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FDA Perspective on Clinical Trial Design for Rare Diseases

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Disclosures

- No Conflicts of Interest
- Nothing to Report
- Opinions expressed are personal and do not reflect those of the FDA

Rare Diseases Program

- The current team
  - Lucas Kempf, MD
    - Associate Director (Acting)
  - Larry Bauer
    - Regulatory Scientist
  - Althea Cuff
    - Science Policy Analyst
  - Tracy Cutler
    - Science Policy Analyst
    - EMA cluster coordina
  - Melania Blank, MD
    - Medical Officer

Rare Diseases Program

- Rare disease have less that 200,000 people
- There are 7,000 known rare disease
- 1 in 10 people are affected by a rare disease

Challenges for Rare Disease Drug Development

- Rare diseases **natural history** is often poorly understood/characterized
- Diseases tend to be progressive, **serious**, life-limiting and life-threatening and lack **approved therapy**
- **Small populations** often restrict study design and replication
- **Phenotypic** diversity within a disorder adds to complexity, as do **genetic subsets**
- Well defined and validated **endpoints**, **outcome measures**/tools, and **biomarkers** are often lacking
- Lack of **precedent** for drug development
- **Ethical** considerations for children in clinical trials

CDER Rare Diseases Program

Mission Statement:

- Facilitate
- Support
- Accelerate

…the development of drug and biologic products for the treatment of patients with rare disorders

Rare Diseases Program Responsibilities

Coordinate development of CDER Policies and Procedures

- Guidance development
- Continuing involvement with Senior FDA staff re: Rare Diseases Program and its role

Assist in development of good science

- Database adjudication committee for NMEs
- Specific projects/peer reviewed publications
- Workshop development
  - Rare disease trial designs

Rare Diseases Program Responsibilities

Coordinate internal training in rare diseases

- 101 course for new reviewers
- 102 advanced training day for review staff

Assist in external training for the rare disease community

- Presentations at national and international meetings
- Workshop development
  - Rare disease trial designs workshop
- Panel Participant/Speaker at Patient Focused Drug Development Workshops
  - FDA
  - Externally Led

Rare Diseases Program Responsibilities

- Review Rare Pediatric PRV requests and Developed procedures for management
- FDA Rare Disease Council member
- NORD Registries Cooperative Agreement with FDA

The problem:

THERE ARE 40 PEOPLE IN THE WORLD WITH THIS DISEASE, NOT 40 MILLION

The Basics

CONTROL GROUPS, RANDOMIZATION, AND MASKING

What We Hear

- Just do a descriptive study
  - Of what?
  - Still needs a plan and sample size
- Chart review
  - Is this something that will be in a chart?
- Case series
- Single arm study
- Open label/unblinded/unmasked

- BUT people forget to ask if it will really improve power if they drop the “usually gold standard” elements
  - Hint: many times end up in a worse place
- It is possible to do a randomized, double blind, controlled study…with N=39

Missing Data

Key Points for Analysis Planning

- Involve patients or family members in study design
- Keep people (participants and study staff) active and invested in the study
- Include efforts to retrieve meaningful data from 'drop-out' cases
- Main (primary) analysis and missing data plans
  - Pre-specification is not enough
  - Assumptions should be plausible given study population, study objectives, and anticipated effects of the test and control product(s)
- Sensitivity analyses should be planned and reasonable
- *SPIRIT Statement discusses in its minimum set of elements to be included in a protocol http://www.spirit-statement.org/spirit-statement/

Strategies to Make a Study More Powerful: Reduce Variability

- Anything that reduces variability in measurements (↓ variance and measurement error leads to ↑power for the same N)
  - Multiple measurements (e.g. take blood pressure three times at the visit and use the average systolic (or diastolic) as the study value for the visit)
  - Standardize equipment across sites
  - Standardize assays before the study begins
  - Central reader
  - Training, manuals, and active frequent QA & QC
  - Interim review of masked data for QC, *in time to modify data management, analysis plan and study procedures, if needed*

Strategies to Make a Study More Powerful: Reduce Variability

- Reduce variability in the interventions
  - Standard of care or usual care are great in theory
  - May not be consistent across sites (countries), over time, etc
  - Must record and evaluate what is done
- Check every step of how the test intervention is handled (and the control, too)
  - Not just product quality/consistency

Adjusting for Baseline Covariates and More….

- To reduce variance (of estimated treatment effects) and increase power (for hypothesis tests about treatment effects)
- Randomization strata (e.g., clinical centers)
- Propensity scores (if you know enough to make them)
- Continuous outcome variable?
  - Including baseline value as covariate adds power (provided correlation between baseline and outcome is positive)
  - Analyzing change scores without adjusting for baseline in ANCVOA only helps if correlation >0.5
  - ANCOVA or similar methods when endpoint is continuous

