Opportunities for Patient Centered Trial Design in Rare Disorders

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SCT | 45TH ANNUAL MEETING

Disclosures

- Dr. Hetanshi Naik consults for Disc Medicine, Mitsubishi Tanabe Pharma, Alnylam Pharmaceuticals, and Recordati Rare Diseases. She is on the Board of Directors of the United Porphyrias Association (non-financial)
- Lina Rebeiz received honoraria as a Patient Ambassador sponsored by Alnylam Pharmaceuticals
- Dr. Jessica Overbey is a statistical scientist at Berry Consultants, LLC, a statistical consulting firm that specializes in the design, conduct, oversight, and analysis of adaptive and platform clinical trials
- Dr. Daniela Varela Luquetti is a medical geneticist and clinical reviewer at the Food and Drug Administration (FDA) in the Division of Rare Diseases and Medical Genetics
- Dr. George Diaz is Vice President, Therapeutic Area Lead, UCDs for iECURE, Inc. and has equity interest in the company.

Session Overview

- Introduction to the rare disorders landscape
- Our amazing panelists
- Moderated discussion of key topics
- Questions from the audience
- Summary

Rare Disease Treatment Landscape

- FDA Rare Disease Definition: a disease or condition that affects less than 200,000 people in the US
- There are 30 million people in the US living with a rare disease
- Of >7,000 known rare diseases, ~90% have no approved therapies

https://www.fda.gov/patients/rare-diseases-fda#orphandrug
https://globalgenes.org/rare-disease-facts/

Rare Disease Treatment Landscape

- FDA Ra… less than 20…
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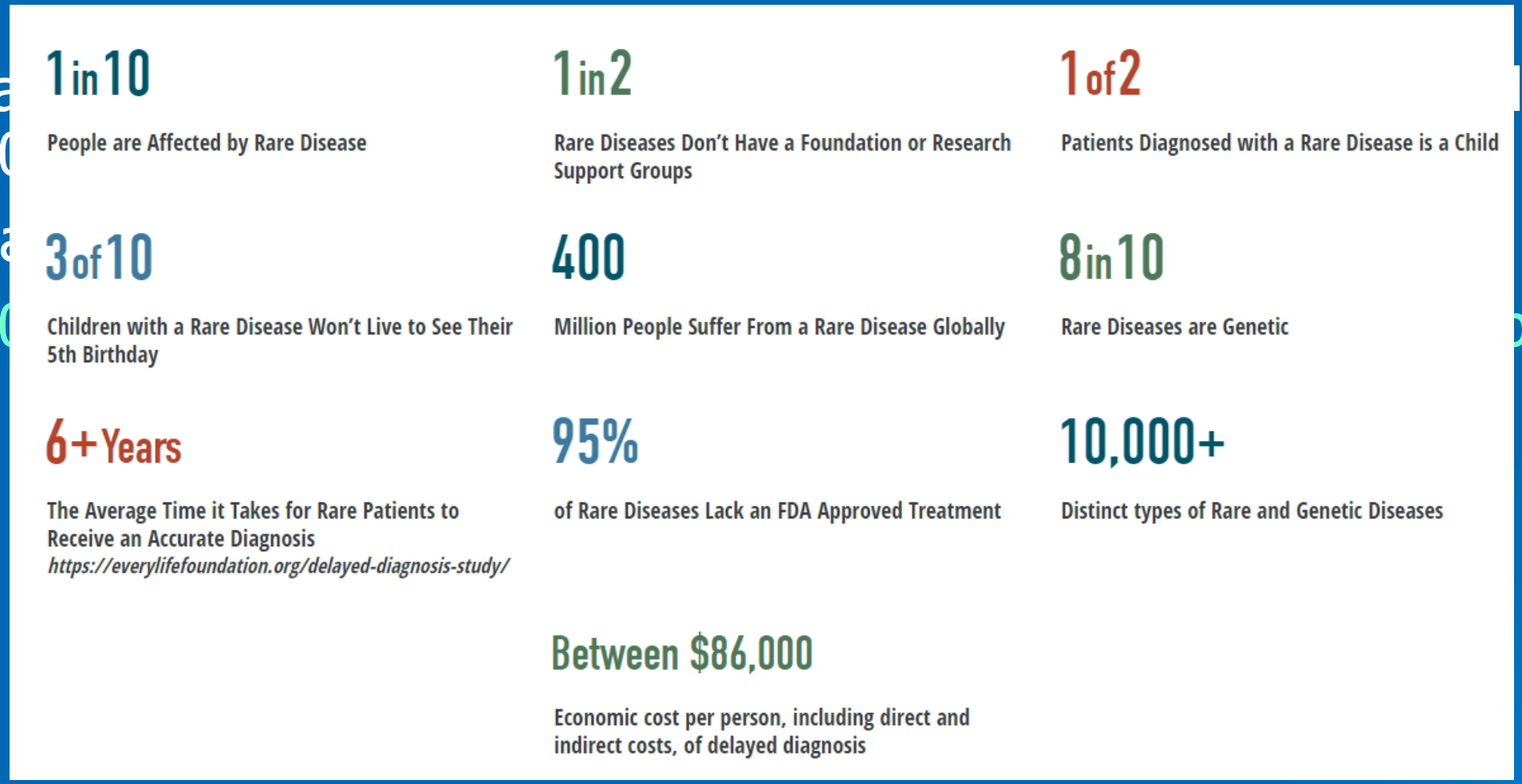

