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Study Designs for Rare Diseases

Keith Hull, MD, PhD
FDA/CDER/DPARP
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Disclosures

- The views presented here do not necessarily reflect those of the Food and Drug Administration

2

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Orphan Diseases

- "Rare disease"
  - any disease or condition which affects <200,000 persons in the US
  - any disease or condition which affects 5 or less people out of every 10,000 in the EU
- 25 million Americans are diagnosed with one of 7,000 rare diseases

4

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Orphan Drug Act

- Passed in 1983 to encourage pharmaceutical companies to develop drugs for "rare" diseases
  - Before 1983
    - 10 treatments had been developed for rare diseases
  - Since 1983
    - >2,000 products in development have been designated as orphan products
      - 2000-2002: 208 products
      - 2006-2008: 425 products
    - >350 drugs and biologics for treatment of rare diseases have been approved by the FDA since 1983

5

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Orphan Drug Act
Incentives

- Financial Incentives
  - Marketing Exclusivity
    - 7 years
  - Tax Credit
    - 50% tax credit for clinical testing expenses
  - Orphan Grant Program
    - Open to foreign or domestic public, private, non-profit, & for-profit entities
    - Phase 1: $200K per year up to 3 years
    - Phase 2 & 3: $400K per year up to 4 years
  - Waiver of FDA User Fees

6

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Orphan Drug Act
Incentives

- Non-Financial Incentives
  - Orphan Products Board
    - DHHS, FDA, NIH, and CDC
    - Helps implement the Orphan Drug Act and promotes coordination among and between members of the public and private sectors
  - FDA Protocol Assistance
    - Direct assistance from FDA in helping sponsors to design clinical trials to meet FDA approval requirements
    - Most helpful for smaller developers

7

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Orphan Drug Act
Drug Development

- Drugs must first receive the "orphan drug" designation from the FDA's Office of Orphan Products Development
  - Review of the product is performed by the individual review Divisions
- Orphan drugs follow the same regulatory development path and need to meet the same standard of evidence as other products
  - Flexibility of study designs are considered given the potential patient population
- Orphan drugs frequently receive expedited review or accelerated approval because they often provide an unmet medical need for a serious or life-threatening disease

8

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Snapshots

"The good news is that we're going to name the disease after you."

9

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Challenges with Studying Rare Diseases

10

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Challenges with Studying
Rare Diseases

- Small numbers of patients available for study enrollment
- Understanding of the disease's clinical course may be incomplete
- Often there are no validated measures of disease activity or disease progression
- What is the standard of care for patients with the disease?

11

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Challenges with Study Design

Choosing a Primary Endpoint

12

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Challenges with Study Design
Choosing a Primary Endpoint

- Which symptoms will be targeted during the trial?
  - "Defining" symptoms of the disease may differ between individuals
  - What degree of change in symptoms is clinically meaningful?
- Composite index of symptoms may be preferable to assessing a single symptom
  - Is the treatment expected to impact all or only a subset of symptoms?

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Challenges with Study Design
Choosing a Primary Endpoint

- Are symptoms progressive, periodic, or do they wax & wane?
- Are symptoms serious or life-threatening?
- How are symptoms measured or assessed?

14

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Challenges with Study Design
Choosing a Primary Endpoint

- Surrogate Endpoints
  - A surrogate endpoint is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of therapy
  - Represents a possible alternative endpoint that could allow more expedient trials and decrease the sample size requirements BUT there must be evidence that effects on the surrogate predict a clinical benefit

15

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Challenges with Study Design
Choosing a Primary Endpoint

- Surrogate Endpoints
  - Pros:
    - Objective
    - Change more rapidly than clinical endpoints
    - Smaller sample sizes required
  - Cons:
    - Validation can be complicated and expensive
      - Demonstrate that drug effect on surrogate predicts drug effect on clinical outcome
      - Fully represents the net effects of treatment on clinical outcome
      - Repeatable

16

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Patient Reported Outcomes
(PRO)

- PRO is a measurement of any aspect of a patient's health status that comes directly from the patient, i.e., without the interpretation of the patient's responses by a physician or anyone else
- PRO need to be meaningful to support an effectiveness endpoint that includes an assessment of its ability to measure the claimed treatment benefit and is specific to the intended population and to the characteristics of the condition or disease treated
- FDA Guidance regarding validation and data inclusion into the package insert is in the final stages of sign-off and should be available soon

17

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Choosing a Study Design

18

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Clinical Trial Designs

- Traditional Randomized Placebo-Control Design
- Alternatives to the randomized Parallel Group Design
  - Randomized Withdrawal Design
  - Crossover Design
  - Add-on Design
  - Dose-Response Design
  - Placebo-Phase Design
  - n of 1
  - Three Stage Design

