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Innovative Clinical Development Solutions

The Trials and Tribulations of a Clinical Research Biostatistician - Where Knowledge Meets the Real World

June 6, 2023

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Agenda

- Opening remarks
  - Our panel of clinical trial statisticians
  - Setting the context - Definitions

PART 1

- Establishing Efficacy: Case Studies in Rare Disease
  - Introduction
  - Rare disease study design challenges: a case study in an ultra-rare population using the Sequential Parallel Comparison Design
  - Leveraging natural history data in drug approvals for rare disease
  - Discussion

Agenda (continued)

PART 2

- Establishing Safety of Medical Products
  - Introduction
  - Integrated analyses of safety data from studies of differing populations/disease states for submission to the FDA
  - The crucial role of the ISC Statistician supporting Data Monitoring Committees in ensuring patient safety and data integrity
  - Discussion

Our Panel

Miganush Stepanians, Ph.D.
President and CEO

Nicole LaVallee, Ph.D.
Senior Statistical Advisor

Heidy Russell, Ph.D.
Senior Director, Biostatistics

Suzanne Granger
Associate Director, Biostatistics

Neil Wohlford
Associate Director, Biostatistics
Leader of DMC Services

Setting the Context – Terminology

Basic mission of a clinical trial statistician: determine whether a medical product is efficacious and safe

- Clinical development program
- Clinical trial protocol
- Statistical Analysis Plan (SAP)
- Primary and secondary efficacy endpoints
- Safety endpoints: adverse events (AE), laboratory data, vital signs, ECG

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PART 1

Establishing Efficacy: Case Studies in Rare Disease

What is a Rare Disease?

- In the U.S., a rare disease is defined as a disease or condition that impacts fewer than 200,000 people.
- More than 10,000 known rare diseases affect about 1 in 10 people (or 30 million people) in the U.S.
- Other countries have their own definitions. European Union defines a disease as rare when it affects fewer than 1 in 2,000 people.

https://rarediseases.info.nih.gov/about

Design Challenges in Rare Disease Trials

- Small populations with serious genetic conditions
- Lack of established Standard of Care
- Ethical concerns on usage of placebo
- Heterogeneity of disease and multi-organ involvement
  - Difficult to define primary endpoint and timing of assessments
- Need for leveraging natural history data
- Need for innovative study designs and statistical methods

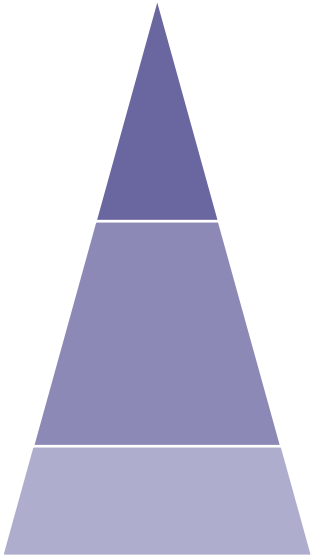
Innovative Designs and Statistical Methods

- Group sequential design
- Sample size re-estimation
- Drop-the-loser design
- Adaptive dose-finding design
- Adaptive enrichment design
- Adaptive randomization

Natural History Data

- Data on the natural course of a disease, symptomology, and patient experience, used to:
  - Select efficacy endpoints and timing of their assessments
  - Derive sample size estimation assumptions
- Use as external control for interventional trial

Natural History Data Collection

	Interventional?	Randomized?	Prospective?	Natural History Data Collection
Randomized Clinical Trial	Yes	Yes	Yes	
Single Arm Clinical Trial with **Natural History Control**	Yes	No	Yes	
Prospective **Natural History** Study	No	No	Yes	
Natural History Registry	No	No	Yes	
Retrospective **Natural History** Study	No	No	No	

Use of Natural History as an External Control

- Most persuasive when:
  - No feasible placebo control
  - No available therapy for comparison
  - Predictable disease progression
  - Objective outcome measure
  - Large treatment effect
  - Similar population and setting

Establishing Efficacy: Case Studies in Rare Disease

Nicole LaVallee, Ph.D.

