

REAGAN-UDALL FOUNDATION FOR THE FDA

Rare Disease Framework Initiative Public Meeting

October 28, 2026 | 1–5pm *(eastern)*



Funded by the U.S. Food and Drug Administration Center for Drug Evaluation and Research under FDA contract 75F40126C00214



REAGAN-UDALL FOUNDATION FOR THE FDA

WELCOME

Susan C. Winckler, RPh, Esq.

CEO, Reagan-Udall Foundation for the FDA

BEFORE WE BEGIN

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Recording

This meeting is being recorded.

Public Comment

Registered commenters will be called in turn, alternating between in-person and virtual.

Materials

The recording and meeting materials will be posted at reaganudall.org.

Agenda

1pm	**Welcome** Susan C. Winckler, Reagan-Udall Foundation for the FDA
1:05pm	**Framework Initiative Discussion** Michael Davis, Karim Mikhail, and Amy Comstock Rick, FDA
1:45pm	**Break**
1:55pm	**Remarks from the Acting Commissioner of Food and Drugs** Kyle Diamantas, JD, Acting Commissioner of Food and Drugs, FDA
2pm	**Public Comment**
5pm	**Adjourn**

Framework Initiative Discussion



Michael Davis, MD, PhD

Director, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration



Karim Mikhail, B.Pharm, MSc

Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration



Amy Comstock Rick, JD

Director, Rare Disease Innovation Hub, U.S. Food and Drug Administration

Outcome Commitments

- Providing greater clarity, consistency, and predictability in regulatory decision-making through tailored guidance and transparent communication.
- Embedding the patient's voice both early and at clearly defined milestones in the drug development and review process.
- Further leveraging external expertise to support customization of regulatory review.
- Building shared resources, robust training, and institutional knowledge on rare disease drug development and review.
- Applying risk-based approaches to chemistry, manufacturing, and controls review and pre-approval inspections.
- Championing the use of cutting-edge science, novel methods and innovative statistical approaches in rare disease drug development.

Engagement on Framework Initiative

Public Meeting: Public meeting occurring on 10/28 to solicit feedback from the general public

Sector-specific Feedback: Thematic roundtables to solicit additional feedback by sector

Input from several sources will inform the **Rare Disease Framework**

Request For Information: open now through Dec. 11 to solicit additional feedback

Internal Engagement: Four internal workstreams & additional efforts to collect staff feedback

Process

- Led by the leadership of CDER, CBER, the Office of the Commissioner, and the FDA's Rare Disease Innovation Hub.
- Internal Workstreams comprised primarily of CDER and CBER SMEs, including:
  - Tailored Approach,
  - External Engagement – patient voice and external experts,
  - Chemistry, Manufacturing, and Controls (CMC), and
  - Framework Initiative Engagement

  will develop recommendations for next steps for FDA.
- Public and internal engagement will inform the Framework Initiative

Outcome Commitments

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Break

The meeting will resume at

1:55pm ET



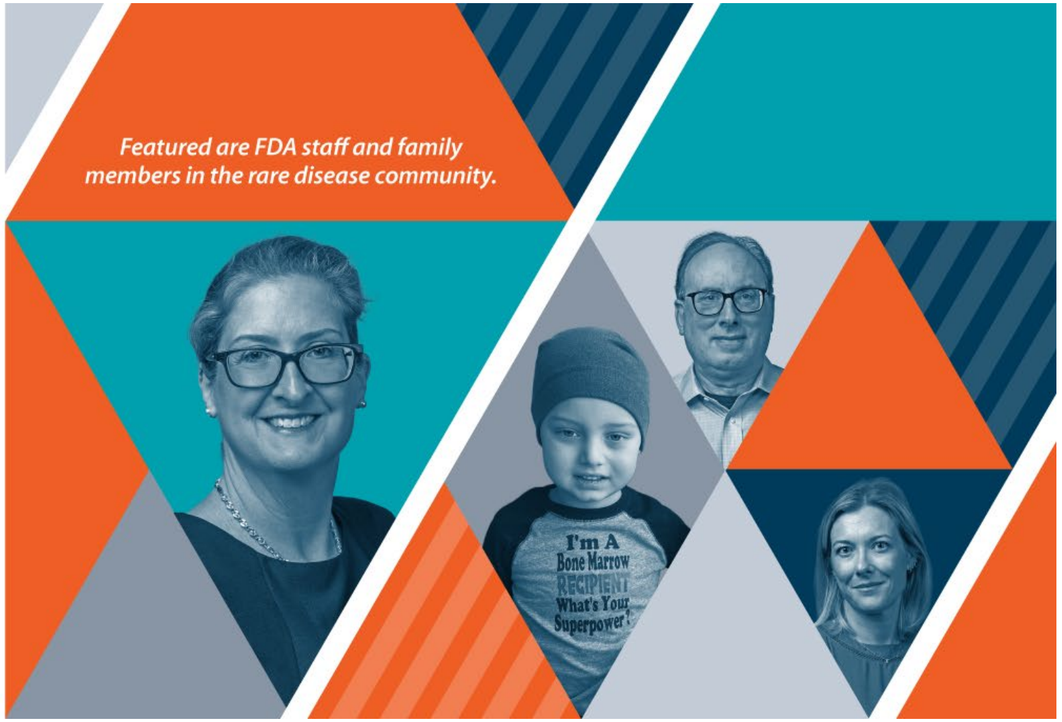
Save the Date

RARE DISEASE DAY2027

YOUR STORIES. OUR STORIES.
An event for patients.

MARCH 5, 2027
9AM-4PM ET

HYBRID EVENT



Hybrid: Attend in-person at FDA White Oak Campus (Silver Spring, MD) or Virtually

For more information:
https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-rare-disease-day-2027-03052027



REAGAN-UDALL FOUNDATION FOR THE FDA

Kyle Diamantas, JD

Acting Commissioner of Food and Drugs

U.S. Food and Drug Administration

IN PERSON AND VIRTUAL

Public Comment

2.5

minutes per commenter

HOW IT WORKS

Here’s how we’ll proceed

Alternating sets

We alternate between in-room and virtual commenters.