19

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Three-Stage Design

- Stage 1: All eligible subjects are randomized into a parallel-arm, placebo-controlled phase
- Stage 2: Subjects who responded to study treatment in Stage 1 enter into a randomized withdrawal phase
- Stage 3: randomization of placebo-treated patients who did not respond in Stage 1 but subsequently responded to open-label treatment are entered into a randomized withdrawal phase

20

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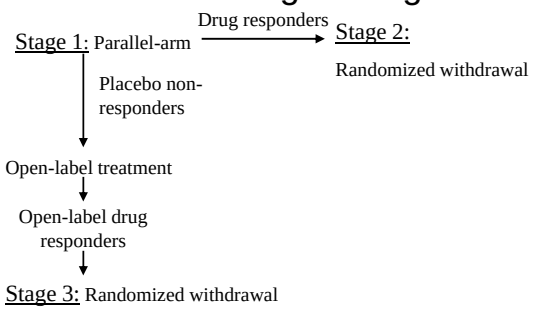
Three-Stage Design



21

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Three-Stage Design

- Pros:
  - Reduces required sample size by 20-30% compared to randomized control trial while maintaining comparable statistical power
  - Provides more information about efficacy
  - Provides information about need for continued treatment
- Cons:
  - Limited experience
  - Ethical issues of placebo treatment
    - Depends on the consequences of non-treatment
  - Same limitations as for Randomized Withdrawal

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Rilonacept (Arcalyst) for the Treatment of Patients with Cryopyrin-Associated Periodic Syndrome (CAPS)

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Background

- Cryopyrin-Associated Periodic Syndromes (CAPS)
  - 200 to 500 patients in the US
- AD disorder due to mutations in *CIAS1*
  - *CIAS1* encodes NALP3 (cryopyrin), a component of "inflammasomes", which regulate caspase-1
  - Caspase 1 regulates the cleavage of pro-IL-1 to active IL-1
- 3 Clinical syndromes associated with CAPS
  - Familial Cold Autoinflammatory Syndrome (FCAS)
  - Muckle-Wells Syndrome (MWS)
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

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Background

- FCAS
  - Symptoms induced by cold exposure
  - Fever
  - Cold-induced urticaria-like lesions
  - Conjunctivitis
  - Arthralgia common
  - Mild myalgias
  - Abdominal involvement rare
  - Symptoms provoked by cold stimuli

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Background

- MWS
  - Urticaria-like rash
  - Conjunctivitis
  - Limb pain and arthralgias common
  - Abdominal pain may occur
  - Sensineural hearing loss may occur in some patients

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Background

- CAPS Treatment at time of Study
  - Literature reports from a small open-label study demonstrating a clinical benefit of patients with CAPS treated with the IL-1 antagonist anakinra (Kineret)
- Rilonacept (Arcalyst)
  - Fusion protein (human)
  - IL-1r and IL-1r accessory protein : Fc IgG1
  - Binds both IL-1α and IL-1β
  - Approved for use in patients with CAPS in March 2008

28

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Rilonacept for CAPS
Challenges for Clinical Trial Design

- Choice of primary endpoint
- Deriving rigorous evidence of efficacy with limited numbers of patients available for study
- Assessing whether chronic treatment needed or just treatment in winter months

29

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Study Design

- Using primary endpoint driven by lowering of C-Reactive Protein would be problematic:
  - Not validated to predict clinical improvement
- Sponsor conducted natural history study to define most common, most bothersome symptoms
- Derived primary endpoint based on a composite symptom scoring
  - 5 symptoms scaled from 0-10 via 0.5 increments
  - For each day, the 5 scores were summed and divided by 5 (daily mean score)
  - For each observation period the daily mean scores were summed then divided by 21 resulting in a mean key symptom score

30

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Study Design

- Modified Three-Stage Design

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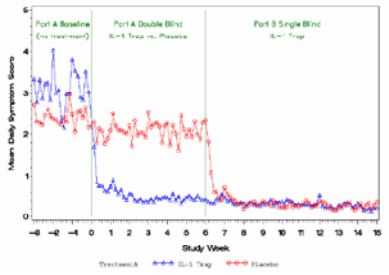
Study Results

- Stage 1 (Part A)

Mean Daily Key Symptom Score by Treatment Group from Week -3 to Week 15 in Study Part A and Part B Single-blind Phase



32

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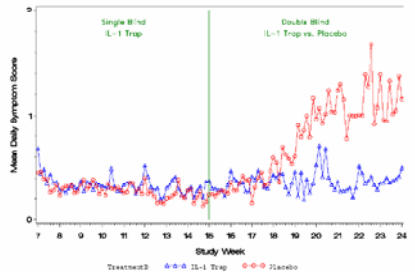
Study Results

