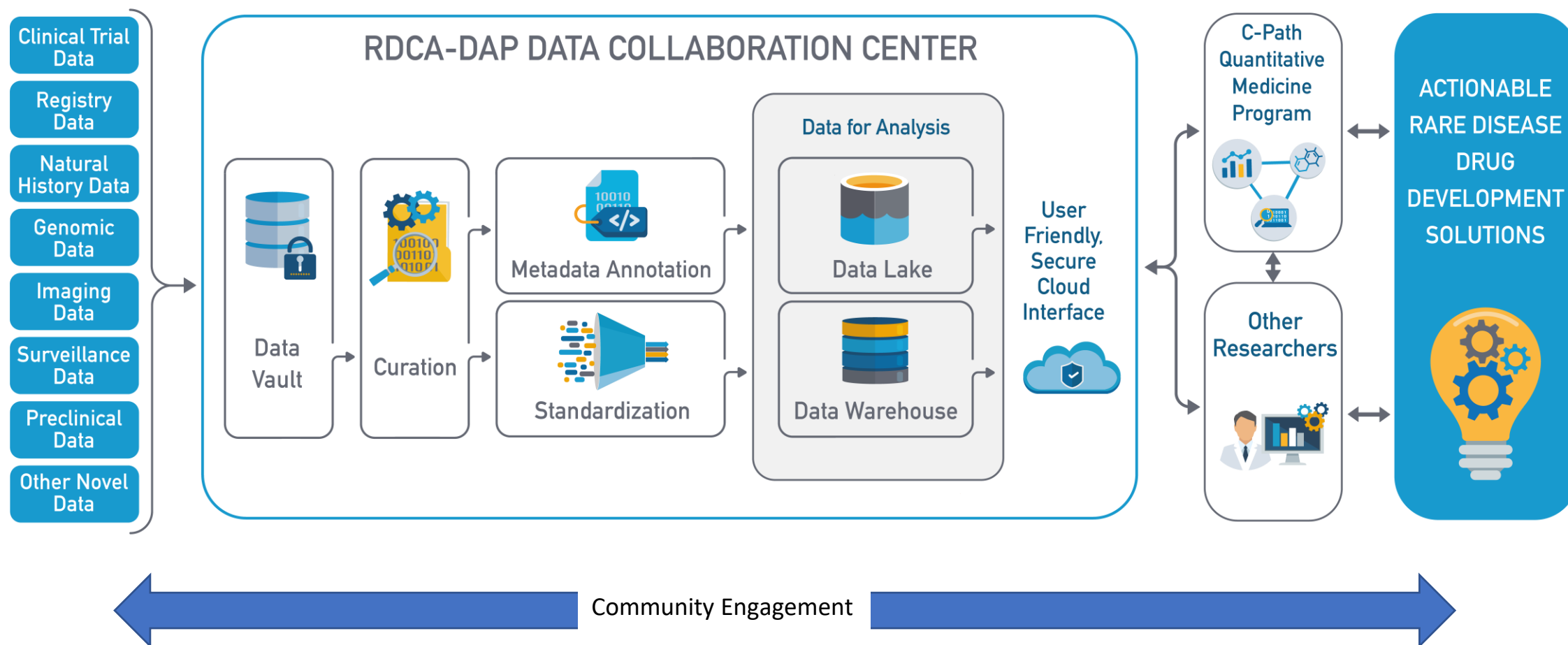
Discovery / Translational / Preclinical		Clinical Development
<b>Characterization of Disease</b> <ul style="list-style-type: none"> <li>• What is known about the disease?</li> <li>• Are there well-defined lab tests—to diagnose the disease?</li> <li>• What is the natural history of the disease?</li> <li>• What causes the disease (pathogenesis)?</li> </ul>	<b>Getting Patient Perspectives on their Disease and Treatment</b> <ul style="list-style-type: none"> <li>• What disease impacts matter most to patients?</li> <li>• What is the landscape of currently available treatments?</li> </ul>	<b>Clinical Study of New Treatments</b> <ul style="list-style-type: none"> <li>• Is the investigational drug available in a form that can be administered?</li> <li>• Pre-clinical safety testing done to inform assessment of safety in humans?</li> <li>• A study design specified?</li> <li>• A study protocol?</li> <li>• IRB review and approval?</li> <li>• IND submitted for FDA review?</li> <li>• Plan for patient enrollment?</li> <li>• Patient access to the trial site?</li> <li>• Plan for study data collection?</li> </ul>

