Clinical Trial Design in Rare Diseases:

Special Considerations

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Disclaimer

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Outline

- Application of US regulatory framework to rare disease product development

- Challenges in trial design for rare diseases

  - Natural history

  - Statistical considerations

  - Dose selection

  - Ethical considerations in pediatric clinical investigations

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Definitions

- Rare disease: disease or condition affecting < 200,000 people in the United States

- Orphan Drug Designation:

    - Investigational product must be intended to treat a rare disease

    - Adequate demonstration of a medical plausibility for the drug's expected benefit

    OR

    - A product for which there is no "reasonable expectation" that the development costs would be recovered from U.S. sales

- Orphan Designation is an incentive to encourage drug development

- Orphan designation applies to specific product AND specific disease

Evidentiary Standard

- 1962 Drug Amendments to the Food, Drug & Cosmetic Act (FD&CA):

  - Require establishment of effectiveness of the drug as a prerequisite for marketing approval

  - Effectiveness established by **"substantial evidence"**

  - Section 505(d) of the FD&C Act:

"Evidence consisting of adequate and well- controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Adequate and Well-Controlled Studies

- Studies that have been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change, placebo effect, or biased observation" (21 CFR 314.126)

- Adequate and well-controlled studies have:

    - Clear statement of purpose
    - Appropriate control for valid comparison*
    - Appropriate selection of subjects
    - Appropriate assignment of subjects to treatment and control*
    - Adequate measures to minimize bias
    - Well-defined and reliable methods of assessing response*
    - Prospectively planned analyses designed with rigor

Adequate & Well-Controlled Studies
21 CFR 314.126

- Traditionally a minimum of 2 adequate and well-controlled studies when each meets its primary endpoint by its prespecified primary analysis with p-value less than 0.05

- 1997: FDA Modernization Act (FDAMA) provided a complimentary statutory standard for demonstration of substantial evidence of effectiveness

    - "**one adequate and well-controlled study and confirmatory evidence**"

Application of regulatory standards in rare disease trials

- Regulations recognize need for flexibility

   21 CFR 314.105(c)

   – "While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards"

   – "The FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information….required to provide for a particular drug to meet the statutory standards."

Use of FDA Approval "Flexibility"
FDA Novel Drug and Biologic Approvals 2006 - 2017
(n = 423)

	Orphan Drug	non-Orphan
2 or more Adequate and well-controlled studies	35%	74%
1 adequate and well-controlled study plus supporting evidence	60%	25%
Other: no adequate and well-controlled study, or atypical program	4%	2%
Accelerated Approval	25%	3%
Regular Approval	75%	97%
"Conventional" Approval (Regular approval based on 2+ AWC studies)	29%	72%
"Flexible" Approval (Accelerated approval and/or approval based on <2 AWC studies	71%	28%

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Trial design in rare diseases: special considerations

1. Disease natural history

2. Statistical planning/considerations

3. Dose selection

4. Ethical challenges

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Disease Natural History

Natural history

- Incompletely/poorly understood natural history

  - Lack of longitudinal data
  - Cross-sectional studies, case reports, retrospective studies
  - Standardized measures to assess outcomes in NH studies are often not optimized for regulatory purposes
  - Tools used in NH studies are often different than tools used in clinical trials (difficult to compare and interpret potential differences if used as historical controls)
  - Often, symptoms are slowly progressive over decades (difficult to study in a longitudinal, systematic way)

- Disease heterogeneity

  - Phenotypic
    - variable manifestations, variable age of onset/rate of symptom progression
  - Genotypic
    - multiple gene variants, variants/polymorphisms in other genes or epigenetic changes may affect phenotypic expression, different disease severity, other genetic factors affecting phenotype

Natural History Studies

- Track course of disease over time

- Identify variables that correlate with disease and outcomes in the absence of treatment

- Generate important information on

  - Genotypes
  - Phenotypic variation/disease subtypes
  - Course, rate of progression – e.g., chronic progression, episodic
  - Major important morbidities, mortality, and time course of each
  - Other elements – often disease specific (biomarkers, etc)
  - **Information Relevant to Patient Focused Outcome Assessments**

Natural history studies within drug development

- Knowledge of disease natural history is **critical** to inform trial design for selection of:

  - Appropriate patient population/subpopulations (most likely to show effect or to have benefit)