https://www.fda.gov/patients/rare-diseases-fda#orphandrug
https://globalgenes.org/rare-disease-facts/

Rare Disease Treatment Landscape: Orphan Drug Act

- Passed in 1983 to incentivize development of rare disease treatments
- Grants companies: tax credits for qualified clinical testing, waiver of prescription user drug fee, and market exclusivity for 7 years after approval
- Regulatory standards remain the same as medications for common diseases

Miller KL, Fermaglich LJ, Maynard J. 2021. Orphanet J Rare Diseases.
https://www.fda.gov/news-events/fda-voices/cder-continues-make-rare-diseases-priority-drug-approvals-and-programming-speed-therapeutic

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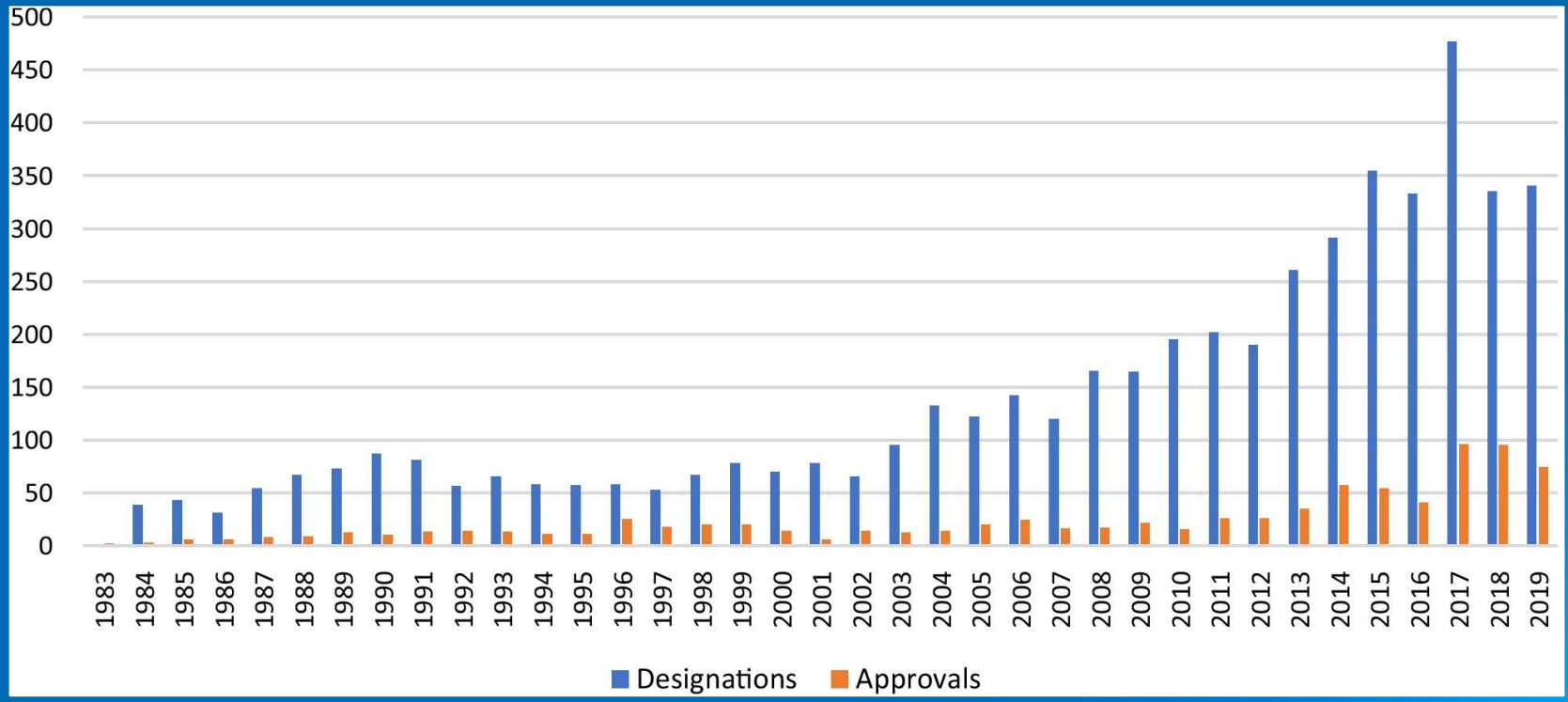