# Centralized and Standardized Infrastructure to Support and Accelerate Rare Disease Characterization

- There is a compelling need for:
  - Efficient comprehensive **characterization of the natural history of a given rare disease** targeted for clinical development
  - Characterization **conducted rigorously with attention to established data quality standards**, in order to be most useful to clinical trial design and regulatory review
- A standardized rare disease **natural history study data platform** is needed to provide a sustainable approach
  - This platform would **provide a disease-neutral background data framework** for the conduct of standardized natural history studies.
  - **Disease-specific needs would be layered onto this framework** to provide a rapid means for standardized, yet customized, development of natural history studies for any given disease.

# RDCA-DAP

- Critical Path Institute and NORD partnering on initiative



# RDCA-DAP: Long-term Goal for Impact on Drug Development



- More efficient and effective clinical trial protocols
- Standardized data that can be extracted in CDISC format for regulatory submission
- Understand variance in disease progression across broad range of patients aiding in development of optimized clinical trial protocols (endpoints, inclusion criteria, length and size of trial)
- Analytics and simulation tools to help optimize your trial protocol for your therapy
- Ability to look at dynamics of change in outcome measures and biomarkers in individual disease states and in related diseases and understand sources of variation in rate of change
- Ability to potentially find and match historical or contemporary control patients to enrich your placebo arm and reduce numbers of patients.

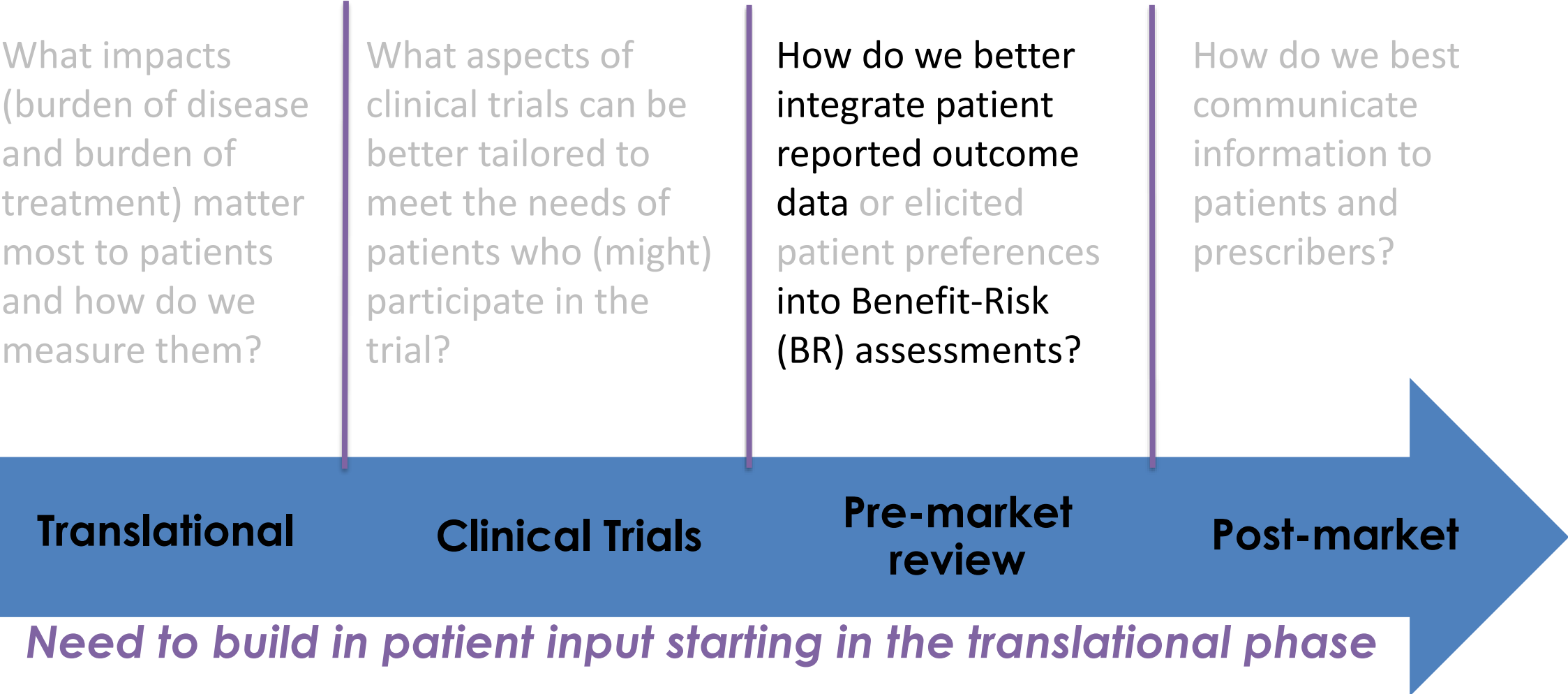
# THE STANDARD CORE CLINICAL OUTCOME ASSESSMENTS AND THEIR RELATED ENDPOINTS GRANT PROGRAM