  - Most efficient/informative trial design (parallel group, cross-over, randomized withdrawal, etc)

  - Sufficient trial duration to see change in outcomes

  - Reliable, disease-specific biomarkers (for dose selection, population selection, stratification, surrogate for approval)

  - Clinically meaningful endpoints

Natural History Studies as Historical Controls

- "Infrequent" application of NH study or registry data
  - "usually reserved for special circumstances"[4], e.g.: Objective endpoint (mortality), large treatment effect
  - Used more frequently in rare diseases than in common diseases

- Historical control limitations:
  - Different baseline characteristics, alternative treatments (confounding- known and unknown variables)
  - Different instruments used to assess outcomes, different assessment frequencies/assessors (bias)
  - Retrospectively collected data with critical limitations
  - Inadequate documentation, missing data
  - Potentially more severely affected patients in NH studies ("healthier" populations tend to participate in clinical trials)
  - Comparability of populations?

[4]21CFR314.126 Adequate and well-controlled studies

Natural History Studies as Historical Controls

- If a natural history external control group is proposed, it should be ideally identified prospectively to ensure comparability to treatment group

  - Natural history external control group created post hoc is very difficult to interpret (unless effect of test drug is large) due to known and unknown confounding

- In many cases, randomized controlled clinical trials remain the fastest way to determine effectiveness:

  - Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials

  - Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)

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Statistical planning/considerations

Statistical considerations

- Lack of study power, alpha considerations
    - Small sample size
    - Often small treatment effect size
- One trial vs 2 trials
    - May depend on disease prevalence
    - Often 1 trial + confirmatory evidence
- Endpoint selection
    - Single primary vs multiple endpoints
    - Composite endpoint (A, B, C, D, or E/ A, B, C, D & E)
    - Continuous vs binary endpoints
    - "totality of evidence" assessment (how?)
    - Survival endpoint (rare, not ethical)
- Choice of trial design
    - Superiority vs non-inferiority
    - Adaptive design (novel approaches)
- Concurrent control vs non-concurrent (historical) control
- Statistical significance vs clinical meaningfulness

Sample Size Considerations

(produced by Di Xiao; idea from John Doan quality control book)
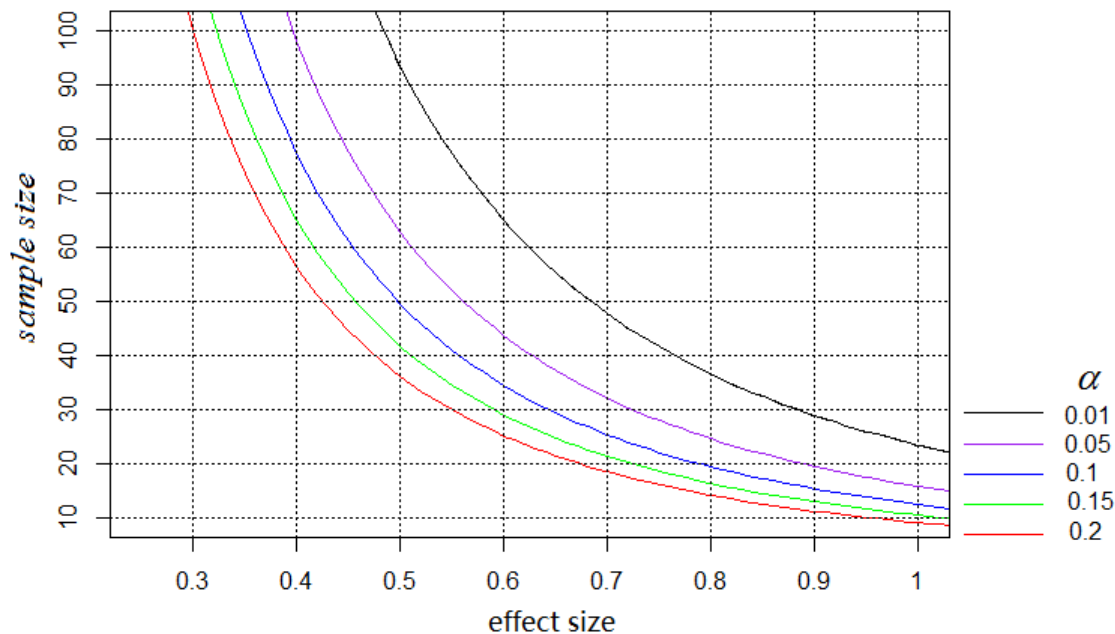
- Assuming the study power is fixed, larger samples are needed when the effect size and/or alpha is smaller