- Rare disease study design challenges: a case study in an ultra-rare population using the Sequential Parallel Comparison Design

Suzanne Granger, M.S.

- Leveraging natural history data in drug approvals for rare disease

Sequential Parallel Comparison Design (SPCD) in a Rare Disease Trial

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Rare Disease Case Study

- Outline
  - Initial Study Design
  - Benefits of Adaptive Design
  - Sequential Parallel Comparison Design (SPCD)
  - Simulations

Rare Disease Characteristics

- Ultra-rare disease (<200 patients reported worldwide)
- Onset usually at <6 years of age
- Life expectancy <2 years in most severe cases
- Currently, no approved treatments

Study Design

- Randomized, double-blind, placebo-controlled, first-in-human trial
- Planned enrollment of 15-20 patients
- Patients randomized 2:1 to active treatment and placebo

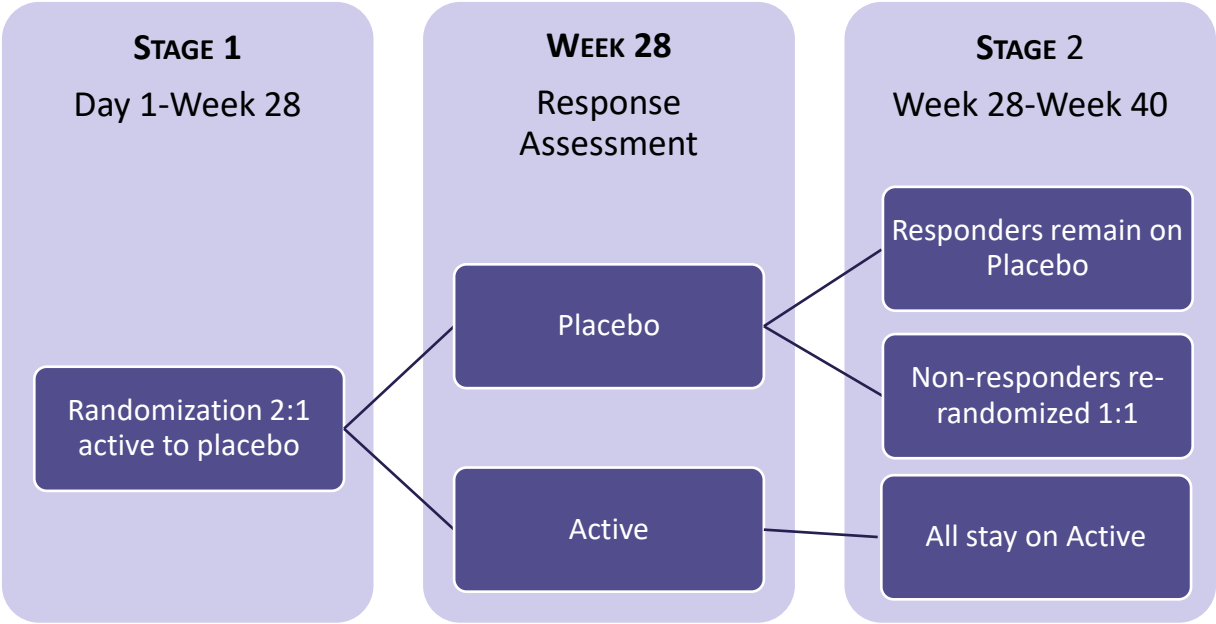
Study Design (continued)

- Initial design, primary endpoint measured at Week 28
- Based on sample size assumptions, >90% power to detect treatment group difference in % change from baseline
- But this is first-in-human trial
  - Is 28 weeks long enough to see a treatment effect?
  - Are sample size assumptions (i.e. expected treatment difference and variability) reasonable?
- How can we improve chance of trial success?