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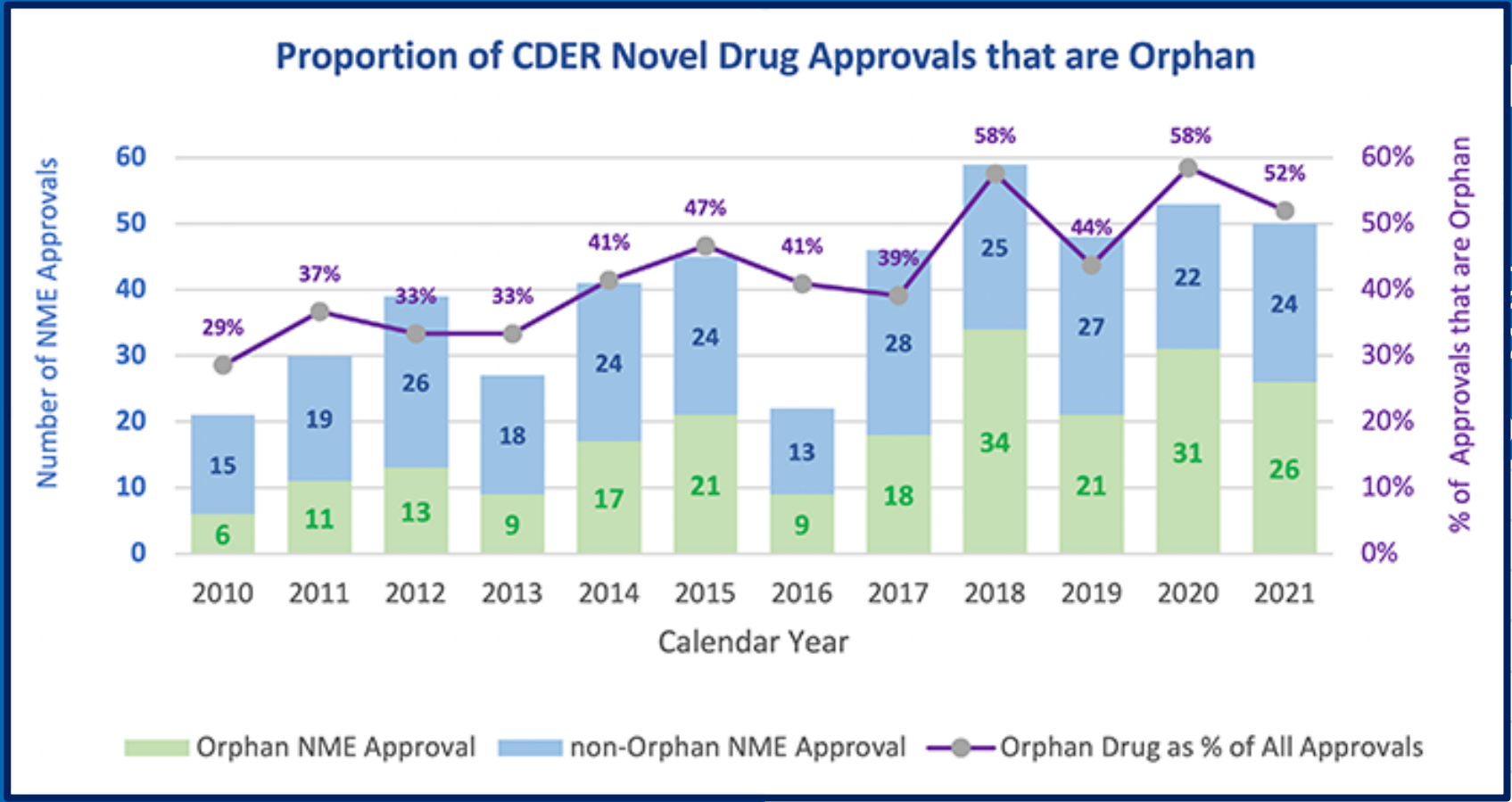