- If the effect size is fixed, to reduce the sample size, alpha may need to be relaxed

Endpoint Selection

- Both continuous and binary endpoints can be based on patients' outcome at a visit or change from baseline
  - Issue: For small trials, baseline data can be greatly imbalanced due to chance
- Continuous endpoints: mean change or % change from baseline
  - Concerns:
    - mainly population comparisons
    - validity of the normality assumptions
    - outliers can have big impact on results
- Binary endpoints can be used to assess individual patients' improvement
  - Concerns:
    - Need to identify a meaningful cutoff to lead to clinical meaningfulness
    - May need many more subjects to detect a drugs' efficacy
- Survival endpoints usually need longer study durations and capture of many events

Multiple Primary Endpoints: Example

- Indication: a very rare, autosomal recessive, lysosomal storage disease (Sly syndrome, MPS VII)
- Efficacy based on the totality of the clinical data.
- No primary selected
- Potential endpoints:
  - Change from baseline in disease biomarker
  - A multi-domain responder index
  - Pulmonary function test
  - Six minute walk test
  - …..
- How do Sponsors propose to assess the totality of evidence?

Composite Endpoint Approaches

- Determine responders based on patients' improvement in each endpoint, meeting pre-specified criteria for

    - A, B, C, D, or E
    - A, B, C, D & E
    - Some variation of this (see guidance and previous slide)

- Once winning on the primary composite endpoint, results of single components should be further examined and described to make sure that the positive findings are not driven by a few components

- No single component should be further tested and claimed in the labeling unless pre-specified under type I error control

    https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf

Statistical Significance vs Clinical Meaningfulness

- When both intervention arm and the placebo have the same variance, a continuous primary endpoint seems to be more powerful than a binary endpoint, however,

  - Need to ensure that statistical significant results will lead to clinical meaningful results

| Example: NDA208794	Mean (SD)	Mean difference from Placebo (97.5% CL)
Study drug 250mg (3 times a day)	-1.4 (1.4)	-0.8 (-1.3, -0.3)[#]
Placebo	-0.6 (0.8)	