Alphabetical order

Within each set, we call on commenters by last name.

Rolling list of three

You’ll hear your name twice before it’s your turn.

2.5 minutes each

A countdown clock on screen shows your time left.

VIRTUAL COMMENTERS

If you’re joining by Zoom

1

When you first hear your name

Accept the Zoom prompt to become a panelist.

2

The second time you hear it

Get ready to deliver your comments.

3

When the speaker before you finishes

Turn on your camera, unmute, and wait for your introduction.

4

Your turn

We bring you on screen. Speak for up to 2.5 minutes.

Prompt arrived early? Production may send the panelist prompt before your name is called. Please accept it.

10 seconds to begin. If you don’t start speaking, we’ll move on and circle back at the end of the set if time allows.

IN-ROOM COMMENTERS

If you’re here with us in person

1

When you first hear your name

Make your way to a Foundation team member, who will direct you to your podium.

2

When it’s your turn

A member of our team will help you onto the stage.

3

At the podium

Speak for up to 2.5 minutes.

Watch the clock. A countdown clock shows the time you have remaining.

A REMINDER

We’re here in listening mode.

No one from the Foundation or the FDA will respond to comments

THANK YOU

Written comments are open through December 11, 2026

In addition to today's public comments, the FDA is accepting electronic and written/paper submissions.

SUBMIT ONLINE
Regulations.gov

DOCKET NUMBER
FDA-2026-N-12214

LEARN MORE
reaganudall.org

PUBLIC COMMENT

Now Speaking

Caryn Alagno



NPHP1
Family Foundation

AAV-5 GENE THERAPY TO HALT VISION LOSS

PUBLIC COMMENT

Now Speaking

Tammy Anderson



Tammy Anderson

Executive Director

Wake Up Narcolepsy

A national nonprofit patient advocacy organization advancing Narcolepsy awareness, education, and research toward treatments and ultimately, a cure.

1. Patient-centered evidence

Involve patients early and measure daily functioning, cognitive difficulties, and quality of life (e.g. difficulty waking, brain fog). Achieve greater inclusivity in clinical trial eligibility.

2. Children with Narcolepsy

Expand pediatric studies, age-appropriate formulations, and evidence that guides care.

3. Pregnancy, maternal and infant health

Close evidence gaps through coordinated data collection and a Narcolepsy pregnancy registry.

PUBLIC COMMENT

Now Speaking

Ron Bartek

PUBLIC COMMENT

Now Speaking

Kara Berasi

PUBLIC COMMENT

Now Speaking

Jyoti Bharadwaj

PUBLIC COMMENT

Now Speaking

Mackenzie Bloom

PUBLIC COMMENT

Now Speaking

William Brown

Nova Brown (Age 8): INPP5K Muscular Dystrophy

Ultra-Rare Subtype ("Low Hundreds or Fewer" - Framework p. 4)
Part of the Congenital Muscular Dystrophy Community



1. Meaningful Measures of Progress (p. 7)

Prioritize upper-limb preservation, stamina, and daily independence across review milestones.

2. Reasonably Attainable Evidence (pp. 7–8)

Accept natural history registries and make external disease experts a structural feature.

3. Cross-Center Consistency (p. 9)

Codify predictable evidentiary flexibility uniformly across CDER and CBER divisions.



William Brown • Parent Advocate (Rochester, NY) • No Financial Disclosures

Docket No. FDA-2026-N-12214

PUBLIC COMMENT

Now Speaking

Tanya Brown

PUBLIC COMMENT

Now Speaking

Mindy Cameron

22 Years Since Diagnosis

JANUARY 2004



OVER

300

INTERVENTIONAL STUDIES



OVER

100

OBSERVATIONAL STUDIES



8

FDA APPROVED TREATMENTS



Mindy Cameron

Mom of 25 year old living with Duchenne Muscular Dystrophy

PUBLIC COMMENT

Now Speaking

Meg Didier

PUBLIC COMMENT

Now Speaking

Nasha Fitter

Name real-world data from *medical records* as evidence.

And publish the standard it has to meet, up front:

1

Pre-specified analyses

2

Source-verified records

3

Audit trails

4

Matching on the factors that drive severity

We built to that standard from day one. Make it the rule, so drug developers don't have to guess.

Nasha Fitter | Parent | Co-founder, FOXG1 Research Foundation | Co-founder, Citizen Health

PUBLIC COMMENT

Now Speaking

Annie Kennedy

PUBLIC COMMENT

Now Speaking

Maria Apostolaros

PUBLIC COMMENT

Now Speaking

Barb Ballard

PUBLIC COMMENT

Now Speaking

Jason Begalke

PUBLIC COMMENT

Now Speaking

Kat Bryant Knudson

A Patient-Driven Path Forward for Rare Disease Drug Development

Realistic. Inclusive. Attainable for All.

1 Use Existing Patient Evidence



Recognize and enable the use of natural history data.

- Provide regulatory clarity on how existing natural history data can be evaluated, standerdized, and used as fit-for-purpose evidence, including potential external controls.
- Enable data sharing across development programs.
- Recognize the significant contributions patients have already made.
- **Patients are not a renewable resource.**

2 Make Drug Development Attainable



Ensure a viable pathway for every rare disease population.

- Support innovative trial designs, cutting-edge science, and novel statistical approaches.
- Leverage existing evidence and shared infrastructure.
- Recognize the realities of rare diseases, including ultra-rare and very small patient populations.
- Ensure the pathway to approval is attainable for all rare disease communities, not just a fortunate few.

3 Include External Experts & Patients



Bring rare disease experts and patients into regulatory science.

- Establish a formal patient research advisory mechanism.
- Include individuals living with rare diseases and independent patient advocacy organizations as meaningful partners and shared leaders.
- Include outside experts in the review process to ensure the right expertise is at the table.
- Ensure the patient voice is meaningfully included throughout the development and regulatory review process — not simply invited to comment on decisions already made.

