Advancing the Development of Pediatric Therapeutics (ADEPT) 10: Addressing Challenges in Neonatal Product Development – Leveraging Rare Disease Frameworks

Join us to discuss common challenges in neonatal and rare disease product development and identify ways to leverage rare disease product development frameworks in the neonatal product development space

February 5-6, 2026

FDA Great Room
White Oak Campus
Silver Spring, Maryland

Registration required and virtual option available

FDA

ADEPT 10 Welcome

An N. Massaro, MD

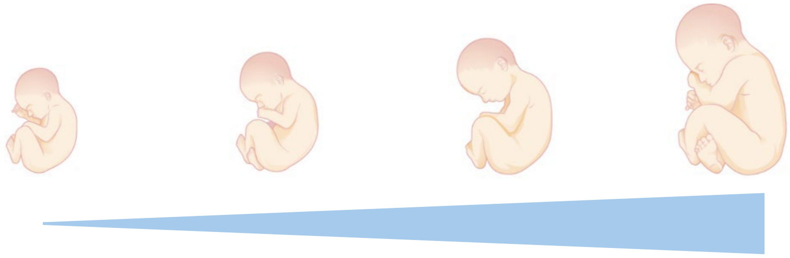
Acting Director

Office of Pediatric Therapeutics
Office of the Chief Medical Officer

Office of the Commissioner
U.S. Food and Drug Administration

Rare Pediatric Disease

Neonatology



Legislation

Expedited Programs

Incentives

Collaboration

ADEPT 10 – Meeting Goals

We will discuss:

- Current landscape of medical product (drugs and biologics) development for neonates and rare diseases
- Gaps and priorities
- Strategies/ future directions

We will not focus on:

- Medical devices
- Fetal therapies
- New approach methodologies

A continuing dialogue…

- Public Meeting: FDA Rare Disease Day 2026 - 02/23/2026 | FDA
- Rare Disease Day at NIH | National Center for Advancing Translational Sciences - 02/27/2026
- Rare Disease Day 2026 – 02/28/2026

- Rare Disease Innovation, Science, and Exploration (RISE) Workshop Series | FDA
- RISE Together: Data Sharing Across the Rare Disease Ecosystem – 03/30/2026

Day 1 Agenda

Welcome and Introductory Remarks

Session I: Setting the Scene- Neonatal and Rare Disease Drug Development

Neonates and Rare Diseases- Why Early Diagnosis and Approved Treatments are Imperative

Recognizing Common Challenges Across Investigations in Neonates and Rare Diseases Populations

-Break-

Session II: Ethical Considerations in Neonatal and Rare Disease Clinical Trials

Introductory Remarks

Panel A Discussion: Weighing benefits and risks when evidence is limited

-Break-

Panel B Discussion: Study design considerations

Day 2 Agenda

Session III: Innovative Strategies for Neonatal and Rare Disease Clinical Trials

Innovative study designs to address small populations

Incorporating novel approaches to facilitate neonatal/rare disease clinical trials

1. *Artificial Intelligence/ Digital Health Technologies in the NICU- Academic Perspective*
2. *AI/DHTs in Neonatology/Rare Disease- Regulatory Perspective*
3. *Leveraging Real World Data in Neonatology/Rare Diseases*
4. *Platform Trials/Master Protocols in Pediatrics*

Selecting Patient-focused Outcomes for Neonatal Conditions and Rare Diseases

-Break-

Day 2 Agenda continued....

Panel Discussion: Leveraging Networks/ Consortia/ Centers of Excellence to Optimize Harmonization and Operational Feasibility of Neonatal/Rare Disease Clinical Trials

-Lunch-

Session IV: Regulatory Landscape and Future Directions for Neonatal and Rare Disease Drug Development

Panel Discussion: Regulatory Perspective: How can Expedited Programs, Incentive Pathways, and other Regulatory Initiatives be Leveraged for Neonatal and Rare Disease Drug Development?

Panel Discussion: Stakeholder perspective: Lessons Learned, Gaps and Future Directions

Summary and Closing Remarks

Introductory Remarks

Mallika Mundkur, MD, MPH
Deputy Chief Medical Officer

Office of the Chief Medical Officer
Office of the Commissioner
U.S. Food and Drug Administration

Session 1: Setting the Scene – Neonatal and Rare Disease Drug Development

Neonates and Rare Diseases: Why Early Diagnosis and Approved Treatments Are an Imperative

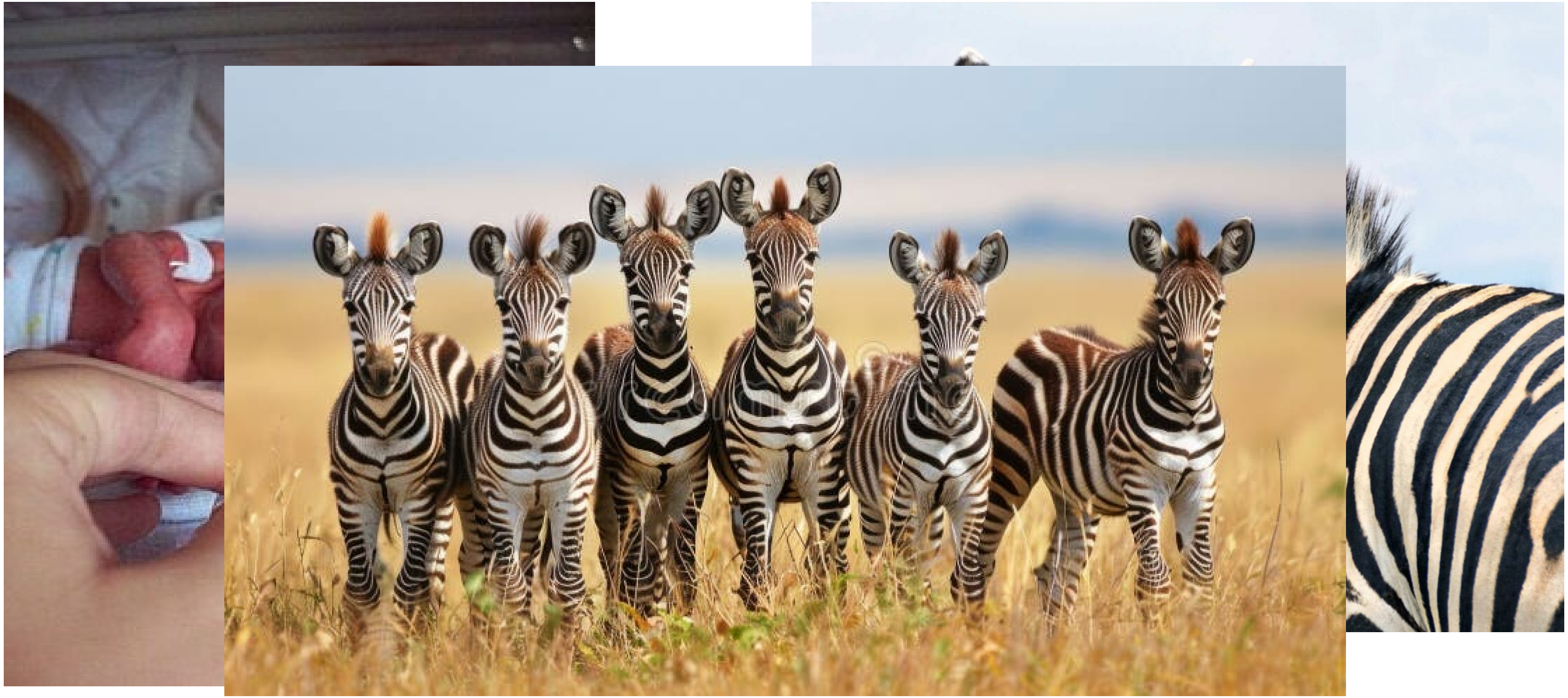
Melissa Lestini, MD

Physician
Neonatal Consultant/Neonatology Team
Office of Pediatric Therapeutics (OPT) | Office of the Chief Medical Officer (OCMO)
Office of the Commissioner (OC) | US FDA

Conflict of Interest and Disclaimer Statement

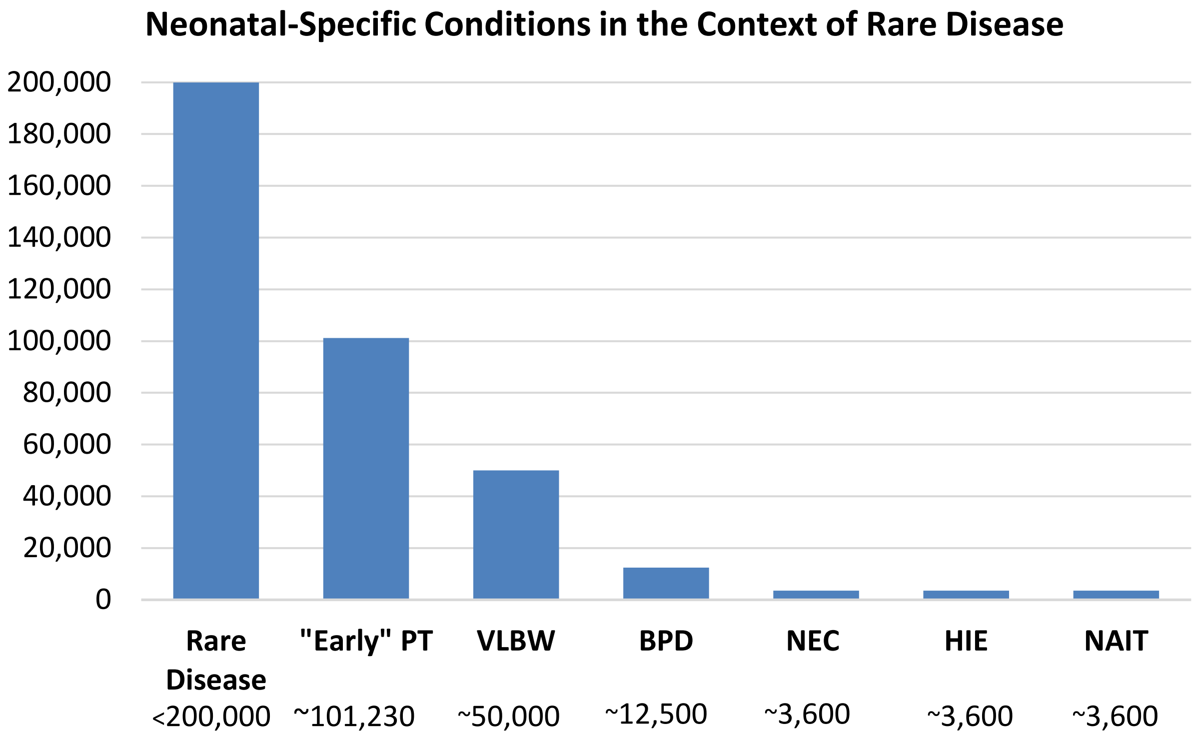
- The views presented here are personal and do not necessarily reflect the views of the FDA
- All specific product development questions should be discussed with the relevant review center and division
- I have no financial conflicts of interest to disclose
- <u>Off-label or unapproved medical product use may be discussed, as it is common practice in pediatrics (especially neonatology)</u>

Neonatal Diseases are Rare Diseases



Neonatal Diseases are Rare Diseases

Rare Disease: Disease or Condition affecting <200,000 persons in the US



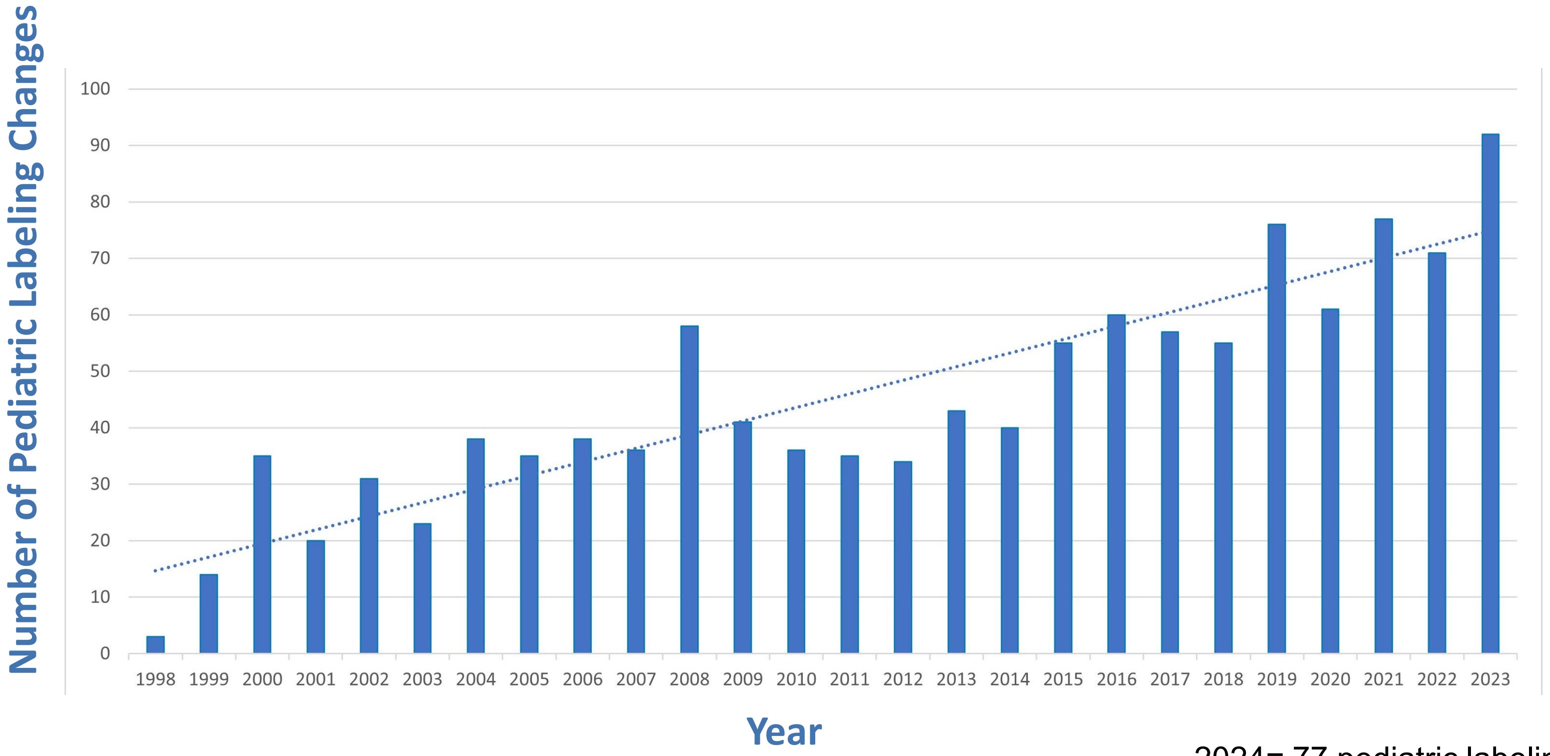
"Early" PT: Early Preterm (≤34 weeks gestation)
VLBW: Very Low Birth Weight (<1500g)
BPD: Bronchopulmonary Dysplasia
NEC: Necrotizing Enterocolitis
HIE: Hypoxic-Ischemic Encephalopathy
NAIT: Neonatal Alloimmune Thrombocytopenia

Overview

- Current state of approved neonatal products
- Challenges to neonatal and rare disease product development
- Early diagnosis and long-term impacts of diseases unique to neonates and rare diseases

Pediatric Labeling Changes

Number of Pediatric Labeling Changes for Drugs and Biologics Pursuant to Pediatric Laws from 1998 to 2023



2024= 77 pediatric labeling changes
2025= complete data pending

Slower progress for the neonatal sub-population…

Labeling Changes for Neonates Pursuant to the Pediatric Rule, BPCA and PREA (April 1999- June 2025)

- Majority of drugs used in neonates are “off-label”[1-3]
- Scientific (& legislative) mandate to address gaps

[1]Laughon et al, JAMA Pediatr 2014; [2]Hseih et al, Am J Perinatol 2014; [3]Stark et al, J Pediatr 2022

A Challenging Combination…

Neonatal Studies

- Rarity of neonatal diseases
- Rapid development of organs and tissues
- Ontogeny of enzymes, receptors, transporters, neurotransmitters
- Complex transitional physiology
- Comorbidities

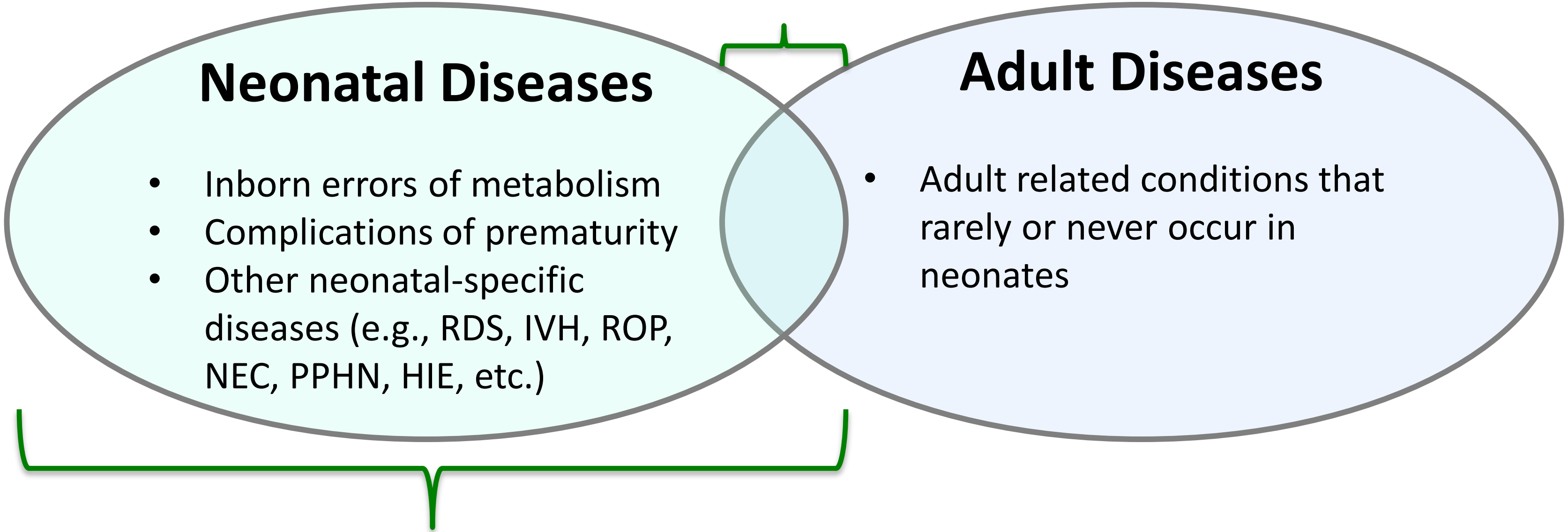
Rare Pediatric Disease Drug Development

- Difficulties with study design
- Lack of definitive outcome measures and assessment tools
- Need for additional safeguards for children as a vulnerable population
- Logistical hurdles to completing trials, especially with the need for longer term follow-up to establish safety and efficacy
- Garnering interest from sponsors and investors

Epps et al, Ther Innov Regul Sci. 2022

Current Paradigm of Neonatal Drug Development

Pediatric extrapolation[1]
PREA (2003)[2]



BPCA/Pediatric Exclusivity (2002)
Orphan Drug Exclusivity (1983)
Rare Pediatric Disease Voucher Program (2012)

[1] E11A Pediatric Extrapolation | FDA
[2] Pediatric Research Equity Act | PREA | FDA

Programs to Promote Rare Disease Product Development

Orphan Drug Act

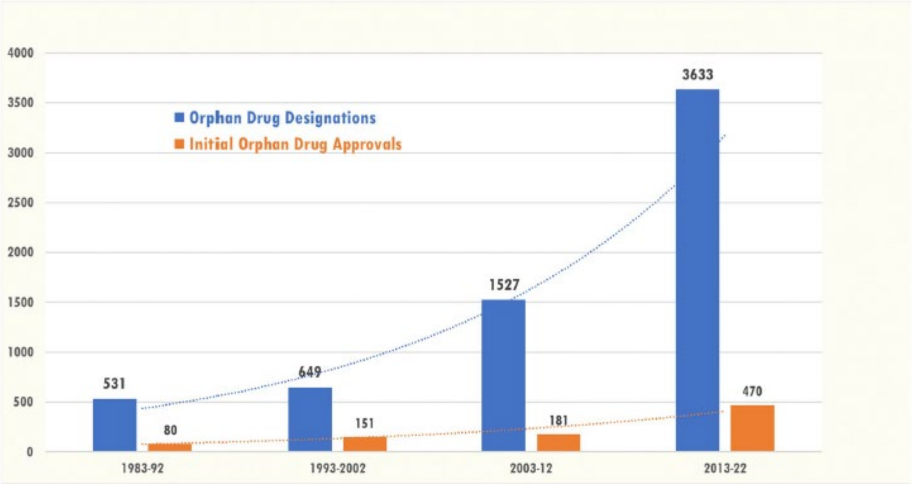
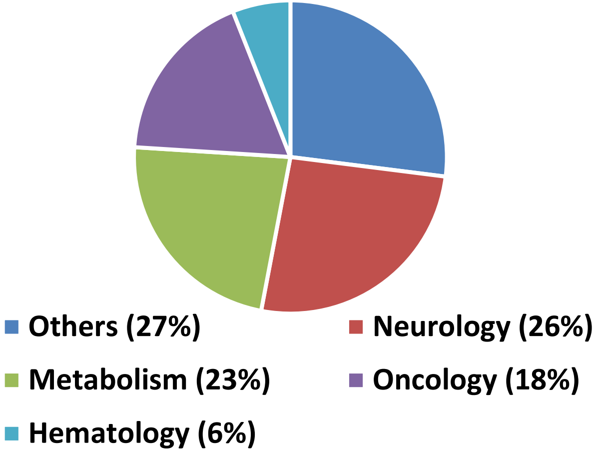


Fig. 1 Total orphan drug designations (n = 6340) and initial orphan drug approvals (n = 882) by decade, 1983–2022

Fermaglich, et al. Orphanet Journal of Rare Disease, 2023

RPD Priority Review Voucher

Percent of RPD Designations by Therapeutic Area (2013-2022)



- 33 Neonatology products designated (6%)
- 4 designations each for neonatal seizures, BPD, NEC and ROP

Mease, et al. Orphanet Journal of Rare Diseases, 2024

Early Diagnosis of Rare Disease

Potential Benefits:

- Timely treatment
- Prevents severe complications (e.g., metabolic and immunologic diseases)
- Improves Quality of Life
- Reduces Health Care Costs
- Empowers Families

Intervening Early: Newborn Screening

- Enables early detection of rare disorders for which early diagnosis and intervention can prevent death or adverse outcomes
- Programs available in all 50 states
- Recommended Uniform Screening Panel (RUSP) (https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp); includes 38 core conditions
- Estimated number of infants detected via DBS screening in the US
  - 6439 in 2006 *(CDC, MMWR 2008)*
  - 6646 in 2015-2017 *(Sontag et al, MMWR 2020)*
  - 7389 in 2021 *(Gaviglio et al, Int J Neonatal Screen 2023)*
- Beyond the numbers… “newborn screening is a lifesaver” (Newborn Screening Stories | Newborn Screening | CDC)

Public Health Impact of Treating Neonatal Diseases

- Disability-adjusted life years (DALYs)= years of life lost due to premature mortality (YLLs) + years lived with disability (YLDs)

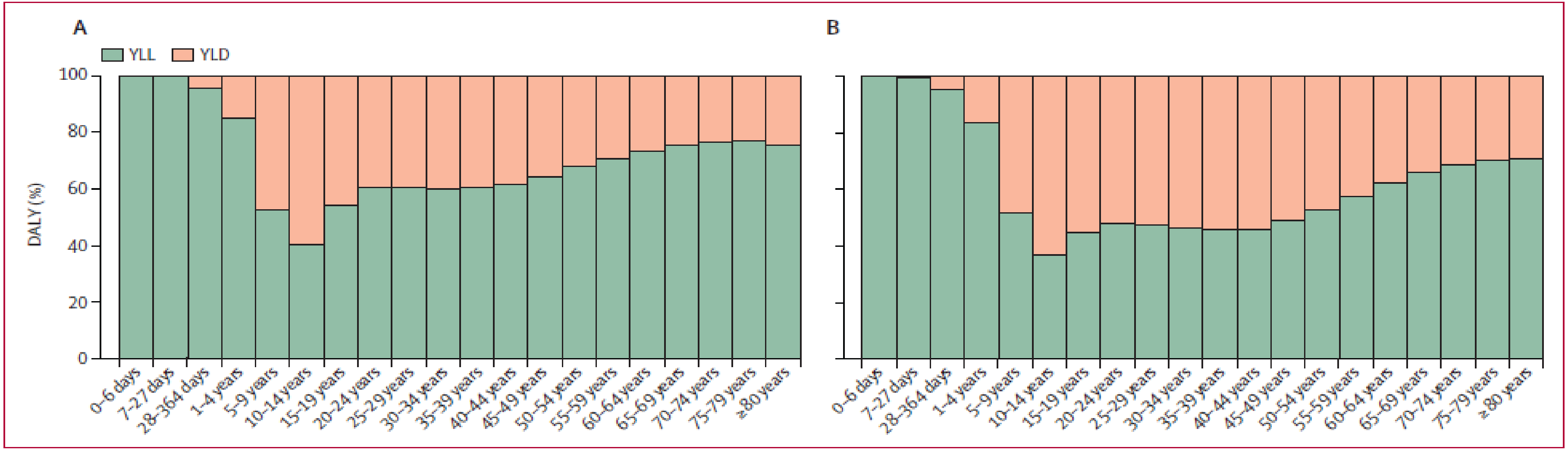


Figure 1: Years of life lost due to premature mortality and years lived with disability composition of total disability-adjusted life years by age and sex, 2010
Composition in male individuals (A) and female individuals (B). DALY=disability-adjusted life years. YLD=years lived with disability. YLL=years of life lost due to premature mortality.