**Robyn Bent, RN, MS**

Director, Patient Focused Drug Development

CDER, U.S. FDA

# Integrating patient input into medical product development and decision making



# Coming Full Circle



Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	PFDD Meetings and Reports provide powerful narrative that gives regulators insights about clinical context and what matters to patients	
Current Treatment Options		
Benefit	Using methodologically sound measures & tools (COAs) to systematically capture what matters most during clinical trials can turn narrative into evidence for regulatory decision making	
Risk and Risk Management		
Benefit-Risk Summary and Assessment		

# Standard Core COA and Endpoints Pilot Grant Program



## Why

- There is **currently little coordination** in development of COAs including within a given disease area
- Reviewers currently may see **multiple independent efforts**
  - Duplication of effort and diversity of measures and proprietary tools that limit affordability and sustainability
  - **Variable quality of tools and resulting data** that limit utility for regulatory decision making
- Goal: Enable development of standard core sets of measures of disease burden and treatment burden for a given area—that would be made publicly available at nominal or no cost



# Standard Core COA and Endpoints Pilot Grant Program



Who: On September 11, 2019 the FDA made the following three awards



Migraine Clinical Outcome Assessment System (MiCOAS)



Clinical Outcome Assessments for **Acute Pain** Therapeutics in Infants and Young Children  
(COA APTIC)



Northwestern University Clinical Outcome Assessment Team (NUCOAT) – **Physical Function**

<https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints>

# The Second Funding Opportunity



The purpose of this second FOA was to solicit applications to support the development of a publicly available core set(s) of COAs and their related endpoints for the following four areas:

- **fluid overload in nephrotic syndrome**
- **age appropriate domains of pediatric daily functioning**
- **the mechanics of swallowing and speech from infancy to adulthood**
- **treatment effects in systemic sclerosis**

The deadline to submit an application to this FOA, [RFA-FD-21-004](#), was October 14, 2020. Awards are expected to be announced in the coming months.

Questions?

**Discussion/Any Other Business**

# Upcoming Topics

**Friday, February 19, 2021**

10:00am-12:00pm EST

- TBD

# **PDUFA VII Closing Remarks**

December 11, 2020

**Dr. Theresa Mullin**

Office of the Center Director  
Center for Drug Evaluation and Research  
Food and Drug Administration