Annual Patient Engagement & Regenerative Medicine Meeting: An FDA CBER Workshop for Patient Advocates

Tuesday, May 24, 2022, 11:00 a.m. – 3:00 p.m. ET

Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Moderated by:
Anne Rowzee, PhD
Associate Director for Policy, OTAT, CBER, FDA
Workshop Agenda

11:00 a.m.  Welcome Session

11:05 a.m.  Natural History Study Overview

11:45 a.m.  Panel Discussion – Perspectives from Patients and Advocates

1:00 p.m.  Lunch

1:30 p.m.  Panel Discussion – How FDA & Other Organizations are Supporting Natural History Studies

2:30 p.m.  Closing Remarks
Virtual Meeting Considerations

- The webinar will be recorded and available online after the event.
- Closed captioning is available in Zoom.
- Use the Q&A box to submit questions throughout the event.
- Use the chat box to share general comments and report technical difficulties.
RegenMedEd Series

- OTAT’s event series about regenerative medicine
- Goals of the RegenMedEd Series:
  - Discuss foundational information about regenerative medicine therapies, including gene therapy and cell therapy
  - Explore opportunities to engage with FDA and advance regenerative medicine research and drug development
  - Hear from FDA, patients, advocates, researchers, and other important stakeholders about their experiences
Session 1:
Natural History Study Overview

Speaker:
Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Our Mission

The Office of Tissues and Advanced Therapies (OTAT) promotes the public health through collaborative, science-based regulation of medical products. This includes facilitating drug development and ensuring safety of individuals. OTAT’s regulatory decisions are data-driven, impartial, and compassionate.
Regenerative Medicine Therapies

- Regenerative medicine involves using stem cells, engineered biomaterials, gene editing, and other technologies to repair or replace damaged cells, tissues, or organs.

- Types of regenerative medicine therapies (RMTs):
  - Gene therapies (including gene editing)
  - Cell therapies
  - Tissues and tissue engineering products
  - Xenogeneic cell products
## FDA’s Role in Regulating RMTs

- **Regulate products over their entire lifecycle—during development and after approval**
- **Provide oversight of clinical trials to protect patient safety and rights**
- **Advance development by providing advice and education to product developers, including academicians and industry**
- **Engage stakeholders to facilitate development of innovative products that meet patient needs**
Drug Development Overview

- Development
- Preclinical
- Phase 1
- Phase 2
- Phase 3
- Biologics License Application
- Post-Marketing

Investigational New Drug Application
Rare Diseases and Gene Therapy

- 80% of rare diseases are caused by a single-gene defect.
- FDA has approved two gene therapies for single-gene disorders.
- 1271 investigational new drug applications for ongoing gene therapy clinical trials.
- Patient participation in clinical research is critical.
How Patients Can Advance Research & Development

- Patient Listening Session
- Public Meeting
- Special Government Employee
- Clinical Trial
- Patient-Focused Drug Development
- Natural History Study
- Patient Registry
Natural History Studies: Defined

- A study that follows a group of people over time who have, or are at risk of developing, a specific disorder.

- A natural history study collects data in order to understand the disorder. Information may include:
  - Age
  - Diagnosis
  - Symptoms
  - Effect on quality of life
  - Test results
  - And more
### Natural History Studies: *Purpose*

- Identify demographic, genetic, environmental, and other variables that correlate with disease development and outcomes.
- Better characterize the disease and the patient population.
- Clarify the impact on the lives of patients and their families.
- Collect patient-reported outcomes and other clinical outcomes that are specific to the disease.
- Inform the clinical drug development process.
Natural History Studies: Types

Retrospective versus prospective natural history studies: Both rely on data collected from patient visits.

**Retrospective:**
- Past
- Often a first step in describing progression
- Data are collected from existing medical records

**Prospective:**
- Ongoing
- Establish definitions and data to be collected ahead of time
- Data are collected from ongoing patient visits
Natural History Studies: Types, continued

Cross-sectional versus longitudinal natural history studies: Both rely on data collected from a cohort.*

**Cross-sectional**
- Data collected over a specified, limited time period

**Longitudinal**
- Data collected at various time points over a long period

*Can be either retrospective or prospective*
Natural History Studies: Protocols

FDA recommends that natural history study protocols specify, in detail:

- Who should be included in the study (inclusion and exclusion criteria)
- What information is to be collected
- When the data will be collected (if prospective)
- How data are to be collected and analyzed
Natural History Studies: Drug Development

- The FDA does not require that natural history studies be conducted for drug development programs.

- To be applied in a drug development program:
  - The FDA recommends an early evaluation of the depth and quality of existing natural history knowledge.
  - Most useful if conducted and data are available prior to drug development program.