Murray et al, Lancet 2012

Global Burden of Disease Study

Leading causes of disease burden worldwide in 2010, 2020, and 2021

Leading causes, 2010	Number of DALYs (millions), 2010
1 Neonatal disorders	236.3 (218.9 to 256.4)†
2 Ischemic heart disease	159.9 (153.8 to 164.9)
3 Stroke	144.3 (137.3 to 150.3)
4 Lower respiratory infections	127.3 (115.4 to 140.0)
5 Diarrheal diseases	104.1 (86.7 to 123.2)
6 Road injuries	74.3 (70.9 to 78.4)
7 HIV/AIDS	67.8 (60.4 to 78.3)
8 Congenital defects	67.5 (55.9 to 82.5)
9 COPD*	67.0 (62.9 to 70.5)
10 Malaria	66.4 (37.7 to 105.9)

Leading causes, 2020	Number of DALYs (millions), 2020
1 Neonatal disorders	192.6 (168.2 to 220.6)
2 Ischemic heart disease	185.1 (175.2 to 194.5)
3 Stroke	158.2 (146.4 to 168.8)
4 COVID-19	123.4 (116.3 to 132.5)
5 Lower respiratory infections	88.2 (78.1 to 99.4)
6 COPD*	78.4 (72.1 to 84.3)
7 Diabetes	76.5 (64.9 to 92.2)
8 Low back pain	69.3 (49.5 to 92.8)
9 Road injuries	65.1 (61.0 to 69.8)
10 Diarrheal diseases	61.6 (49.8 to 75.5)
11 Malaria	55.4 (21.5 to 110.5)
13 Congenital defects	54.5 (47.3 to 65.1)
22 HIV/AIDS	42.3 (39.0 to 47.5)

Leading causes, 2021	Number of DALYs (millions), 2021
1 COVID-19	212.0 (198.0 to 234.5)
2 Ischemic heart disease	188.3 (176.7 to 198.3)
3 Neonatal disorders	186.3 (162.3 to 214.9)
4 Stroke	160.4 (148.0 to 171.7)
5 Lower respiratory infections	82.5 (72.9 to 93.2)
6 COPD*	79.8 (74.0 to 86.0)
7 Diabetes	78.9 (66.8 to 94.5)
8 Other COVID outcomes**	77.4 (59.7 to 101.9)
9 Low back pain	70.2 (50.2 to 94.1)
10 Road injuries	65.1 (60.7 to 69.8)
11 Diarrheal diseases	59.3 (47.4 to 73.2)
13 Malaria	55.2 (22.6 to 108.7)
14 Congenital defects	52.3 (45.2 to 62.6)
24 HIV/AIDS	40.3 (37.2 to 44.8)

Injuries

Non-communicable diseases

Communicable, maternal, neonatal, and nutritional diseases

† Uncertainty intervals are a range of values that are likely to include the correct estimate of health loss for a given cause.

* Chronic obstructive pulmonary disease.

** Other pandemic-related mortality; includes excess mortality associated with the pandemic.

[Global Burden of Disease 2021: Findings from the GBD 2021 Study | Institute for Health Metrics and Evaluation]

Long-term Individual and Family Impact

Social/Emotional/Behavioral Outcomes in Hypoxic Ischemic Encephalopathy

- Increased anxious and depressive symptoms at 3-6 years
- Oppositional behavior, attention problems, hyperactivity, somatic complaints and anxiety at school age
- Higher rate of cognitive impairment and learning disabilities compared to peers

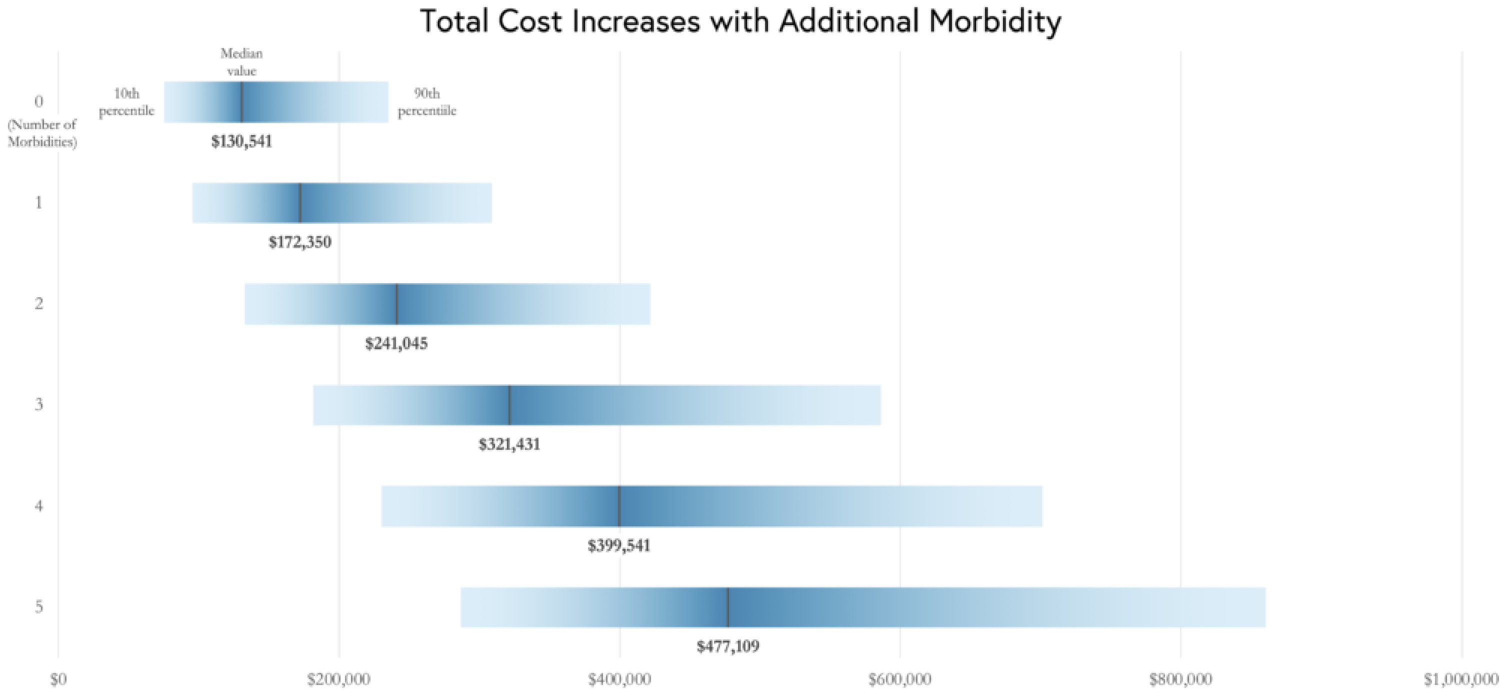
Christoffel, et al. Pediatric Research 2025

Severe BPD's Impact on Families

Fig. 1 Correlations between child outcomes and total family impact module score. Line thickness represents strength of correlation.

Farrell, et al. J Perinatology 2025

Cost of Preterm Birth



Study sample consists of a cohort of infants born preterm without major congenital anomalies (birth weight between 400 and 1999 grams and gestational age from 24-to-30 weeks) admitted in the first three postnatal days between January 1, 2009, and December 31, 2018. Data are drawn from the Pediatric Health Information System (PHIS) and includes 19,232 patients from 30 children's hospitals across the United States.

Lai & Lorch, Journal of Pediatrics, 2023

Life-time cost of Prematurity

National Aggregate and Incremental Cost of Preterm Births in 2016

Category of Cost	Total ($)	Per Preterm Birth ($)
Medical Care for Affected Child	17,126,625,946	44,116
Maternal Delivery Costs	1950,230,570	5024
Early Intervention Services (EI)	702,014,493	1808
Special Education Services	622,589,060	1604
Assistive Devices	10,820,563	28
Lost Labor Market Productivity	4750,215,975	12,236
Total	25,162,496,608	64,815

Per Preterm Infant Incremental Lifetime Cost by Gestational Age in 2016

Gestational Age	Per Preterm Infant Birth ($)	% Medical
< 28 weeks	344,355	82%
28–31 weeks	186,731	79%
32–36 weeks	28,367	67%
All Preterm (<37 weeks)	64,815	76%

Waitzman, et al. Semin Perinatol, 2021.

Leveraging rare disease product development resources for diseases unique to the neonate…

- FDA Rare Disease Innovation Hub
- CBER Rare Disease Program
- CDER's Accelerating Rare disease Cures (ARC) Program
- Orphan Drug Designation program
- Rare Pediatric Disease Priority Review Voucher program
- Humanitarian Use Device (HUD) program
- Grant Programs to Support Development of Medical Products for Rare Diseases
- About BPCA - BPCA | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development

FDA Neonatology Program

Congressionally mandated

Established in response to the FDA Safety and Innovation Act (FDASIA) which mandates that the Agency maintain expertise in neonatology

Cross-cutting

Housed in the Office of Pediatric Therapeutics, Office of the Chief Medical Officer, Office of the Commissioner, FDA; allows for awareness and coordination of Agency-wide initiatives

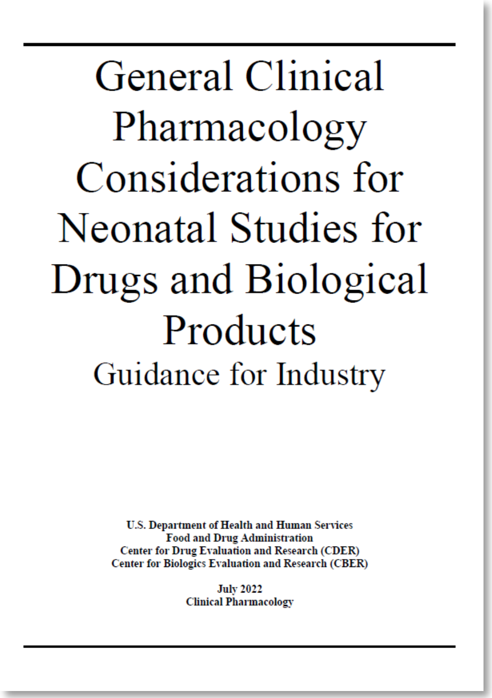
Consultation

Supports all FDA Centers by providing expertise in neonatal and perinatal medicine to support and promote product development for neonates

Collaboration

Collaborates with interested parties to improve and accelerate neonatal product development

Neonatology Resources



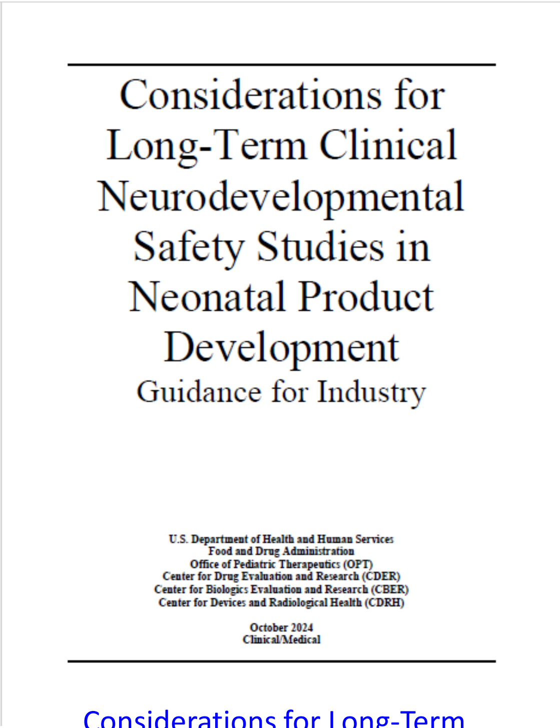
General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products

Guidance for Industry

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

July 2022
Clinical Pharmacology

[General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry | FDA]



Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

October 2024
Clinical/Medical

[Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development | FDA]

U.S. FOOD & DRUG ADMINISTRATION

Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development

Guidance for Industry

What is covered in this guidance?

This guidance provides a framework for considering neurodevelopmental evaluations that could be useful to assess long-term safety of a medical product intended for use in neonates.

Why is this guidance important?

Treatment with medical products during the neonatal period coincides with a time of critical growth and physiologic development. Short-term safety evaluations typical for adults or other populations may fail to identify important adverse effects in the neonatal population, as latent effects may follow early-life exposures.

Domains for evaluating neurodevelopmental clinical outcomes for safety

General	Neurodevelopmental
Physical health	Sensory
Health conditions	Motor
Feeding problems	Cognition
Somatic growth	Emotional and behavioral health
Sleep	Communication
Quality of life and global function	Social functioning
Receipt of developmental interventions and educational services	Adaptive functioning

www.fda.gov

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about the considerations for long-term clinical neurodevelopmental safety studies in neonatal product development, read the guidance.

1

[Guidance Snapshot Pilot | FDA]

Summary

- Neonatal conditions that are “common” in the NICU are rare diseases
- There is a critical unmet need for product development for conditions unique to neonates and rare diseases
- Detecting, diagnosing and treating conditions in the neonatal period greatly impacts public health
- Rare disease product development resources can be leveraged to advance therapies for conditions unique to neonates

U.S. FOOD & DRUG ADMINISTRATION

Uncommon Cures

Recognizing Common Challenges Across Investigations in Neonates and Rare Diseases Populations

Marshall Summar, MD
Uncommon Cures

The Speaker has no conflict to report.

How I got here

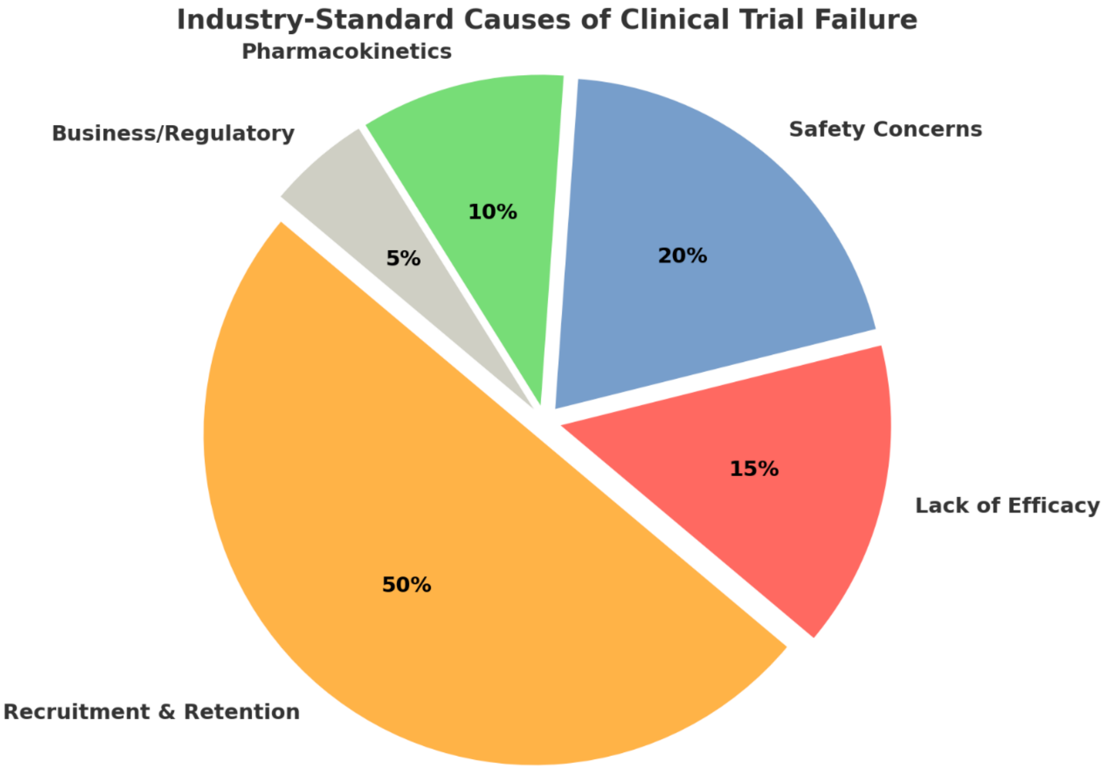
- Started in rare disease during pediatrics training in 1985
- Worked as a General and Biochemical Geneticist from 1988 to present
- Was geneticist and executive committee for Vanderbilt's General Clinical Research Center (NIH) and steering committee and project evaluator for Vanderbilt Institute for Clinical and Translational Research (NIH) from 1990 to 2010
- Directed GCRC and then CRC at Children's National for 4 years as well as CTSA exec. committee
- Built and led Rare Disease Institute at Children's National and clinical trials program avg. 35 trials ongoing
- Participated or led in over 130 Rare Disease Clinical Studies
- Board Chairman of National Organization for Rare Disorders for > 5 years, Board member 9 years
- NIH Rare Disease Clinical Research Network founding study member 2004
- NIH NCATS Council
- Helped build IAMRARE Registry Program and National Clinical Centers of Excellence Program at NORD
- Chaired inaugural Patient Centered Ooutcome Research Institute Rare Disease Advisory Committee
- Co-chaired BWHI Rare Disease Diversity Coalition Research Group
- **<u>IN OTHER WORDS: After 40 years, I've had the opportunity to make or be a part of every rare disease clinical trial mistake you can make and had some time to think over the reasons and possible solutions.</u>**

Likely Number of Patients per Rare Disease Frequency in the U.S., EU, and Japan for Over 3000 Diseases With Known Prevalence

Prevalence Category (per 100,000)	Number of Diseases	U.S. Patient Range	EU Patient Range	Japan Patient Range
< 0.1	2,970	< 341	< 449	< 123
- <10 cases worldwide (N=1)	~1,188	0-1	0-1	0-1
- 10 to 100 cases	~891	0-5	0-6	0-2
- 100 to 1,000 cases	~594	4-43	6-56	2-15
- 1,000 to 8,000 cases	~297	43-341	56-450	15-123
0.1 - 0.9	41	341 - 3,069	449 - 4,041	123 - 1,107
1 - 9	84	3,410 - 30,690	4,490 - 40,410	1,230 - 11,070
10 - 90	33	34,100 - 306,900	44,900 - 404,100	12,300 - 110,700

Total diseases with <150 patients in the U.S.: ≈ 90%, EU: ≈ 89%. Japan: ≈ 95%.
Total diseases with <50 patients in the U.S.: ≈ 88%, EU: ≈ 82%. Japan: ≈ 93%.

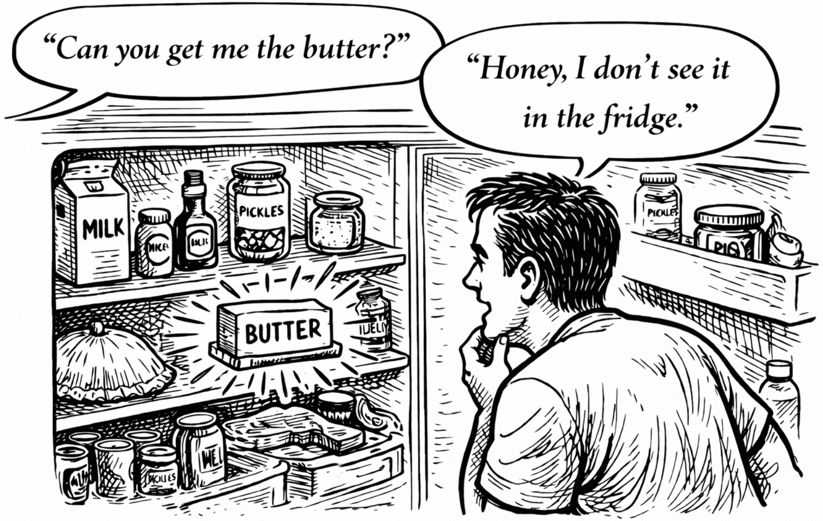
Why Do Clinical Trials Fail >75% Of The Time?