Modified Study Design

- Increase treatment period to 40 weeks
- Perform analysis at 28 weeks and 40 weeks
- Week 28 analysis only viewed by the study IDMC, and sponsor will remain blinded
- Study continues to Week 40, regardless of Week 28 results

Sequential Parallel Comparison Design



Sequential Parallel Comparison Design (continued)

Let δ_1 = Stage 1 treatment effect, all patients

δ_2 = Stage 2 treatment effect, re-randomized placebo non-responders (NR)

w = weight for Stage 1 treatment effect, between 0 and 1

Test H_0: $w\delta_1 + (1-w)\delta_2 = 0$

weighted average treatment effect from Stage 1 and Stage 2

Sequential Parallel Comparison Design (continued)

- Advantages
  - Increases number of patients who receive active treatment
  - Eliminates placebo responders from Stage 2 comparison
  - Improves power of test at Week 40 compared to Week 28

- Analyze by MMRM Method (Doros et al, 2013)
  - Uses all data collected in repeated measures model
  - Accounts for data missing at random

Simulations for Type 1 Error and Power

- Stage 1 sample sizes of 14:7, 8:8
- Stage 1 weight, w, of 0.5, 0.6, 0.7, 0.8, 0.9
- % change from baseline to Week 28 (from protocol)

  Active: mean -40% and SD 30%

  Placebo: mean +20% and SD 30%
- % change from Week 28 to Week 40

  Placebo NR → Placebo: mean of +10%

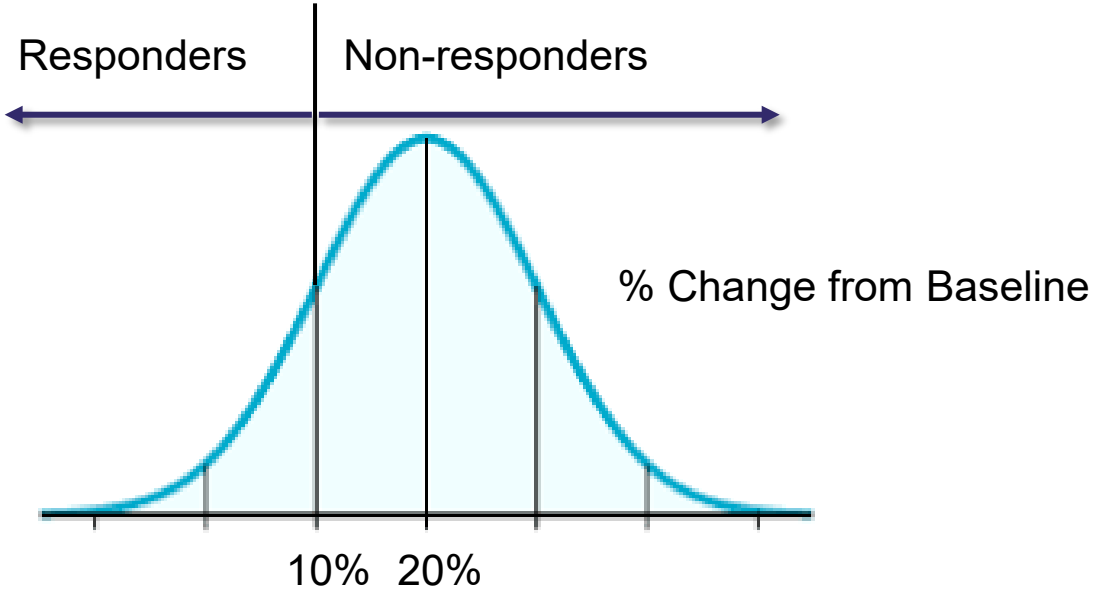
  Placebo NR → Active: means of -5%, -10%, -15%, -20%, -30%

  All others: mean of 0%

Simulations (continued)