- Data should be collected for a sufficient duration to capture clinically meaningful outcomes and determine variability in the course of the disease.
### Natural History Studies: Benefits to Disease Research in Clinical Development

These studies can inform important aspects of drug development:

<table>
<thead>
<tr>
<th></th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Refines the target patient population</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Identifies and develops clinical outcomes</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Identifies and develops biomarkers</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Informs design of future clinical trials</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Serves as external control (in limited circumstances)</td>
</tr>
</tbody>
</table>
Natural History Studies: *Purpose in Rare Disease Research*

- The progression of rare diseases is often poorly described.
- Natural history data can be critical for drug development.
- When knowledge about the disease is insufficient to guide clinical development, a natural history study may help in designing an efficient drug development program.
Enhancing Collaboration

There are many ways stakeholders can work together to advance regenerative medicine; FDA encourages:

- Drug developers to invite patients / advocates to their meetings with OTAT
- Patient groups to take on natural history studies and patient registries
- Patient groups to work together
- Groups to begin collaboration early
Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

wilson.bryan@fda.hhs.gov
Contact Information, continued

- **Regulatory Questions:**
  - OTAT Main Line – 240 402 8190
  - Email: OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

- **OTAT Learn Webinar Series**

- **CBER website**

- **Phone:** 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch:** ocod@fda.hhs.gov

- **Manufacturers Assistance and Technical Training Branch:** industry.biologics@fda.hhs.gov

- **Follow us on Twitter**
Break

11:40 a.m. to 11:45 a.m. ET

Stay tuned! Our next session will begin at 11:45 a.m. ET.
Session 2:
Perspectives From Patients and Advocates

Moderator:
Karen Jackler, MPH
Patient Engagement Program Manager
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Meet Our Panelists

Leah Schust Myers  
Founder, Executive Director  
FamilieSCN2A Foundation

Amanda and Bailey Regalado  
Type 2/3 New Family Representatives,  
Gaucher Community Alliance

Bradley Williams, PhD  
Director of Research & Diagnostic Innovation,  
Jain Foundation

Bruce Marshall, MD  
Executive Vice President and Chief Medical Officer,  
Cystic Fibrosis Foundation
Conflict of Interest Disclosure

I have nothing to disclose.
**Who We Are**

WE ARE AN ORGANIZATION CREATED BY PARENTS OF CHILDREN DIAGNOSED WITH RARE FORMS OF EPILEPSY AND AUTISM AS A RESULT OF A CHANGE IN THE SCN2A GENE.

**Mission**

TO IMPROVE THE LIVES OF THOSE AFFECTED BY SCN2A-RELATED DISORDERS THROUGH RESEARCH, PUBLIC AWARENESS, FAMILY SUPPORT AND PATIENT ADVOCACY.

**Vision**

TO FIND EFFECTIVE TREATMENTS AND A CURE FOR SCN2A-RELATED DISORDERS.

**Values**

URGENCY
INTEGRITY
COLLABORATION
INCLUSION
SCN2A-related disorders

- Leading single-gene cause of neonatal-onset seizures and autism spectrum disorder
- Diagnosed exclusively through genetic testing
- Average time to diagnosis is 5 years, much longer in underserved communities
- Precision treatments mean nothing without precision diagnostics
What is important to US (the patients and caregivers)

SCN2A Community Poll

<table>
<thead>
<tr>
<th>SCN2A Families</th>
<th>reduce seizures</th>
<th>increase communication</th>
<th>cognition / alertness</th>
<th>improve behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>
How do you measure improvement in a clinical trial?

- What exactly needs to be measured?
- What does the instrument actually measure?
- Is it appropriate for our severely affected group?
What is already out there

- Standardized scores decrease with age—cannot distinguish why
  - Regression?
  - Plateauing?
  - Slow acquisition of skills?

Berg et al., Epilepsia, 2020
New or adapted?

Create new measurement tools?
- Work
- Time
- Money

OR—
- Understand the population
- Adapt already validated measurement tools
SCN2A: Clinical Trial Readiness Study (CTRS)

This study will provide information on the reliability of specific measurements over a short period of time and the rate at which they change over time in an individual child.

Early data is showing Vineland III is potentially useful, as it has separate expressive and receptive scales.