So What's Different About Rare Disease Trials?

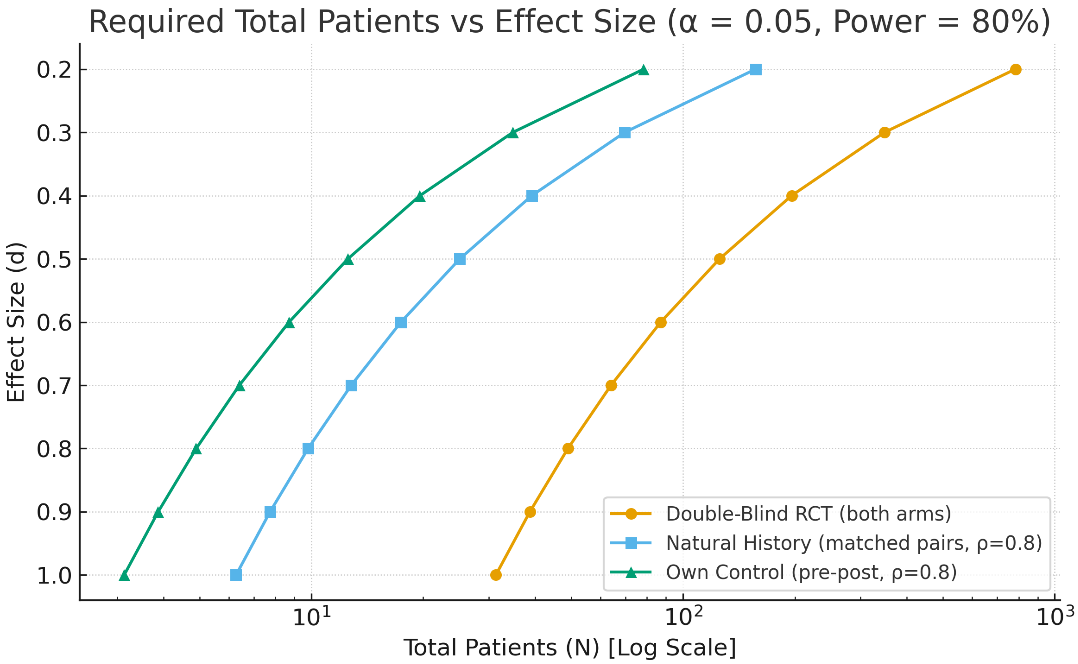
1. **They Are Rare—By Definition**
Patient numbers are limited. Building an "ideal" model for treatment response isn't always feasible.
2. **Genetic Heterogeneity**
Each patient may carry different primary and modifier genes, leading to wide variability in disease severity and trajectory.
3. **Sparse Natural History and Outcome Data**
Available evidence often comes from small case series, lacking longitudinal depth or standardized outcome measures.
4. **Challenging Patient Identification**
Diagnosis is often delayed or missed; recruitment depends on complex referral and diagnostic networks.
5. **Effect Size and Event Frequency Are Unclear**
Small, heterogeneous samples make estimating statistical parameters—like effect size and outcome variance—especially difficult.

False Negatives Are A Major Risk in Small Populations



- Small N + heterogeneity = diluted group means
- Between-patient variance overwhelms treatment effect
- RDBPC designs maximize Type II error in rare disease
- Result: biologically active therapies are abandoned prematurely

"This is not regulatory evasion — this is variance control."



Effect size d	RCT total N (both arms)	Natural history total N (matched pairs, correlation=0.8)	Own-control total N (correlation=0.8)
0.2	784	156.8	78.4
0.25	501.8	100.4	50.2
0.5	125.4	25.1	12.5
0.8	55.8	11.2	5.6
1	31.4	6.3	3.1

Why Own-Control Designs Outperform RCTs in Rare Disease

"Your average groups"

Core Problem: Extreme Heterogeneity

- Rare diseases show wide variability in genotype, severity, and trajectory
- "Matched" treatment and control groups are rarely biologically comparable
- Randomization does not eliminate imbalance when N is small

Why Between-Group Comparisons Lose Sensitivity

- Inter-patient variance often exceeds treatment effect size
- Group means obscure meaningful individual responses
- True biological signals are diluted → false negatives

Why Within-Patient Comparisons Are More Informative

- Each patient provides their own biologically matched control
- Change from baseline or slope change reduces noise
- Sensitivity driven by intra-patient correlation, not cohort size

Key Point (Bottom Line)

In heterogeneous rare diseases, the most reliable comparison is often the patient against themselves, not against another patient.

Natural History Studies: Designing Success Before the First Patient Is Dosed

1. Endpoint Validation
- Identify outcomes that change reliably over time
- Avoid insensitive or biologically misaligned endpoints

2. Disease Trajectory & Variability
- Define true progression rates and phenotypic spread
- Support slope-based and own-control analyses

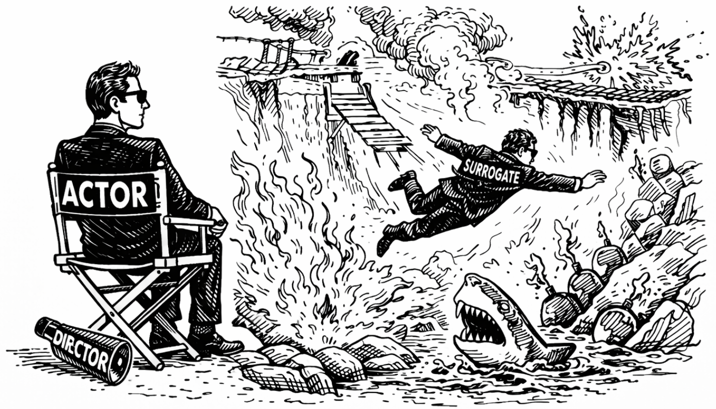
3. Safety Context
- Distinguish disease events from treatment toxicity
- Anticipate expected serious adverse events

4. Trial Feasibility
- Pre-identify characterized, motivated patients
- Reduce screen failure and recruitment delays

5. Community & Infrastructure
- Align patients, clinicians, and investigators early
- Enable external controls (e.g., IAMRARE / NORD)

"Always good to have a map before you go."

The Use of Surrogate Markers



"Sometimes it's easier and more reliable to get it done with a substitute."

Used when

- A true primary outcome takes too long to measure (like long term brain development)
- A manifestation has been causally linked to a biomarker (hyperammonemia and encephalopathy)

Can Be

- Imaging
- Psychological testing
- Metabolite or bio-molecule
- Symptom or finding tightly linked to primary outcome
- Performance or Quality of Life Metric

- Are not historically the preferred method of proof by agencies but they are coming around.

Pediatric Inclusion – A Scientific Imperative

•**Children Make Up the Majority:** ~70% of rare diseases begin in childhood—excluding them perpetuates delays in diagnosis and treatment.

•**Strong Scientific Justification:** Many therapies show their largest effect in children, allowing for smaller, more efficient trial designs.

•**Access Equity:** Children should not be denied participation when inclusion is safe and scientifically supported.

Point of Maximal Impact
Where Signal Is Largest

- Disease biology most malleable early

- Less accumulated damage → larger effect potential

- Adult-only trials often test *after* PMI has passed

- Result: false assumption of inefficacy

"PMI, make your impact where it will make the biggest difference."

Off-Label Use Is the Real Safety Risk
The Paradox of “Protecting” Children

- 50–90% of hospitalized children receive off-label drugs
- Exposure occurs **without** dosing, PK, or safety rigor
- Adult-first paradigm shifts risk *out of trials* and *into practice*

Pediatric Safety Is Not Predictable From Adults

- Ivacaftor → pediatric liver toxicity
- Nusinersen → infant hypersensitivity
- SSRIs → suicidality signal only in youth

Early Pediatric Inclusion Can Improve Trial Success

- Combined adult + pediatric trials show higher success rates
- Larger aggregate N
- Broader effect size distribution
- Earlier regulatory clarity

Aligning Therapy Type with Ethical Sustainability

- **Gene Therapy as an Ethical Strength:** One-time or limited-dose gene therapies offer potentially curative benefit—ideal for settings where chronic treatment access is uncertain.

- **Small Molecule and Oral Drugs Still Critical:** Lower-cost or repurposed therapies remain viable and sustainable options, especially when approved in-country.

- **Select Trials Based on Real-World Fit:** Trials should reflect local healthcare capacity, reimbursement potential, and follow-up feasibility.

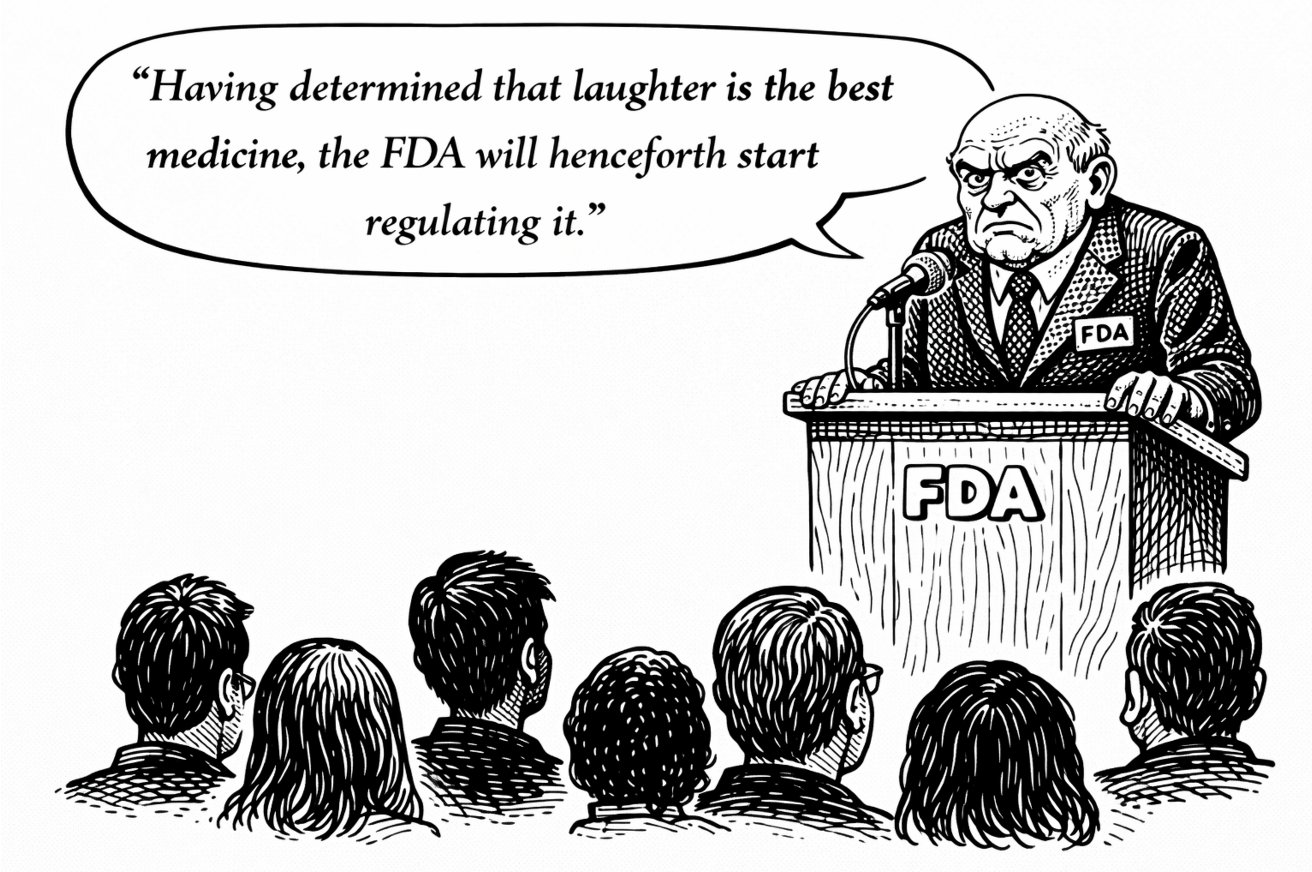
- **Plan for Post-Trial Access:** Ethical trial design includes early planning for registration, access, or continued supply after study completion.

What All This Means for Regulators

- Own-control ≠ lower rigor
- Early pediatric inclusion ≠ higher risk
- Worst error in rare disease = missing a real signal
- Design flexibility improves both science and safety

Take-Home Message

1. Rare disease trials often fail because designs amplify noise (heterogeneity), not because therapies fail.
2. Patient-as-own-control and adaptive models can preserve signal in small populations.
3. Pediatrics should be included early — not for equity alone, but for scientific truth.


"Having determined that laughter is the best medicine, the FDA will henceforth start regulating it."
FDA
FDA

Break

Session 2: Ethical Considerations in Neonatal and Rare Disease Clinical Trials

Session 2 Agenda

- Applying ethical considerations to pediatric studies, highlighting challenges in neonatal and rare disease
- Panelist introductions
- Panel discussions:
  - Weighing benefits and risks when evidence is limited
  - Study design considerations

U.S. FOOD & DRUG ADMINISTRATION

Ethical Considerations in Neonatal and Rare Disease Clinical Trials

Applying 21 CFR 50 Subpart D

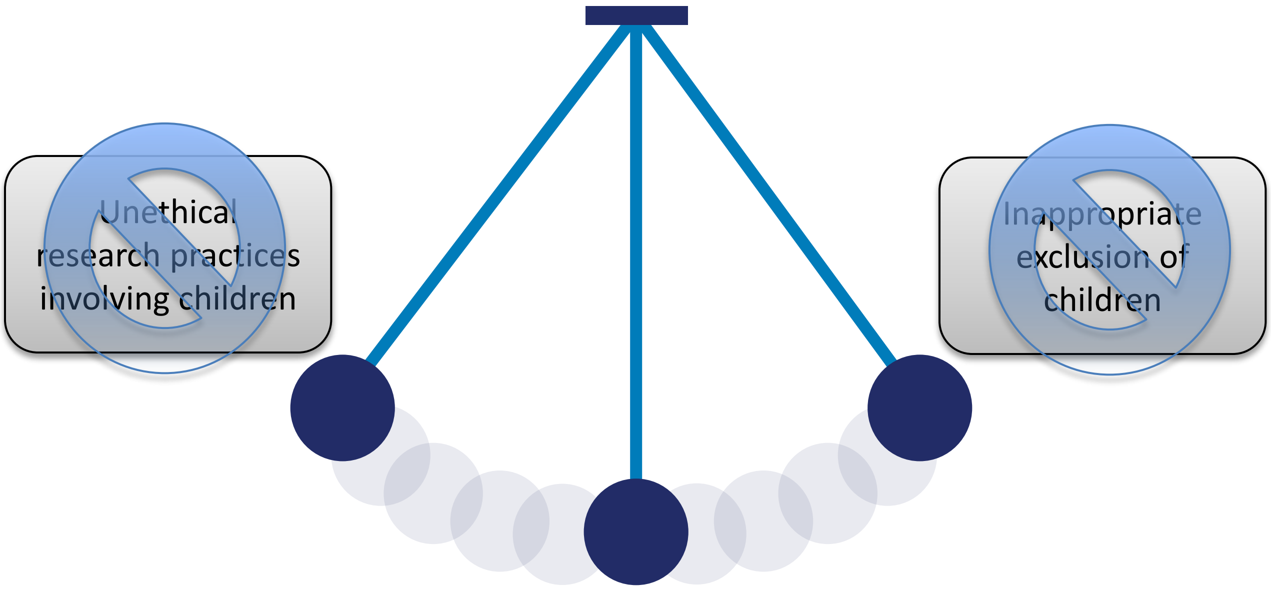
Dalia Feltman MD, MA
Physician Ethicist

Office of Pediatric Therapeutics (OPT)
on detail to Office of Clinical Policy (OCLP)
Office of the Chief Medical Officer (OCMO)
Office of the Commissioner (OC)

Overview

- Principles of human research protections
- Additional Safeguards for Children

Protecting Vulnerable Pediatric Patients



Protection for research participants
AND
Benefits for children from research advances

Scientific necessity

- Value of question for children's health
- Design for success
- Is the enrollment of children necessary?
  - Adults able to consent should enroll before children
  - Can extrapolation be used?

21 CFR 50 SUBPART D

ADDITIONAL SAFEGUARDS FOR CHILDREN

21 CFR 50 Subpart D Additional Safeguards for Children in Clinical Investigations

Section	Topic
50.50	IRB duties
50.51	Clinical investigations not involving greater than minimal risk
50.52	Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.
50.53	Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.
50.54	Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
50.55	Requirements for permission by parents or guardians and for assent by children.

Is there a Prospect of Direct Benefit?

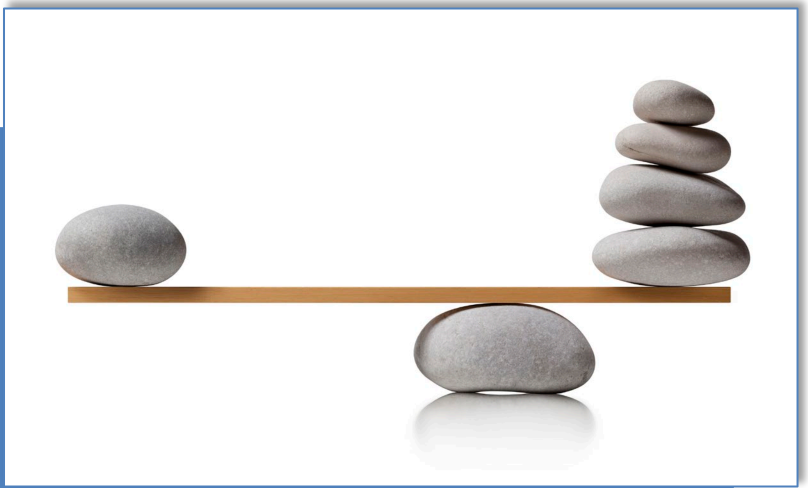
YES: Consider 50.52

- The risk is justified by the anticipated benefit to the subjects:
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

NO: Consider 50.53

- Limit: minor increase > minimal risk
- Intervention or procedure… reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- Likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition

Weighing the Evidence: Benefits and Risks

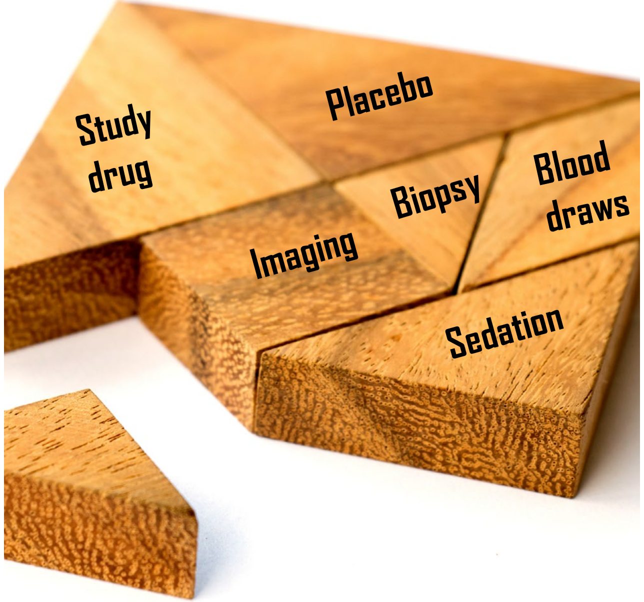


- Non-clinical studies
- Clinical studies
  - Therapeutics
  - Indications
  - Populations
- Alternative therapies
- Evidence to support:
  - Proof of concept
  - Dose/duration/method of administration
  - Risks

Prospect of Direct Benefit

- Prospect of direct benefit: Comes directly from the intervention to the patient
- A research intervention that presents no prospect of direct benefit can present no more than a “minor increase over minimal risk” and meet other 21 CFR 50.53 criteria

Component analysis for pediatric studies



"To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively."

-The National Commission 1977

Ground Rules for Comparator Arms

Clinical equipoise
(genuine uncertainty)
required to allow randomizing child to study arms

Control arm designs:

- Inert placebo
- Sham procedure
- Standard therapy alone vs.
- Study product add-on to standard therapy

Placebo arms allowed when:

There is no established effective intervention

OR

When use of an established effective intervention as comparator would not yield scientifically reliable results

AND

When withholding an established effective intervention would expose participants to no more than a minor increase over minimal risk

Protecting Children in Research:
A shared responsibility among all parties

- Sponsors, Monitors, Contract Research Organizations, Clinical Investigators (CIs), Institutional Review Boards (IRBs) and regulators all play a role
- Responsibilities overlap – system of checks and balances
- Each party is independently responsible for compliance
- Parents ultimately decide whether their child may enroll

Discussion Panel A: Weighing Benefits and Risks When Evidence is Limited

Moderator: Dalia Feltman, MD, MA (OPT/OCMO/OC, FDA)

Panelists:

Robert Nelson, MD, PhD (Johnson and Johnson)

Alison Bateman-House PhD, MPH,MA (NYU Grossman School of Medicine)

Elliott Mark Weiss, MD, MSME (Seattle Children's Hospital)

Panelists continued...

Matthew A. Rysavy, MD, PhD (McGovern Medical School at UTHealth Houston)

Allyson Berent, DVM, DACVIM (The Foundation for Angelman Syndrome Therapeutics [FAST])

Ashley O'Neil, CRNP (It's a NICU World)

Discussion Panel B: Study Design Considerations

<u>Moderator:</u> Dalia Feltman, MD, MA (OPT/OCMO/OC, FDA)

<u>Panelists:</u>

Robert Nelson, MD, PhD (Johnson and Johnson)

Alison Bateman-House PhD, MPH,MA (NYU Grossman School of Medicine)

Elliott Mark Weiss, MD, MSME (Seattle Children's Hospital)

<u>Panelists continued…</u>

Matthew A. Rysavy, MD, PhD (McGovern Medical School at UTHealth Houston)

Lindsey Wahlstrom, MPH, CPH (Rona's FUN LAB)

Jennifer Degl, MS (NICU Parent Network)

End of Day 1 of Workshop

Advancing the Development of Pediatric Therapeutics (ADEPT) 10: Addressing Challenges in Neonatal Product Development – Leveraging Rare Disease Frameworks

Join us to discuss common challenges in neonatal and rare disease product development and identify ways to leverage rare disease product development frameworks in the neonatal product development space

February 5-6, 2026

FDA Great Room
White Oak Campus
Silver Spring, Maryland

Registration required and virtual option available

FDA

Advancing the Development of Pediatric Therapeutics (ADEPT) 10: Addressing Challenges in Neonatal Product Development- Leveraging Rare Disease Frameworks

Day 2 Agenda

Session III: Innovative Strategies for Neonatal and Rare Disease Clinical Trials

Innovative study designs to address small populations

Incorporating novel approaches to facilitate neonatal/rare disease clinical trials

1. *Artificial Intelligence/ Digital Health Technologies in the NICU- Academic Perspective*
2. *AI/DHTs in Neonatology/Rare Disease- Regulatory Perspective*
3. *Leveraging Real World Data in Neonatology/Rare Diseases*
4. *Platform Trials/Master Protocols in Pediatrics*

Selecting Patient-focused Outcomes for Neonatal Conditions and Rare Diseases

-Break-

Day 2 Agenda continued....