- δ_1 and δ_2 set to 0 to assess Type 1 error
- Assume multivariate normal distribution for baseline, Week 28, and Week 40 observations
- For simplicity, correlation between time points was fixed at 0.5 for both treatments
- Run in SAS with 10,000 datasets per scenario

Simulations (continued)



Placebo Patients at Week 28, N(20,30)
Non-response rate = 0.631

Simulation Results

- If number of placebo non-responders was 2 or less, then MMRM failed (about 6% of replications)
- Power was at least 88% even when treatment effect in Stage 2 was 1/4 of that in Stage 1
- Power increased as Stage 1 weight increased
- Type 1 error was slightly inflated (0.052-0.065)

Note: For sample sizes of 20 per group, Type 1 error was preserved

References

Doros, G, et al. A repeated measures model for analysis of continuous outcomes in sequential parallel comparison design studies. Statistics in Medicine 2013;32:2767-2789.

Haber, H, et al. Analysis Methods for a Sequential Parallel Comparison Design (SPCD). PharmaSUG 2015, Paper #PO23.

Case Study

Retrospective Natural History Study in Ultra-Rare Neurologic Disease as an External Control

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Objectives

- Obtain summary of available data
  - Inform and support clinical trial design
  - Target population
  - Identify potential endpoints for interventional studies
- Provide data to serve as a control
  - Comparable clinical manifestations

Natural History Study: Feedback from FDA

- Interpretable
  - Control patients must be as similar as possible
- Study observations
  - Performed using the same methodology
  - Similar timing

Retrospective Data Collection

- Selection of the patient population involves two steps
  - Selection of eligible sites
  - Identification and selection of eligible patients within each site
- Clinical data abstracted from collected medical records
  - Variables selected include endpoints that will be compared with the study endpoints

Analysis Plan

- Formalized by writing protocol for retrospective data abstraction
- Formalized retrospective data analysis
  - Statistical analysis plan - provide insights into the completeness of data for key outcomes of interest

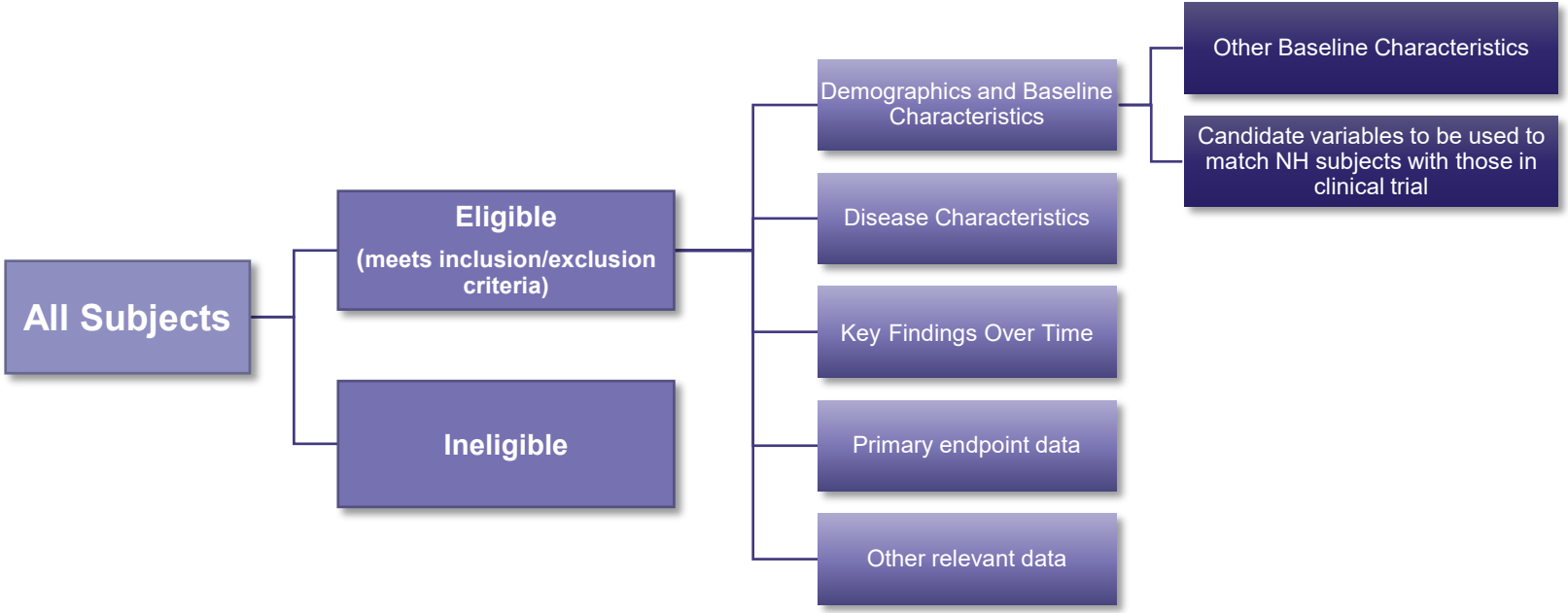
Data Abstraction: Time Point Definition Complications