Also, the CSBS captures social behavior and communication together, with very little floor/ceiling effect.
SCN2A-related disorders defined

- 1,000+ self-identified patients in 2021
- Estimated incidence: 1/9,000–1/10,000
- Diagnosis can be made only through genetic testing
- Treatment with sodium channel blockers for GoF variants has shown to be most useful
- No treatment for LoF
- Severe, life-limiting comorbidities, including:
  - Refractory Epilepsy
  - Autonomic Dysfunction
  - Cortical Visual Impairment
  - Gastrointestinal Dysfunction (reflux & constipation)
  - Movement Disorders (chorea, ataxia, dystonia)
  - Neuropathic Pain
  - Sleep Disorders
  - Urology Problems

### SELF-CARE

<table>
<thead>
<tr>
<th>Task</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dress themselves</td>
<td>5%</td>
</tr>
<tr>
<td>Drink from a cup</td>
<td>12%</td>
</tr>
<tr>
<td>Use spoon and fork</td>
<td>21%</td>
</tr>
<tr>
<td>Brush own teeth</td>
<td>5%</td>
</tr>
<tr>
<td>Use a touchscreen</td>
<td>22%</td>
</tr>
<tr>
<td>Scribble or write</td>
<td>14%</td>
</tr>
<tr>
<td>Wash and dry hands</td>
<td>9%</td>
</tr>
<tr>
<td>Use a touch screen</td>
<td>5%</td>
</tr>
<tr>
<td>Are completely independent for toilet use</td>
<td>5%</td>
</tr>
</tbody>
</table>

### COMMON MEDICAL CONDITIONS

- **Lungs**: 20% reported conditions affecting the lungs. These were related to low muscle tone, aspiration and tracheostomies.
- **Endocrine Dysfunction**: 18% reported endocrine dysfunction. 9% precocious puberty.
- **Dental**: 13% Teeth grinding. 11% Late baby teeth.
- **Musculoskeletal**: 20% Dystonia. 38% Hypotonia. 17% Spasticity. 23% Scoliosis.
- **Vision**: 71% had vision/eye concerns. 41% Cortical-visual impairment. 13% Difficulty judging distance, depth, visual-motor impairment.
Learning more

**EATING**

44% are completely dependent on a caregiver for feeding

Feeding tube
- 20% Exclusively G-tube fed
- 9% Partially G-tube-fed

Can drink or eat these foods with no difficulty*

- 60% water
- 66% solids (apple sauce)
- 57% Bite-sized soft food like piece of bread or banana
- 46% Bite-sized crunch food like crackers
- 23% Bite-sized piece of chewy food like meat
- 20% Bite into a crispy food like an apple

*Non G-tube dependent only

**LABOR – DELIVERY – FIRST MONTH**

- 23% - pre-term
- 35% - complications during labor & delivery
- 22% - emergency c-section

53% - evaluated & treated for serious condition in neonatal period

- 32% problems feeding
- 9% failure to thrive
- 20% jaundice
- 12% breathing problems/apnea
- 16% encephalopathy
- 34% neonatal epilepsy

40% admitted to NICU

25% NICU admission >=1 month

**MOTOR**

- 75% Moderate to severe gross motor delay

21% walk outside independently for distances

- Cannot control head
- Cannot sit independently
- Have to be lifted or hoisted

12% pick up raisin with thumb and forefinger

18% cannot grasp objects with their hands

21% and older depend on a mobility device for any distance
89% Moderate to severe language delay

72% inconsistently or rarely communicate even with people they know (e.g. family)

29% speak a few or more words
16% speak as their primary form of communication
15% communicate by sign or device only
56% have no symbolic language

15% use >100 words/signs/symbols
8% combine 3+ words into sentences
23% understand >100 words/signs/symbols
Our impact is evolving

- We are most proud of OUR COMMUNITY!
  - Education, financial, and emotional support
- 2021 was the year of the VOICE
  - FDA listening session
  - Launched Clinical Trial Readiness Study
- 2022 is the year for Building Towards a Cure
  - Clinical trials beginning
  - Scheduling a patient-focused drug development (PFDD)
In summary

• Non-seizure outcomes are critical to clinical trial readiness for rare neurodevelopmental disorders, such as SCN2A

• Rare diseases—rare outcomes
  • Not meaningfully assessed with instruments standardized for the typical population

• Alternative approaches are promising
  • Growth scores
  • Adapted
  • Out of range

• Full understanding of the disease and the drivers of outcomes is critical
Thank You!
Meet Our Panelists

Leah Schust Myers  
Founder, Executive Director  
FamilieSCN2A Foundation

Amanda and Bailey Regalado  
Type 2/3 New Family Representatives,  
Gaucher Community Alliance

Bradley Williams, PhD  
Director of Research & Diagnostic Innovation,  
Jain Foundation

Bruce Marshall, MD  
Executive Vice President and Chief Medical Officer,  
Cystic Fibrosis Foundation
I have nothing to disclose.
Bailey Regalado (Age 13)

Hometown: Midlothian, Texas

Hobbies/Interests: Horse riding, dogs

Dreams for the Future: Hopes for a cure, easier access in the U.S. to necessary medications, and trade in port/weekly infusions for a pill
Diagnosis: Neuronopathic Gaucher disease

Age of Diagnosis: 10.5 months

Medical History:
- 3 ports placed for infusions
- Plate/screw implants on right side of hip
- 2 strabismus repair surgeries
- Tonsil and adenoid removal
- Cochlear implant surgery
Bailey Regalado (Age 13)