Panel Discussion: Leveraging Networks/ Consortia/ Centers of Excellence to Optimize Harmonization and Operational Feasibility of Neonatal/Rare Disease Clinical Trials

-Lunch-

Session IV: Regulatory Landscape and Future Directions for Neonatal and Rare Disease Drug Development

Panel Discussion: Regulatory Perspective: How can Expedited Programs, Incentive Pathways, and other Regulatory Initiatives be Leveraged for Neonatal and Rare Disease Drug Development?

Panel Discussion: Stakeholder perspective: Lessons Learned, Gaps and Future Directions

Summary and Closing Remarks

Session 3: Innovative Strategies for Neonatal and Rare Disease Clinical Trials

Innovative Trial Designs to Address Small Populations

ADEPT 10: Addressing Challenges in Neonatal Product Development – Leveraging Rare Disease Frameworks

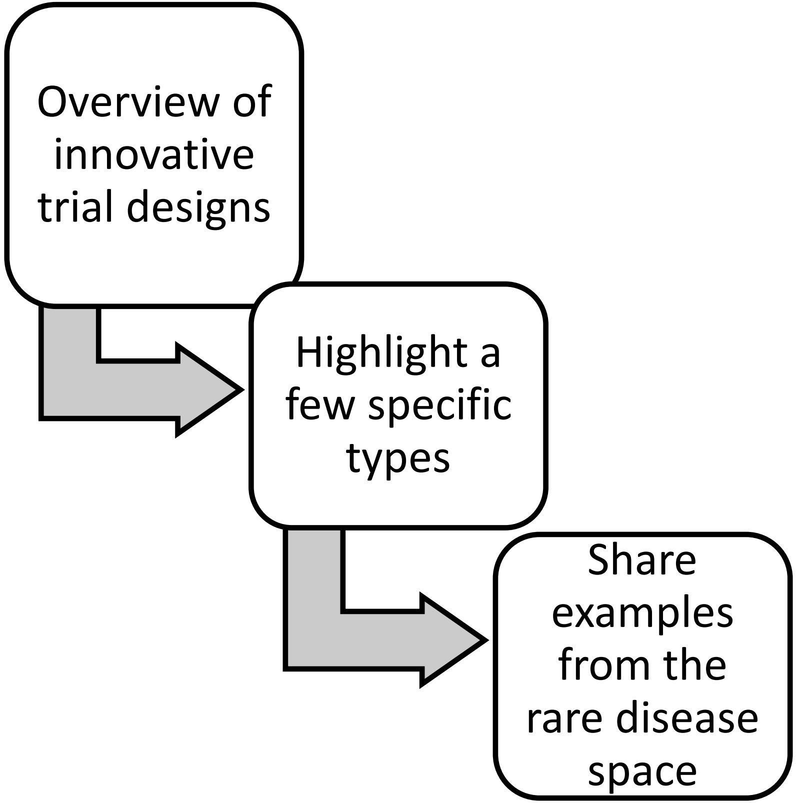
February 6, 2026

Rebecca Rothwell Chiu
Acting Deputy Office Director
Office of Biostatistics (OB), Center for Drug Evaluation and Research (CDER), FDA

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.

Today’s Talk


Overview of innovative trial designs
Highlight a few specific types
Share examples from the rare disease space

What is an innovative trial design?

- No fixed definition - What is considered innovative or novel can change over time
- Generally used to refer to trial designs that have ***rarely or never*** been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications
- Can also include ***the novel application*** of complex trial design features to a given indication even when those design features have been used in other indications

Innovative Design Examples

Novel adaptive designs

Externally-controlled single arm trials

Use of real-world evidence

Formal incorporation of "prior" information to increase clinical trial efficiency (e.g., borrowing external or historical info)

Master protocols (umbrella, basket, or platform trials)

Common Challenges in Rare Disease Drug Development

- Limited number of patients available for trials
- Poorly understood natural history
- Often serious, life-threatening, and lacking approved therapies → high unmet need
- Lack of consensus and experience with endpoints, optimal timing of assessment, expected effect size
- Genotypic and phenotypic diversity within a disorder

How can innovative designs help?

Innovative designs aim to **maximize clinical trial efficiency** and **improve decision making** by…

- Decreasing number of patients needed to study or increase the power/precision for a given sample size
- Accelerating product development
- Optimizing product development

Potential Challenges of Innovative Designs

- Necessitate careful consideration of analysis plans and simulations to avoid:
  - Increasing the chance of erroneous conclusions
  - Introducing bias in estimates
- Logistical challenges to ensuring trial conduct and maintaining trial integrity, especially with adaptive approaches
- Gains in efficiency may be offset by losses elsewhere (e.g., lead time)
- For Bayesian approaches, may be limited by prior information available and required assumptions
- Gains may be limited by scientific constraints
- Adaptive changes can impact interpretability of the results

Bayesian Approaches

New draft guidance!

Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott Goldie at Scott.Goldie@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

January 2026
Biostatistics

https://www.fda.gov/media/190505/download

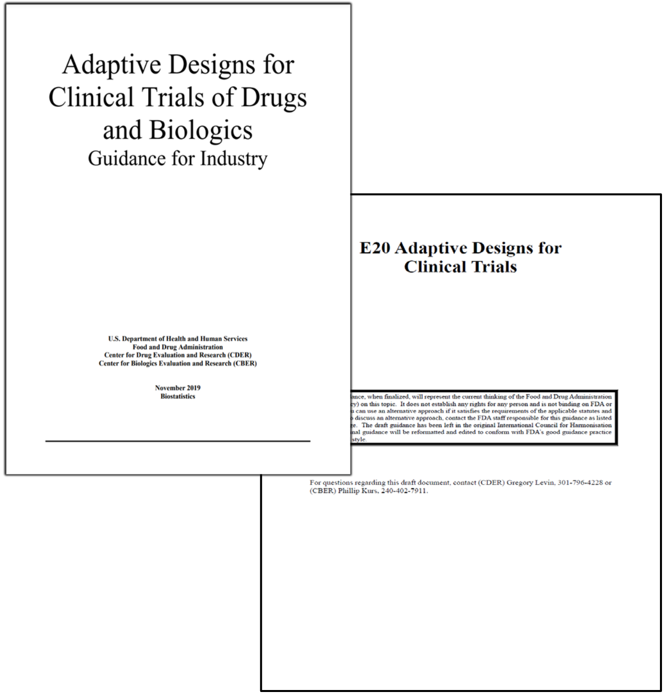
- Combines what you already know (**prior information**) with **new data** from your study to get an updated understanding (**posterior information**)
- In most cases, “borrow” or “leverage” previously available trial data.
  - Can improve efficiency and reduce the amount of new data that needs to be collected

Bayesian Example: Belimumab in cSLE

- **Rare Disease Setting:**
  - Childhood-onset systemic lupus erythematosus (cSLE)
  - Difficult to design and recruit adequately powered pediatric studies.
  - Pediatric and adult patients showed similar disease characteristics, drug responses, and safety profiles
- **Bayesian Analysis Approach:**
  - Post-hoc analysis combined pediatric data with adult belimumab study results
  - Used robust mixture prior that combined a skeptical prior (assuming no treatment effect) with a meta-analysis of treatment effects observed in adult studies.
- **Key Results:**
  - When adult data received ≥55% prior weight, the 95% credible intervals excluded no treatment effect
  - Post-hoc analysis (in addition to secondary endpoints, PK, safety) supporting FDA's approval of belimumab as the first treatment specifically indicated for cSLE.

Pottackal G, Travis J, Nie L, Chiu R, Neuner R, Levin G, Niu J, Marathe A, Mulugeta LY, Nikolov NP. Application of Bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the United States. Lupus. 2025 Aug;34(9):943-952. doi: 10.1177/09612033251349930. Epub 2025 Jun 27. PMID: 40577570.

Adaptive Designs


Adaptive Designs for Clinical Trials of Drugs and Biologics
Guidance for Industry

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

November 2019
Biostatistics

E20 Adaptive Designs for Clinical Trials

For questions regarding this draft document, contact (CDER) Gregory Levin, 301-796-4228 or (CBER) Phillip Kurs, 240-402-7911.

- Allow for **prospectively planned modifications** to one or more aspects of the design, based on **accumulating data**
- Examples include:
  - Group sequential designs
  - Sample size adaptations
  - Adaptations to patient population
  - Adaptations to treatment arm allocation
  - Adaptations to patient allocation
  - Adaptations to endpoint selection
  - Adaptations to multiple features simultaneously

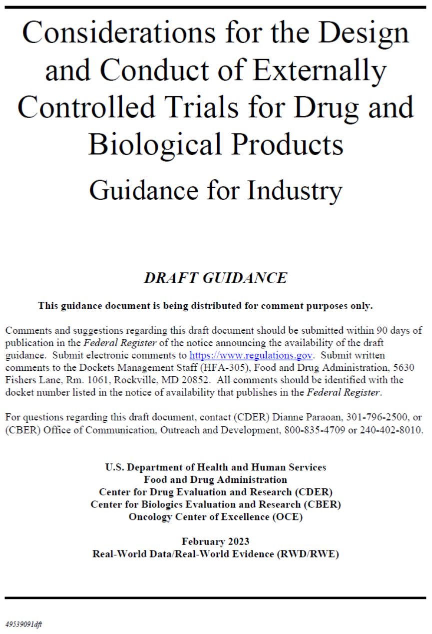
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry
https://www.fda.gov/media/188961/download

Novel Adaptive Design Example: EMAS

- **Rare Disease Setting:**
  - Children and adolescents with epilepsy with myoclonic-atonic seizures (EMAS)
  - Consistent treatment effects observed across related indications
- **Novel Design Elements Proposed:**
  - Bayesian methods proposed to formally incorporate study results from historical studies of the same drug in related populations into the primary analysis of the proposed study in the EMAS population
  - Inclusion of an interim analysis to **adapt the sample size** based on Bayesian predictive probabilities and a prespecified algorithm.
- **Potential Benefits:**
  - Reduce the number of patients needed in the study, making the study more feasible
  - Dynamic borrowing approach may mitigate concern of borrowing non-compatible patient data
- **Challenges**
  - Simulations needed to assess operating characteristics, compare model choices
  - Sensitivity analyses needed to assess impact of assumption deviations

CID Paired Program Trial Design Case Study: https://www.fda.gov/media/172312/download?attachment

Externally Controlled Trials



Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

49539091dft

https://www.fda.gov/media/164960/download

- Outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people **external to the trial** who had not received the same treatment
- Examples:
  – Data from earlier (historical) clinical trials
  – Real world data (RWD) sources
- May be appropriate when:
  – Known that patients would not have spontaneous improvement on a well-defined and meaningful endpoint without treatment
  – Drug is expected to lead to large improvement

External Control Example: Copper Histidinate in Menkes disease

- **Rare Disease Setting**:
  - Menkes disease affects only 1 in 50,000-250,000 live male births
  - Neurodegenerative disorder caused by a genetic defect that impairs a child's ability to absorb copper
  - Most children not surviving past 3 years
- **External Control Design**:
  - Two single-arm trials comparing 66 treated patients to 17 untreated patients from contemporaneous external control groups
  - Primary endpoint: overall survival
- **Results:**
  - Early treatment (within 4 weeks of birth) showed 78% reduction in death risk, with nearly half surviving beyond 6 years versus no untreated patients surviving past 6 years
  - First approved treatment for Menkes disease

https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/211241s000lbl.pdf
FDA Approves First Treatment for Children With Menkes Disease | FDA

Master Protocols

Master Protocols for Drug and Biological Product Development
Guidance for Industry

DRAFT GUIDANCE

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

December 2023
Biostatistics / Clinical / Medical

https://www.fda.gov/media/174976/download

- **Master protocol** - an overarching protocol with multiple **substudies** to evaluate one or more therapies in one or more disease subtypes
  - **Basket trial –** evaluates a single therapy in *multiple diseases or subtypes*
  - **Umbrella trial -** evaluates *multiple therapies* for a single disease
  - **Platform trial -** evaluates *multiple therapies* for a single disease in a *perpetual manner*, therapies allowed to enter or leave the platform over time

Master Protocol Example: Tissue Agnostic Drug Development in Rare Solid Tumors

- Basket trials enable drug development based on specific molecular alterations (biomarkers) across multiple cancer types rather than traditional tumor location-specific development
- **Example**:
  - Selpercatinib received accelerated approval in 2022 for RET gene fusion-positive solid tumors based on one non-randomized, multi-cohort, multi-center, open-label clinical trial (LIBRETTO-001) with 41 patients representing 14 different rare tumor types
  - Primary analysis combined all patients across tumor types together, with 44% achieving objective response despite variable response rates and small numbers within individual tumor types
  - Subgroup analyses by tumor type also evaluated
  - FDA approval supported by genetically-based biologic rationale and existing evidence from related cancers, enabling treatment access for rare, genetically defined patient subgroups

Retevmo Product Labeling https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213246s011s013lbl.pdf

Other Innovative Approaches

- Choice of analysis, e.g.,
  - Use of global tests
  - Novel approaches to longitudinal data
  - Non-inferiority margin derivation
- Choice of endpoints
  - Using novel clinical outcome assessments
  - Composite clinical endpoints
  - Surrogate endpoints
  - Incorporating digital health technology (DHT)
- Use of AI to advance development

Considering Innovative Approaches in Rare Disease

- Remember the basics of trial design (e.g., randomization, blinding) and why they are fundamentally important
- Evaluate the bias-variance tradeoff when deviating from the basics
  - May improve statistical efficiency (power and precision) at the cost of potential bias
  - Example: use of non-concurrent controls in a platform trial design
- To determine the level of acceptance, often requires careful consideration of:
  - Feasibility constraints
  - Unmet need
  - Potential sources of bias (e.g., temporal changes in control arm)
  - Methods to address potential bias (may require novel approaches and simulation)

Further Information on Innovative Approaches and Rare Diseases

- FDA continues to encourage use of Complex Innovative Designs via Prescription Drug User Fee Act (PDUFA) VII (fiscal years 2023-2027)
  - **CID Paired Meeting Program** to discuss specific complex innovative design development programs and promote learning
- The Center for Drug Evaluation and Research (CDER) Center for Clinical Trial Innovation (C3TI) is a hub to improve the efficiency of drug development through innovative clinical trial approaches.
- CDER's Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D) aims to better understand and address the unique challenges in bringing rare disease products regulated by FDA CDER to the market.
  - Videos | Case Studies | Public Report of External Stakeholder Analysis | Additional Resources
- Rare Disease Endpoint Advancement (RDEA) Pilot Program created to support novel endpoint efficacy development for drugs that treat rare diseases

Acknowledgments

- Contributions from:
  - Dr. Wonyul Lee
  - Dr. Greg Levin
  - Dr. Mark Levenson
  - Dr. Pallavi Mishra-Kalyani
  - Dr. Lei Nie
  - Dr. James Travis
  - Dr. Arup Sinha
- Office of Biostatistics Master Protocols Working Group
- Office of Biostatistics Bayesian Working Group
- Office of Biostatistics Rare Disease Committee
- Complex Innovative Trial Design Working Group

Department of Pediatrics
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

AI and Digital Health Technologies in the NICU

DR. RYAN M. MCADAMS

Healing Humanity. Shaping AI.

ADEPT 10

Disclosure

- Consultant: GE Healthcare
- No relevant financial relationships with manufacturers of products or providers of services discussed in this CME activity
- I **do not** intend to discuss unapproved or investigational uses of commercial products/devices

In the NICU,
“n of 1”
is really
“n of many.”

Individually
rare.
Collectively
common.

AI Advances since 2022

LLMs: ChatGPT and similar LLMs bring natural language AI to mainstream

Generative AI for Images & Video: Photorealistic images and videos from text, revolutionize content creation

AlphaFold & Protein Structure Prediction: Accelerates drug discovery and rare disease research

Multimodal AI Systems: AI integrates text, images, audio, and video simultaneously

Scientific Discovery: Autonomous systems generate hypotheses and discover new antibiotics and materials

The Time is Now: The Predictive NICU Imperative

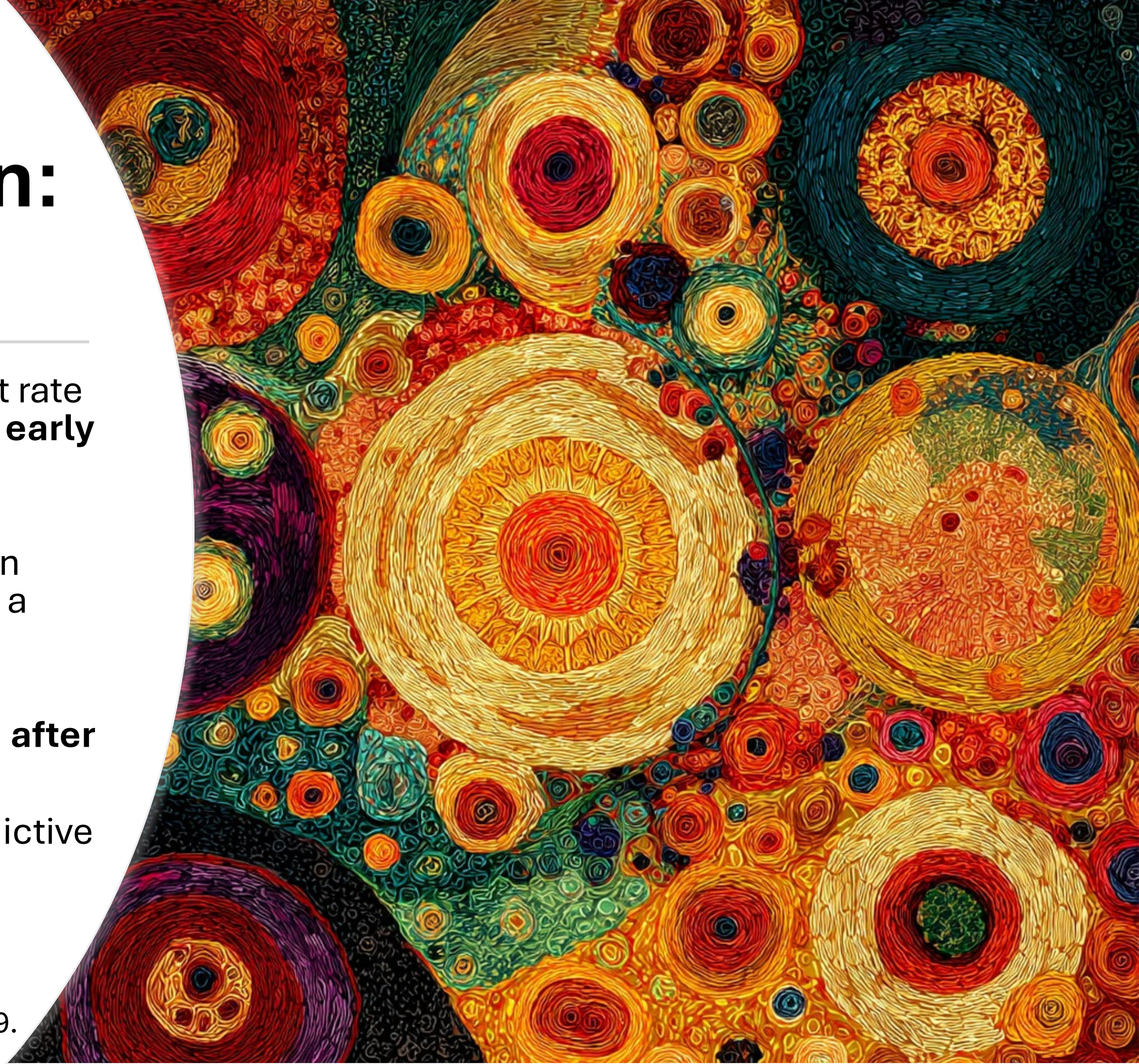
- NICUs generate vast multidimensional datasets.
- Complex phenotypes
- High disease burden
- Machine learning is ready for clinical integration.
- Shift from reactive to proactive, predictive care.

AI in Clinical Use

- **Mostly pre-clinical:** Impressive retrospective results, limited prospective, multi-center clinical validation.
- **Generalizability remains the core risk:** Models often do not travel well across sites, devices, and populations.
- **We validate models, not systems:** Few tools are evaluated as real interventions that change care and outcomes.

Infection Detection:
HeRO Monitoring

- **What it does:** Analyzes neonatal heart rate variability and decelerations to detect **early physiologic signatures of deterioration/sepsis**
- **Clinical impact: Reduces mortality** in very low birth weight infants (shown in a large multicenter RCT)
- **Important nuance: Does not reduce sepsis incidence**, but **reduces death after sepsis occurs**
- **Regulatory status: FDA-cleared** predictive monitoring tool (not a diagnostic)



Fairchild KD. Curr Opin Pediatr. 2013 Apr;25(2):172-9.