- Baseline - earliest timepoint at which subject meets all inclusion criteria
- Subsequent encounters
  - Categorize into intervals
  - Selection of events for analysis

Data Abstraction: Encounters

- Baseline ➡ among eligible patients, determine the earliest time point (age, in months) at which the patient has a specific score on the validated scale at or prior to 30 months of age.
- Subsequent encounters
  - AGEDIFF = age at post-baseline assessment – age at baseline
- Identify further subset with assessment 24 (+/- 3) months after baseline assessment

Data Abstraction



Natural History Study: Why This was Acceptable?

- ☑ No feasible placebo control
- ☑ No available therapy for comparison
- ☑ Predictable disease progression
- ☑ Objective outcome measure
- ☑ Large treatment effect
- ☑ Similar population and setting

Propensity Scores

- Selection bias can occur in the treated vs. untreated group assignment
- Statistical technique to estimate the effect of a treatment/intervention by accounting for the covariates that predict receiving treatment
- In randomized studies, randomization allows for unbiased assessment of treatment effect

Propensity Score Methods

- Inverse Probability Treatment Weighting (IPTW)
- Propensity Score Matching
- Stratification
- Regression Adjustment
- Combination of methods

Part 2

Establishing the Safety of Medical Products

Marketing Authorization of a Medical Product

- When evidence on the medical product's safety and effectiveness has been obtained to meet FDA's requirements, the sponsor submits to FDA a new drug application (NDA) or Biologic License Application (BLA)
- The application is reviewed by FDA experts including chemists, pharmacologists, physicians and statisticians
- NDA/BLAs may include analyses of safety and efficacy on pooled data from all applicable clinical trials

Integrated Summary of Safety (ISS)

Goal of ISS: provide a comprehensive picture of the safety of a compound under consideration for marketing approval

- Why do we need integrated analyses of safety data?
  - Detect rare AEs & patterns in data indicative of safety signals
  - Conduct sub-group analyses with respect to key demographics and baseline characteristics
- Integrated analyses are detailed in an SAP
  - Best practice: submit to FDA & request feedback

Data Monitoring Committee (DMC)

- A group of experts (physicians and a biostatistician) independent of the sponsor/investigators of clinical trial
- Review ongoing data to monitor the safety of trial participants and ethical conduct of the clinical trial
- Review interim efficacy results to potentially stop the trial early for overwhelming efficacy or futility or modify the trial
- Meet periodically and vote to recommend whether the study should stop or continue with or without modifications

Independent Statistical Center (ISC)

- Team of statisticians/programmers and DMC coordinators
- Prepare DMC reports and set up meeting
- Facilitate efficient review of results by the DMC
- Ensure unblinded results are only accessible to DMC, ISC and others if allowed by the DMC Charter

Establishing Safety of Medical Products

Heidy Russell, Ph.D.

