Advancing Rare Disease Therapies Through an FDA Rare Disease Hub

The hybrid public meeting will begin shortly

Wednesday, October 16, 2024

Time: 10am – 2:30pm ET

This activity is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of $89,000 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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Welcome

Susan C. Winckler, RPh, Esq.

Chief Executive Officer

Reagan-Udall Foundation for the FDA

Hybrid Meeting

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Joining online:
Microphone and video will remain off during the meeting

This public meeting is being recorded
The slides, transcript, and video will be available at www.ReaganUdall.org

Today's Agenda (Eastern Time)

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10am	Welcome & Opening Remarks
10:05am	Principal Deputy Commissioner Remarks
10:15am	A Conversation with The Rare Disease Innovation Hub Co-Directors
10:50am	The Rare Disease Innovation Hub: Looking Ahead
11:05am	Public Comments
12:20pm	Lunch
12:50pm	Public Comments
2:30pm	Adjourn

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Principal Deputy Commissioner Remarks

Namandjé Bumpus, PhD

Principal Deputy Commissioner

U.S. Food and Drug Administration

A Conversation with The Rare Disease Innovation Hub Co-Directors

- **Patrizia Cavazzoni, MD,** Center for Drug Evaluation and Research, FDA
- **Peter Marks, MD, PhD,** Center for Biologics Evaluation and Research, FDA

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The Rare Disease Innovation Hub: Looking Ahead

- **Kerry Jo Lee, MD,** Center for Drug Evaluation and Research, FDA
- **Julie Tierney, JD,** Center for Biologics Evaluation and Research, FDA

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Stakeholder Comments

Virtual Public Comment Process

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1) Commenters will be called by last name in alphabetical order, by topic.
2) Check your chats to see if we've asked you to confirm your name.
3) When your name is first called, use the "Raise Hand" function to identify yourself. Click "Join as panelist" when prompted.
4) Once you are introduced as the next speaker, turn on your camera and unmute.
5) You will have 10 seconds to begin speaking once introduced. If you do not begin speaking within that time frame, we will move to the next commenter.
6) The timer will start as you begin to speak and will count down from 3 minutes. Once time runs out, you will be muted, and we will introduce the next commenter.

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Topic 1 (VIRTUAL): Cross-cutting disease-related, scientific, regulatory, or policy issues (those not related to a particular disease or condition) that should be prioritized for consideration by the Rare Disease Innovation Hub

Reagan Udall: Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub

- Include data collected between when a trial closes and when an application is filed
- Address composite endpoints for heterogenous ultra rare diseases
- Consider “adequate and well controlled” *studies* vs. “adequate and well controlled” clinical trials
- Funding from drug companies should not be considered a conflict, rather, the only way patient organizations can do their valuable work
- Patient organizations should be able to interact with FDA without drug companies present
- Patients need open lines of communication with FDA reviewers
- FDA reviewers need to provide patient groups with feedback on what is useful and not- and why

HAYSTACK PROJECT
The Voices of Rare & Ultra Rare

Kara K. Berasi, PharmD, MS

Kara.Berasi@haystackproject.org

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Gabrielle Conecker

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Curtis Hanson

Organization
Salla Treatment and Research Foundation

STAR is a 501 (c) 3 tax-exempt charitable organization located in New York State and a new member of the Chan Zuckerberg Initiative's "RARE AS ONE" cohort of rare disease advocacy organizations.

We have a community of families from 17 countries around the world and all across the US!

"Salla disease "is named after the region in Finland where disease first noted, and "Salla Disease" is the most mild form of this rare, congenital form of Free Sialic Acid Storage Disorder.

STAR strongly supports the Promising Pathways Act (2.0) – a bipartisan bill to create a conditional approval pathway for drugs.

Our community includes newborn babies, young children, teens and adults. There is a wonderful consortium of researchers (the FSASD Consortium) working in the lab to find drug candidates and potential cures. Please 'fast track' these discoveries when they are made.

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Mary Kohler

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Danny Miller

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Kathleen Troeger

In-Person Public Comment Process

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Commenters will be called by name in alphabetical order.

- We will announce the commenters in sets of three, so you know when your slot is coming up
  - The first time your name is called: **MOVE TO THE STAGE STAIRS**
  - Second time your name is called: **MOVE TO THE OPEN PODIUM**
  - Once you are introduced, you will **SPEAK FROM THE PODIUM.**

Commenters will have 3 minutes to speak. A countdown timer will be provided.