Every patient deserves a pathway forward.

Kat Bryant Knudson
Founder and CEO, The Speak Foundation | Living with limb-girdle muscular dystrophy (LGMD)

PUBLIC COMMENT

Now Speaking

Hassan Danesi

PUBLIC COMMENT

Now Speaking

Kimberly Dimicco

PUBLIC COMMENT

Now Speaking

Lindsay Ellington

PUBLIC COMMENT

Now Speaking

Lana Escamilla

Lana Maria Escamilla

Patient and Patient Advocacy Director, Wilson Disease Association Board of Directors



Wilson disease is a rare, genetic disorder that prevents the body from removing excess copper, leading to toxic copper buildup in the liver and brain.

Wilson disease is fatal if not diagnosed and treated.

Tetrathiomolybdate "TM" saved my life in 2000

Twenty-six years later, TM is still not available, but this summer the FDA did authorize Monopar to submit its New Drug Application for ALXN1840 on a rolling basis and the first sections are now under review.

THREE POINTS

- First, fit-for-purpose evidence must reflect what is at stake.
- Second, patients must be at the table when risk and benefit are weighed.
- Third, sponsors and patients need consistency and predictability

THANK YOU

PUBLIC COMMENT

Now Speaking

James Flint

PUBLIC COMMENT

Now Speaking

E'Lissa Flores

BIO Key Priorities for Consideration

1

Fit-for-Purpose Evidence

Use the totality of evidence while maintaining scientific rigor within existing statutory standards.

2

Fit-for-Purpose CMC

Apply risk-based approaches to CMC evidence while maintaining product-quality standards.

3

Innovation into Practice

Advance methods from pilots and workshops into routine regulatory use and for updating guidances.

4

Early FDA–Sponsor Alignment

Align early and throughout development on evidence, endpoints, design, CMC, and uncertainty.

5

Patient Input Throughout

Clarify how patient experience and preferences inform decisions across the lifecycle.

6

Consistent Implementation

Use Hub, cross-Center learnings, and internal & external expertise for consistent Agency-wide application

Implementation is Key: Scientific rigor & practical fit-for-purpose approaches must be paired with consistent application across Centers & review divisions to maximize the Framework's impact

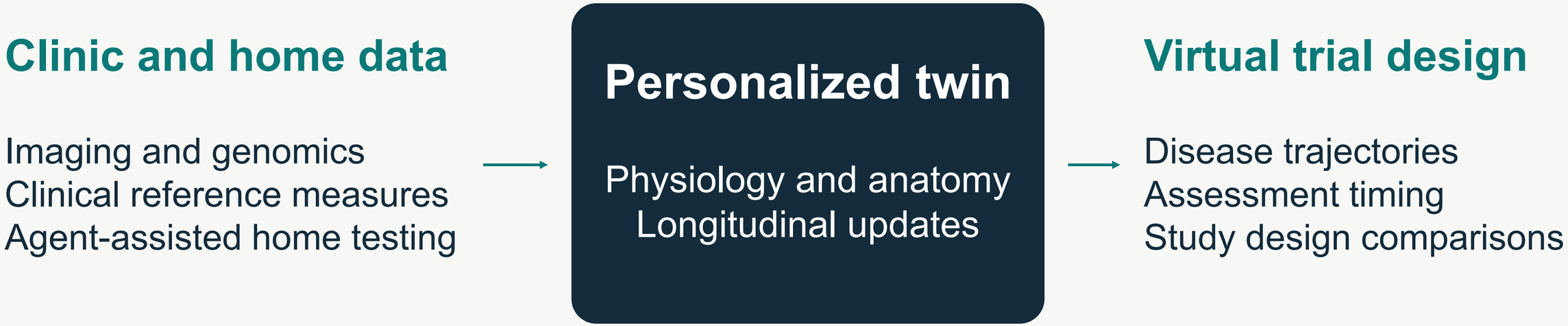
PUBLIC COMMENT

Now Speaking

Kemar Earl Green

Personalized digital twins for rare-disease trials

Rare neurological diseases and other rare diseases with neurological manifestations



Requires validation for its intended use, human oversight and explicit uncertainty.

Proposed FDA priority

Build on existing programs to evaluate these platforms and clarify acceptable evidence for trial design and analysis.

Kemar Earl Green, NeuroAgent AI

PUBLIC COMMENT

Now Speaking

Raphael Hebert

From Commitment to Meaningful Change

Three priorities:



Fit-for-Purpose Evidence

Rigorous, flexible & realistically attainable



Regulatory Accountability

Consistent & transparent implementation



Meaningful Patient Influence

Hearing & incorporating

Time is not an abstract consideration.

ALS illustrates the urgency. These recommendations serve all Rare Diseases.

IAM ALS

PUBLIC COMMENT

Now Speaking

Pamela Gavin

PUBLIC COMMENT

Now Speaking

Charlie Gayer

Scientific rigor without flexibility can stifle innovation

A fit-for-purpose framework should preserve high evidentiary standards while allowing evidence generation to reflect each rare disease and patient population.

1

Recognize the reality of very rare diseases

Few diagnosed patients, experienced clinicians and trial centers can make conventional approaches, including placebo control, difficult to enroll, sustain or justify.

2

Respect small and precious populations

Patients' willingness to enroll, travel and accept uncertainty and treatment burdens should help shape what is feasible, ethical and informative.

3

Enable earlier substantive FDA dialogue

Alignment on strategy and trial design, even before clinical data exist, can prevent avoidable delays and conserve patient participation.

PUBLIC COMMENT

Now Speaking

Christine Green

Finding Hope *for* FRIZZLE (FRRS1L)



FRIZZLE (FRRS1L) GENETIC DISEASE

Frizzle (FRRS1L) is an ultra-rare and devastating genetic disease that causes patients by age of 2 years old to have uncontrolled epilepsy, rapid regression, and global loss of all motor function.