- Integrated analyses of safety data from studies of differing populations/disease states for submission to the FDA

Neil Wohlford, M.S.

- The crucial role of the ISC statistician supporting DMCs in ensuring patient safety and data integrity

Integrated Analyses of Safety Data from Studies of Differing Populations/Disease States for Submission to the FDA

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Key ISS Decisions

- Goal of ISS - to integrate data together to detect the safety signal
  - Decision #1: how to combine the studies in a meaningful way to achieve the goal
    - ‘Study Pools’
  - Decision #2: how to combine the treatment groups
    - ‘ISS Analysis Groups’
  - Decision #3: how to analyze the combined data

ISS Planning Considerations

ISS Planning

- Study Design
- Patient Population
- Treatment Group
- Dosage and Length of Exposure

ISS Analysis Decisions

Analysis Rules and Methods:
- Retain derivation rules from individual studies
- Apply global rules
- Apply special rules if required by study design

Study Pools:
- Pivotal studies pool
- Placebo-controlled studies pool
- Healthy volunteers pool
- All patients pool
- "Other indication" pool

ISS Analysis Groups:
- Placebo
- Drug X in "Marketed Dose"
- Drug X in Doses other than Marketed Dose
- Active Controls

Other Planning Considerations: Data Pooling Approach

Two Main Data Pooling Strategies:

- Create the integrated datasets by first pooling the individual study data without derivation rules applied and then apply derivation rules globally afterward
- Create the integrated datasets by pooling the individual study data with study-specific derivation rules already applied

Other Planning Considerations: Handling Subjects Enrolled in Multiple Studies

Each subject is counted once in the risk set for all applicable treatment groups

Analysis rules assign AEs to the applicable treatment group

Challenges for visit based variables

Other Planning Considerations: Subgroup Analyses

- Standard subgroups by demographic variables (e.g., age group, sex, race)
- Additional subgroups by baseline characteristics of interest (e.g., stratification factors at randomization, selected baseline disease history)

Other Planning Considerations: Handling of Missing Data

- Usually no imputations for missing safety data
- Exceptions:
  - Missing AE severity
  - Missing AE partial dates

Case Study

- Drug development program with 24 clinical trials to be integrated
- ISS primary objective
  - To characterize the integrated safety profile of Drug X in subjects with disease A (indication disease)
- ISS secondary objective
  - To evaluate the overall safety profile across all other studies in subjects exposed to Drug X

Case Study (continued)

Abbreviations:

R = randomized

DB = double-blind

PG = parallel-group

PC = placebo-controlled

AC = active-controlled

SP = special population (hepatic impaired subjects)

OLE = open-label extension

Case Study (continued)

ISS Planning

Study Design:

- 2 R, DB, PG, AC studies with OLE (patients with disease A)
- 2 R, DB, PG, PC and/or AC studies with placebo run-in period (patients with disease B)
- 1 R, DB, PG, AC study with OLE (patients with disease C)
- 3 parallel-group studies (HV)
- 5 single-arm studies (HV, patients, SP)
- 10 crossover studies (HV)
- 1 study with Part 1 being parallel-group design and Part 2 being crossover (HV)

Diseases A and C impact the same organ while disease B impacts a different organ.