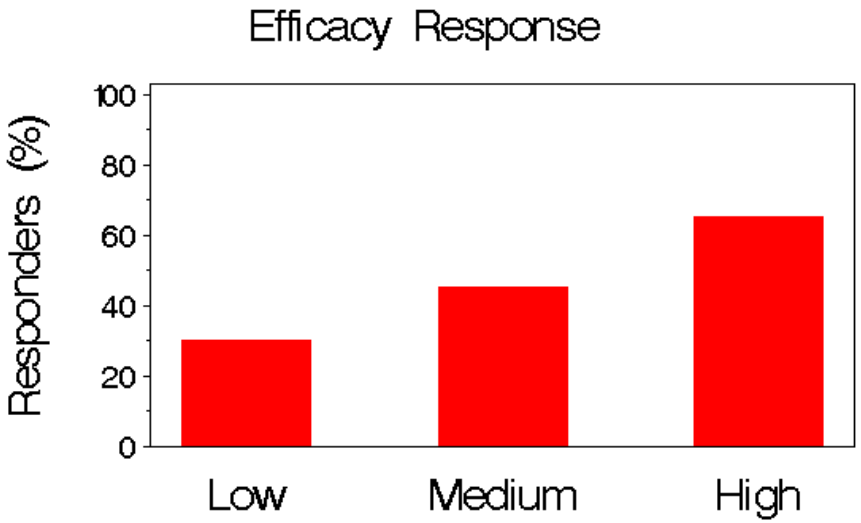
Strategies: Randomization

- Patients may be wary of randomization to placebo
  - Use an “active” control, standard of care…rarely is the study arm “nothing”
  - Reminder that new is not always better
- Use 2:1 or higher allocation, skewed toward experimental treatment
- Allow early rescue treatment

Randomization Strategies: Change "when" on Experimental Product

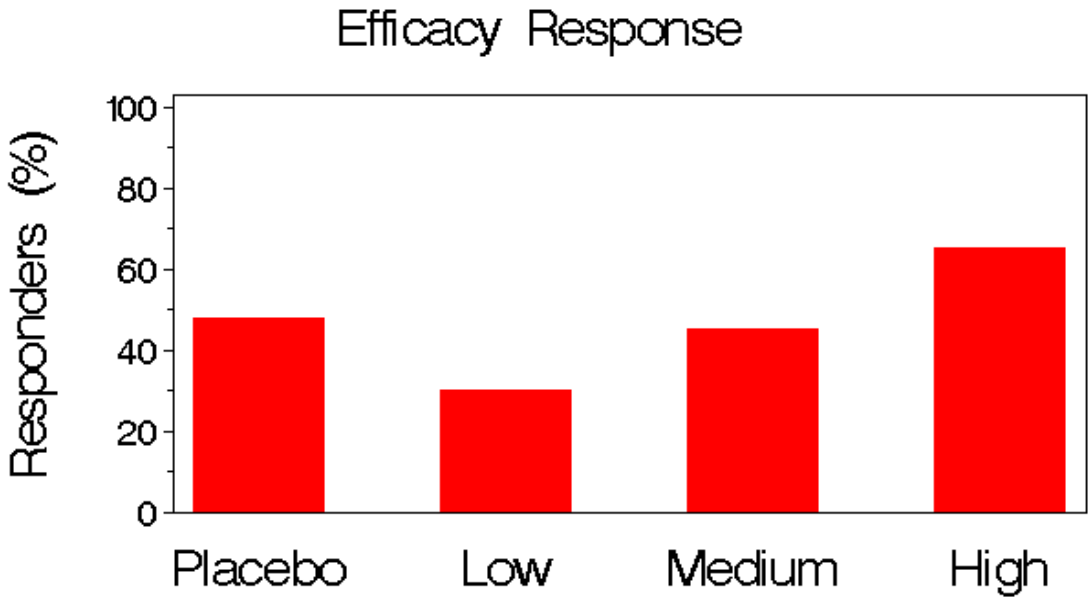
- Waitlist control (not waiting for Godot), stepped wedge, delayed start
- Randomized withdrawal designs
- N-of-1 designs, crossover designs
- Allow placebo patients to switch to experimental treatment for a safety follow-up phase
  - Caution: efficacy data collected after the point of switching is difficult to interpret

Do Not Forget Placebo: Evidence of a dose response?



Steve Ruberg's classic pair of articles on dose response Stephen J. Ruberg Ph. D. Journal Of Biopharmaceutical Statistics Vol. 5, Iss. 1,1995

Sometimes not including the arm is far more costly than "wasting" patients on the arm



ROOM FOR INNOVATION

Adaptive Designs and Interim Analyses

- Pre-planned adaptations can help maximize use of the scarce resource here – patients!

- Interim looks for safety, futility, and early evidence of efficacy through traditional design, e.g., group sequential, all useful in small trials, particularly if slow enrollment expected

Share a Study?

- Umbrella trials
  - Multiple sponsors (willing?)
  - Multiple treatments
  - Sharing controls
  - Within disease subtype or histology
- Basket trial?
  - One drug
  - Single mutation
    - Screening, gene mutations
    - Targeted therapy
  - Variety of tumor types

Type I Error, Multiplicity, Oh My!

- Well-defined endpoints, measured as accurately and reliably as possible, are critical to success of small trials
- Type I error control should be specified for multiple primary endpoints to ensure interpretability of results, but also ‘totality of the evidence’
- FDA Multiple Endpoints in Clinical Trials Draft Guidance, January 2017

Study Conduct

- Quality control is a critical element in ensuring the validity of a study's findings
- For rare diseases, also important because

quality = efficiency

FDA Want to Make the Correct Decision

Want enough information to be able to make an evidence based decision

Problem Solver, Risk Mitigator

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