RARE DISEASE: FRAMEWORK FEEDBACK

- **IMPLEMENT NOW:** Feedback that can be implemented at an internal US FDA level needs to be made now. This includes improved and more open **communication** with sponsors, clearer **expectations**, increased engagement with external **experts**, **endpoints** that are meaningful to rare disease patients, and fit-for-purpose analysis of genetic variants, including variants of uncertain significance (**VUS**).
- **DIALOGUE:** Implement clear, collaborative, and compassionate FDA communication**.** Establish a more open and flexible communication process that recognizes the urgency and human impact of ultra-rare diseases. **Complement existing FDA meetings with meaningful dialogue, early guidance, and shared problem-solving** between FDA, developers, and patient organizations.
- **EXPERT SIGN-OFF:** Provide a path that includes the **recognition and value of external expert scientists, researchers, and clinicians** as part of the IND package evaluation.
- **VARIANTS of UNCERTAIN SIGNIFICANCE (VUS)**: **allow rigorous expert clinical assessment alongside laboratory classification**, with expert panel review when needed, to establish causality for variants of uncertain significance**.** Requiring every variant to meet traditional evidence thresholds places an unrealistic burden on ultra-rare populations and risks excluding patients from needed treatments even when experts can establish that their variant causes their disease.
- **CONSISTENT GUIDANCE:** ensure pre-IND guidance aligns with FDA expectations at IND submission. **Communicate evolving agency-level expectations early** and throughout development, not only in formal meetings—before small programs commit precious time and scarce resources to strategies that may no longer meet them.
- **TOX/CMC:** Tailor toxicology and manufacturing requirements for first-in-human studies to each program's risk-benefit context, with greater flexibility and clearer guidance for life-threatening, ultra-rare diseases. Requiring mature toxicology and CMC packages before first-in-human studies can create significant barriers for ultra-rare diseases, where resources are limited, patient populations are extremely small, and development pathways may not fit traditional models. Particularly for life-threatening and severely debilitating diseases, **these requirements must be proportional to the risk-benefit context of that program**.

THANK YOU

- Thank you for the US FDA's continued efforts to improve the drug development process for rare diseases and for the opportunity to speak today.

PUBLIC COMMENT

Now Speaking

Jon Hagstrom

AATD is the ‘middle case’ rare disease that this Framework *must* get right

- ~100k patients but only 10-15k identified. We’re too big for the September 2025 ultra-rare evidence principles, but too small to conduct conventional trials
- End points *have to be recruitable* in a small population with a slowly progressing disease.
- Restoration of functional AAT is not merely a biomarker – it is *direct evidence that the therapy has corrected the fundamental molecular defect*. It should be accepted as a primary endpoint for approval.
- Treat well-run registries and natural histories as part of the total evidence base.

PUBLIC COMMENT

Now Speaking

Jessica Haywood

PUBLIC COMMENT

Now Speaking

Lauren Holder

The Many Faces of Huntington's Disease















After brain surgery to hopefully slow disease. I'm a mom to 3. One who has Down syndrome and autism. I need to live to raise my girls.



8w Love Reply Share 9

"Our lived experience IS expertise."

"Perfection cannot become the enemy of progress."



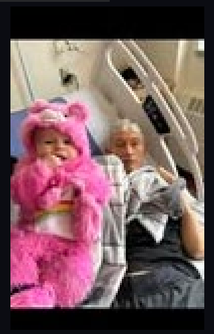


"When we delay access, that is function lost that our families cannot get back. - Heather & Nathan













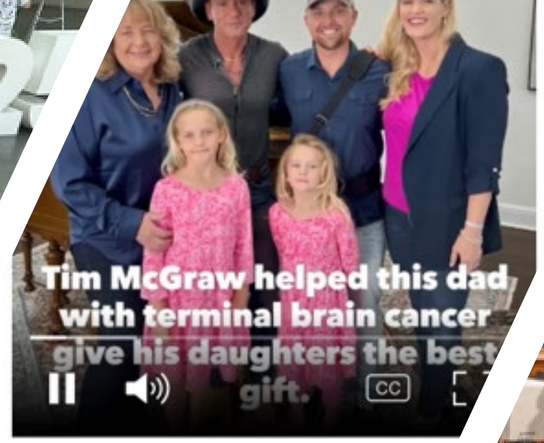
PUBLIC COMMENT

Now Speaking

Michael Hugo







Dad with terminal brain cancer sings special duet for daughters with Tim McGraw





Michael Hugo

Diagnosed with Glioblastoma in 2022
Now facing recurrence

PUBLIC COMMENT

Now Speaking

Matthew Kahn

PUBLIC COMMENT

Now Speaking

Sharon King

PUBLIC COMMENT

Now Speaking

Mike Lehmicke

Principles of a Fit for Purpose Rare Disease Framework

Fit-for-purpose review of rare disease therapies based on attainable evidence, particular disease state, and population

Randomized controlled trials should not be the default. 75% of CGTs were approved by FDA based on single-arm trials (85% in EU)

Consistency and predictability of FDA's rare disease drug development and review regulatory requirements

Maintain alignment with the sponsor. Ensure consistency between review teams.

FDA engagement with external parties—including patients, disease experts, and researchers—to inform review decision-making

Evidentiary standards, including clinical endpoints, should be informed by the patient voice and disease expert opinion

Considerations for chemistry, manufacturing, and controls (CMC) specific to rare disease therapies

Apply prior knowledge and platform principles to accelerate development

Alliance *for* Regenerative Medicine

PUBLIC COMMENT

Now Speaking

Mackenzie Liebowitz

Trust decides who stays in a rare disease study

One person leaving a 20-person rare disease trial takes 5% of the evidence.