Symptoms:
- Enlarged spleen and liver
- Moderate to profound hearing loss in both ears
- Cognitive impairment
- Epilepsy
- Bone fragility
- Frequent hospitalization due to respiratory illness
- Exhaustion
- Avascular necrosis in right hip
Meet Our Panelists

Leah Schust Myers
Founder, Executive Director
FamilieSCN2A Foundation

Amanda and Bailey Regalado
Type 2/3 New Family Representatives,
Gaucher Community Alliance

Bradley Williams, PhD
Director of Research & Diagnostic Innovation,
Jain Foundation

Bruce Marshall, MD
Executive Vice President and Chief Medical Officer,
Cystic Fibrosis Foundation
Brad Williams, PhD
Director of Research, Jain Foundation
Living with Dysferlinopathy, aka limb-girdle muscular dystrophy type 2B/R2

Disclosures:
• Employee of the Jain Foundation
• The Jain Foundation, and I personally, are entitled to receive contingent payments from Sarepta Therapeutics based on drug commercialization milestones.

What is dysferlinopathy?

- Autosomal recessive type of muscular dystrophy
- Typical onset 15-30 years age
- Estimated 2,000-3,000 patients in the United States
Clinical Outcome Study in Dysferlinopathy (COS)

- 190+ participants, all genetically diagnosed with LGMD2B/R2
- 15 clinical centers in 8 countries
- 2013-2018—each participant followed longitudinally 3-5 years (6-8 visits)
- Several outcome measures evaluated for use in clinical trials
- 11 papers published (so far) on COS findings

Clinical centers located in California, Missouri, North Carolina, Ohio, and Maryland in the United States and in Australia, France, Germany, Italy, Japan, Spain, and the UK.
Findings and Benefits of COS

- Identified best outcome measure ("NSAD" adapted from DMD, now used in clinical trials in other LGMD subtypes)
- Identified:
  - Which patients will be most sensitive to detecting a treatment effect
  - Number of participants needed for a trial
- "Dress rehearsal" for an interventional trial
  - Familiarized clinicians with the disease, evaluation methods, and working together
- Learnings about the disease are informing the development of a standard of care
Start your natural history study *before* there’s a treatment to test in a clinical trial—otherwise you’ll have to play catchup later.
Meet Our Panelists

Leah Schust Myers
Founder, Executive Director
FamilieSCN2A Foundation

Amanda and Bailey Regalado
Type 2/3 New Family Representatives, Gaucher Community Alliance

Bradley Williams, PhD
Director of Research & Diagnostic Innovation, Jain Foundation

Bruce Marshall, MD
Executive Vice President and Chief Medical Officer, Cystic Fibrosis Foundation
The Cystic Fibrosis Foundation Patient Registry

Bruce Marshall, MD
Executive Vice President and
Chief Medical Officer
Disclosures

Bruce Marshall has no personal disclosures to make. However, to advance drug development and a search for a cure, his employer the Cystic Fibrosis Foundation (CFF) has contracts with several companies to help fund the development of potential treatments and/or cures for cystic fibrosis. Pursuant to these contracts, CFF may receive milestone-based payments, equity interests, royalties on the net sales of therapies, and/or other forms of consideration. Resulting revenue received by CFF is used in support of our mission. See “How Drugs Get on the Pipeline” on the CFF website for more information.

Additionally, CFF may license CFF Patient Registry data to some companies to monitor drug safety as part of the U.S. Food and Drug Administration’s required Phase 4 clinical trials process and to encourage research aimed at improving the care of people with CF, while maintaining our obligation and commitment to protect the privacy of Registry participants. In connection with these licenses, and upon request, CFF may also assist company researchers in interpreting CFF Patient Registry data to aid in designing, analyzing, and interpreting real world studies in CF.
Cystic Fibrosis Foundation - 1955

**Mission:** To ensure the development of the means to cure and control Cystic Fibrosis (CF) and to improve the quality of life for those with the disease
A therapeutic regimen for patients with cystic fibrosis.

LeRoy W. Matthews, M.D.,* Carl F. Doershuk, M.D.,** Melvin Wise, M.D.,
George Eddy M.D., Harry Nudelman, M.D., and Samuel Spector, M.D.