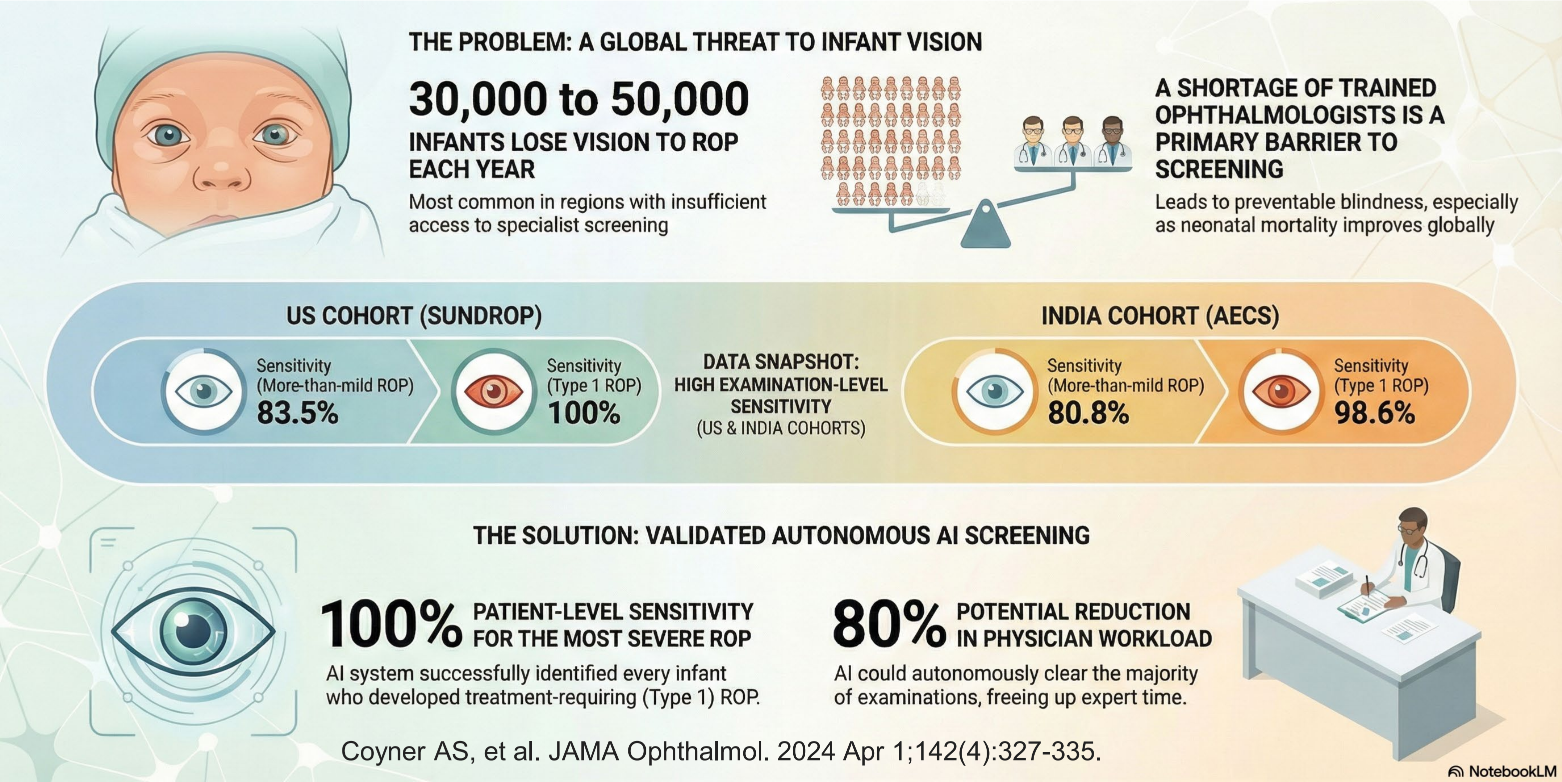
AI for Retinopathy of Prematurity Screening

i-ROP DL

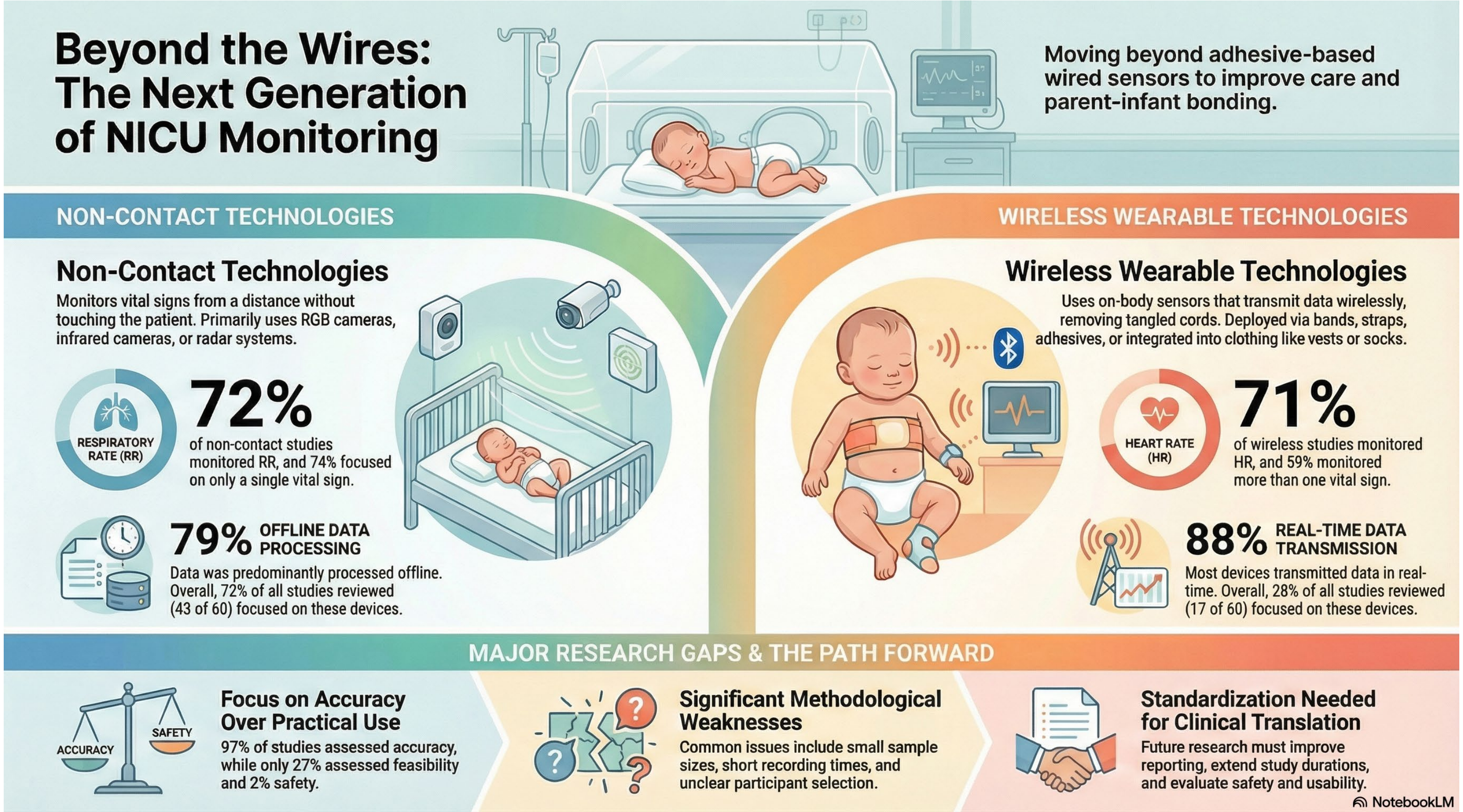
•AI for ROP severity / plus disease from retinal images

Expert-level research performance

Breakthrough Device status — **not yet FDA-approved**



Coyner AS, et al. JAMA Ophthalmol. 2024 Apr 1;142(4):327-335.



Senechal E, et al. Pediatr Res. 2025 Nov 12.

Battling Time: Neonatal Rare Diseases

7 Million Infants

Born with genetic disorders annually worldwide

18% of NICU Admissions

Harbor a Mendelian disease

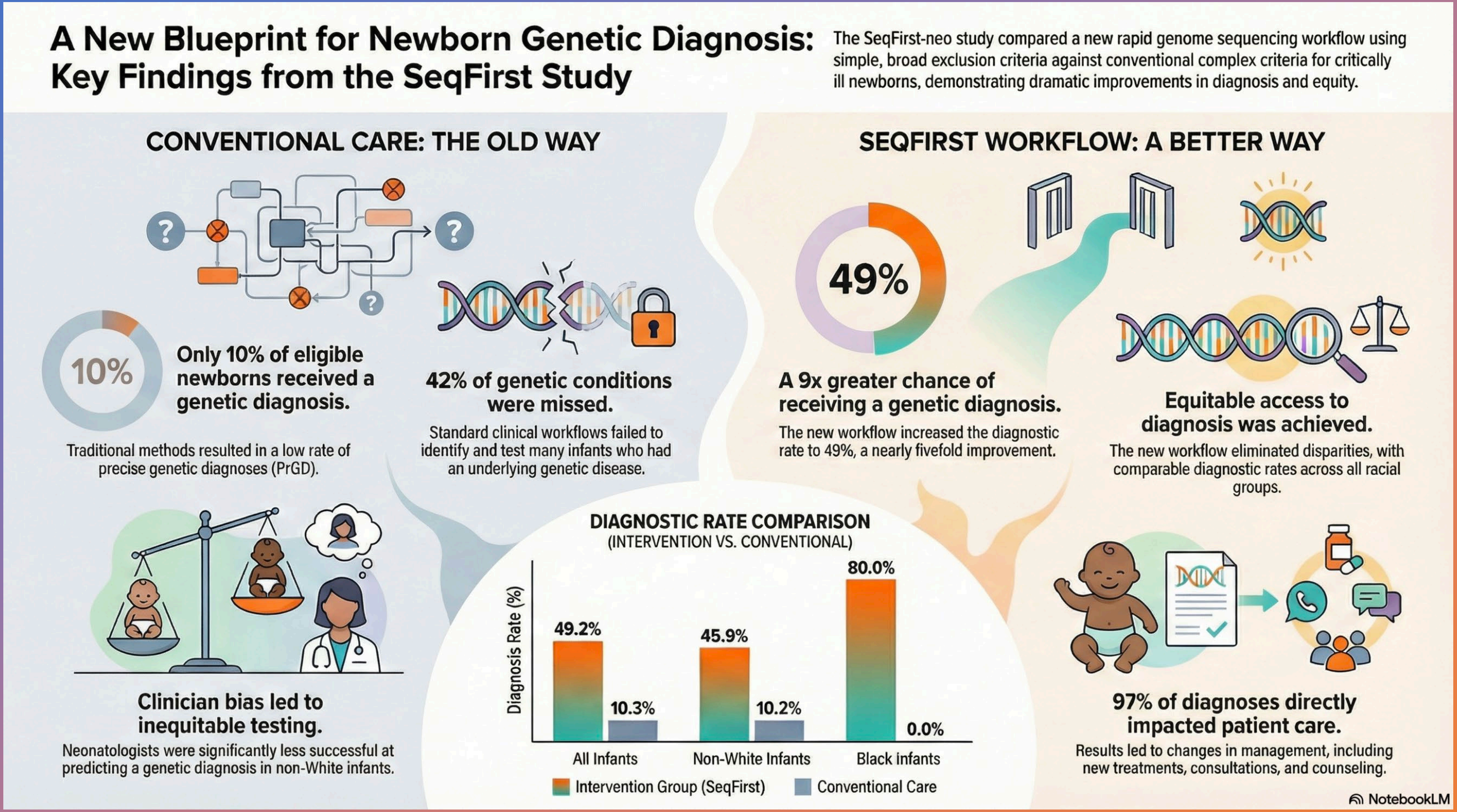
Resource Constraint

Only a fraction can receive rWGS despite >35% diagnostic rate

The Operational Bottleneck

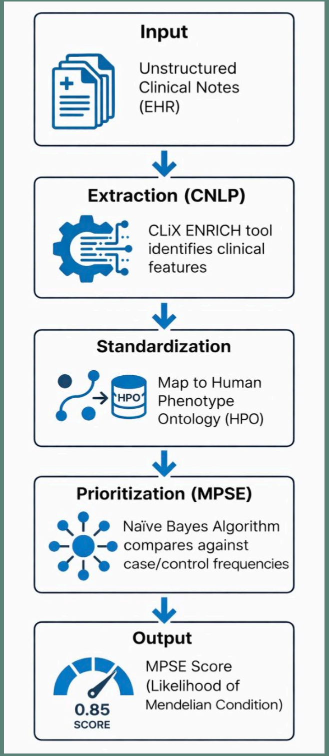
- Large NICUs see >1,000 admissions/year.
- Disease trajectories change minute-to-minute.
- Manual review is static (e.g., Day 7) and cannot keep up.

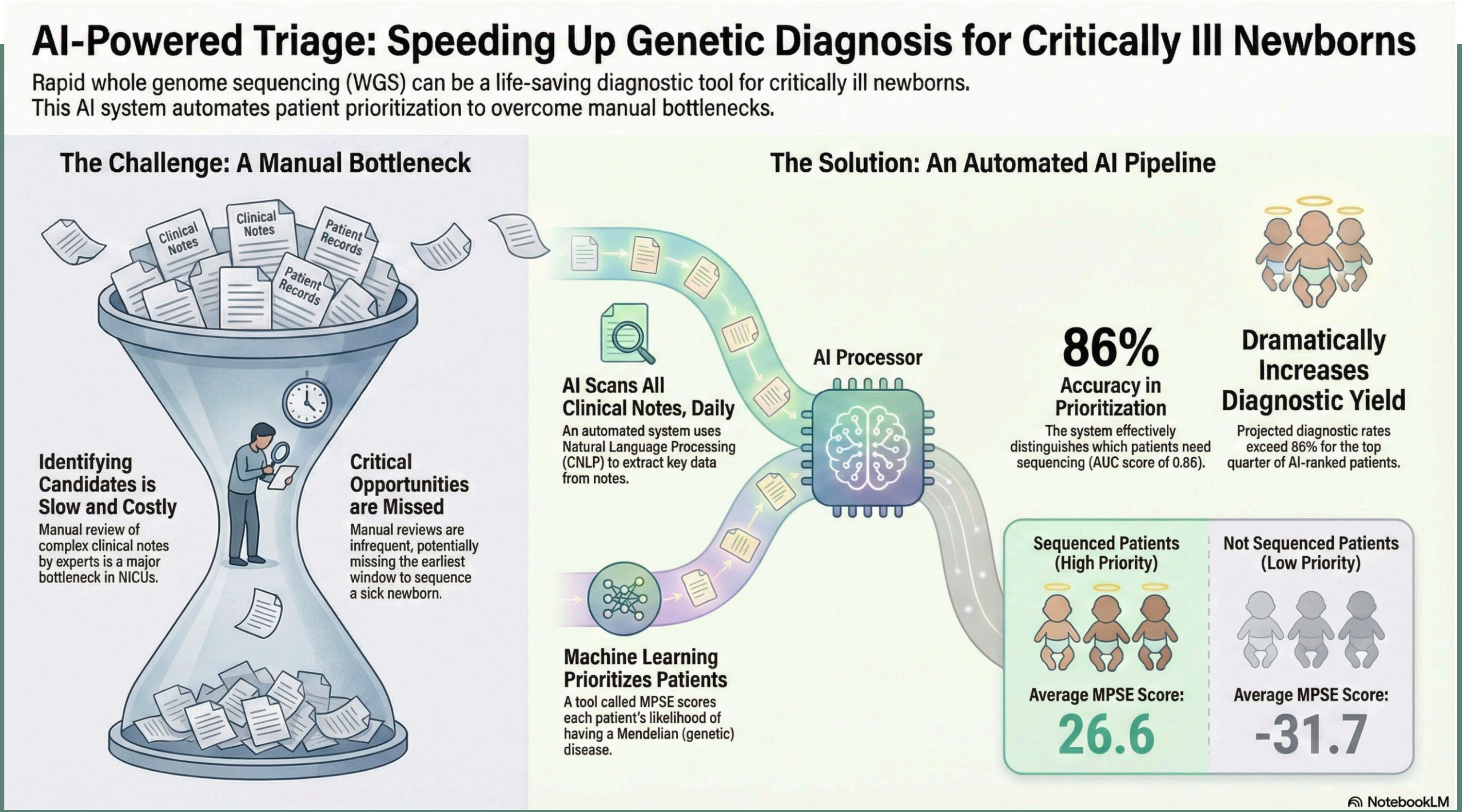
Diagnostic Yield of rWGS: >35%



Wenger TL, et.al. Am J Hum Genet. 2025 Mar 6;112(3):508-522.

Unstructured Notes to Probability





Peterson et al. Genome Medicine (2023) 15:18

Article | Open access | Published: 28 January 2026

Advancing regulatory variant effect prediction with AlphaGenome

Žiga Avsec, Natasha Latysheva, Jun Cheng, Guido Novati, Kyle R. Taylor, Tom Ward, Clare Bycroft, Lauren Nicolaisen, Eirini Arvaniti, Joshua Pan, Raina Thomas, Vincent Dutordoir, Matteo Perino, Soham De, Alexander Karollus, Adam Gayoso, Toby Sargeant, Anne Mottram, Lai Hong Wong, Pavol Drotár, Adam Kosiorek, Andrew Senior, Richard Tanburn, Taylor Applebaum, ... Pushmeet Kohli

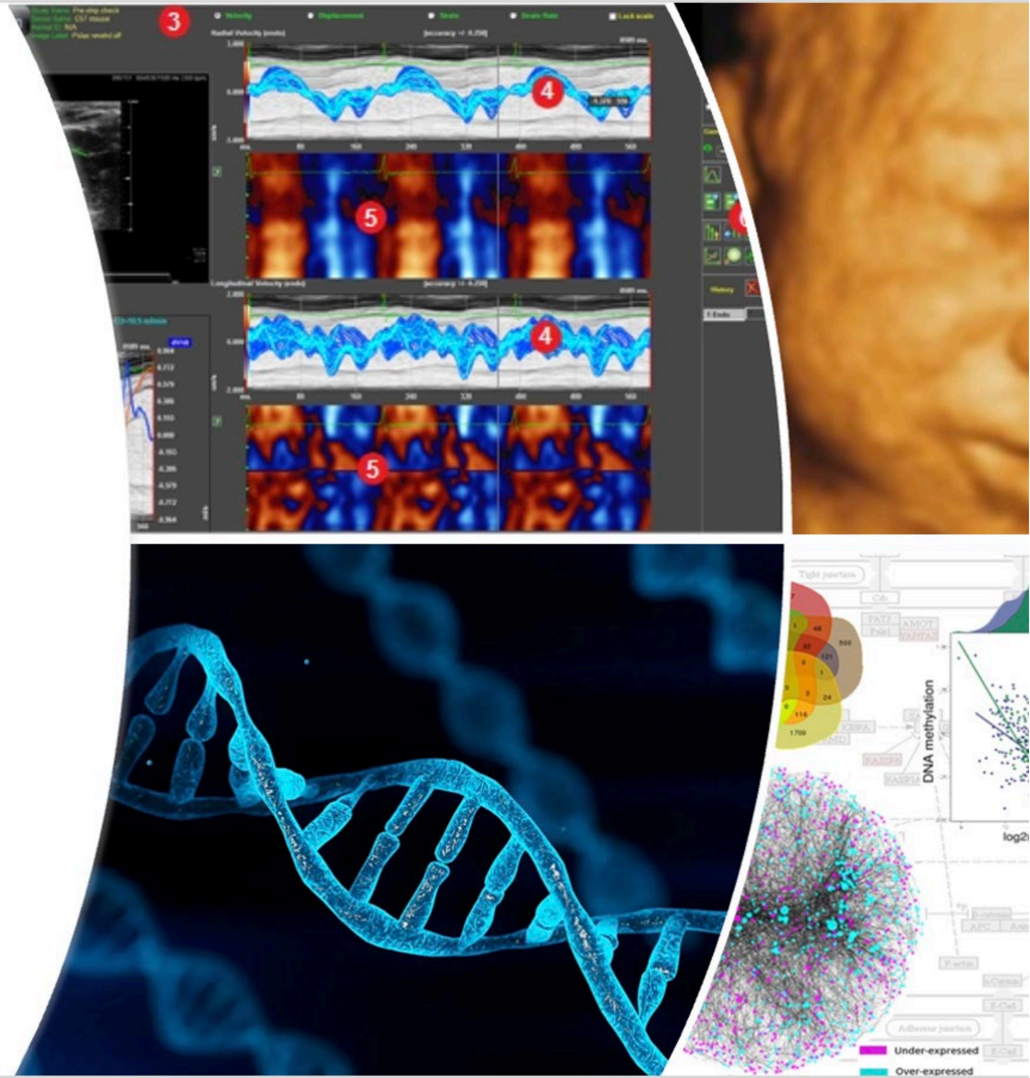
+ Show authors

Nature **649**, 1206–1218 (2026) | Cite this article

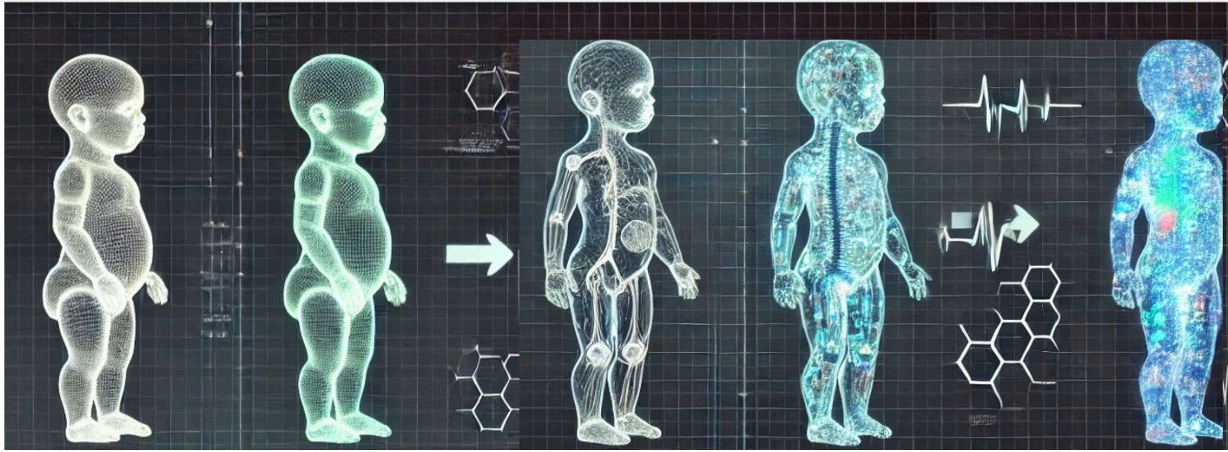
- **Potential to Predict the functional impact of a newborn's genome** across splicing, gene expression, and chromatin regulation—directly from DNA sequence
- **Represents a shift from annotation-based to mechanism-informed genomics**, focusing on how variants may disrupt biology rather than only where they occur
- **Points toward in-silico functional testing to support rare disease diagnosis in the NICU**, particularly for currently uninterpretable non-coding and regulatory variants

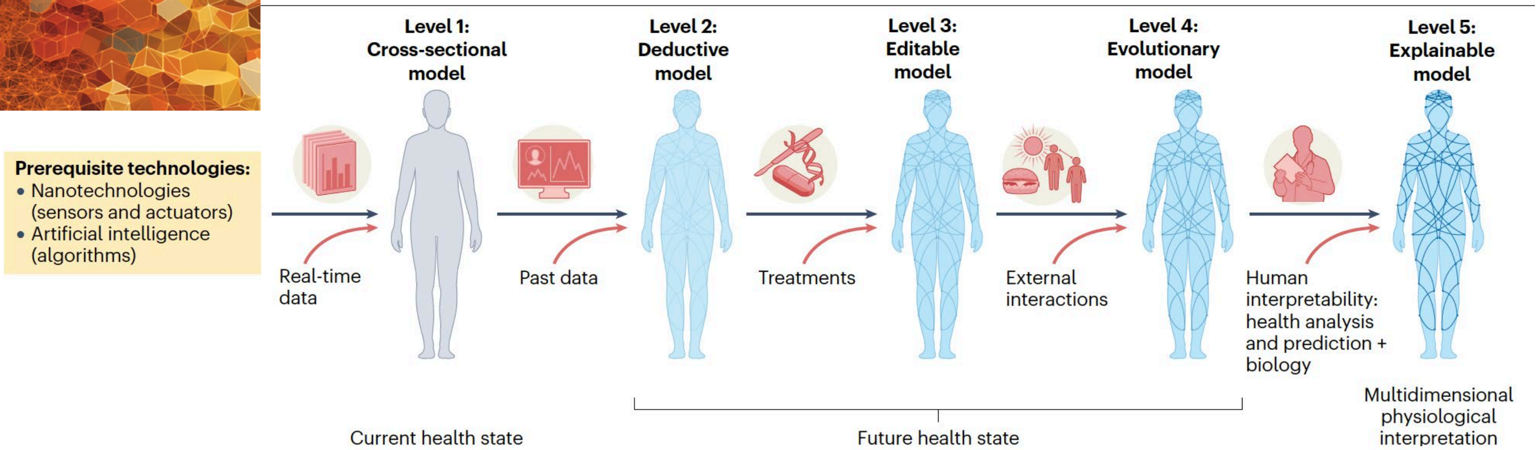
Tomorrow's NICU: Next-Generation AI

- **Rare Disease Discovery:** AI mining multi-omics data (genomics, proteomics, metabolomics) to identify undiagnosed genetic and metabolic disorders within hours of presentation
- **Precision Dosing:** Real-time AI optimization of oxygen, medications, nutritional support based on individual physiology and genetics
- **Integrated Decision Support:** Multimodal AI combining images (ultrasound, MRI), continuous physiologic signals, labs, and EHR—providing holistic clinical guidance



Human Body Digital Twins





Tang, C., *et al.* A roadmap for the development of human body digital twins. *Nat Rev Electr Eng* **1**, 199–207 (2024).

