Quality Data Facilitates Regulatory Flexibility

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Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

Rare Disease Drug Development?

Foundation
- Screen endpoints instead of patients
- Patient Focused Drug Development
- Real World Evidence

Design
- Randomized, Double Blind, Placebo Controlled Trials
- 21st Century Cures: Complex Innovative Design
  - Flexibility
  - Seamless designs
  - Platform trials
- EMA & FDA alignment

Build
- Quality – MRI examples

The upside down house in Bispingen, Germany

Foundation

Screen Endpoints for Feasibility

- Natural history poorly described
- Leverage rare disease advantage: when study participants known before enrollment
- Screen endpoints instead of patients
  - Formal cognitive testing
  - Endpoints for potential to demonstrate response to treatment

Patient Focused Drug Development

- Neurological Manifestations of Inborn Errors of Metabolism, June 10, 2014
  - Informed our advice for PMRs
- Led by FDA or Patient Groups
- Patient Reported Outcome Measures
- Patient Focused Drug Development
  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm

https://www.fda.gov/downloads/drugs/newsevents/ucm436454.pdf

Real World Evidence

- Primary Sclerosing Cholangitis ICD codes
- Mobile data collection
- Inform natural history
- Limitations for rare disease
- Strengthening the Reporting of OBservational studies in Epidemiology (https://www.strobe-statement.org)
- Constancy assumption

Design

Patients deserve the best

- Randomized, double-blind, placebo-controlled trials whenever possible
- Placebo arm includes standard of care
- Duration sufficient for clinical benefit
- Endpoints for clinical benefit
- Escape criteria
  - Blinding to maintain trial integrity
- Open label extensions

Seamless Designs

Feasibility Snapshot

Endpoint screening

Practice visits

PRO development

Placebo

Low Dose

Medium Dose

High Dose

Phase 2

PD Biomarker

PRO development

Higher Dose

Optimum Dose

Phase 3

Biomarker → Clinical Outcomes

PRO & Biomarker

Functional endpoint: 6MWT, PFTs, metabolic crises

Phase 4

Approval

21st Century Cures

- Complex Innovative Designs Pilot Program
  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm617212.htm
- Flexibility
- Bayesian approaches
- Adaptive designs
- Platform trials

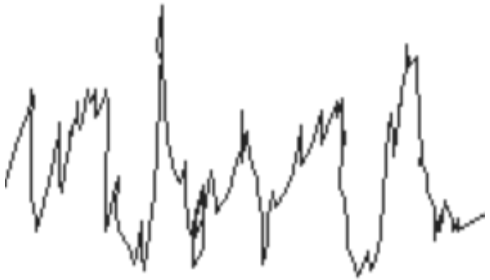
FDA & EMA Alignment

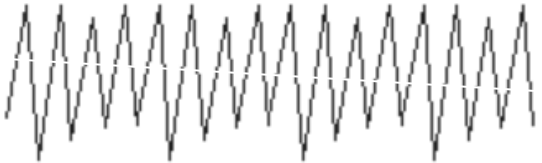
- We want to make trials feasible
- DGIEP is glad to work with EMA and other regulatory authorities for alignment
- Consultative advice
- EMA & FDA cluster calls
- Parallel Scientific Advice

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OfficeofInternationalPrograms/UCM557100.pdf

Quality

Quality: separates signal from noise





What we can see without science

Lousy Study

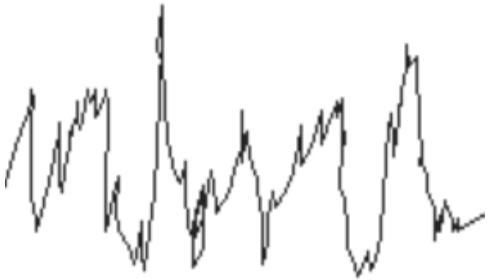
Failed trial No new treatment

Quality Example: MRI

- Same protocol
- Same scanners
- Phantoms
- Blinded central reader
- Blinded re-reads
- ARIC Quality Assurance & Control Manual

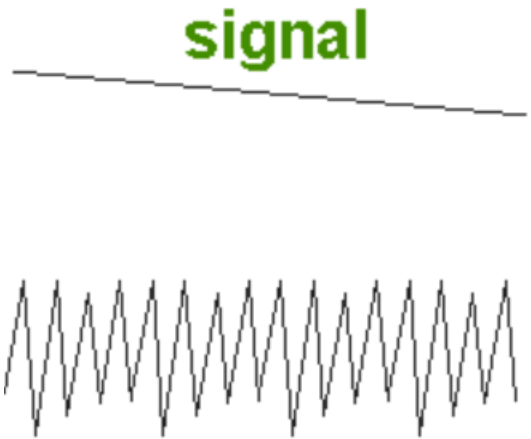
https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/document.cgi?study_id=phs000280.v4.p1&phd=4530#sec12.0

Quality: separates signal from noise



What we can see without science

Quality randomized trial



New treatment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