CLEVELAND, OHIO
The Cystic Fibrosis Foundation Patient Registry: Design and Methods of a National Observational Disease Registry


Annals ATS Volume 13 Number 7 July 2016
• Generalizability
  - 81%-84% of individuals with CF in the United States enrolled

• Lost to follow up
  - Retention rate for the 2009 cohort through 2013 was 90.6%

• Completeness
  - 95% of encounters and 90% of hospitalizations in the medical record captured

• Accuracy
  - Registry data matched the medical record 82.6% to 99.9% of the time depending on the data element
Uses of the Cystic Fibrosis Foundation Patient Registry

- **Disease Surveillance**: Track progress in curing CF and the impact of treatments.
- **Framework for Clinical Trials**: Test promising new therapies.
- **Post-Marketing Surveillance Studies**: Ensure safety and effectiveness of approved products.
- **Quality Improvement**: Provide all patients with high-quality care.
- **Comparative Effectiveness Research**: Promote evidence-based clinical decision making.
Identification of the Cystic Fibrosis Gene: Genetic Analysis

Bat-sheva Kerem, Johanna M. Rommens, Janet A. Buchanan, Danuta Markiewicz, Tara K. Cox, Aravinda Chakravarti, Manuel Buchwald, Lap-Chee Tsui

Science; 1989; 245(4922): 1073-1080
Cystic Fibrosis

- Complex, multisystem chronic disease
- Nearly 40,000 people with CF in the United States and >100,000 worldwide
- Autosomal recessive, genetic disease
- CFTR gene-major mutation (F508del) and >2,000 variants
- CFTR modulator drugs address basic defect
### CFTR Modulators by Year, 2014-2020

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Eligible</th>
<th>Pct Eligible on Modulators</th>
<th>Total on Modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>1,763</td>
<td>60.6%</td>
<td>1,069</td>
</tr>
<tr>
<td>2015</td>
<td>10,433</td>
<td>48.3%</td>
<td>5,040</td>
</tr>
<tr>
<td>2016</td>
<td>12,815</td>
<td>52.3%</td>
<td>6,701</td>
</tr>
<tr>
<td>2017</td>
<td>15,189</td>
<td>58.8%</td>
<td>8,936</td>
</tr>
<tr>
<td>2018</td>
<td>17,076</td>
<td>69.0%</td>
<td>11,788</td>
</tr>
<tr>
<td>2019</td>
<td>23,116</td>
<td>69.2%</td>
<td>16,005</td>
</tr>
<tr>
<td>2020</td>
<td>23,304</td>
<td>86.1%</td>
<td>20,067</td>
</tr>
</tbody>
</table>
Median Predicted Survival Age, 1989–2020  In Five Year Increments
Annual Number of Transplant Procedures

<table>
<thead>
<tr>
<th>Year</th>
<th>Liver</th>
<th>Lung</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>17</td>
<td>226</td>
<td>10</td>
</tr>
<tr>
<td>2016</td>
<td>21</td>
<td>269</td>
<td>9</td>
</tr>
<tr>
<td>2017</td>
<td>17</td>
<td>255</td>
<td>10</td>
</tr>
<tr>
<td>2018</td>
<td>23</td>
<td>257</td>
<td>13</td>
</tr>
<tr>
<td>2019</td>
<td>20</td>
<td>244</td>
<td>14</td>
</tr>
<tr>
<td>2020</td>
<td>21</td>
<td>91</td>
<td>10</td>
</tr>
</tbody>
</table>
Number of Pregnancies in Women 14 to 15 Years with CF, 2000, 2005, 2010, 2015, 2020

- 2000: 180
- 2005: 193
- 2010: 222
- 2015: 235
- 2020: 619
How Rare Disease Patients Can Move Scientific Discovery Forward
Break

1:00 p.m. to 1:30 p.m. ET

Stay tuned! Our next session will begin at 1:30 p.m. ET.
Session 3:
How FDA & Other Organizations Are Supporting Natural History Studies

Moderator:
Devaveena Dey, PhD
Scientific Reviewer
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Meet Our Panelists

Captain Julienne Vaillancourt, RPh, MPH
Rare Disease Liaison and Policy Advisor
CBER, FDA
U.S. Public Health Service
Commissioned Corps

Katherine Needleman, MS, PhD, RAC
Director
Orphan Products Grants Program,
Office of Orphan Products Development, FDA

Eric Sid, MD, MHA
Program Officer
Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences, National Institutes of Health
CBER Support of Natural History Studies for Rare Diseases

CAPT Julienne Vaillancourt, RPh, MPH
CBER Rare Disease Liaison
May 24, 2022
CBER Advises And Encourages Natural History Studies Of Rare Diseases

- Regulatory meetings with individual sponsors
- Regulatory correspondence to sponsors (proprietary) on a case-by-case basis
- FDA-held public meetings
- CBER talks at stakeholder-held meetings
- Patient engagement meetings
- One-on-one interactions with patient advocates
Regulatory Guidance Addressing Natural History Studies

- **Rare Diseases: Natural History Studies for Drug Development (Draft, 3/2019)**
- **Rare Diseases: Common Issues in Drug Development (Draft, 1/2019)** *
- **Human Gene Therapy for Rare Diseases (Final, 1/2020)**
- **Human Gene Therapy for Retinal Disorders (Final, 1/2020)**

“...the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized.” *(lines 115-116)*
CBER-Supported, NORD-Sponsored Natural History Study of MLD