*assessing change from bowel movement/day averaged over 12 weeks

# p<0.001

Assessing Clinical Meaningfulness

Figure 1: Cumulative Proportion of Patients with Carcinoid Syndrome Diarrhea Reporting Change in Overall Average Bowel Movement Frequency
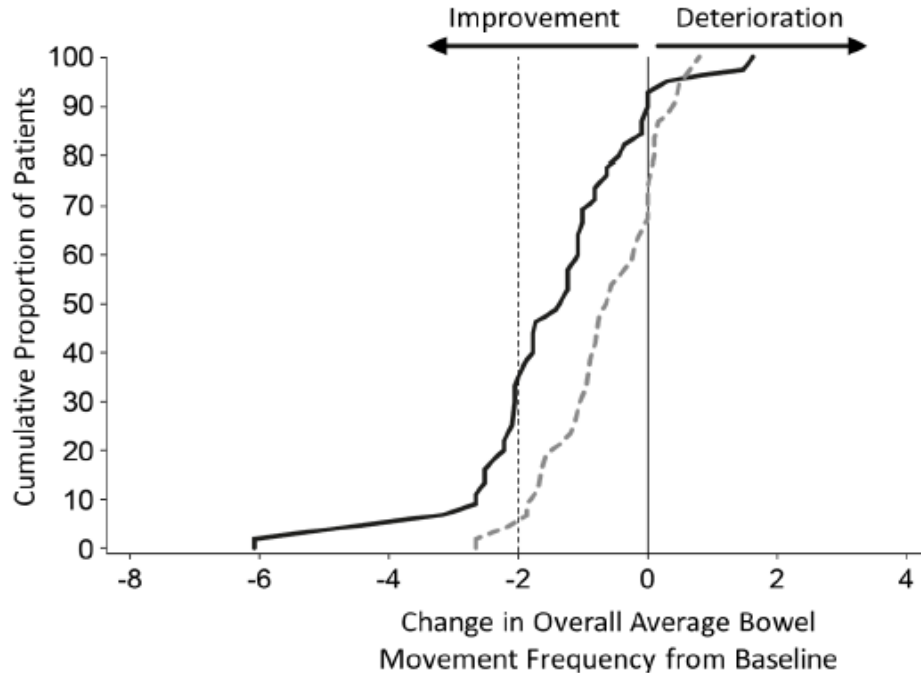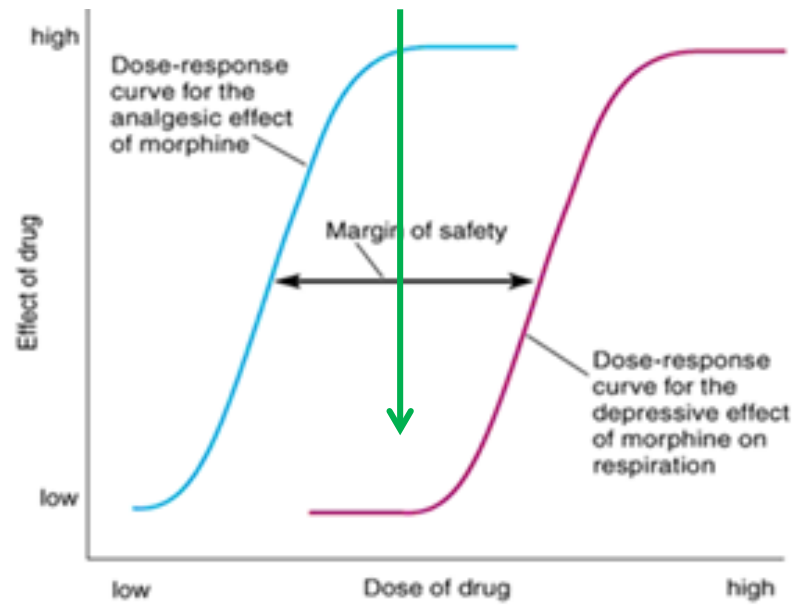
*extracted from FDA label (solid line is for drug and dashed line for placebo)

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Dose selection

Basic Principles of Dose-Finding

- Optimal dose: the most efficacious dose with minimal toxicity *(or acceptable safety profile)*
- Optimal dose selection depends on exposure-response (E-R) curves for efficacy and toxicity
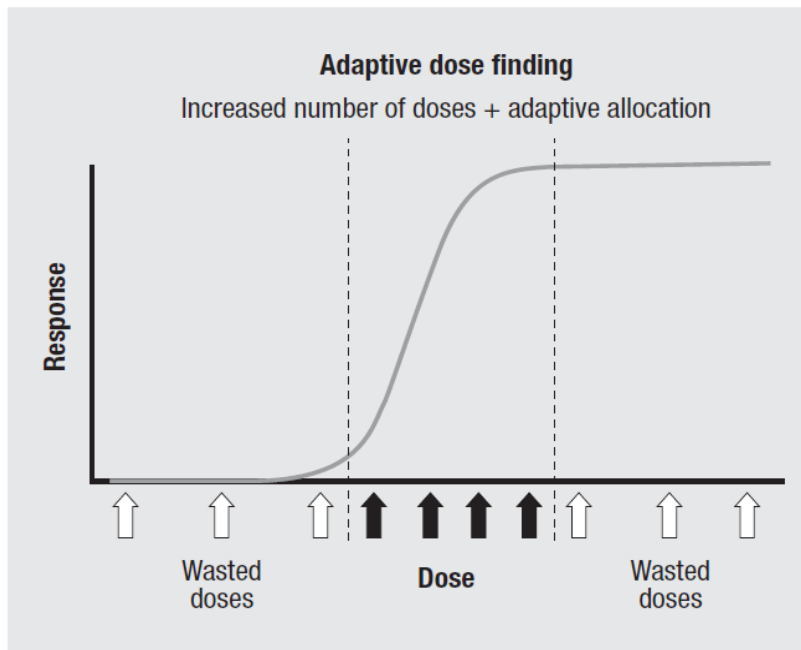
Dose-Finding Challenges in Rare Disease Trials

- Small patient population

- Rapidly progressive phenotypes
  - Survival endpoints not feasible for dose-finding