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Topic 1 (IN-PERSON): Cross-cutting disease-related, scientific, regulatory, or policy issues (those not related to a particular disease or condition) that should be prioritized for consideration by the Rare Disease Innovation Hub

Meet Davidson

NPHP1 Family Foundation

Developing an AAV-based NPHP1 gene replacement therapy for the retina

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Jamie Babin

Biotechnology Innovation Organization (BIO) Rare Disease Committee Member Feedback

There are several key points we believe the Hub should prioritize:

1) Improved Coordination & Consistency across FDA Centers
2) Enhancing Communication with External Stakeholders
3) Facilitating Expertise Discussions – FDA Reviewer Training
4) Advancing Scientific Research and Innovation
   - Utilizing *real-world evidence*
   - Conducting *Natural History Studies*
   - *Innovative clinical trial designs* - Collaborate with CDER's C3TI
   - Establishing effective biomarkers & surrogate endpoints and create a clearer framework for Accelerated Approval pathways
5) Host Multistakeholder Scientific Workshops & Forums
6) Incorporating Continuous Multi-Stakeholder Feedback
7) Creating a Strategic Roadmap & Metrics of Success for Short and Long-term Goals

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Richard Horgan

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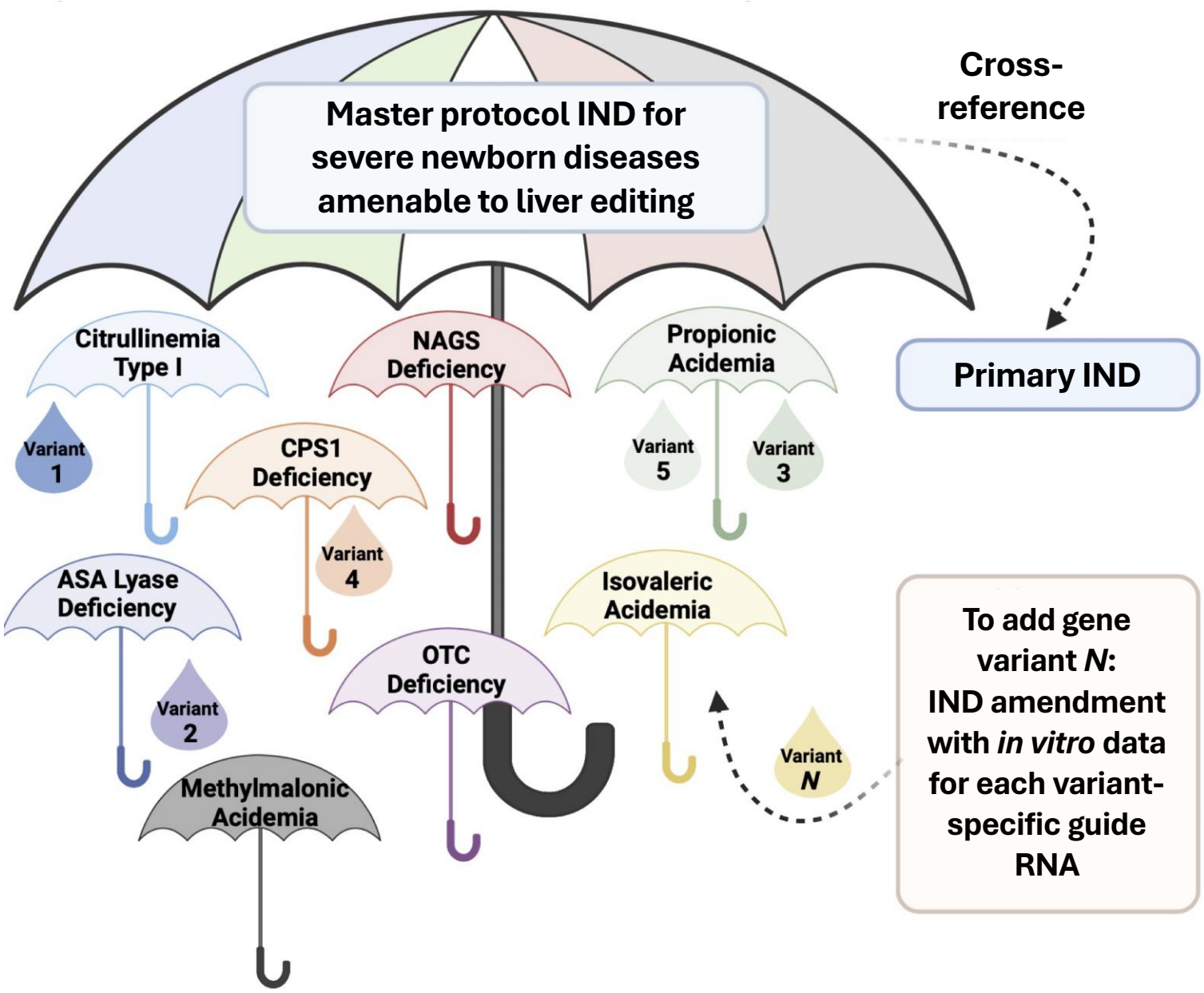
Edward Kaye