The Natural History of Metachromatic Leukodystrophy (MLD)

- Novel framework for building regulatory-grade natural history studies incorporating patient information
- Dynamic data collection via NORD’s IAMRARE® registry platform and CBER’s SHAPE App
MLD HOME Study
ClinicalTrials.gov Identifier# NCT04628364

Primary Study Aims

Design & implement a natural history study for MLD to serve as a source of external control data, to augment or replace concurrent controls in clinical trials

Pilot test & develop guidance on how to design, conduct, & analyze the data from a natural history study to support adaptive trial designs for regulatory use

Reduce burden of participation in trials & provide a potential solution to patient recruitment challenges, particularly for randomized clinical trials

Design approaches that support remote participation in studies
MLD HOME Study

Study Update:
• Status: Recruiting
• 26 registered participants as of April 30, 2022

Learn More:
• Visit the website to find out more or to enroll

Thank you to everyone “in the village” who has contributed to this study in one way or another!
SHAPE App: Survey for Health and Patient Experience

CBER-supported mobile app developed by IBM

- Platform for collecting patient experience data via surveys
- Easy to use
- Allows reporting of real-time events
- Compatible with mobile and desktop devices

Use of app not limited to HOME Study (currently open-sourced)

- May be configured for other study types (e.g., clinical trials, registries)
- Available on Apple App Store or Google Play
- To find out more visit: https://patientexperience.app
Other FDA Efforts That Support Natural History Studies

**Rare Disease Cures Accelerator Data Analytics Platform**

- FDA-supported initiative led by Critical Path Institute (C-PATH) in collaboration with NORD and FDA/CDER
- Provides a centralized and standardized infrastructure to support and accelerate rare disease characterization
- Integrates patient-level data from multiple sources such as natural history studies in a regulatory grade format
- **Goal:** accelerate therapy development across rare diseases
- Learn more [on C-PATH's website](#)

**Natural History Studies Grant Program**

- Administered by FDA’s Office of Orphan Products Development
- Launched in 2016
- Supports efficient & innovative natural history studies that advance medical product development in rare diseases and conditions with unmet needs
Summary

- Natural history studies can inform regenerative medicine therapy development for rare diseases
- CBER advises and encourages conducting natural history studies for rare diseases
- Several FDA-issued guidances address natural history studies
- The MLD HOME study and the SHAPE App are innovative ways that CBER supports natural history studies
- CBER participates in other FDA efforts that support natural history studies
Thank you!

Julienne.Vaillancourt@fda.hhs.gov
Meet Our Panelists

**Captain Julienne Vaillancourt, RPh, MPH**
Rare Disease Liaison and Policy Advisor
CBER, FDA
U.S. Public Health Service
Commissioned Corps

**Katherine Needleman, MS, PhD, RAC**
Director
Orphan Products Grants Program,
Office of Orphan Products Development, FDA

**Eric Sid, MD, MHA**
Program Officer
Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences, National Institutes of Health
Orphan Products Grants Program: Supporting Natural History Studies

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD
May 24, 2022
FDA Rare Disease Interactions
**Mission:** To promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations

### DESIGNATION PROGRAMS

<table>
<thead>
<tr>
<th>Designation Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Orphan Drug Designation &amp; Exclusivity</td>
</tr>
<tr>
<td>2. Rare Pediatric Disease (RPD) Designation</td>
</tr>
<tr>
<td>3. Humanitarian Use Device Designation (HUD)</td>
</tr>
</tbody>
</table>

### GRANT PROGRAMS

<table>
<thead>
<tr>
<th>Grant Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Orphan Products Clinical Trials Grant Program</td>
</tr>
<tr>
<td>2. Orphan Products Natural History Grant Program</td>
</tr>
<tr>
<td>3. Pediatric Device Consortia Grant Program</td>
</tr>
<tr>
<td>4. Rare Neurodegenerative Disease Grant Program</td>
</tr>
</tbody>
</table>
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 80 product approvals, publications, regulatory milestones, impact on field
- Focus on efficiency and innovative trial designs

**Natural History (NH) Grants**
- Currently funding 8 grants
- Impact in clinical trial development, collaborations with industry and patient groups and publications
OOPD’s NH Grants Program: When It Began

- **Launched** the Natural History Grants Program in 2016
- **Goal:** To support drug development for rare diseases through an increased understanding of the impacts and course of rare diseases
- Overwhelming response in terms of interest and applications
- **Funded 6 studies** in FY2017 with $2M budget (2 with support from National Institutes of Health’s [NIH] National Center for Advancing Translational Sciences [NCATS])

- Reissued a new **funding opportunity** in 2018: Focus narrowed, focus on efficiency, innovation, patient input and infrastructure, changes to budget
- **Goal:** To support studies that advance medical product development through the characterization of the natural history of rare diseases and conditions with unmet needs
- **Funded 2 studies** in FY2019
OOPD Natural History Grant Awards