TOPIC 3 · PRINCIPLE 2

Define the patient-input milestones and write them into regulation

Understanding the Disease (NHS) → **Pre-IND** → **Pivotal design** → **During the trial** → **FDA review** → **Post-approval**

At each one: **Invite → Ask → Listen → Implement → Close the loop**

TOPIC 2

Apply them the same way in every division and both centers, then publish what patients said and what it changed



Mackenzie Liebowitz (Abramson), MPH, BCPA, CHES, CPH

linkedin.com/in/mackenzie-liebowitz · mackenzie@tactteamconsulting.com

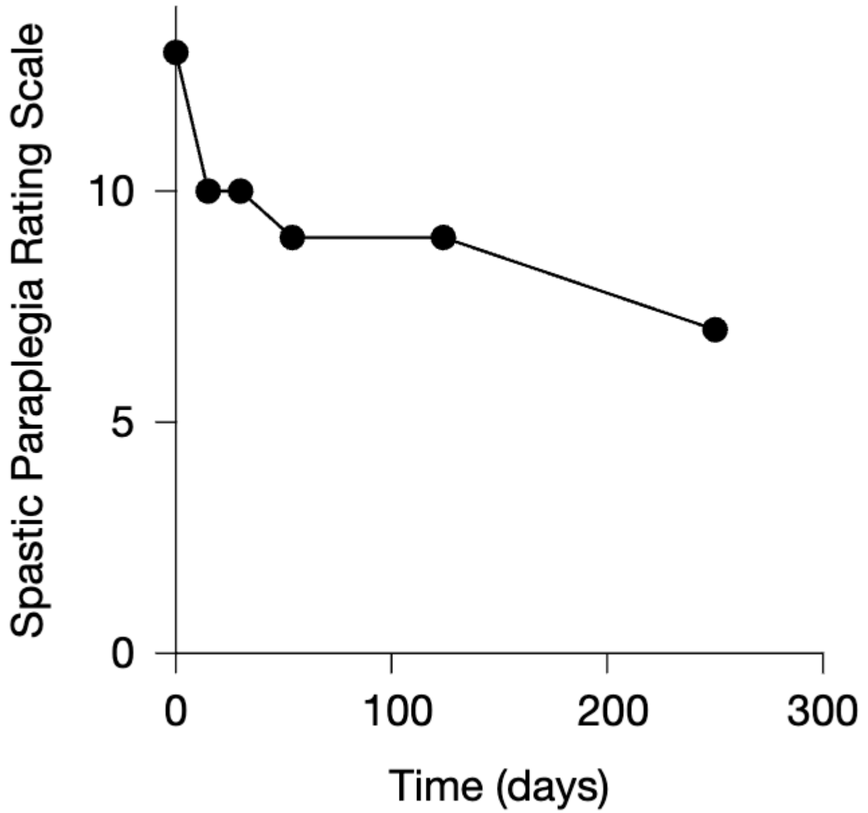
PUBLIC COMMENT

Now Speaking

Michael Pacold

HPDL Encephalopathy as a Prototype for the Rare Disease Review Framework

- Ultra-rare (~2000 worldwide) pediatric mitochondrial disease caused by loss-of-function variants in HPDL. We discovered that HPDL is required for a novel metabolic pathway: mammalian CoQ10 headgroup synthesis (Banh *et al*., *Nature* 2021, PMID 34471290)
- This discovery enabled metabolite replacement therapy of HPDL deficiency with CoQ10 headgroup intermediates under a compassionate use SPIND (170119) with good effect (Shi, Miller *et al*., *Nature* 2025, PMID 40634618)
- Approval of metabolite replacement therapy will benefit from proposed framework, particularly clinical trial design for ultra-rare diseases



Shi, Miller *et al*., *Nature* 2025, PMID 40634618

PUBLIC COMMENT

Now Speaking

Angie Howell



A Race Against Time

EARLY DETECTION SHOULD MEAN EARLY ACCESS.

For rare but aggressive genetic diseases,
waiting for symptoms may mean
waiting too long.

JADE | AGE 19 | FUS-ALS

FIND IT EARLY.

ACT IN TIME.

HOPE FOR THOUSANDS OF TOMORROWS.

PUBLIC COMMENT

Now Speaking

Amit Khanna

PUBLIC COMMENT

Now Speaking

Tim Kline

Fit-for-purpose evidence, applied consistently

What we have seen

Ultra-rare cancer

Approved on a single-arm study. A randomized trial is not feasible in a population this small.

Pediatric rare disease

In Phase 3: too few patients to enroll in the US alone. Non-US natural history and PK data must bridge the gap.

Our asks of the Framework

1. **Bring rare cancers in.** Apply the Framework through OCE, so rare tumors get the same fit-for-purpose standards.
2. **Agree on evidence sources up front.** Ex-US natural history, external controls and Bayesian borrowing.
3. **Make post-approval obligations feasible.** Offer alternatives when a confirmatory trial cannot enroll.
4. **Right-size CMC.** Risk-based CMC review and inspections for small-batch orphan products.

KAKEN ADI bioscience

PUBLIC COMMENT

Now Speaking

David Liepert

Recognise the pre-specified within-person series as attainable evidence for individualised therapies

Two measures FDA names

- A physiological measure from a sensor — a digital health technology (DHT guidance, 2023)
- A patient-reported outcome — a clinical outcome assessment (PFDD Guidance 4, 2023)
- One instrument carries both

One pre-specified series

- Expected change stated before each remeasurement
- Stable baseline and repetition before a change is read
- Dimensions reported separately, never averaged
- Pooled across patients sharing a starting state

What the record supplies

- The natural history — the patient's own, from diagnosis
- The patient as their own control, variance shown
- The post-approval record on agreed metrics
- Evidence for the group, not only the person

The one sentence we ask the framework to carry: a sponsor may meet the natural-history, within-patient and post-approval expectations of the Plausible Mechanism Framework with a digital health technology and a clinical outcome assessment built to FDA's existing guidances, pre-specified as one series.

We seek no recognition of any product and make no accuracy claim for any reading.

PUBLIC COMMENT

Now Speaking

Mary Anne Meskis

Dravet Syndrome Foundation

Presented by: Mary Anne Meskis, CEO

Realize the full promise of natural history data to reduce the burden of placebo and sham arms.