Casey McPherson
~~Chmn of TCAR~~
~~Founder of Everlum~~
~~CEO of Chrysalis Genetics~~
Rose's Dad



Cross-reference

Primary IND

To add gene variant *N*: IND amendment with *in vitro* data for each variant-specific guide RNA

CGE
Somatic Cell Genome Editing

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Heidi Ross

Impactful issues in Rare Disease Trials for FDA

- Trial Time
  - Design
  - Recruitment (age!)
  - Regulatory cycle/scheduling
- Trial Cost
  - Time
  - Design
  - Recruitment mandates
- Trial Design
  - Predictability and consistency
  - Point of Maximal Impact (PMI) for age groups (fear of children)
  - Dialogue (IMPACT meeting)
  - Risk acceptance/toleration

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Topic 2 (VIRTUAL): Rare disease-specific (but not application-specific) scientific, regulatory, or policy issues that should be prioritized for consideration by the Rare Disease Innovation Hub

The International Niemann-Pick Disease Registry (INPDR)

- The INPDR maintains a global disease-specific patient registry to better define the natural history of the Niemann-Pick Diseases
- Global collaboration is key to support data collection and research studies which use registry data
- Dialogue with patients, advocacy groups, clinicians, researchers, regulators and industry members is a core principle of the INPDR
- Engagement with the Rare Disease Innovation Hub can support the Mission and Vision of the INPDR and reduce drug development challenges faced by the Niemann-Pick Disease community

Shwachman-Diamond Syndrome

What patients are most worried about is the
INVISIBLE threat of Leukemia

The FDA Rare Disease Innovation Hub should develop a mechanism to work with PAGs and other stakeholders to develop **biomarkers** and **endpoints** meaningful to patients. In our case, to assess across a variety of applications the
INVISIBLE threat of Leukemia

Eszter Hars, Ph.D.
President, SDS Alliance
Mother to a child with SDS

www.SDSAlliance.org
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SHWACHMAN-DIAMOND SYNDROME ALLIANCE

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Mary McGowan

REAGAN-UDALL FOUNDATION FOR THE FDA

Jennifer McNary

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Elad Sharon

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Topic 2 (IN-PERSON): Rare disease-specific (but not application-specific) scientific, regulatory, or policy issues that should be prioritized for consideration by the Rare Disease Innovation Hub