Enhancing the Human Experience

IoT-Enabled Micro-Environments: AI autonomously adjusts incubator settings (light, sound, temperature) based on the baby's physiological state.

Transparent Parent Communication: AI synthesizes complex clinical data into clear, jargon-free daily progress reports for families.

Data-Driven Prognostics: AI provides personalized, risk-stratified insights for long-term developmental counseling.

Family Bonding: Reduced clinical alarms and clearer communication reduce parental anxiety and enhance the opportunity for bonding.

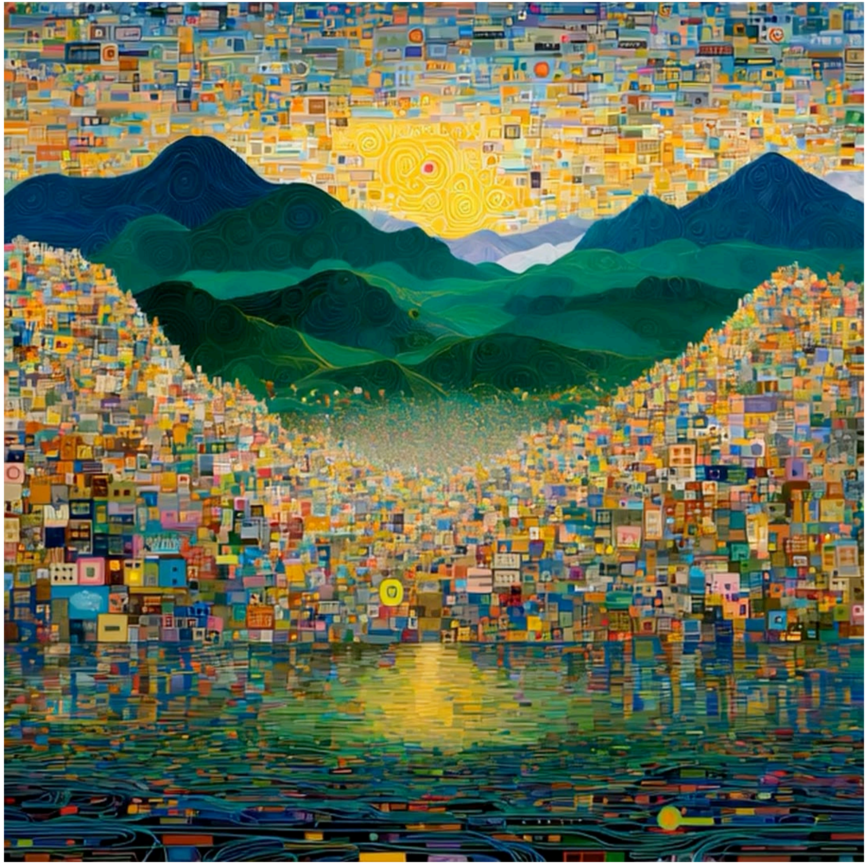
Safety, Ethics, and Governance

Bias Mitigation: Models must be rigorously tested to ensure equitable performance

Transparency: AI must be a Clinical Decision Support tool; the "why" of the recommendation must be interpretable.

Accountability: The human clinician retains full legal and ethical responsibility for the final decision in all scenarios.

Governance: Continuous safety audits must be performed by cross-functional teams (Clinical, Ethics, Data Science) for ongoing validation.



Key Takeways

- **The NICU Is Ready:** Data-rich environment with strong collaborative infrastructure
- **Current Tools Work (But Are Underused):** HeRO and ROP-AI show benefit; barriers are adoption, integration, and trust
- **Pipeline Is Promising:** BPD, NEC, rare diseases — needs external validation and real-world trials
- **Data Is the Foundation:** Multicenter, standardized, diverse datasets are essential
- **Fairness & Transparency Are Non-Negotiable:** Bias audits, demographic validation, clinician-interpretable
- **Implementation Requires Governance:** Reimbursement, liability clarity, monitoring, human oversight

The Promise:
Precision Neonatology

With thoughtful regulatory guidance and collaborative infrastructure, and a commitment to safe, reliable, and broadly applicable AI, neonatal care can be transformed—enabling earlier diagnosis of rare diseases, personalized interventions, and improved outcomes for the most vulnerable patients.

The opportunity is now.

U.S. FOOD & DRUG ADMINISTRATION

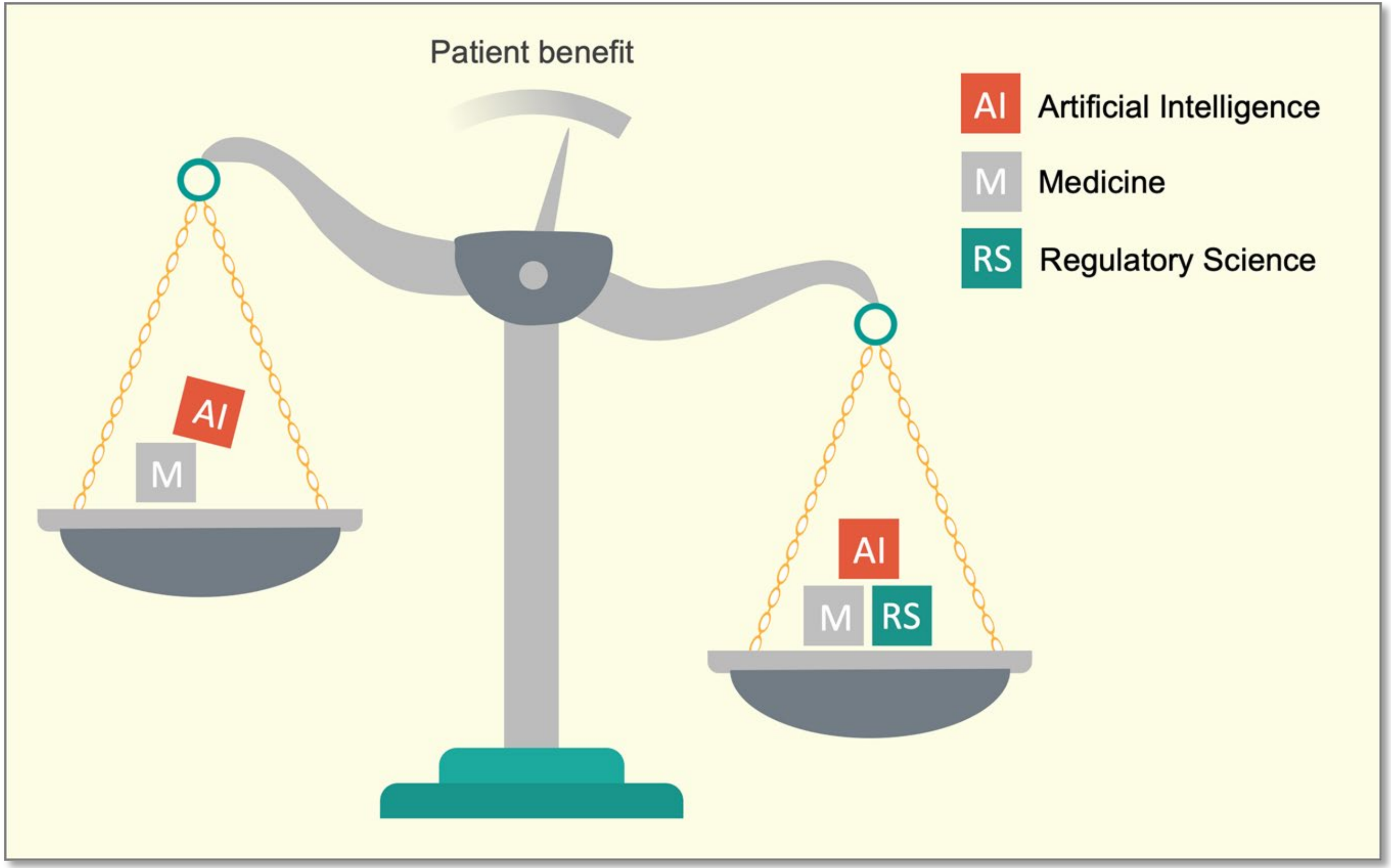
AI/DHTs in Neonatology/Rare Disease- Regulatory Perspective

Hussein Ezzeldin, PhD

Senior Public Health Advisor, Office of Medical Policy, CDER

The views expressed in this presentation do not necessarily represent the policies of the FDA.

FDA is Advancing AI Regulatory Science



Source: : https://www.nature.com/articles/s41746-022-00721-7

Artificial Intelligence at FDA

FDA

2019

- MIDD Initiated (2018)
- CoPs (including AI/ML)
- Trainings
- AI Tracking and Framework Activities

GMLP Guiding Principles

2022

Duke Margolis Expert Workshop

2023

Discussion Papers

Qi et al Landscape Analysis

2024

Areas of Focus

Duke Margolis AI in RWE July 2024

CDRH Glossary

CTTI Workshops

August 2024

October 2025

2025

Considerations for the Use of AI

AI-Enabled Device Software Functions

PCCP

2026

Guiding Principles of Good AI Practice in Drug Development

https://www.fda.gov/science-research/artificial-intelligence-and-medical-products/artificial-intelligence-fda-publications

Artificial Intelligence in Drug Development

Discovery

- Drug Target Identification, Selection, and Prioritization
- Compound Screening and Design

Nonclinical Research

- PK/PD and toxicologic studies
- Dose range finding

Clinical Research

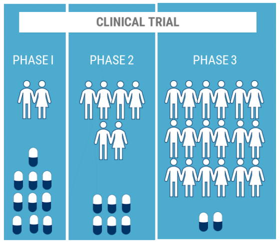


Image source: cbinsights.com

- Dose range finding
- Site selection
- Recruitment and Retention
- Adherence
- Data collection, management, and analysis
- RWD analyses
- Clinical endpoint assessment

Manufacturing and Postmarket Safety Monitoring


- Advanced pharmaceutical manufacturing
- Post-market safety surveillance or pharmacovigilance (PV)

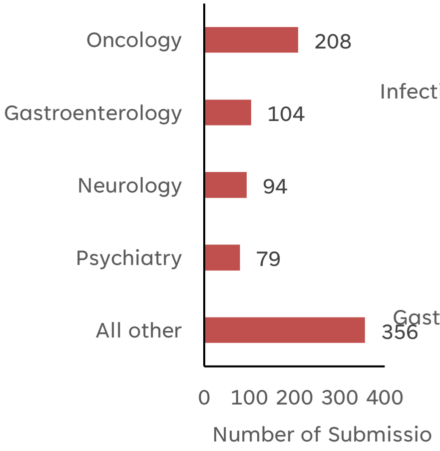
CDER & CBER has received 1000+ submissions with AI

Number of Submissions with AI by Year

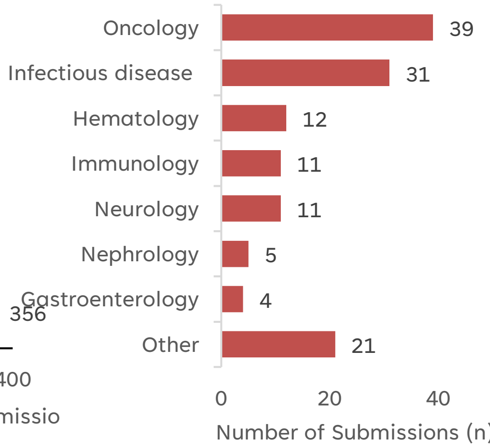
CDER	Year								
Submission Type	2016	2017	2018	2019	2020	2021	2022	2023	2024
IND	-	-	2	6	12	128	153	174	248
NDA, ANDA, BLA	1	1	1	1	1	2	22	17	50
DDT, CPIM	-	-	-	-	1	2	-	10	9
Tota	**1**	**1**	**3**	**7**	**14**	**132**	**175**	**201**	**307**

CBER	Year								
Submission Type	2016	2017	2018	2019	2020	2021	2022	2023	2024
IND	4	4	8	9	14	12	21	29	7
BLA	2	1	4	2	1	6	6	4	0
Total	6	5	12	11	15	18	27	33	7

Submissions by Therapeutic Area



CDER



CBER

Acknowledgement: Qi Liu, Menglun Wang (CDER), Sylvia Cho, Jessica Zhou, Ujwani Nukala, Aneesha Sahu (CBER)

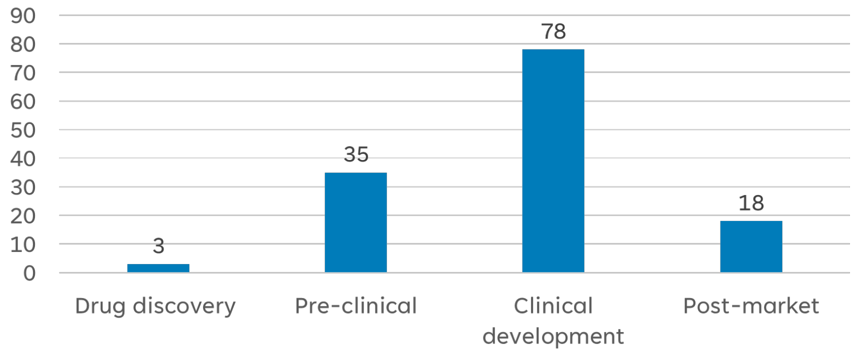
CDER & CBER has received 1000+ submissions with AI

Therapeutic Development Life Cycle

	Year					
Drug Development Stage (n)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Discovery and Development	-	-	-	-	1	3
Preclinical Research	-	-	-	-	-	8
Clinical Research	1	1	3	5	12	118
Post-Market Safety Monitoring	-	-	-	2	1	3

ABBREVIATIONS: Investigational New Drug (IND); New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biologics License Application (BLA); Drug Development Tool (DDT) Qualification Programs, Critical Path Innovation Meeting (CPIM)

SOURCE: Internal databases maintained by the FDA Center for Drug Evaluation and Research (CDER)

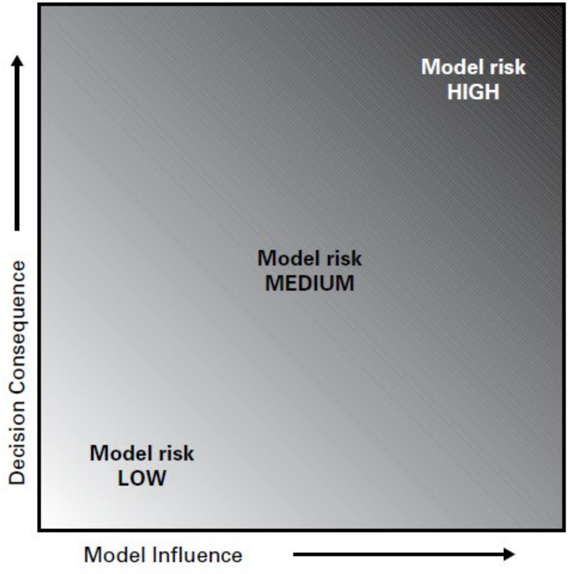


CDER

CBER

Acknowledgement: Qi Liu, Menglun Wang (CDER), Sylvia Cho, Jessica Zhou, Ujwani Nukala, Aneesha Sahu (CBER)

A Risk-Based Approach, Anchored in the Context of Use



GENERAL NOTE: Darker shades indicate greater model risk.

Depending on model risk, the level and stringency of "credibility evidence" may differ

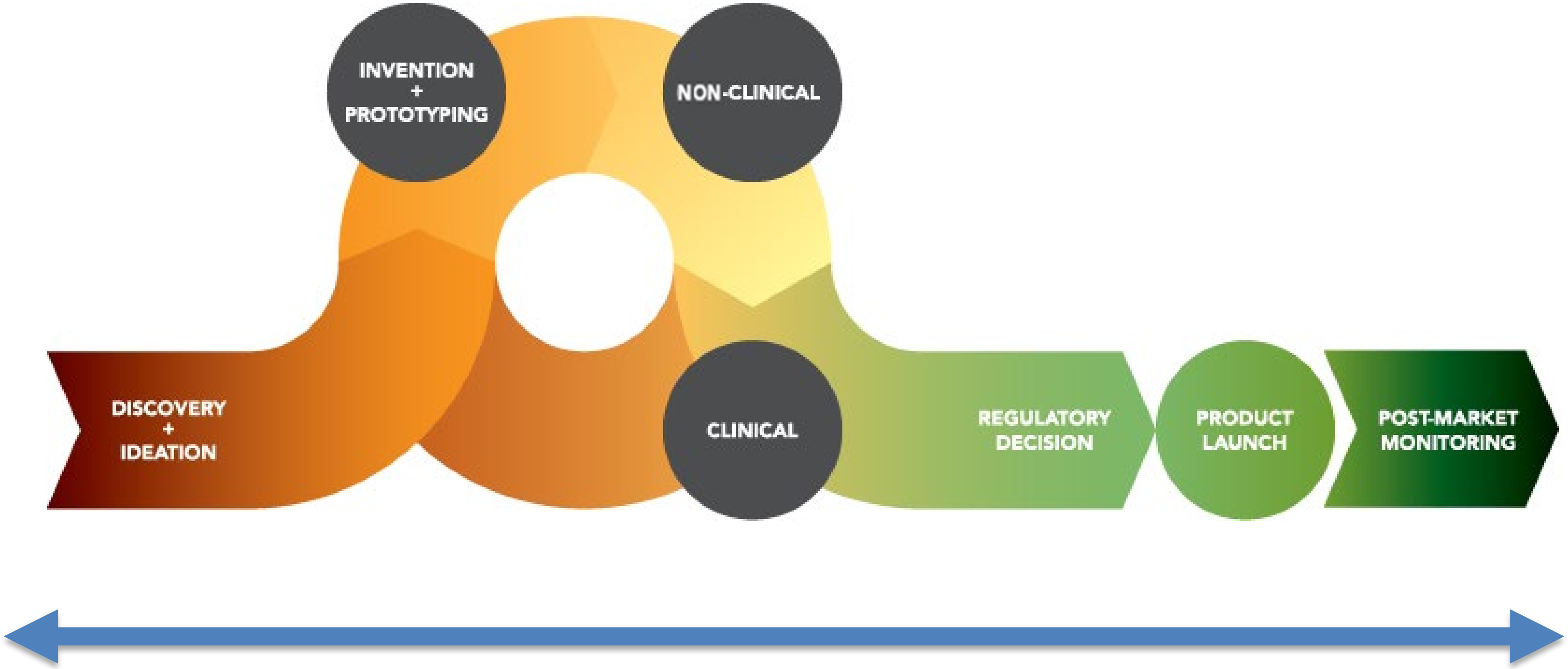
Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for model influence and decision consequence are determined independently.

SOURCE: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6966181/

Digital Health: Part of a Patient's Lifestyle

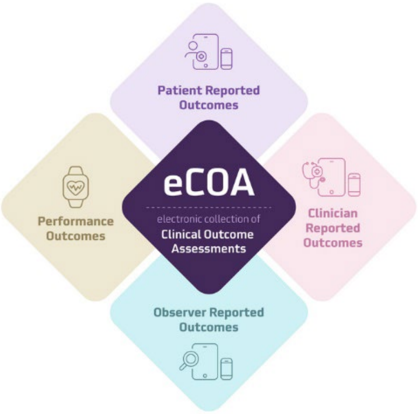
Patient-generated health data (PGHD) collected from digital health technologies (DHTs) allows us to understand patient behavior in the context of their daily lives

DHTs Offer Opportunity Across the TPLC



Digitally-Derived Endpoints

- Clinical Outcome Assessments (eCOA)
- Remote Monitoring Technologies
- Interactive Applications
- Digital Biomarkers
- Multi-Modal Digital Health Platforms
- Digital Pathology/Imaging



eCOA

Remote Monitoring

Digital Biomarkers

Encouraging Early Engagement Depending on COU

CDER/CBER have several pathways for engagement that depend on COU

Examples of Engagement Pathways

Nonclinical Research

Clinical Research

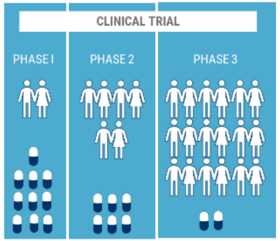


Image source: cbinsights.com

Manufacturing and Postmarket Safety Monitoring

- Model-Informed Drug Development Program
- Real-World Evidence (RWE) Program
- Rare Disease Endpoint-Advancement Pilot Program
- Digital Health Technology (DHT) Program
- Complex Innovative Trial Design Meeting Program
- CDER Center for Clinical Trial Innovation (C3TI)
- Emerging Drug Safety Technology Program (EDSTP)
- CDER's Emerging Technology Program (ETP)
- CBER's Advanced Technologies Team (CATT)

Conclusion

- **Multiple-fold** increase in AI/ML submissions from 2016 to 2024
- The data shows AI/ML applications are **primarily** occurring in **clinical drug development** phases
- **Risk-based regulatory approach** essential to balance innovation with public health protection
- **Verification** and **validation** are critical to ensure the **fitness-of-purpose** of DHT for the intended **COU**
- **Early engagement** with FDA is highly encouraged

Acknowledgment

- **CDER/CBER Colleagues**
  - Gabriel Innes, Cecilia Almeida, Qi Liu, Hao Zhu, Jennifer Shepherd, Janice Maniwang, Annie Saha
  - Sylvia Cho, Ujwani Nukala, Whitney Steele, Jessica Zhou, Weidong Gu, Jane Mutanga, William Ryan, Brien Hampton, Maryland Hatch, Stephen Chang, Richard Forshee
- **Former FDA Colleagues**
  - Barbee Whitaker, Aneesha Sahu, *Chris Joneckis, Elizabeth Valenti, Steven Anderson, Tala Fakhouri*


LINK-SPOT
SECURITY
SYSTEM-PREF.
CLOUD
SEARCH
PROFILE
46
73
37.2
36
75
-9
SUMMARY:

Thank you!