- Slower (not rapidly) progressive phenotypes
  - Lack of established clinical endpoints, or clinical endpoints require long duration for evaluation
  - Correlation of biomarker with clinical endpoints is unclear

- Lack of PK-PD correlation in many cases, depending on the site of action

Innovative Approaches:
Adaptive Design in Early Phase Trials

Adaptive dose finding

Increased number of doses + adaptive allocation

Response

Dose

Wasted doses

Wasted doses

- Traditional dose finding: few doses; some dose levels not informative
- Adaptive dose finding: few pts on many doses initially; Dose assignment based on responses of previous subjects (maximize information about dose response curve); **Requires that drug response is rapidly observable relative to accrual rate**

Ref: Bornkamp. J Biopharm stat 2007

Innovative Approaches:
Dose PK/PD Simulation

Canakinumab: Mab developed for treatment of Muckle-Wells syndrome in adults and children 4 years and older
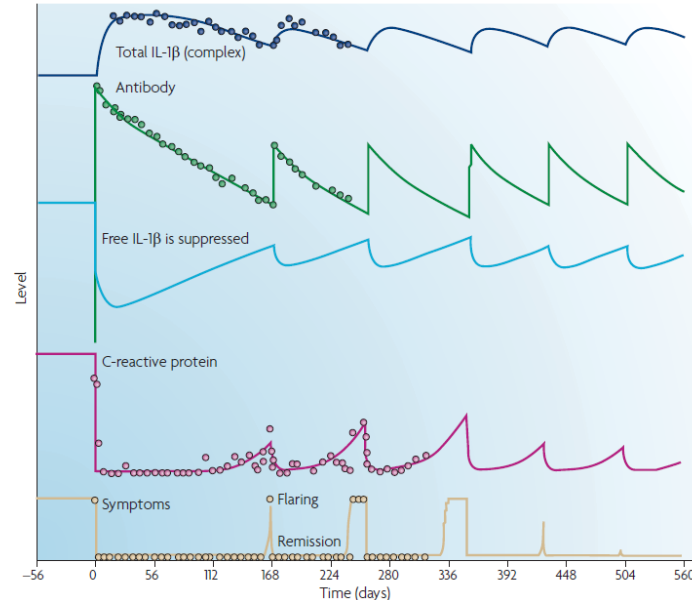- Rare genetic disorder characterized by fever, urticaria, joint pain, malaise

Phase 1/2 study in ~20 pts with MWS
- Total IL-1β (complex) increases after dosing and can be measured
- Reduction in free IL-1β correlates with change in clinical signs and symptoms

Modeling and simulation strategy:

- **Model to integrate** clinical data on relationship between activity of the therapeutic target (IL-1β), markers of inflammation & remission of symptoms

- **Simulation to propose dosing** to achieve desired response for the majority of patients (80% probability that 90% of patients would remain flare-free for 2 months)

- Dosing regimen investigated and confirmed in a Phase III trial

Ref: Orloff et al. The future of drug development: Advancing Clinical Trial Design. Nature Reviews. 2009

Nonclinical Considerations for Dose Selection

- Toxicology data
    - What is the safety margin from in vivo toxicological studies?
    - Are expected toxicities able to be monitored and/or reversible?
    - For large molecules, are there differences in the pharmacology between test species and humans (i.e. is the NOAEL from test species relevant to human testing)

- In vivo PK–PD experiments:
    - Characterize the relationship between dose, exposure, and biomarker changes, and efficacy studies in appropriate disease models when applicable
    - Cross-species allometric scaling to derive initial human dose

- In vitro pharmacology experiments
- Data on receptor binding affinity and receptor occupancy (RO) data to define target exposures in humans

Clinical Considerations for Dose Selection

- Target population
  - Is there a role for an enrichment strategy?
  - Is dose-response relationship expected to apply across genotypes?

- Dose selection/refinement
  - What is the relationship between receptor occupancy (RO) and downstream biological effects? Is the human dose-RO relationship sufficient for initial dose selection?
  - Is there an intermediate or PD/biomarker endpoint that can inform dose titration or dose refinement? Is drug response rapidly observable relative to accrual rate?
  - Will the half-life of the drug/biologic allow for adequate dose titration?
  - What is the optimal timing and extent of does adjustment? What is the expected carryover effect for an intra-patient dose-escalation trial?
  - When is the use of a maximum tolerated dose approach warranted?