PRIORITIES FOR ULTRA RARE DISEASE FDA REVIEW AND APPROVAL

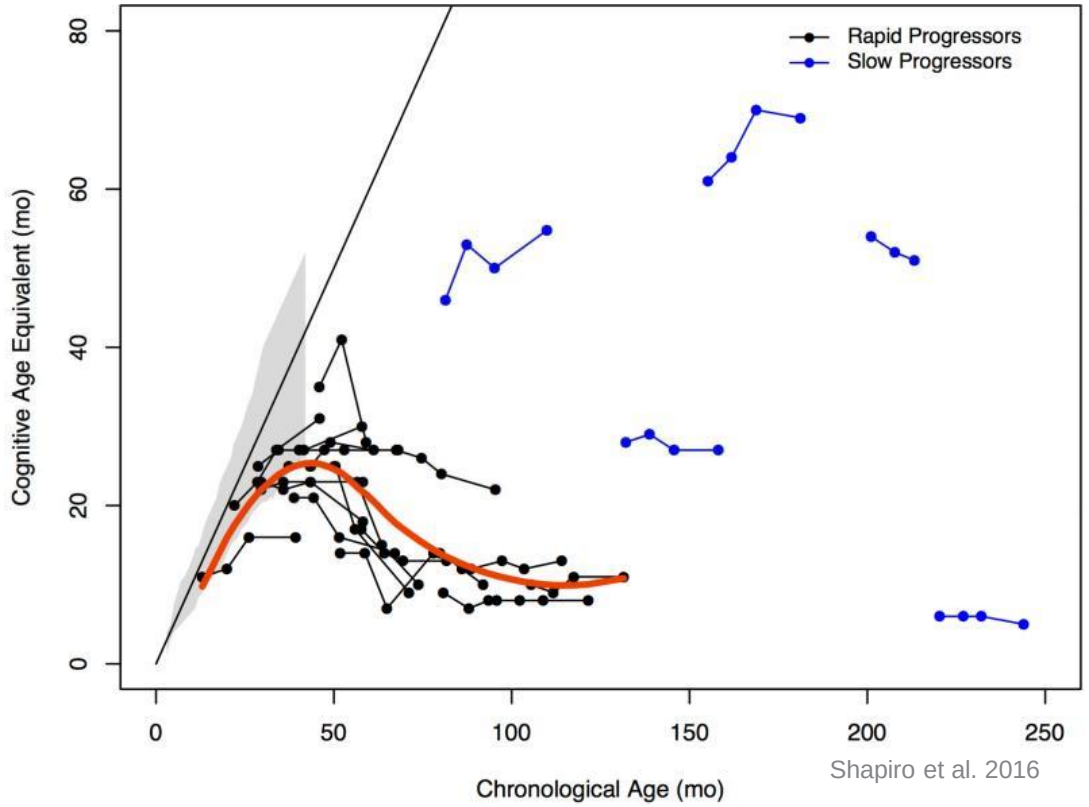
- **Consistent approaches to regulatory standards** across FDA Centers, Divisions, and therapeutic modalities

Example: Approaches to **open label studies** vs. **randomized studies** in a rare disease area requires consistency to continue to promote innovation across multiple therapeutics modalities including genetic medicines (e.g. gene therapy) and novel delivery mechanisms (e.g. brain-targeting therapies)

- **Innovative study designs to accelerate Full Approval** or conversion from Accelerated Approval to Full Approval

Example: How can we leverage **natural history studies** and **duration of follow-up** with registry data for conversion to Full Approval without requiring patients to continue in randomized studies after reasonable likelihood of benefit has been established

COGNITIVE GROWTH TRAJECTORY BY AGE IN MPS IIIA COMPARED TO NORMATIVE GROWTH



Shapiro et al. 2016

Natural history data demonstrates that at ~40 months, cognitive function plateaus and then declines compared to normal development (diagonal line); Thus, continued gain in cognitive skills after ~40 months would be consistent with clinical benefit

FDA Rare Disease Innovation Hub

Proposed Priority Initiatives:

Establishing Cross-functional Consultation Processes

Supporting the Creation of a Knowledge Management System

Advancing Ultra-rare Policy

Enhancing Advisory Committees' Rare Disease Knowledge

Leading the Evolution of Patient Focused Drug Development

Facilitating Pre-competitive Scientific and Regulatory Science Conversations

EVERYLIFE FOUNDATION FOR RARE DISEASES

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Becca Reef

EveryONE MEDICINES

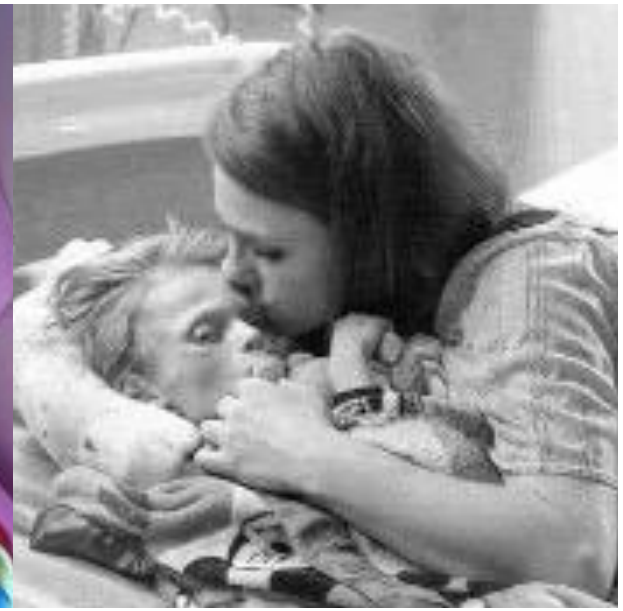
Time is not just of the essence for children with neurodegenerative disease, it is the enemy. New regulatory pathways are needed.