Clear guidance is needed. Not only on success stories, but on what might make a dataset incompatible for use as a comparator to the therapeutic arm of a study

The patient voice should be a regular touchpoint, not a checkbox.

The FDA should engage the patient community and incorporate the patient voice throughout the development timeline of each product.

Benchmarks are necessary for reflection

How will we measure the success and impact of the new framework?

In developing the framework, we must always be asking: What are the consequences for patients if a treatment is not approved, and how can we identify pathways that enable approval while appropriately managing risk?

PUBLIC COMMENT

Now Speaking

Amanda Moore

APPENDIX CANCER AND RARE CANCER TRIALS

Same mutation. Different organ. No access.

INNOVATIONS IN THE TREATMENT OF APPENDIX CANCER

Appendix tumors commonly carry KRAS and GNAS mutations. Patients are still screened out of trials for drugs that target them because of where the tumor started.

1

Default to inclusion when a rare cancer patient carries the target. Sponsors state any reason to exclude.

2

Tell patient groups early what data standards registries must meet to be usable in review.

3

Give rare cancers the same fit-for-purpose flexibility as other rare diseases, in writing.

Amanda Moore | Founder and Executive Director, Appendicure | appendicure.com

PUBLIC COMMENT

Now Speaking

Hetanshi Naik

PUBLIC COMMENT

Now Speaking

Miro Pastrnak

RARE TRIALS SUMMIT

Miro Pastrnak, PhD
Rare Disease Research

The flexibility exists. Predictability is missing.



Accelerate RARE Working Group A

1

Focus area 1 · Fit-for-purpose review

Agree the evidence plan up front

Before new data: what matters, what is known, and what counts as success.

2

Focus area 2 · Predictability

Publish evidence-reuse rules

Say what a characterized platform need not repeat, and what it still must.

3

Focus area 3 · Patient engagement

Ask families what matters

Let patients define meaningful change and how much uncertainty is acceptable.

4

Focus area 4 · CMC

Apply “known or shown”

Show each element for the product, or justify it as known from the platform.

Not a lower bar. Where a randomized trial is feasible and ethical, use it.

PUBLIC COMMENT

Now Speaking

Sandra Smieszek

PUBLIC COMMENT

Now Speaking

Devyn Smith

PUBLIC COMMENT

Now Speaking

Charlene Son Rigby

PUBLIC COMMENT

Now Speaking

Allison Martin

PUBLIC COMMENT

Now Speaking

Jewell Martin

PUBLIC COMMENT

Now Speaking

Tracy Mayne

PUBLIC COMMENT

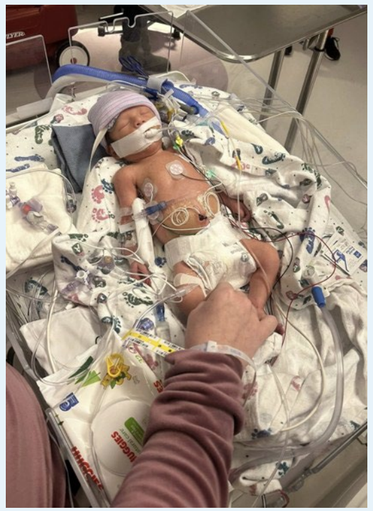
Now Speaking

Reenie McCarthy

“

Please do not forget our children.





Barth Syndrome Foundation®

In genetic mitochondrial disease, children are often most vulnerable to abrupt and devastating bioenergetic crises, all too frequently leading to sudden death.

Do not assume that the fragility of these children suggests that they are living with a different disease requiring distinct development efforts which are even more infeasible in a further segmented population.

Do consider ways to expedite access to novel therapies to children as soon as your risk analysis permits.

They do not have time to wait, and expanded access is a highly imperfect solution.”

Kate McCurdy, Chair, Barth Syndrome Foundation

shared with permission of the families

PUBLIC COMMENT

Now Speaking

Paul Melmeyer

PUBLIC COMMENT

Now Speaking

Jason Menzo

Too large for n-of-1. Too small for industry. Where is their path?

n = 1–2

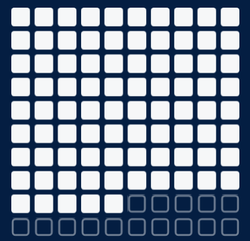
Individualized (n-of-1) therapy

Single-patient IND, paid by families and philanthropy

e.g., milasen; KJ Muldoon

THE MISSING MIDDLE: A HANDFUL TO ~1,000

NO RELIABLE PATH TO APPROVAL



84.5%

of all rare diseases affect **fewer than 1 in a million people**, roughly 340 or fewer Americans each

1,000+

A defined, hard-won path

NDA/BLA; patient groups often seed research, industry develops

Still long, costly and uncertain

Why the middle can’t attract investment

Costs don’t shrink

Much of the cost is fixed. Revenue falls with every patient fewer.

Every gene starts over

No defined way to carry platform data to the next gene.

No agreed endpoints

Slow diseases, no agreed way to show benefit in a feasible trial.

Investors can’t price an unpredictable path. RDEP (Rare Disease Evidence Principles, 2025) and plausible-mechanism guidance (2026) are a start. **A predictable pathway would change the math.**

Sources: Orphanet (Nguengang Wakap et al., 2020); FDA ASO guidance (2021); FDA RDEP (2025); FFB PDUFA VIII comments (2026)

PUBLIC COMMENT

Now Speaking

Allison Mintz

PUBLIC COMMENT

Now Speaking

Samarendra Mohanty

PUBLIC COMMENT · RARE DISEASE FRAMEWORK HYBRID PUBLIC MEETING

Addressing Heterogeneity of Group of Rare Disease Genotypes

Policy, not science, is the rate-limiting step

01 · The arithmetic of heterogeneity

Disease-by-disease development hinders patient access

- ~300 genes cause inherited retinal degenerations; few populations support a standalone program
- Gene-agnostic therapy treats the surviving cell, not the mutated gene: one drug substance, many diseases
- Common Mechanism of Action should permit broad prior-knowledge leveraging
  - Plausible Mechanism
- Composite endpoint for totality of evidence: no single endpoint captures heterogeneous phenotype
- **Opportunity:** leverage commonality, cross-indication evidence