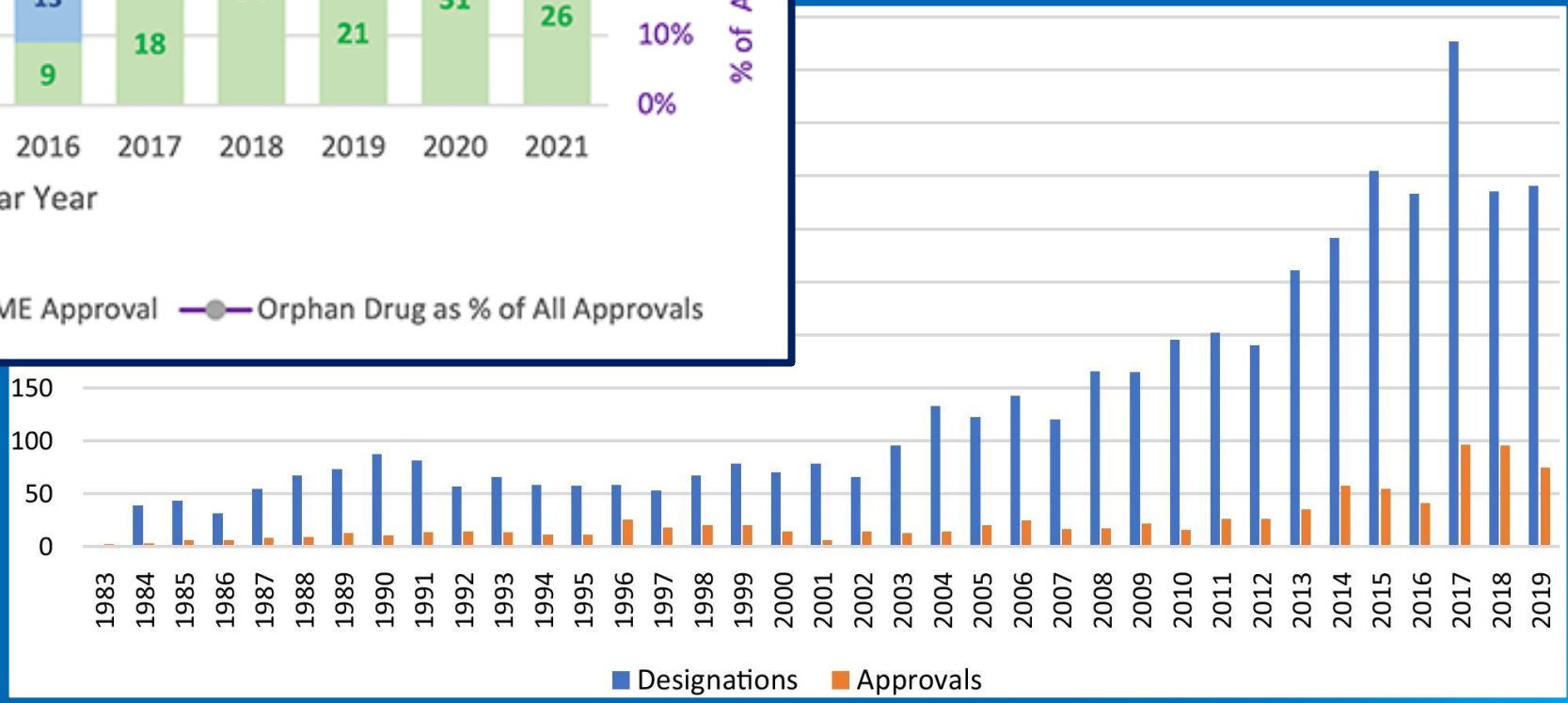

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Rare Disease Treatment Landscape: FDA Programs & Guidance

- Various expedited review processes/programs
- Rare Pediatric Disease Designation and Voucher Programs
- Individualized Antisense Oligonucleotide Drug Products
- Patient-Focused Drug Development
- Enhancing Diversity of Clinical Trial Populations

https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs
https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or-life

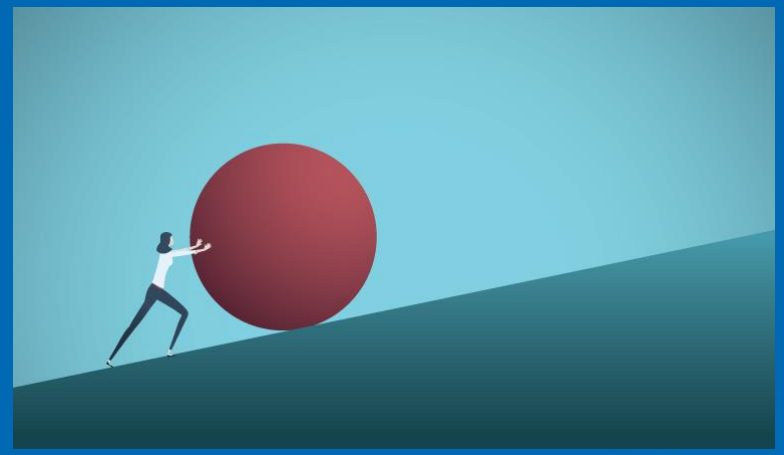
Rare Disease Treatment Landscape: Biotech

- >100 Rare Disease Biotech Companies
- Increasing partnership deals with large biopharma companies
- Partnership deals frequently fail to lead to a marketed therapy – recent review of acquisitions using public M&A information identified 5 leading causes for failure:
  - Scientific validation of therapeutic targets
  - **Translation of targets into clinically relevant outcomes**
  - **"Regulatory issues"—companies not fully able to address regulatory guidance or lacking efficacy evidence per regulatory bodies (FDA/EMA)**
  - Valuation discrepancies
  - Intellectual property issues
- Financial risks

Levine JA, Stemitsiotis. 2023.. Nature Reviews Drug Discovery.