- Other trial design elements
  - Is there a role for a seamless adaptive Phase 2/3 trial design   to maximize use of patients?
  - Selection of a control arm
  - Sparse PK sampling in all patients for exposure-response analysis

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Ethical Considerations

Additional Safeguards for Children
21 CFR 50, subpart D

- Research involving children must either:

  - be restricted to "minimal" risk or a "minor increase over minimal" risk absent a potential for direct benefit to the enrolled child (21 CFR 50.51/53)

  OR

  - present risks that are justified by anticipated <u>direct</u> benefits to the child, the balance of which is at least as favorable as any available alternatives (21 CFR 50.52)

Additional Safeguards for Children
21 CFR 50, subpart D

- To conduct a pediatric clinical trial, the ethical challenge is to establish sufficient evidence using either preclinical animal models or adult human clinical trials to conclude:

  - "Low risk" pathway: absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably low risk (minimal, minor increase over minimal), or…

    - 21 CFR 50.51/50.53

  - "Higher risk" pathway: administration of investigational product to children presents a sufficient prospect of direct benefit to justify "higher" risks

    - 21 CFR 50.52

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Prospect of Direct Benefit (PDB) 21 CFR 50.52

- A "**direct** benefit" may improve the health or well-being of the individual child and results from the research intervention being studied
  - not from other clinical interventions included in protocol

- What is the available evidence (either from adult humans or animal models) about the intended clinical effects of the product (intervention)?
  - Does the available data make us reasonably comfortable that children might directly benefit from the product?
  - Are the dose and duration of treatment with the product appropriate/sufficient to offer the intended benefit?
  - For diagnostic procedures, would the procedure normally be done as part of routine clinical care? Would the data impact clinical care?

"First-in-Children" Trial
21 CFR 50.52

- Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a "first-in-children" clinical trial under 21 CFR 50.52?
  - The data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks of product administration varies with the severity of the disease and the adequacy of alternative treatments

- Proposal: Sliding Threshold
  - <u>Structure</u> (generally insufficient for PDB)
  - <u>Function</u> (based on mechanism of action)
    - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
    - Transgenic Technology (human target + mouse)
  - <u>Clinical Disease</u> Model
    - Surrogate endpoints
    - Clinical endpoint (e.g., survival) (FDA "Animal Rule")

Placebo (Sham) Control: ethical considerations

- Sham procedures (and placebos) do not offer any prospect of direct benefit to the enrolled child.

- Two types of risk

  - Risk of placebo itself may be "minimal" unless placebo is invasive (e.g. sham injections)
  - Risk of harm from not receiving "proven" or "effective" treatment.

- Both types of risk must be no greater than a "minor increase over minimal risk" (21 CFR 50.53)

  - This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.

Case Study

- Multinational, placebo-controlled, study of an investigational product, in children ≥ 7 years old–
  - Product (or placebo) administered (double blind) by lumbar puncture every other week for 1 year
- LP presents more than a minor increase over minimal risk
  - LP use justified in children receiving the active product due to the prospect of direct benefit from the treatment
  - Children receiving placebo via LP offered no prospect of direct benefit, but exposed to greater than minor increase over minimal risk
- Thus, LP in a placebo group would not be in compliance with 21 CFR 50, subpart D
  - Alternative use of sham control
  - Patient receives "sham" LP involving local anesthetic injection only, patient and caregiver (as well as assessors) remain blinded to treatment

Conclusions

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- Drug development in rare diseases presents multiple unique challenges that require careful planning (ideally before IND stage), collaboration, and (often) creative/novel approaches

- Knowledge of disease natural history, which is fundamental in designing any trial, is often lacking or incomplete in rare diseases

- Statistical approaches to rare disease trials require creativity and flexibility

- Interpretation of treatment effects from a statistical vs a clinical perspective can differ (not specific to rare disease trials) but is more difficult in rare disease trials where often the treatment effect may be small

- Important ethical and regulatory/legal considerations often apply to rare disease trials, in which disease are pediatric-onset and most available patients are children

- Choice of appropriate and ethical controls in rare disease trials is challenging and often needs to be tailored to individual disease and drug development program

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Thank you!

Questions/Comments:

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