02 · Retina is Central Nervous System (CNS) tissue

Carry the neurodegeneration precedent to the eye

- Retina: developmental and anatomical extension of brain
- CNS programs accept intermediate clinical endpoints (ICE) in slowly progressive, heterogeneous disease
  - Retinal degenerations share those features: slowly progressive, variable baseline
- Agency supports adaptive, open-label extension trials along with known natural history
- **Opportunity:** extend existing regulatory flexibility to retinal neurodegeneration, which is known to cause irreversible loss of rods & cones

Three suggestions

Draft guidance on cross-functional prior-knowledge leveraging for a shared substance · A defined route for composite and intermediate endpoints in gene/disease-agnostic programs · Frequent informal Sponsor-Agency interaction for the multi-indication programs

Samarendra K. Mohanty, President & Chief Scientific Officer, Nanoscope Therapeutics, Inc.

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Edward Neilan

Comments on FDA's New Framework for Rare Disease Review

Edward Neilan, MD, PhD – Global Head, Pediatric & Rare Disease Center of Excellence, IQVIA

- We thank FDA for committing to build an improved framework for rare disease drug development and regulatory review, one fit-for-purpose for diseases affecting small populations
- Over the past 10 years, IQVIA has helped sponsors conduct 513 rare disease trials, including more than 52,000 patients in 96 countries
- The unmet medical needs are huge, and patients urgently need safe & effective new treatments and clinical development paths tailored to what evidence is meaningful and reasonably attainable
- Sponsor's need clarity and predictability to continue to invest in rare disease drug development
- Regulatory approaches should continue to evolve alongside advances in science, including gene-targeted therapies
- Some approaches worthy of greater use include: Accelerated Approval, the Therapeutic Technology Platform Designation Program, the Plausible Mechanism Framework, Bayesian statistical methods, innovative trial designs, including single-arm studies, and risk-based safety and CMC considerations
- In addition to FDA staffing, training, and revisions of guidances, formal rule making is likely important
- IQVIA stands ready to offer advice or assistance as may be appropriate, based on IQVIA's clinical development experience and/or our healthcare-related databases and analytics

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Jackie O’Neil



Jackie O’Neil, MS

Director of Chemistry, Materials, Controls (CMC)

17 years in Pharmaceutical Development • 4 new drugs brought to market

Patient Living with a Connective Tissue Disorder

Advocate for Expanding Clinical Evidence and Regulatory Pathways for Existing Medicines

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Sierra Phillips

Jack needs a path to treatment. His childhood cannot wait.







Building on FDA's progress through ARC, the Hub, and C-Path

1. Support us at day zero

Build evidence FDA can use.
Before a candidate exists.

2. Make evidence achievable

Sound studies. Attainable data.
Outcomes defined with families.

3. Include disease expertise

Define when families and experts help FDA interpret evidence.

Warsaw Breakage Syndrome (WABS)

Gene: DDX11. Autosomal recessive.
Known U.S. patients: <20
Documented worldwide: <50

Clinical features: Microcephaly, growth restriction, sensorineural hearing loss, developmental / speech delay, intellectual disability, epilepsy.

Sierra Phillips, Founder, Warsaw Breakage Syndrome Foundation,
one of the 200 patient organizations that make up REN, the Rare Epilepsy Network.

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Nichole Riek

How We Compressed a 5-Year Drug Development Timeline Into <6 months?



Collaboration between academia, industry, and government across every step of the drug development process enabled accelerated timeline.

Confidential - Company Proprietary

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Liza Squires

Key Principles for Consideration in the FDA Rare Disease Framework

Enabling effective, indication-appropriate, patient-centered drug development

Consistent evidence standards across therapies for an indication

Requirements tailored to the indication and patient population

Consideration of within-participant controlled trial designs

Understanding that trial design and endpoint selection are interconnected

Regulatory flexibility regarding fit-for-purpose endpoints

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Michael Templin

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Steven Thompson

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Now Speaking

Sarah Tompkins

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Anne Yang

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Matthew Zirwas

Many Rare Diseases Have Easy Solutions

- Case reports, series, and small trials show a ‘blockbuster’ drug works
- The drug has a huge safety database: thousands of patients in pivotal phase 3 trials
- Without an indication, insurance denies coverage as ‘experimental’
- Why companies won’t study it, from least to most important, and the fix (for approved drugs with 1,000+ patients already studied in other phase 3 trials):
  - Few, scattered patients who won’t accept true placebo → **Cap the trial at 0.1% of US patients (floor of 10), use historical controls and consider standard of care plus randomized to drug or placebo**
  - Tiny market → **Exclusivity extends for all indications, up to 6 months, proportional to US population**
  - Rare-disease complications get blamed on the drug and land on the blockbuster label → **New adverse events stay on that indication’s label unless they replicate. If it didn’t show up in 1,000+ trial patients and it does in a 20 person trial in a rare disease, it’s either random or a specific drug/disease interaction, not just the drug**

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Yoko Rosenbaum

Rare Disease Company Coalition

Our Mission

The Rare Disease Company Coalition represents life science companies dedicated to discovering, developing, and delivering treatments for patients living with a rare disease.

Our Members

Collectively, RDCC members have delivered over 100 approved products to market and have 230+ ongoing development programs.

Our Message

Greater regulatory predictability, efficiency, and consistency are essential to fostering innovation, attracting investment, and accelerating the development of therapies for rare disease patients.