Challenges in Rare Disease Trial Design

- Small populations
- Phenotypic diversity & genotypic heterogeneity
- Endpoint challenges:
  - High variability in biomarkers
  - Identifying clinical endpoints that are important to patients and acceptable to regulators
  - Limited natural history data
- Progressive disease course—urgent needs
- Ethical issues enrolling vulnerable patients with no treatment alternatives

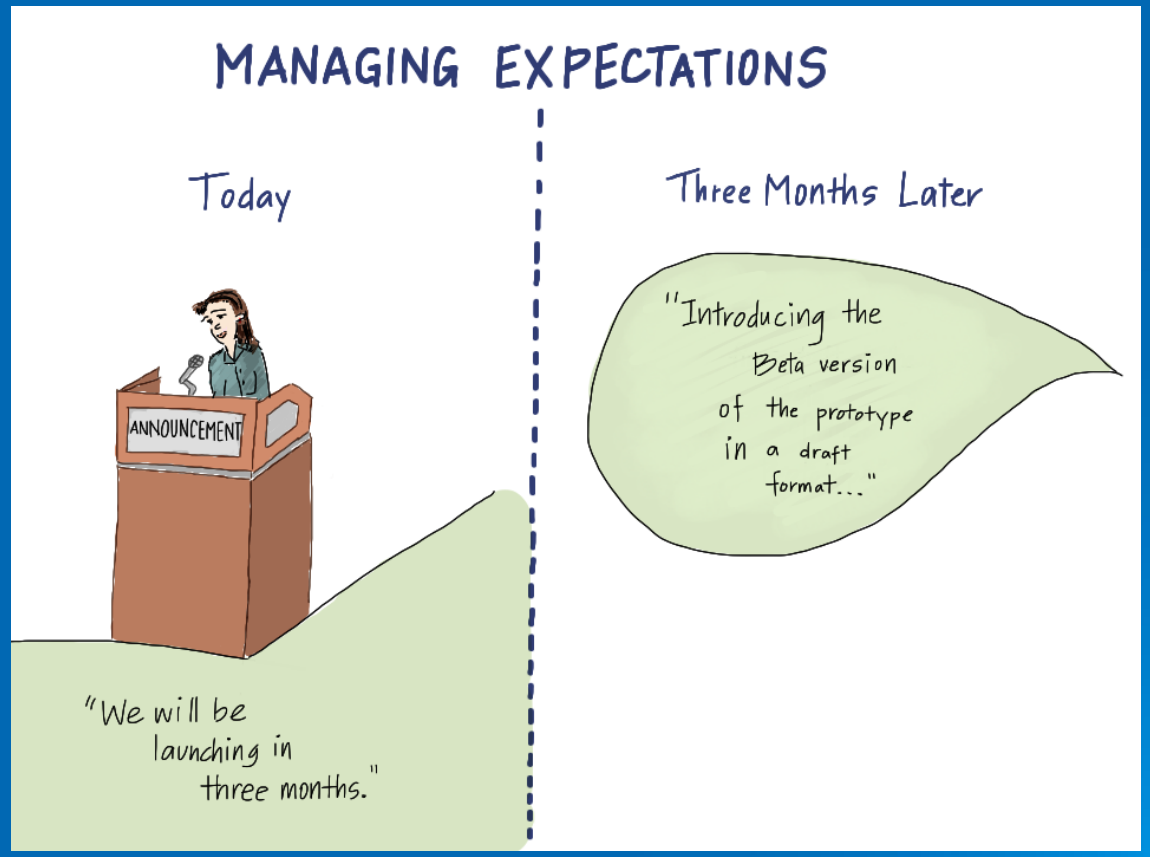


Challenges in Rare Disease Trial Implementation

- Complex trials—logistical issues
- Specific biomarkers not all labs measure
- Maximize data from one trial—combined phase 1/2, etc.
- Large pediatric representation
- Limited physician experts
- Small patient population spread across wide geographic area