FY2019
1. University of Texas MD Anderson Cancer Center, PI: Elizabeth Grubbs, Prospective Study in Medullary Thyroid Cancer
2. Vanderbilt University Medical Center, PI: Jonathan Soslow, Prospective Study in Cardiac Disease in Duchenne Muscular Dystrophy

FY2017
1. Children's Hospital Corp, PI: Wen-Hann Tan, Prospective Study in Angelman Syndrome
2. Children's Hospital of Philadelphia, PI: David Lynch, Prospective Study in Friedreich Ataxia
3. Columbia University Medical Center, PI: Adi Cohen, Prospective Study in Pregnancy & Lactation Associated Osteoporosis
4. University of Iowa, PI: Alicia Gerke, Retrospective Study in Sarcoidosis
5. University of Tennessee Health Science Center, PI: Kenneth Ataga, Prospective Study in Sickle Cell Anemia to Determine Biomarkers of Endothelial Function Changes in Chronic Kidney Disease
6. Virginia Commonwealth University, PI: Nicholas Johnson, Prospective Study in Myotonic Dystrophy Type 1 to Determine Biomarkers and Clinical Endpoints
Applications of Natural History Studies

Facilitate Drug Development
Inform Clinical Trial Design
Potential to Serve as Historical Controls
Inform Clinical Trial Design
Define Target Population
Develop Clinical Outcome Measures
Develop Biomarkers
Natural History Studies
Planning for Future Cycles

• **Needs/Wants/Things to Consider**
  • Studies to provide optimal support to rare disease product development
  • Standardized approaches to ensure data quality
  • Well-defined and documented protocols before study initiation
  • Collaborative and efficient approaches
  • Use of patient engagement
  • Ability to exert a broad impact
  • Plans for data dissemination

• **Budget**

• **Focus**
Orphan Products Natural History Grants: New Funding Opportunity

**Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (R01)**
- Receipt Date: February 13, 2024
- FOA Number: RFA-FD-22-001

**Purpose:** To support efficient and innovative natural history studies that advance medical product development in rare diseases/conditions with unmet needs

**Focus:** Efficiency, innovation, impact, data quality and interpretability, leveraging patient input, infrastructure and financial resources, future use of data

**Contact:** Katherine Needleman, Director, Orphan Products Grants Program
E-mail: katherine.needleman@fda.hhs.gov
Eligibility and Number of Awards

Eligibility:
• Foreign or domestic, public or private, for-profit or nonprofit entities (state and local units of government) are eligible; Federal agencies may not apply
• Orphan Drug Designation not required for grant application
• Must qualify as rare disease, as generally defined in the U.S. Orphan Drug Act: diseases or conditions with a prevalence of fewer than 200,000 persons in the U.S.

Awards:
• Number of awards is contingent upon FDA appropriations and submission of a sufficient number of meritorious applications
• ~$2 million to fund 2 to 4 applications, depending on the types of studies funded
• Funding dependent on quality of application and availability of Federal funds
Funding

• Prospective Studies:
  – $400,000/year for up to 4 years
• Retrospective Studies:
  – $150,000/year for up to 2 years
General Review Process

1. Initial review by OOPD for responsiveness; notifications of nonresponsiveness
2. All responsive applications are individually reviewed and scored by independent ad hoc experts for technical merit
3. Applications discussed at review panel
4. Scoring based on criteria in RFA
   - Funding based on scores
5. Summary statements issued to applicants with review specifics
6. Prefunding checklist and funding of top scored applications
Orphan Grantee/FDA Connect Meetings

• Early interaction with FDA review divisions is beneficial for NH studies
  – To connect and support communication among FDA review staff, funding agencies, and grantees
  – To discuss key challenges faced by the investigator and strategies to address these challenges
Ways to Engage With OOPD and NH Studies

• Importance of community-wide effort
  • Patients Matter Video on OOPD and NH program

• Become a reviewer

• Help with recruitment

• Future proposals
OOPD Contact Information

For more information on OOPD programs go to

www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov
Or at katherine.needleman@fda.hhs.gov
Call us at 301-796-8660
Meet Our Panelists

Captain Julienne Vaillancourt, RPh, MPH
Rare Disease Liaison and Policy Advisor
CBER, FDA
U.S. Public Health Service
Commissioned Corps

Katherine Needleman, MS, PhD, RAC
Director
Orphan Products Grants Program,
Office of Orphan Products Development, FDA

Eric Sid, MD, MHA
Program Officer
Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences,
National Institutes of Health
Session 3: How FDA & Other Organizations Are Supporting Natural History Studies

Eric Sid, M.D., M.H.A.