CRITICAL PATH INSTITUTE 20 YEARS OF IMPACT

Real-World Data as a Foundation for Neonatal Drug Development

Neonates as Therapeutic Orphans — and How Pre-Competitive Data Infrastructure Can Change That*

Kanwaljit Singh, MD, MPH, MBA

Executive Director, International Neonatal Consortium

Critical Path Institute

**Neonates remain therapeutic orphans. More than 90% of NICU drugs are off-label, and no new drugs have been approved for major neonatal diseases in 30+ years*

Why Neonates are Therapeutic Orphans

Neonatal drug development faces structural constraints that incentives alone cannot overcome:

- Very few drugs are developed or labeled specifically for neonates.
- **>90% of NICU drugs are off-label, no new therapies in 30+ years** *(Major neonatal diseases [e.g., BPD, NEC, brain injury, sepsis] have seen no new approved therapies).*

Rapidly evolving physiology

- Week-to-week changes in PK/PD, organ maturity, and biology make extrapolation from adults or older children unreliable.

Neonatal-specific diseases

- Major neonatal conditions (e.g., BPD, brain injury, NEC, sepsis) lack adult analogues, limiting applicability of adult-anchored development pathways.

Lack of validated endpoints and biomarkers

- Few regulatory-accepted efficacy or safety measures make trials risky, underpowered, and prone to failure.

High-risk, low-reward development environment

- Fragile patients, ethical constraints, small populations, and perceived liability skew the risk–benefit calculus, reducing industry willingness to invest.

The off-label cycle

- Widespread off-label use fills the clinical gap, creates the perception that existing practice is “good enough,” and further disincentivizes dedicated neonatal trials — perpetuating reliance on off-label therapy.

👉 **Neonates are not excluded only due to lack of intent — but also due to lack of fit-for-purpose tools and data.**

👉 **Breaking this cycle requires quantitative, data-driven solutions.**

C-Path's International Neonatal Consortium

Why Collaboration is Essential

- Neonatal drug development challenges are too complex for any single company or institution.
- Unique physiology, small numbers, ethical constraints, and lack of biomarkers require shared solutions.
- Progress demands a neutral, pre-competitive space, where stakeholders pool expertise and data.
- **Critical Path Institute's International Neonatal Consortium (INC) serves as that home.**

👉 **Take-Home Message:** INC exists because no one can solve neonatal drug development alone — it takes a global village working together in a neutral, science-driven partnership.

Critical Path Institute's International Neonatal Consortium (INC)

- Public-private partnership of diverse stakeholders consisting of Industry members, academic researchers, nurses, families, and regulators
- Mission to accelerate drug development in neonates
- Operating as a pre-competitive collaboration to:
  1. Address the measurement and assessment of clinical outcomes in neonates, through teams that share data and expertise to advance regulatory science
  2. Improve the predictability of neonatal drug development

"By uniting stakeholders from research institutions, drug developers, regulatory agencies, patient advocacy and other organizations, INC can develop practical tools that can be incorporated into clinical trials for neonates, which will then lead to more successful, efficient trials and provide this population with better treatments." stated Dr. Janet Woodcock,, *efficient trials and provide this population with better treatments."*

~Dr. Janet Woodcock, CDER Director, May 2015

Quantitative Tools Are Needed to De-Risk Neonatal Drug Development

The Path Forward to De-Risk Neonatal Drug Development Requires New Tools: To integrate neonates into drug development, we need **more than incentives** — we need **quantitative, fit-for-purpose tools** that can meaningfully **de-risk decision-making**:

- **Innovative trial design methods** to improve feasibility in small, heterogeneous, and ethically constrained populations
- **Validated biomarkers and endpoints** to enable efficient, interpretable trials
- **Regulatory-grade data platforms** to reduce uncertainty across development programs

These tools depend on availability of data: Biomarkers, endpoints, dosing models, and trial simulations are **inherently quantitative** — and require:

- **Scale** (to capture rare events and variability)
- **Longitudinal data** (to reflect rapidly evolving neonatal physiology)
- **Heterogeneity** (to understand real-world clinical trajectories)

👉 **Traditional neonatal clinical trials alone cannot generate this evidence.**

What IS abundantly available — uniquely in neonatology — is high-resolution real-world EHR data on nearly every NICU patient.

Every premature infant admitted to the NICU generates longitudinal, granular clinical data across diagnoses, labs, therapies, and outcomes — **if that data can be curated, harmonized, and made analyzable.**

👉 **In neonatology, real-world data is not a convenience — it is a necessity for de-risking drug development.**

INC Real-World Data & Analytics Platform (RW-DAP)

Operationalizing Real-World Data to De-Risk Neonatal Drug Development

CRITICAL PATH INSTITUTE 20 YEARS

What It Is

- A **large-scale, curated neonatal EHR resource** comprising ~380,000 NICU patients across ~30 hospitals.
- **Longitudinal, high-resolution clinical data** capturing demographics, diagnoses, labs, medications, respiratory support, and outcomes across the NICU stay and beyond.
- Curated and hosted within **C-Path's secure, regulatory-aligned analytics environment**, leveraging RDCA-DAP infrastructure.

Why This Matters for Neonatal Drug Development

- Neonatal trials alone **cannot generate the scale, longitudinal depth, or heterogeneity** needed to support quantitative tools.
- RW-DAP provides a **standardized, harmonized real-world data foundation** across health systems, designed specifically for **regulatory science use cases**.
- Enables characterization of **disease trajectories, outcome variability, and real-world clinical practice** that directly inform trial planning and interpretation.
- **Value is not in the volume — it is the curation, harmonization, and governance required to make RWD fit for regulatory use.**

How RW-DAP De-Risks Development for Regulators and Sponsors

- **External control arms** to complement trials in rare, small, or ethically constrained neonatal populations.
- **Predictive models and trial simulation tools** to inform feasibility, sample size, endpoint selection, and enrichment strategies.
- **Regulatory-grade reference tools** (e.g., lab value reference curves, disease progression models) to reduce uncertainty in safety and efficacy assessment.

Impact: INC's Neonatal Lab Values Initiative (Neo-LV)

CRITICAL PATH INSTITUTE 20 YEARS

The problem

No standardized neonatal lab reference ranges → **inconsistent safety assessment and trial design**

High inter-site variability → **regulatory review and cross-study comparison are difficult**

The RW-DAP–enabled solution

Large-scale, real-world NICU data used to **harmonize key hematology, chemistry, liver, and metabolic labs**

Percentile-based reference curves stratified by *gestational* and *postnatal* age

Generated using a **standardized, reproducible framework** aligned with regulatory expectations

How this de-risks neonatal drug development

Reduces ambiguity in **what constitutes "normal" vs. safety signal** in neonates

Improves **trial design, safety monitoring, and cross-study comparability**

Provides a **regulatory-grade reference tool** that sponsors and reviewers can interpret consistently

INC Lab Values GUI

Select analyte(s) from the dropdown menu: *

PLT

Select age bin(s) from the dropdown menu: *

Moderate to Late Preterm (32–36)

Show scatter?

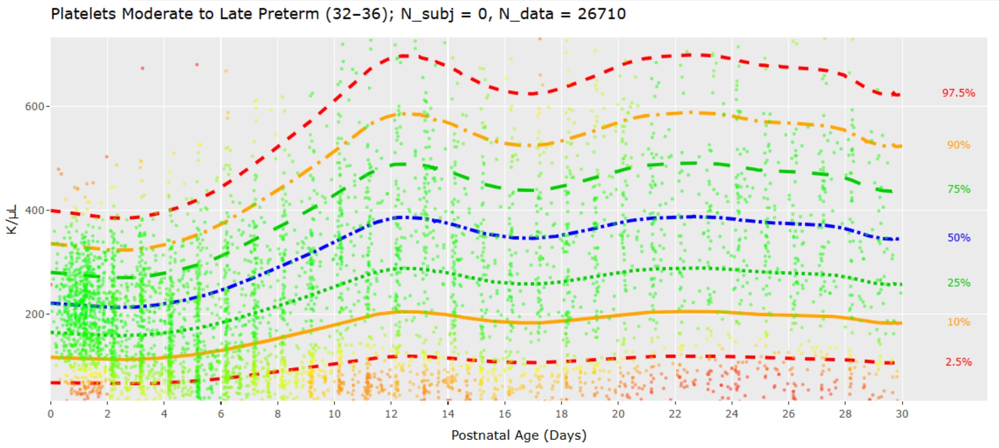
Show color coding?

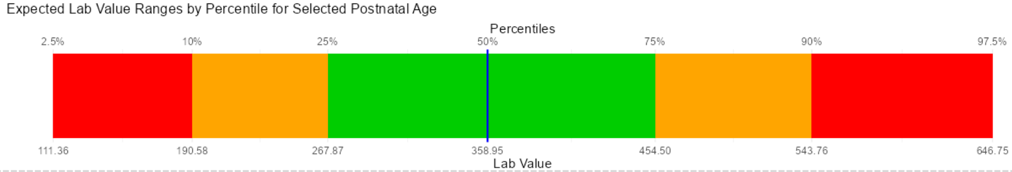
[Optional] Enter a postnatal age (in days):

15

Submit

Reference Curves | refineR Models





👉 **Take-Home Message: This is a concrete example of how real-world data can be transformed into a quantitative tool that de-risks neonatal trials and regulatory decision-making.**

This tool is publicly available for use at: https://cpath.shinyapps.io/lvgui/

Next-Generation RWD Use Cases to De-Risk Neonatal Trials

CRITICAL PATH INSTITUTE 20 YEARS

From RWD Infrastructure to Advanced Trial-De-Risking Tools

The challenge

- Neonatal trials are often **underpowered, delayed, or ethically constrained**
- Small, heterogeneous populations and limited endpoints restrict conventional RCT designs
  RWD-enabled use cases (built on RW-DAP)

External Control Arms (ECAs):

- High-quality comparator data when randomization is infeasible

Digital Twins:

- Predictive models that reflect individual neonatal trajectories using longitudinal clinical data

Trial Simulation:

- Test feasibility, endpoints, and enrichment strategies *before* enrollment

Why this matters for regulators and sponsors

- These approaches are **adjuncts to RCTs**, not replacements
- Provide **context and interpretability** for single-arm or underpowered studies
- **De-risk development** by reducing trial failure risk and improving design decisions

👉 **Take-Home Message:**

As neonatal RWD infrastructure matures, advanced tools like ECAs and trial simulation become a natural extension — strengthening, not replacing, the gold standard of RCTs.

Circling Back: Why INC Exists

Neonates remain therapeutic orphans

→ >90% off-label use, no new drugs approved for major neonatal diseases in 30+ years.

This gap persists not from lack of intent — but from lack of fit-for-purpose tools.

→ Unique physiology, neonatal-specific diseases, and trial feasibility constraints require new approaches.

Addressing these barriers demands new, quantitative tools

→ regulatory-grade data platforms, validated endpoints and biomarkers, and innovative trial-de-risking methods.

No single organization can solve this alone.

→ Progress requires regulators, industry, academia, and advocacy working together in a neutral, pre-competitive setting.

👉 **That is why INC exists.**

Final Take-Home Message

INC provides the global, pre-competitive table where collaborative science can finally translate into safe, effective therapies for neonates.

For more information, please contact us: incinfo@c-path.org
Visit our website: https://c-path.org/inc/
Contact me directly: ksingh@c-path.org, Cell: (617) 953-1480

Platform Trials Experience & Lessons Learned
from the
Pediatric Trials Network

Danny Benjamin MD PHD
Distinguished Professor of Pediatrics Duke University
Chair, Pediatric Trials Network of NICHD

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

What is the Pediatric Trials Network?

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

An infrastructure for investigators to conduct trials that improve pediatric labeling and child health

- –Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- –Performs studies to improve dosing, safety information, labeling, and ultimately child health
- –Focus on off-patent therapeutics

Definitions and Overview

- Master protocols: answer more than one question at a time
  - Platform trial: multiple treatments or diseases are evaluated within the same protocol
  - Basket trial: one therapy is tested on more than one disease
  - Umbrella trial: multiple therapies are tested for a single disease

- For today
  - 3 slides on experience
  - 3-4 lessons learned and applied across neonatology/rare diseases

- Three stages of research

1. No one can do this
2. We cannot do this
3. We have always done this

Summary of Platform Trials That We Have Designed, Completed Enrollment, and Submitted Data to FDA

- **POPs**: PK and a modest amount of safety
  - Child receiving molecule per standard of care; consent for 1 to 5 drops of blood during standard of care laboratory
  - PTN uses POPS as a funnel: 33,000 biologic samples, >100 validated assays (>200 methods), >50 analyses completed
    - Screening of: Investigators, Sites (300 across PTN trials), Molecules (145), Populations
    - Emerging and difficult populations—neonates (2,700 samples), ECMO (2,000), obesity (6,000), breast feeding (3,000), COVID
- **Cuddle** (Breast Milk Study): PK and a modest amount of safety
  - Mothers receiving medicine per standard of care—sample from mother's blood, breast milk, and infant
- **SCAMP:** Safety and efficacy of antibiotics in premature infants
  - Preterm infants with complicated intra abdominal infection randomized to 5 different molecules, at doses stratified by postmenstrual age. (stricture and resistance)
- **LAPS:** Long-term safety of anti-psychotic medicines
  - (vs 48 weeks in label), >500 children
- **ACTIV-1:** During the pandemic, PTN faculty and staff were asked by NIH to lead a platform study in adults
  - enrolled 1,971 abatacept; infliximab; cenicriviroc; or placebo; international study ACTIV-1

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

Pediatric Trials Network: Platform Trials

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

1. POPS: Pediatric Opportunistic PK Study NCT04278404
2. CUDDLE: Mother-infant dyads, breast milk NCT03511118
3. SCAMP: complicated abdominal infections in infants NCT01994993
4. LAPS: Long term anti-psychotic safety study NCT03522168
5. ECMO: extra-corporeal membrane oxygenation NCT01431326
6. ANA: Anesthetics and Analgesics NCT03427736
7. Children with Obesity NCT04278404
8. Children with Down Syndrome NCT04278404
9. AED: Anti-epileptic drugs used in obese children NCT02993861
10. Anti-Staph Trio: antibiotics to treat S. aureus NCT01728363
11. Dosing of Therapeutics in COVID NCT04278404

Molecules studied

Acyclovir
Alfentanil
Aminocaproic acid
Amiodarone
Amphotericin B deoxycholate
Ampicillin
Anakinra
Aripiprazole
Aspirin
Azithromycin
Baclofen
Bosentan
Bumetanide
Caffeine
Cefdinir
Cefepime
Ceftazidime
Cidofovir
Ciprofloxacin
Citalopram
Clavulanic acid
Clindamycin

Clobazam
Clonidine
Clozapine
Colchicine
Cyclobenzaprine
Dexamethasone
Dexmedetomidine
Dextroamphetamine
Diazepam
Digoxin
Dolutegravir
Dopamine
Doxycycline
Efavirenz
Emtricitabine
Enoxaparin
Epinephrine
Fentanyl
Fluconazole
Fosfomycin
Fosphenytoin
Furosemide
Gabapentin

Granisetron
Guanfacine
Haloperidol
Hydralazine
Hydrocholorothiazide
Hydrocortisone
Hydromorphone
Hydroxychloroquine
Hydroxocobalamin
Hydroxyurea
Inflectra
Ketamine
Ketorolac
Labetalol
Levetiracetam
Levofloxacin
Lidocaine
Lisinopril
Lithium
Lorazepam
Lurasidone
Meropenem
Metoclopramide

Metformin
Methadone
Methylphenidate
Methylprednisolone
Metoclopramide
Metronidazole
Midazolam
Milrinone
Molindone
Morphine
Nalbuphine
Nicardipine
Nifedipine
Norepinephrine
Olanzapine
Ondansetron
Ondansetron
Oseltamivir
Oxcarbazepine + MDH
Oxycodone
Pantoprazole
Pentobarbital

Piperacillin/ Tazobactam
Posaconazole
Pralidoxime
Pravastatin
Propofol
Propylthiouracil
Quetiapine
Ravuconazole
Remdesivir
Ribavirin
Rifampicin
Rifampin
Risperidone
Rocuronium
Rosuvastatin
Ruxolitinib
Sertraline
Sevelemer carbonate
Sildenafil
Simvastatin
Sodium nitroprusside
Spironolactone

Sumatriptan
Tenofovir
Terbutaline
Ticarcillin
Timolol
Tobramycin
Tocilizumab
Topiramate
Tranexamic acid
Trazodone
Trimethoprim-Sulfamethoxazole (Bactrim)
Valganciclovir
Valproic acid
Vasopressin
Venlafaxine
Verapamil
Voriconazole
Warfarin
Ziprasidone
Zolpidem

Platform Trials Lessons Learned: Stakeholders and Partners

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

- Infrastructure and Collaboration
  - POPS1 in 2010, extensive pediatric-specific site infrastructure for opportunistic studies
  - Limited compensation, but the prospect of 20 therapeutics or more meant that each site could support a full-time coordinator
- Key stakeholder input: families, child advocates, professional societies, AAP, NIH, PTN, EMMES, FDA, investigators, and sites
- Expertise: this is not a trial design for a widget approach
- Flexibility in bioanalytical methods and how you get the samples (no extra sticks)

- Industry and NIH more broadly:
  - Economics of 2 or 3 molecules vs. 20 or 30 molecules
  - Flexibility of sponsors (agencies or companies) and stakeholders is central

Platform Trials Lessons Learned: Flexibility

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

- Flexibility to fill critical knowledge gaps:
  - Opportunistic protocols can be designed to allow for studying variations in PK based on subgroup – i.e. patients on continuous renal replacement therapy, patients with obesity, those with potential drug-drug interactions, etc.
  - Flexibility in sampling schemes depending on the properties of the molecules of interest: the four antiepileptics in AED01 had wide variations in PK properties and the protocol allowed for varying sampling schemes

- Industry application
  - flexibility and compromise around protocol details and sampling schemes, balancing the sites and disease, and the other partners

Platform Trials Lessons Learned: Looking Forward

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

- Lessons from BPCA are uniquely positioned to innovate in clinical trials; these lessons learned can be applied to not just molecules, but other care questions
- "Reverse engineering" studies:
  - Start with a professional guidance document (e.g., osteomyelitis, traumatic brain injury, or neonatal HIE), usually ~20 recommendations
  - Select all the recommendations with low or very low quality of evidence
  - First randomize at the site, because children get sick at night & you don't want to fail
  - Then stack subsequent interventions with different questions at different times
  - E.g., severe traumatic brain injury,
    - what is target intra-cerebral pressure (ICP) monitoring;
    - then randomize at the individual: if ICP exceeds limits, do you use salt or mannitol to reduce ICP;
    - then, if you fail first line therapy, what do you do; primary endpoint 12 months after injury
    - then, how best to improve cognitive outcomes 12-24 months after injury

Long-term goal to answer dozens of questions with each trial

BPCA and Platform Trials Lessons Learned: 'Real World Evidence'

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

- The current state of the electronic health record and the medication administration record, timing of drug administration is not rigorously recorded.
  - Calculating PK parameter estimates with short half-lives
  - Sites require training on the accurate documentation of timing of drug administration and sample collection. Very variable and not always correlated to children's hospitals or major medical centers.
  - Intensive sampling or documentation needs, and trained research-naïve sites on research processes and maintaining high data quality

- Then pushed the models through the Pediatrix (Mednax) data warehouse to evaluate exposure-seizure risk linked to ampicillin
- Industry—as many of you know, a pediatric department has 15 or more clinical divisions, and thus, 15 or more potential performance levels

Selecting Patient-Focused Outcomes for Neonatal Conditions and Rare Diseases

Michelle Campbell, PhD
Office Neuroscience
Center for Drug Evaluation and Research

Clinical Benefit

- A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.
  - How long a patient lives
  - How a patient feels or functions in daily life

- Clinical benefit is described in labeling in terms of the outcome of interest measured

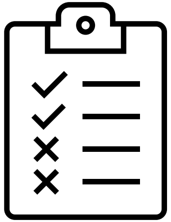
What We Think About Everyday

- Is there clinical benefit?
- Is this benefit clinically meaningful to patients?
- Statistical significance alone does not mean the trial result is clinically meaningful
- We are interested in within-patient clinically meaningful change

Why Does Therapy Type Matter?

- Clinical meaningfulness will differ based on the type of therapy
- For example:
  - Symptomatic therapy, a reduction in symptoms may be a desired effect
  - Therapy targeting an underlying pathophysiology, delaying disease progress or staying in “current” state longer may be the desired effect

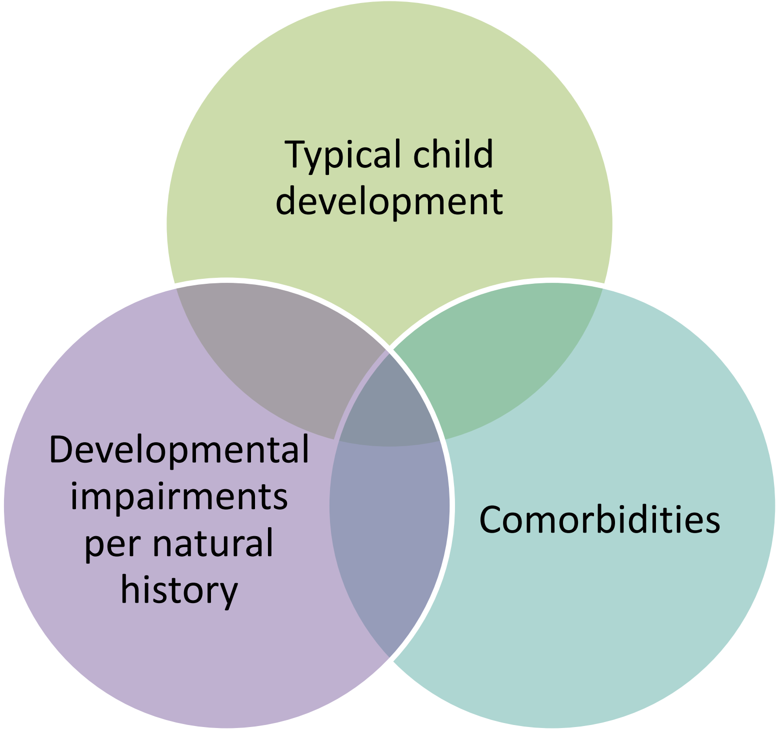
Examples of the Kinds of Issues Seen in Drug Development Programs



- Heterogeneity of symptoms, severity, progression in rare disease population pose a challenge to distinguishing potential effect of the investigational drug
- Clinical Outcome Assessments and endpoints are poorly designed, lacking precision, or otherwise not providing valid and reliable measures
- Use of laboratory tests and biomarkers that have not been validated or standardized
- Clinical trials that are too-short relative to the time of measurable disease progression
- Clinical trials that are underpowered or otherwise uninformative

- **These issues can lead to program delays and failures**

Understanding Pediatric Development



Selecting outcomes at the intersection:

- Typical child development,
- Developmental impairments anticipated from the known natural history/disease trajectory,
- Additional comorbidities conferred by the disease/condition,
- Can it be measured **validly** and **reliably implemented** within the **context** of the clinical trial?