Challenges in Rare Disease Trial Participation

- High burden on patients - intense time commitment
- Not accessible to all patients
- Informed consent
- Patient expectations



Recent Progress in Rare Disorder Trials

- Reduce patient burden: decentralized trials, home health companies, digital health tech
- Real world, "patient-powered" data registries
- Leveraging "non-traditional" trial designs
- Focus on patient-reported outcome measures

Panelists

Lina Rebeiz	Clinical Trial Participant
Daniela Varela Luquetti, MD, PhD	Acting Team Lead & Senior Clinical Analyst, Division of Rare Diseases and Medical Genetics, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine – CDER, FDA
Jessica Overbey, DrPH	Statistical Scientist, Berry Consultants
George Diaz, MD, PhD	VP, Therapeutic Area Lead for Urea Cycle Disorders, iECURE

Lina Rebeiz
Patient & Clinical Trial Participant

- Role:
  - Clinical Research Coordinator at Massachusetts General Hospital in Boston, working with the porphyria team
  - Completing her Masters in Biochemical Sciences at Tufts University

- Experience:
  - Diagnosed with Acute Intermittent Porphyria (AIP) around 10 years ago, when she was a freshman at Johns Hopkins University
  - Since her diagnosis, she has had a particular interest in the Porphyrias
  - She has spoken publicly about her experience as both a patient with AIP and a researcher of the Porphyrias at various hospitals, pharmaceutical companies, and medical conferences

Daniela Varela Luquetti, MD, PhD
FDA

- Role:
  - Scientific and medical review lead for Investigational New Drug (IND) applications, Biologics License Applications (BLAs) and New Drug Application (NDAs) supporting development and approval of safe and effective drug and biologic products for rare genetic metabolic diseases.
  - Provide consults to other FDA Divisions as a rare disease expert.
  - Provide recommendations to sponsors on clinical trial design, efficacy endpoints, and safety monitoring that are scientifically and regulatorily appropriate (traditional and innovative).

- Experience:
  - Primary and secondary clinical review of BLA, NDA, INDs, and pre-INDs, consults.
  - Former academic scientist in medical genetics, medical genomics, and epidemiology of rare diseases at the University of Washington (2009-2020).
  - Designed and conducted research studies on identifying risk factors for genetic and non-genetic craniofacial disorders.
  - Co-founded and directed a multinational research consortium for craniofacial microsomia.

Jessica Overbey, DrPH
Statistician

- Role:
  - Collaborate with various stakeholders to design complex, innovative and implementable clinical trials

- Experience:
  - Supported projects in several rare populations: Porphyrias, SBMA, RHF in LVAD patients, hereditary angioedema, Gaucher's disease, Mucopolysaccharidosis
  - Worked on a variety of designs in these populations: single-arm, N-of-1 series, adaptive designs
  - Leveraged a variety of statistical methods: Bayesian modeling, historical borrowing, disease progression modeling
  - Former lead statistician of the Porphyrias Consortium and Co-chair of the RCDRN's Statistics and Epidemiology Special Interest Group

George Diaz, MD, PhD
Industry

- Role:
  - Lead the clinical development of iECURE's first in human gene editing products to address unmet needs in urea cycle disorders.

- Experience:
  - Former Division Chief, Division of Medical Genetics and Genomics at Icahn School of Medicine at Mount Sinai
  - Founding Director, NORD Center of Excellence
  - Site PI for RDCRN Urea Cycle Disorders Consortium 2003-2022
  - PI for multiple industry-sponsored studies for rare disease including UCDs, Acid Sphingomyelinase deficiency, Arginase deficiency employing small molecule, RNA and gene therapy approaches.