*Division of Rare Diseases Research Innovation, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*
Disclosures

- No conflicts of interest
“Advance rare diseases research to benefit patients”
Rare Diseases & Translational Science

Translation is the **process of turning observations** in the laboratory, clinic, and community **into interventions** that improve the health of individuals and the public.

- **Research** on rare diseases has **collective** obstacles
  - Small population sizes
  - Limited research studies

- **Patients** with a rare disease face **common** challenges
  - Narrow clinical understanding
  - Lack of treatments
Example: Jansen’s Metaphyseal Chondrodysplasia (JMC)

Lead Investigators: Thomas Gardella, PhD, and Harald Jueppner, MD, Massachusetts General Hospital

- Extremely rare: ~25 cases known
- Disease of bone development
- Caused by genetic mutations in PTH receptor type 1 (PTHR1)
- No effective treatment options

How do you do drug development for such a small patient population?

Jansen’s Disease Foundation
- Connect key partners
- Engage patient community in clinical research

MGH Clinical Researchers
- Provide scientific and disease expertise
- Care for patients

NCATS Preclinical Support
- Provide drug development expertise and coordination
- Enable transition from preclinical to clinical

NIH Clinical Center
- Natural history study
- Execute clinical trials

https://ncats.nih.gov/trnd/projects/active/jansens-metaphyseal-chondrodysplasia
Therapeutic Development Starts and Ends with Patients

Outreach

Patient advocates helped to initiate collaborations
- Clinicians
- Researchers
- Drug developers

Participation in natural history studies

Academic Research

Identification of potential therapeutic candidate

Initial testing in mouse models of disease

Preclinical Drug Development

Manufacture & formulation of drug candidate

Toxicology studies

Regulatory IND support

Development of clinical assays

Clinical Planning

Natural history

Phase 1/2 trial

Treatment

Potential benefit to children from drug leading to improved quality of life
Clinical Trial Readiness

Who do you treat? Who will conduct the trial?
What is the desired treatment outcome?
WHERE
Where are the patients? Where are the experts?
HOW
How should the trial be conducted?
WHY
Why is this the best proposed treatment?
WHEN
When is the best time to treat a condition?
<table>
<thead>
<tr>
<th>Toolkit For Patient-Focused Therapy Development</th>
<th>RaDaR Rare Diseases Registry Program</th>
<th>GARD Genetic and Rare Diseases Information Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who:</strong> Patient Groups</td>
<td><strong>Who:</strong> Patient Groups &amp; Scientists</td>
<td><strong>Who:</strong> Patients/Caregivers/Public</td>
</tr>
<tr>
<td><strong>What:</strong> Research &amp; Development</td>
<td><strong>What:</strong> Patient Registries</td>
<td></td>
</tr>
<tr>
<td>Educational Website</td>
<td>Educational Website</td>
<td></td>
</tr>
<tr>
<td>- Educational information, resources, and best practices for collaborating with researchers, industry, and regulators on therapy development</td>
<td>- Stepwise educational information, resources, and best practices for starting a registry and best practices around registry data governance and stewardship</td>
<td><strong>Contact Center</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Health Information Website</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- General Information about rare diseases and finding support</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>New Website in Development!</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Focuses on providing access to information for patients/caregivers and to develop via user experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RareDiseases.info.nih.gov</td>
</tr>
</tbody>
</table>
Rare Disease Registry (RaDaR) Website

Data is the currency that research uses to measure success

Registries Translate Stories into Data

https://registries.ncats.nih.gov
A complete reimagining of the GARD website is in development to scale the translation of complex disease ontology data into accessible and actionable information for patients and caregivers. 

https://rarediseases.info.nih.gov
Problem: With the current commercial drug development model, companies cannot recover the costs required to develop gene therapies to treat rare and ultra-rare genetic diseases, because these diseases affect relatively few patients.

Solution: Create tools to streamline the gene therapy development process, aiming to reduce associated costs and encourage companies to pursue gene therapies for rare genetic diseases.

https://fnih.org/our-programs/AMP/BGTC

https://ncats.nih.gov
Closing Remarks - Top Takeaways

1. Natural history studies can advance the development of regenerative medicine therapies.

2. Patients and families are the experts in their diseases, and their voice is critical.

3. There are many opportunities for patients, advocates, and experts to join or support clinical research.

4. The FDA is committed to engaging with and supporting patients and patient advocacy groups.
Stay Connected!

Helpful Resources:

- Visit CBER’s website
- Sign up for our newsletter, “What’s New @ CBER”
- Follow us on Twitter: @FDACBER
- Learn more about natural history studies:
  - Rare Diseases: Natural History Studies for Drug Development
  - Patients Matter: How Rare Disease Patients Can Move Scientific Discovery Forward
Thank you!

Workshop materials will be available in the coming weeks on FDA.gov.

Stay tuned for future RegenMedEd events in 2022!