Assessing Clinical Benefit in Heterogenous Rare Diseases: Focus on the Concepts

- **Primary and secondary endpoint concepts** should represent aspects of health most meaningful to the broadest range of patients, across ages and stages of disease progression

- **Outcomes concepts assessed** should be reflective of what is expected to change or stabilize within the duration of the trial

- **Multiple COAs should be considered**, and timing of implementation should reflect windows within which a treatment effect can be observed

- **Qualitative insights** generated from caregivers, clinicians, and patients are valuable to understand:
    - the most important concepts that can improve with treatment
    - stability or improvement thresholds that are deemed clinically meaningful

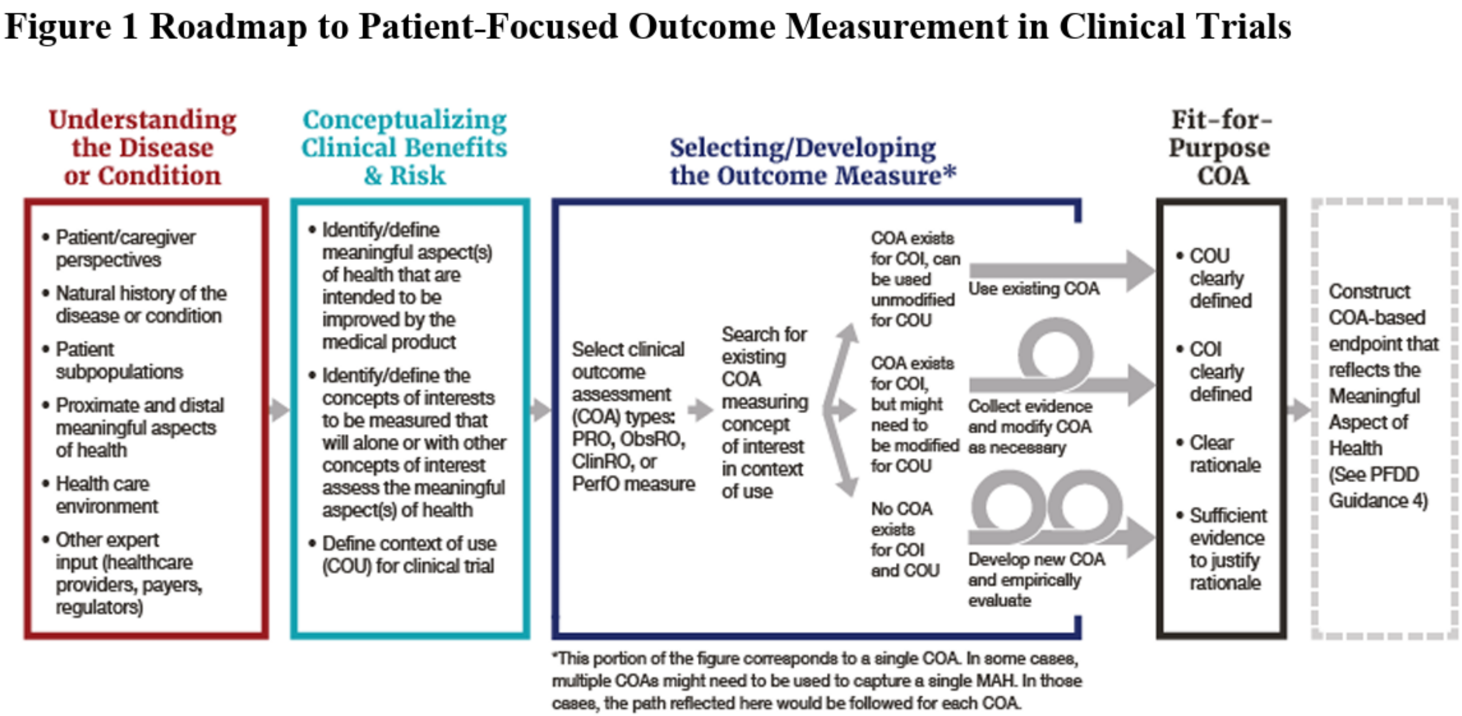
[1] Multiple Endpoints in Clinical Trials Guidance for Industry (fda.gov)

Contents of slide courtesy of Dr. Ebony Dashiell-Aje

Options to Measure Outcomes in Neonates and Rare Disease

- Biomarkers
  - Potential to support and inform efficacy
  - Discussion with review division is needed
- Clinical Outcome Assessments
  - Observer-Reported Outcomes
  - Clinician-Reported Outcomes
  - Performance Outcomes
  - Possible utility for using DHTs to collect data

Roadmap to Patient-Focused Outcome Measurement



Guidance 3: https://www.fda.gov/media/159500/download

EXAMPLES

Spinal Muscular Atrophy (SMA)

- Autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in brainstem and spinal cord, leading to weakness and muscle atrophy
- Type 1 (infantile-onset) SMA is fatal, usually by age of 2 due to respiratory failure and infection
- Three approved therapies since 2016:
  - Nusinersen: ASO
  - Onasemnogene abeparvovec: Gene Therapy
  - Risdiplam: small molecure SMN2 splicing modifier

Spinal Muscular Atrophy (SMA) Infantile Onset: Nusinersen

- Randomized, double-blinded controlled study with 82 patients
  - 2:1 randomization
- Endpoint: Proportion of responders with improvement in motor milestones in Section 2 of Hammersmith Infant Neurological Exam

Spinraza® (nusinersen) Original Review dated 12/23/2016
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000TOC.html , Accessed Febuary 3, 2026

Spinal Muscular Atrophy (SMA) Infantile Onset: Nusinersen

Table 3. Motor Milestone Response and CHOP-INTEND Results of the Final Analysis of Patients with Infantile-Onset SMA (Study 1)

Endpoint	SPINRAZA-treated Patients (n=73)	Sham-control Patients (n=37)
Motor function		
Motor milestones[1]		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)[2,3]	37 (51%) P<0.0001	0 (0%)
CHOP-INTEND[1]		
Proportion achieving a 4-point improvement	52 (71%) p<0.0001	1 (3%)
Proportion achieving a 4-point worsening[4]	2 (3%)	17 (46%)

[1]At the final analysis, CHOP-INTEND and motor milestone analyses were conducted using the Efficacy Set (SPINRAZA n=73; Sham-control n=37).
[2]Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
[3]According to HINE section 2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening), defined as a responder for this primary analysis.
[4]Not statistically controlled for multiple comparisons

Spinraza® (nusinersen) Label dated 4/10/2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209531s013s014lbl.pdf Accessed February 3, 2026

Spinal Muscular Atrophy (SMA) Infantile Onset: Risdiplam

- Open-label 2-part study with 62 patients
  - Part 1: Dose finding
  - Part 2: Assessed safety and efficacy
- Endpoint: Ability to sit without support for at least 5 seconds

Evrysdi® (risdiplam) Original Review dated 8/7/2020, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000TOC.html
Accessed Febuary 3, 2026

Spinal Muscular Atrophy (SMA) Infantile Onset: Risdiplam

Table 3 Key Efficacy Results at Month 12 and Month 24 (Study 1, Parts 1 and Part 2)

Efficacy Endpoints	Proportion of Patients Parts 1 & 2 at Month 12	Proportion of Patients Parts 1 & 2 at Month 24
Motor Function and Development Milestones	N = 58 [a]	
BSID-III, Item 22: sitting without support for at least 5 seconds	32.8%	60.3%
Survival and Event-Free Survival	N = 62 [b]	
Alive without Permanent Ventilation	87.1%	83.8%

[a] Results were pooled from all patients who received the recommended dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n = 58).

[b] Results were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n = 62).

Evrysdi® (risdiplam) Label dated 1/26/26, https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/219285s001,213535s016lbl.pdf
Accessed Febuary 3, 2026

GUIDANCES

Long-Term Clinical Neurodevelopmental Safety

FDA

Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

October 2024
Clinical/Medical

Rare Disease Guidance

Rare Diseases: Considerations for the Development of Drugs and Biological Products
Guidance for Industry

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

December 2023
Rare Diseases

https://www.fda.gov/media/119757/download

Human Gene Therapy for Rare Diseases

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

https://www.fda.gov/media/113807/download

Rare Diseases: Natural History Studies for Drug Development
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases

https://www.fda.gov/media/122425/download

Methodologic Guidance Documents

1. Collecting Comprehensive and Representative Input
2. Methods to Identify What is Important to Patients
3. Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments
4. Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Final Thoughts

1. Neurological diseases are often heterogenous (within and between patients), with the disease lifecycle spanning multiple developmental periods

2. Natural history studies are important in the understanding of disease progression

3. Include all stakeholder perspectives
   - Clinicians and patients have different perspectives. Missing out on the patient/caregiver perspective is to potentially miss capturing the most important outcomes

4. Plan your measurement strategy to include all potential eligible participants including understanding their capabilities

5. Use the entire endpoint hierarchy

6. Additional evidence (e.g., through embedded interviews) may be required to evaluate clinically meaningful change in COA scores given small sample sizes

Resources

- Patient-Focused Drug Development Guidance Series: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
- Accelerating Rare disease Cures (ARC)Program: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program
- Leader 3D Public Report of External Engagement Report: https://www.fda.gov/media/176557/download?attachment=
- Rare Disease Endpoint Advancement (RDEA) Pilot Program: https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program
- Guidance Documents for Rare Disease Drug Development: https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development
- Multiple Endpoints in Clinical Trials: Guidance for Industry: https://www.fda.gov/media/162416/download
- Murray LT, Howell TA, Matza LS, et al. Approaches to the Assessment of Clinical Benefit of Treatments for Conditions That Have Heterogeneous Symptoms and Impacts: Potential Applications in Rare Disease. *Value Health*. 2023;26(4):547-553. doi:10.1016/j.jval.2022.11.012

Thank You

FDA U.S. FOOD & DRUG ADMINISTRATION

Break

Panel Discussion: Leveraging Networks/ Consortia/ Centers of Excellence to Optimize Harmonization and Operational Feasibility of Neonatal/Rare Disease Clinical Trials

Moderator: Shannon Hamrick, MD (OPT/OCMO/OC, FDA)

Panelists:

Rachel G. Greenberg, MD, MB, MHS (Pediatric Trials Network, Duke Clinical Research Institute)

Augusto Santos Schmidt MD, PhD (Neonatal Research Network, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health)

Panelists continued…

Klaus Romero, MD, MS, FCP (Critical Path Institute)

Debra Regier, MD, PhD (RareCap, Levine Children's Hospital, Advocate Health)

Ralph Bax, MD, MA (Paediatric Medicines Office, Scientific Evidence Generation Department, Human Division, European Medicines Agency)

Sarah Zaidi, MD (OPT/OCMO/OC, FDA)

Lunch

Session 4: Regulatory Landscape and Future Directions for Neonatal and Rare Disease Drug Development

Panel Discussion: Regulatory Perspective: How can Expedited Programs, Incentive Pathways, and other Regulatory Initiatives be Leveraged for Neonatal and Rare Disease Drug Development?

Moderator: Cynthia Rothblum-Oviatt, (RDT/DRDMG/CDER, FDA)

Panelists:

Ralph Bax, MD, MA (PMO/SEDG/HD, EMA)

Janet Maynard, MD, MHS (ORPURM/CDER, FDA)

Najat Bouchkouj, MD (OTP/CBER, FDA)

Panelists continued…

Erika N. Torjusen, MD, MHS (OOPD/OCMO/OC, FDA)

Amy C. Rick, JD (Rare Disease Innovation Hub, FDA)

FDA Expedited Programs for Serious Conditions: Overview and Key Features

Intended to facilitate and expedite development and review of drugs and biologics that address unmet medical needs in serious or life-threatening conditions

Program	Key Features
Priority Review	• Shorter clock for review of marketing application 6 months (compared to 10 months for standard review) • If approved, drug would be significant improvement(s) over existing therapy
Accelerated Approval (AA)	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint reasonably likely to predict clinical benefit • Drug provides meaningful advantage over available therapies • Postapproval confirmatory trials to verify clinical benefits
Fast Track (FT) Designation	• Non-clinical or clinical data demonstrate potential to address unmet medical need • Process allowing frequent communication • Rolling review; eligibility for Priority Review if criteria met
Breakthrough Therapy (BT) Designation	• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies • Intensive guidance, organizational commitment, rolling review, actions to expedite review
Regenerative Medicine Advanced Therapy (RMAT) Designation	• Product must be a regenerative medicine therapy with preliminary clinical evidence indicating potential to address unmet medical need. • Statute addresses flexible approaches to satisfy postapproval requirement • All FT and BT features, including early interactions to discuss any potential surrogate or intermediate clinical endpoints

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February 2019
Draft Guidance: Accelerated Approval - Expedited Program for Serious Conditions, December 2024
Draft Guidance: Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway, January 2025
Draft Guidance: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, September 2025

FDA Programs Supporting Rare Disease Drug Development and Regulatory Interactions

Rare Disease Endpoint Advancement (RDEA) Pilot Program	• Collaborative mechanism for sponsors to work with FDA on novel efficacy endpoint development • Provides up to 4 meetings • Advances rare disease drug development programs
Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program	• Accelerates development of certain CBER- and CDER- novel drugs and biological products for rare diseases • Provides additional support mechanisms for rare disease therapeutic development • Selected participants have access to frequent advice from FDA staff to address product-specific development issues (e.g., clinical study design, choice of control group, fine-tuning the choice of patient population, leveraging nonclinical information, and product characterization)
Rare Disease Evidence Principles (RDEP)	• Facilitates approval of drugs for rare diseases with very small patient populations • Addresses conditions with significant unmet medical need and a known genetic defect that is the major driver of the pathophysiology

Cellular and Gene Therapy Guidance Documents: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
RDEA Program: https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program
START Pilot Program: https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/support-clinical-trials-advancing-rare-disease-therapeutics-start-pilot-program
OTP Learn: https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otp-learn
OTP Events, Meetings and Workshops: https://www.fda.gov/news-events/otp-events-meetings-and-workshops

Office of Orphan Products Development (OOPD)

DESIGNATION PROGRAMS

1	**Orphan Drug Designation (ODD) & Exclusivity** • Designation prior to submission of a marketing application • Exclusivity determination post approval
2	**Rare Pediatric Disease (RPD) Designation** • Joint review with Office of Pediatric Therapeutics • Prior to filing of a marketing application
3	**Humanitarian Use Device (HUD) Designation** • Prior to submission of a Humanitarian Device Exemption (HDE) application

GRANT PROGRAMS

1	Orphan Products Clinical Trials Grant Program
2	Pediatric Device Consortia Grant Program
3	Orphan Products Natural History Grant Program
4	Rare Neurodegenerative Disease Grant Program

https://www.fda.gov/about-fda/office-chief-medical-officer/office-orphan-products-development

Rare Disease Innovation Hub

U.S. FOOD & DRUG ADMINISTRATION

- **Mission**: Create a focal point that will further enhance the synergy between CBER and CDER and strengthen collaborations across FDA to accelerate development of rare disease therapies, especially for those diseases with smaller populations.

- **RDIH Goals**:
  - Goal 1: Further Advance Regulatory Science of Rare Disease Therapies
  - Goal 2: Enhance and Strengthen Coordination and Alignment Between Medical Product Centers, with Particular Focus on CDER and CBER
  - Goal 3: Create a Centralized Point of Contact for External Partners

- **2026 Strategic Agenda**:
  - RISE Workshops
  - Rare Disease Day – February 23, 2026
  - Engagement with industry and patient community on innovative methods and designs
  - RDIH as community point of contact (non-product specific)
  - Patient voice in drug development process

Panel Discussion: Stakeholder perspective: Lessons Learned, Gaps and Future Directions

Moderator: Gerri Baer, MD (DHN/ CDER, FDA)

Panelists:

Yuliya Yasinskaya, MD (DRDMG/CDER, FDA)

Annapurna Poduri, MD, MPH (Harvard Medical School)

Susan McCune, MD (Scendea)

Panelists continued...

Antonello Pileggi, MD, PhD, MSCTI (Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health)

Ronald J. Bartek (Friedreich's Ataxia Research Alliance [FARA])

Betsy Pilon (Hope for HIE)

Summary and Closing Remarks- *Lynne Yao, MD (FDA)*

ADEPT 10: Addressing Challenges in Neonatal Product Development—Leveraging Rare Disease Frameworks

Lynne P. Yao, M.D.
Director, Division of Pediatrics and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U.S. FDA

Current State

- FDA has made great strides in increasing the availability of pediatric-specific labeling of drugs and biological products
- Labeling of drugs for use in neonates lags significantly
  - Drugs used in neonates for conditions that affect a broader age range
  - Drugs used specifically to treat conditions related to prematurity
- “We are failing in neonatology”
- Goals of this meeting to understand challenges and discuss potential solutions that leverage rare disease frameworks

Disclosures and Disclaimer

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
- These are my final thoughts, and any omissions should be regarded as my oversight and not a reflection of everyone's important contributions to this meeting.

Final Thoughts

- Neonates and Rare Disease Similarities
  - Limited numbers
  - Poorly understood natural history
  - High unmet need, serious life-threatening
  - Standard of care treatments
    - May not be approved
    - May not be that great
  - Lack of consensus and experience with endpoints; timing of assessment, expected effect size
  - Ethical considerations, including true understanding of risks
    - Not necessarily measurable
    - Based on moral judgement
    - Parents and patients need to be involved
  - Failing to approve a drug that actually works

Final Thoughts: Other Challenges

- Navigating Uncertainty
  - Uncertainty is an every day lived experience—doing nothing also constitutes risk
  - Families are not reckless; transparency with families and need to understand data even if it is limited
  - Need to navigate uncertainty responsibly; avoid conflating uncertainty with recklessness
  - Consider the degree of uncertainty that can be tolerated; avoiding “worship at the alter of p=0.05”
- Conducting clinical trials when there is loss of equipoise lost
- Recognizing systematic exclusions of certain populations and the consequences of this (e.g., decrease in interpretability and generalizability)

Final Thoughts: Differences

- What is different about neonatal drug development?
  - Urgent sometimes emergent need to enroll—how do we simplify this process?
  - Off-label use is the norm—how do change this situation?
  - Diseases of the neonate are rare disease but also occur in complex situations and are often critically ill
  - Neonatal conditions may be able to be measured more quickly to assess clinical endpoints? But maybe not?
  - Regulatory differences: difficulties to require; some incentives may not be enough

Final Thoughts: Potential Solutions

- Need to derisk and create interest: Starting the Revolution!
  - Get out of the echo chamber

- How can we derisk (how are these areas different than for successful rare diseases):
  - Innovative clinical trials
  - Identify endpoints (meaningful endpoints and surrogate endpoints)
  - Standardizing data collection—help to increase interpretability of RWD, safety,
  - AI tools and simulation tools; DHT
  - Education/changing culture of the NICU
  - Take advantage of available numerous expedited programs (START pilot program no longer accepting applications)
  - EARLY and HELPFUL interactions with regulators

Final Thoughts: Potential Solutions

- Engaging Parents and Caregivers Early and Often
  - Hire Mommatologists!
  - Seek input from NICU staff, especially nursing staff
  - Should be included in all phases of drug development
  - Should be included as part of meetings with regulators and investors
  - Benefits are not limited to clearer understanding of the drug development path but also can increase uptake and access after approval

Final Thoughts: Potential Solutions

- Improving methods of communication
  - IRB composition need parents
  - Coercion—a real ethical issue in rare diseases
  - Can we be clear about what the clinical trials are really setting to understand:
    - “Selling hope”; is that honest?
    - Really “selling an option when an option doesn’t exist”
    - “Selling the idea that we can giving back to the community”
  - Palliative care needs to be involved in research (they are good explainers) getting care givers and researcher on the same page
- Increasing early communications with regulators
  - Engage patients and parents in all phases of communications
  - Engage regulators across regions; create a pathway for interactions with more than one regulatory authority in a single meeting

Final Thoughts: Potential Solutions

- Increasing efficiency of Clinical Trial Operations
  - Improved and plain reading ICF
  - The Revised Common Rule (45 CFR 46), effective Jan 21, 2019, modernizes human subject protections by enhancing informed consent, focusing on providing "key information" first, and facilitating understanding rather than just presenting facts
  - FDA has issued guidance about guidance, “Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards”
  - Early patients/parent input

Final Thoughts: Potential Solutions

- Harmonization
  - How to harmonize not just regulators or data; but how to harmonize the practicality of protocol implementation so that the trials can be conducted without “moral distress” or “clinical priority over following the protocol”
  - Standardization of common/core data elements across networks
  - Creation of federated data networks
  - Incentives for data sharing

What's Next?

- How to use the mountains of data already collected:
  - Development of standardized disease definitions; definitions that are clinically relevant and practical
  - Consider how data can be used to fill gaps in knowledge
  - Create federated databases from regional databases or proprietary databases that already exist
  - Consider incentives for data sharing
  - Repurposing of drugs that are already approved for other conditions
- Grow and integrate collaborations that already exist
  - Across regulatory authorities
  - Across health care systems
  - Across patient advocacy groups
  - Across rare disease groups
  - "Create a beautiful chorus rather than an echo"
- Embrace emerging technologies and innovative trial designs
  - Carefully consider how AI/DHT can be implemented and consider prioritization
  - Whole genome sequencing
- Consider strategies that increase alignment in clinical development programs
- Increase education of the entire ecosystem
  - practitioners, investigators, regulators, parents, caregivers, advocates, industry, payers, and venture capitalists

Thanks

- All the presenters, panelists, and especially our parent and family advocates
- OPT and the organizers of ADEPT 10
- All attendees, including on-line participants

Thank You

End of Day 2 of Workshop

THANK YOU FOR JOINING US!

Please continue the dialogue…

- Public Meeting: FDA Rare Disease Day 2026 - 02/23/2026 | FDA
- Rare Disease Day at NIH | National Center for Advancing Translational Sciences - 02/27/2026
- Rare Disease Day 2026 – 02/28/2026

- Rare Disease Innovation, Science, and Exploration (RISE) Workshop Series | FDA
- RISE Together: Data Sharing Across the Rare Disease Ecosystem – 03/30/2026