IT'S TIME FOR A TREATMENT FOR GM1 GANGLIOSIDOSIS

136 Years Before Any Clinical Trials

Fatal, Chronic, Neurodegenerative

At diagnosis



Near death

1883 — First description of Tay-Sachs / GM2

1968 — GM1 gangliosidosis described as a distinct condition

2015 — Cure GM1 Founded

CUREGM1 FOUNDATION

2019 — NIH IV AAV9 trial begins

2023 — Lysogene bankrupt, Passage Bio program shelved

2024 — Sio GTx liquidation, Sanofi AMETHIST study terminated, GEMMA Bio founded

2025 — Azafaros trial planned

Lunch

The meeting will resume at 12:50pm ET

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Topic 3 (IN-PERSON): Rare disease-related activities or initiatives currently being undertaken independently by CDER or CBER that you believe would benefit from being undertaken by the Rare Disease Innovation Hub as a joint activity

We cannot lose another generation.

- **Shift the clinical trial model** to reflect the unique challenges of rare disease research.
- No more double-blind, placebo-controlled for pediatric rare diseases.
- Natural history observational studies exist.
- Our current system is doing harm.
- Need consistency across CBER and CDER.
- Must have patient and caregiver representation and systematic integration into the Rare Disease Innovation Hub.

Swift action to change the paradigm for rare disease clinical trials can save this generation.

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Kath Gallagher

REAGAN-UDALL FOUNDATION FOR THE FDA

Deven McGraw

FDA Rare Disease Innovation Hub – Advancing U.S. Rare Disease Therapeutic Development so American Patients Have Access to American Innovation

Kasper Roet, PhD, CEO and Co-founder, QurAlis

Challenges related to preclinical package requirements and assessments should be a priority in the Hub's comprehensive cross-center strategic agenda

Advancing Regulatory Science in Early Phase Development	• Dedicated workstream for specific guidance development and FDA reviewer training in preclinical and pre-IND development phases • Dedicated and experienced reviewers to work closely with industry and academia on new regulatory science techniques for preclinical toxicology and early phase risk/benefit assessments calibrated to disease state severity as well as available therapies
More Rapid Pace of Engagement and Constructive Communications With Sponsors	• Hub consultation obtained prior to FDA's written feedback • Participation and actionable guidance from hub leadership in a timely manner as part of these critical interactions
Expand START Program to Early Phase Development	• Expand START program to further accelerate drug development so that sponsors have the ability to address program-specific early phase development issues, such as alignment and agreement on enabling toxicology plans to support clinical development

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Topic 4 (VIRTUAL): Approaches that the Rare Disease Innovation Hub should follow for engagement with patients and caregiver groups, industry organizations, and scientific/academic organizations

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Robert Kalwinsky

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES




Advancing Rare Disease Therapies Through FDA Rare Disease Innovation Hub

Formal Mechanism for Advocacy Group Engagement

- Advocacy groups should co-create, not just consult.
- Develop clinical outcomes that reflect patient needs.

Structured Platform for Ongoing Collaboration

- Continuous engagement throughout drug development.
- Influence trial design, regulatory guidelines, and evaluation.

Integration into Decision-Making

- Advocacy groups help define patient-centered criteria.
- Focus on quality-of-life improvements and real-world impact.

Patient-Centered Protocol Development

- Direct involvement of rare disease patients and families in trials.
- Ensure protocols are both scientifically sound and patient-focused.

Formal Assessment of Patient Involvement

- Transparent system to track and evaluate patient engagement.
- Hold companies accountable for incorporating patient input.