- Stage 2 (Part B)

Mean Daily Key Symptom Score by Treatment Group from Week 6 Single-Blind Phase to Week 24 Randomized Withdrawal Phase in Part B



33

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Summary

- Mechanisms is place to help develop drugs for rare diseases
- Rare diseases present challenges regarding optimal study design
- Variety of alternative study designs available that can provide adequate data to demonstrate the efficacy of a new therapy while minimizing prolonged exposure to an ineffective therapy
- Important to devise clinically meaningful endpoints to characterize the benefits of new therapies

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Back-up Slides

36

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Traditional Randomized Placebo-Control Design

- Subjects are randomized to one of two (or more) treatment arms
- Parallel-groups are almost always double-blinded
- Treatment arms include a control arm and active treatment arm(s)
- Typically used to evaluate differences in effect of different interventions over a period of time

37

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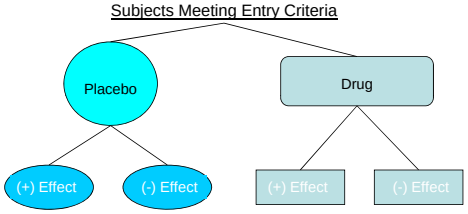
Traditional Randomized Placebo-Control Design



38

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Traditional Randomized Placebo-Control Design

- Pros:
  - Considered the gold standard of trial designs
  - Minimization of bias
- Cons:
  - Potential ethical issues with placebo control group

39

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Randomized Withdrawal Design

- Subjects who have responded positively to an experimental treatment are randomized to continue receiving the treatment or to receive a placebo
- The return of symptoms can be used as study endpoint

40

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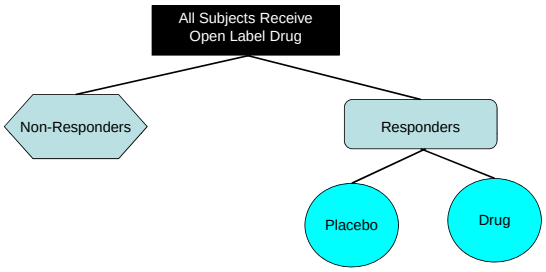
Randomized Withdrawal



41

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Randomized Withdrawal Design

- Pros:
  - Subjects continue to receive study drug only if they respond to treatment
  - Minimizes the time subjects receive placebo
  - Means of enriching the study population
  - Can be useful to assess long-term effectiveness
- Cons:
  - Need to study in a stable chronic disease where the usual course is predictable
  - Ethical issues of placebo treatment
    - Depends on the consequences of non-treatment
  - Carryover may reduce likelihood of flaring in subjects switched to placebo

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Crossover Design

- Compares two (or more) treatments by randomly assigning each subject to receive the treatments being tested in a different sequence
- Once one treatment is completed, patients undergo a "washout" period then receive the second intervention
- Each subject serves as their own control

43

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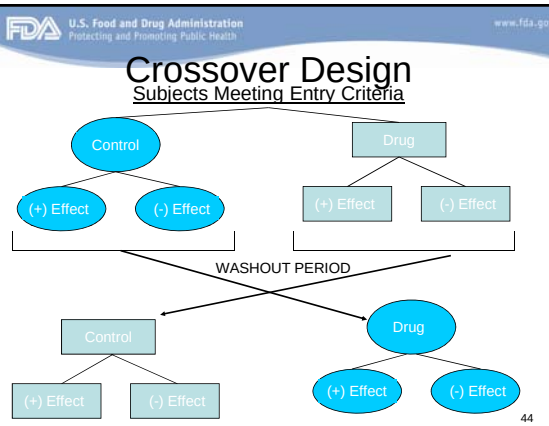
Crossover Design



44

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Crossover Design

- Pros:
  - Requires fewer subjects
  - Can assess response to short periods of therapy
  - May be less variability than in basic randomized clinical trial
- Cons:
  - Potential carryover of treatment effect
  - Cannot use if the intervention is not reversible
  - Cannot use if disease is not stable over time
  - Analysis may be complicated by dropouts and missing data
  - May be longer than standard randomized clinical trial

45

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Add-On Design

- Placebo-controlled study where subjects are enrolled while maintained on standard of care therapy
- Subjects are subsequently randomized to receive either placebo or active treatment
- Problematic if potential for synergistic toxicities between study drug and background medication

46

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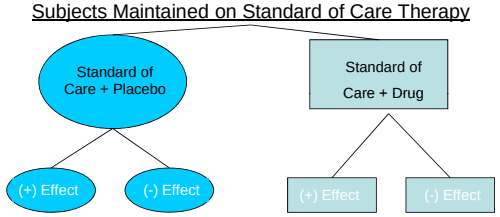
Add-On Design