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Anthony Saleh

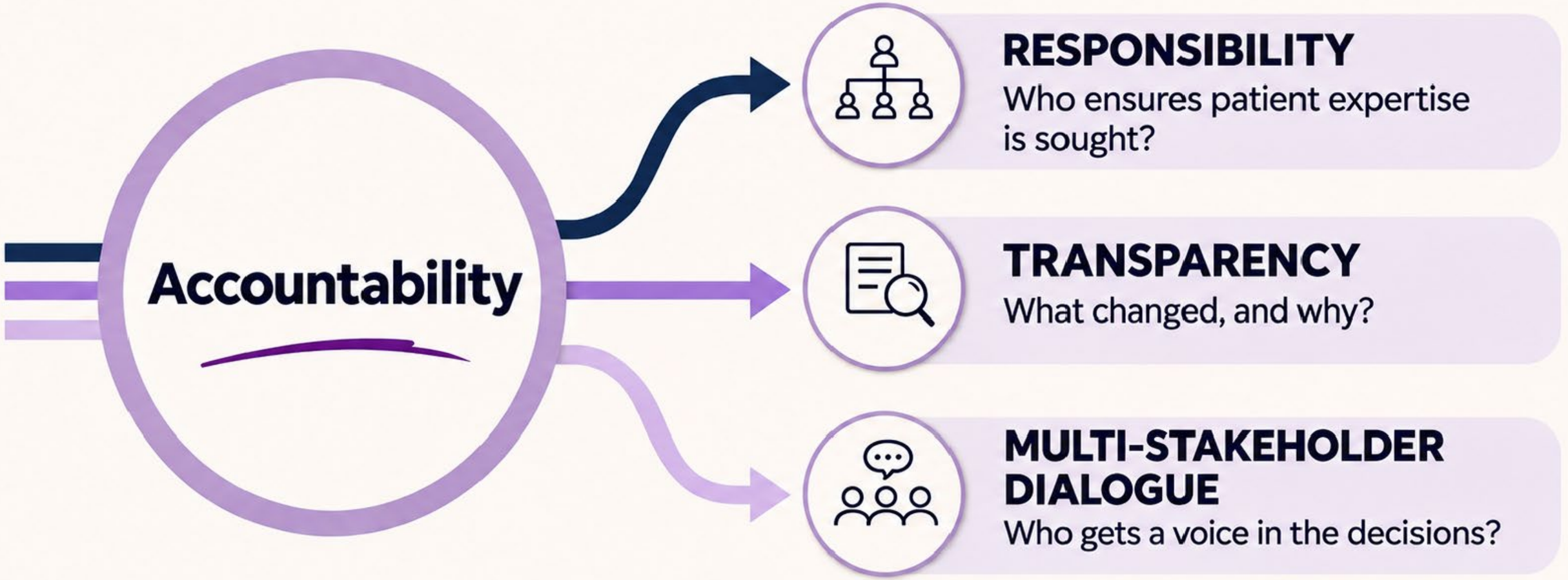
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Hillary Savoie

How do we know the patient voice is heard?

Measure the influence of patient expertise, not just the frequency of consultation.



Hillary Savoie, PhD | hillary@hillarysavoie.com | hillarysavoie.com

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Tricha Shivas

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Amy Simon

Fit-for-Purpose Evidence for Precision Genetic Medicines

Amy Simon, M.D., Chief Medical Officer, Beam Therapeutics, a gene editing company focusing on rare diseases

1 Measure efficacy by mechanism of action

- Clarify when fixing the root cause is enough for approval
- Confirm long-term outcomes after approval
- 6-month primary endpoint when the edit is rapid and permanent

2 Match endpoints to the disease

Example, Alpha-1 antitrypsin deficiency:

- FEV1 misses lung loss seen on CT scan
- Layer serum AAT, then CT densitometry, then FEV1
- Predictable path to qualify rare-disease endpoints

3 Use placebo only when truly needed

- Clear criteria for external controls
- Scale trials to the size of the effect
- Shared natural history datasets for all sponsors

Not a lower bar on safety, but benefit-risk should reflect the unmet needs rare disease patients face

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Michele Sloan

Rare disease treatment development

A patient perspective on TUBB4A-related leukodystrophy

Treatment already underway	Can FDA define an expedited, safety-focused trial model when a treatment is already in several patients and more qualified patients are ready, building toward treatment for all eligible patients?
Trials for older patients	Adults with more complex disease may have equal or greater need for potentially life-saving treatment, and many have waited longest. Trials should include them and fit measures to disease stage.
Natural-history data access	Create a workable path to institutionally held data from studies funded fully or partly by NIH. Credit and compensate investigators fairly. Current costs can block small biotechs.

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Elaine Towle

Building a Rare Disease Framework that Reflects the Patient Voice

Challenges

- Small patient populations
- Heterogeneous symptoms
- Lifelong disease progression
- Limited traditional endpoints

What FDA Can Do

- Recognize patient-identified outcomes
- Provide flexible evidentiary pathways
- Support innovative trial designs
- Improve cross-division coordination

Meaningful Outcomes for PWS Patients

- Reduced food-related anxiety
- Better behavioral regulation
- Improved sleep
- Greater independence
- Improved quality of life for patients and families

"The patient voice should not simply inform the process. It should help shape the evidence we collect, the outcomes we measure, and the decisions we make."

Prader-Willi
SYNDROME ASSOCIATION | USA
SAVING AND TRANSFORMING LIVES

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James Valentine

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Monica Weldon

A Disease-Class Framework for Rare Disease Clinical Trials

Patient reports → Pre-set endpoints → **One registry** → Control and confirmation

1	**Use existing data to design trials**	Patient reports become endpoints in one registry Benefit: a missed primary no longer ends a trial
2	**Promising Pathway in FDA's rules**	Time-limited conditional approval, rare diseases Benefit: earlier access, confirmed by the registry
3	**Evidence expectations on a deadline**	Minimum evidence package by disease class Benefit: sponsors stop guessing what is enough
4	**Consortium for small sponsors**	Neutral manager, independence test, firewalls Benefit: shared data and capacity, fair terms

Goal: a level playing field for small sponsors. **Pilot:** 2 to 3 diseases, 24 months.

Monica Dudley-Weldon, BS, MSL | Monica Weldon Consulting LLC

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Trey Putnam

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

MEETING ADJOURNED

Thank You

The meeting recording and transcript will be available on our website next week.

www.reaganudall.org