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Fungal Diseases are Rare Diseases

Rare Disease Innovation Hub

16 October 2024

ROB PURDIE

MANAGING DIRECTOR, MYCARE

MEMBER, WHO TASKFORCE OF AMR SURVIVORS

PCORI AMBASSADOR

RPURDIE@FIGHTFUNGUS.ORG

MYCARE
MYCology Advocacy, Research, & Education

FightFungus.org

Kristen Vanags

Director of Community Engagement

flok Health | flok.org

Rare Disease Hub Patient Engagement Priorities from the Perspective of flok Health

- Establish Equitable Representation of Patient Advocates in Decision Making
- Emphasize Patient QOL in Endpoint Definition
- Prioritize Patient-Generated Data in Product Development
- Regularly Communicate Hub Progress in a Way that Encourages Patient Engagement
- Build Capacity of Rare Disease Organizations to Enable Their Robust Participation in FDA Programs

Key Suggestions for FDA to Support Rare Disease Therapies:

1. IND approval for Rare Disease can significantly **enhance the chances of securing NIH research funding**

2. A streamlined documentation process minimizes overlap between IND and NIH applications

3. The structured Rare Disease Innovation Hub landing page provides a clear information and solution map for efficient navigation, rather than just being a collection of programs or news.

IND Submission (FDA)	NIH R01 Grant Application
Cover Letter	Cover Letter
Preclinical Data, Protocol, IB	Research Strategy
Chemistry, Manufacturing, and Controls (CMC)	Facilities & Other Resources & Equipment
Previous Clinical Experience	NIH BioSketches
Safety Assessment	Human Subjects or Animal Studies
Informed Consent	ICF Process and Materials
Environmental Assessment	Biological & Chemical Resources
Budget Information	Budget with Justification
Collaborator Letters	Letters of Support

Resources

- CBER Rare Disease Program
- CDER's Accelerating Rare disease Cures (ARC) Program
- October 16, 2024, public meeting, "Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub" – *register for the event
- FDA Rare Disease Innovation Hub to Enhance and Advance Outcomes for Patients

CHOC

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Topic 4 (IN-PERSON): Approaches that the Rare Disease Innovation Hub should follow for engagement with patients and caregiver groups, industry organizations, and scientific/academic organizations

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Simone Day

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Kristin Hatcher

Advancing Rare Disease Therapies: The Role of Broad-Based Genetic Testing

Therapy Starts with a Genetic Diagnosis

- Broad-Based Testing: Whole genome sequencing (WGS) and whole exome sequencing (WES) provide comprehensive insights.
- Ending the Diagnostic Odyssey: These technologies reduce the time and uncertainty in diagnosing rare diseases.
- Impact: Enables targeted therapies, improving patient outcomes.

Understanding Biology to Develop Therapy Begins with Gene Discovery

- Broad-Based Testing: WGS and WES facilitate the discovery of novel genes and pathways.
- Impact: Reveals potential therapeutic targets, aiding in the development of novel therapies.

Clinical Trials Require Genetic Testing to Assemble Cohorts

- Broad-Based Testing: WGS and WES help identify suitable candidates by providing comprehensive genetic profiles.
- Impact: Leads to more efficient and effective trials, accelerating the path to new treatments.

Structured and Sustained Patient Engagement

Tailor Engagement Strategies to Fit Each Drug Development Journey

- Ensure it is empowering & effective for the rare disease community
- Solidify the formal role for patient advocacy organizations as key stakeholders
- Replace passive advisory boards with active engagement in all pivotal meetings

Champion Training, Development & Collaborative Partnerships

- Create incentives for academia to transition research to practical drug development.
- Recognize successful collaborations through awards and funding opportunities.
- Collaborate with medical schools to include patient engagement training.
- Emphasize patient perspectives in future research curricula.

Strengthen Trial Substructures

Use Existing Data

- Leverage historical and registry data to reduce patient burden and timelines.
- Foster transparency by sharing lessons from both successful and failed studies.

Trauma-Informed Trial Design

- Incorporate patient and caregiver feedback into trial designs.
- Ensure support resources are available for participants.

Flexible Trial Methodologies

- Engage stakeholders in discussions on innovative trial designs.
- Host workshops to educate on innovative study models.

Cross-Border Collaboration

- Facilitate communication to connect patients with clinical trial opportunities globally.
- Streamline regulatory discussions through inclusive working groups.

An Integrated Approach

- ~~Outreach~~ → Engagement
  - Joint Advisory Boards
  - Feedback loops
- Evidence Based Policy
- Centralized Rare Disease Toolbox
- Shared Data Platforms and Registries

PRAXIS

DARE FOR MORE®

Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub

Hybrid Public Meeting

Thank you for attending!

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