47

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Add-On Design

- Pros:
  - Subjects receive standard of care at a minimum
  - Useful for diseases where it is unethical to possibly leave subjects untreated
- Cons:
  - Not useful where mechanism of action of study drug shared with standard of care
  - Provides no information regarding the drug as monotherapy

48

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Dose-Response Design

- Subjects are randomized into one of several different dose groups of drug
- A placebo group may not be needed but can be useful to demonstrate effect size of drug
- A positive study should demonstrate increasing efficacy with increasing dose

49

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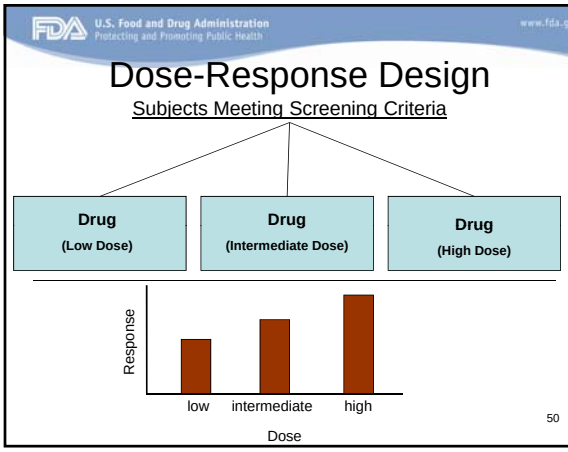
Dose-Response Design



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Dose-Response Design

- Pros:
  - All subjects receive potentially beneficial drug
  - May establish efficacy by demonstrating superior results with higher rather than with lower doses
- Cons:
  - Must understand the dose-response relationship of drug to choose appropriate doses
  - May be difficult to interpret results if inadequate dose-response even if drug is effective
  - Difficult to assess treatment effect size

51

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Placebo-Phase Design

- Subjects are randomized into groups that begin receiving active treatment at different time points from baseline
- A positive study should demonstrate similar efficacy in all groups but in a temporal manner consistent with the time they received active treatment

52

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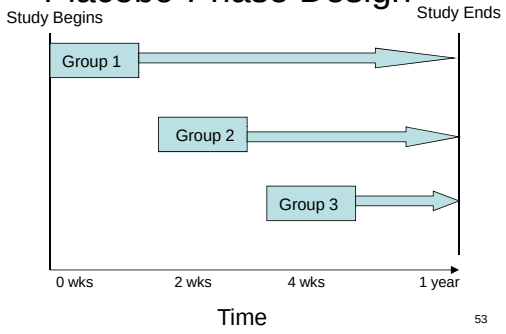
Placebo-Phase Design



53

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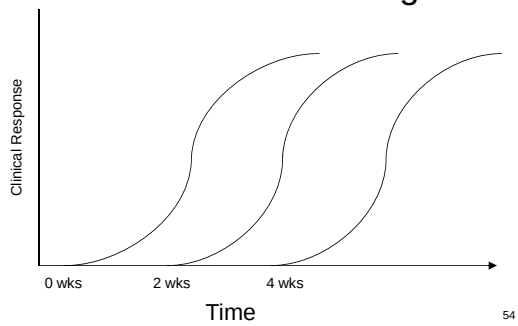
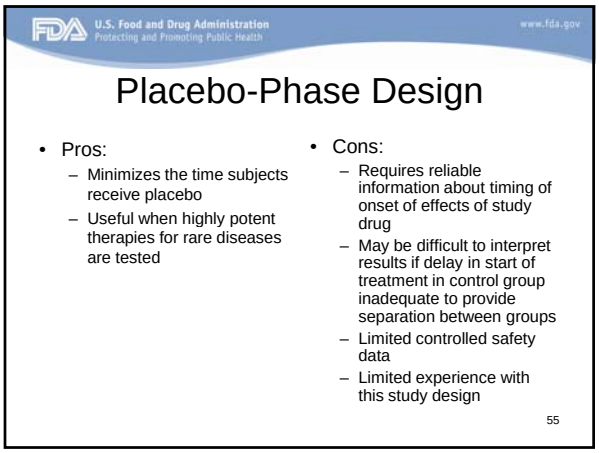
Placebo-Phase Design



54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Placebo-Phase Design
• Pros:
– Minimizes the time subjects receive placebo
– Useful when highly potent therapies for rare diseases are tested
• Cons:
– Requires reliable information about timing of onset of effects of study drug
– May be difficult to interpret results if delay in start of treatment in control group inadequate to provide separation between groups
– Limited controlled safety data
– Limited experience with this study design
55