ISS Analysis Decisions

Study Pools:

- Disease A study pool
- Disease B study pool
- Disease A & C study pool
- Healthy volunteers study pool
- All studies study pool

Analysis Rules and Methods:

- Retain the derivation rules from individual studies in patients with disease A since the other studies followed similar derivation rules and methods for analyses
- Special rules: AE assignment to treatment in crossover studies and studies with OLE

Case Study (continued)

ISS Planning

Patient Population:

- 2 studies in patients with disease A
- 2 studies in patients with disease B
- 2 studies in patients with disease C
- 17 studies in healthy adults
- 1 study in healthy adults and subjects with mild or moderate hepatic impairment

ISS Analysis Decisions

Study Pools:

- Disease A study pool
- Disease B study pool
- Disease A & C study pool
- Healthy volunteers study pool
- All studies study pool

Case Study (continued)

Treatment Group:
- Drug X
- Placebo
- Active control of interest
- Other active treatments

Dosage and Length of Exposure:
- DB 400 mg for 114 weeks with OLE
- DB 800 mg for 112 weeks with OLE
- DB 200, 400, 800 mg for 8 weeks with OLE
- DB 200, 400, 500, 800 mg for 4 weeks with run-in
- 400 mg single dose for 110 weeks
- 20, 50, 100, 250, 500, 1000 mg single dose in oral suspension form
- 500 mg single dose fasted or fed conditions

ISS Treatment Groups:
DB Placebo
DB Active Control of Interest
DB 400 mg Drug X
DB 800 mg Drug X
DB 400/800 mg Drug X
All Drug X

Case Study (continued)

Other ISS Considerations:

- Data Pooling strategy: Create the integrated datasets by pooling individual study data with study-specific derivation rules already applied
- Handling of subjects enrolled in multiple studies
  - Programmatic exploration of subjects' characteristics (i.e., sex and birth date)
  - No subjects were enrolled in multiple studies
- Subgroup analyses: age group, sex, race, baseline disease severity
- Handling of missing data: No imputations for missing data points except for applying derivation rules for AE partial dates in some of the studies to keep the analysis rule consistent across.

The Crucial Role of ISC Statistician Supporting DMCs in Ensuring Patient Safety and Data Integrity

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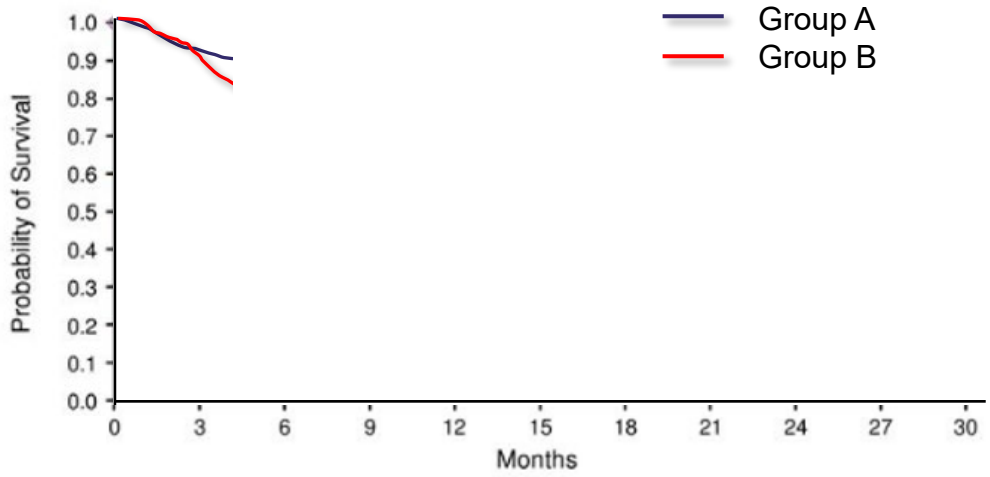
Example 1 - Oncology Trial

- Phase 3 oncology trial
- First in class therapy
- Overall Survival (OS) as Primary Endpoint
- Experimental therapy versus chemotherapy (open label)
- DMC will meet every 3 months to review masked safety
- Kaplan-Meier figure of OS for risk/benefit
- No stopping for futility
- One planned efficacy look at ~2/3 of total planned events

First Meeting



What the DMC saw

- OS Kaplan-Meier
- Still Masked

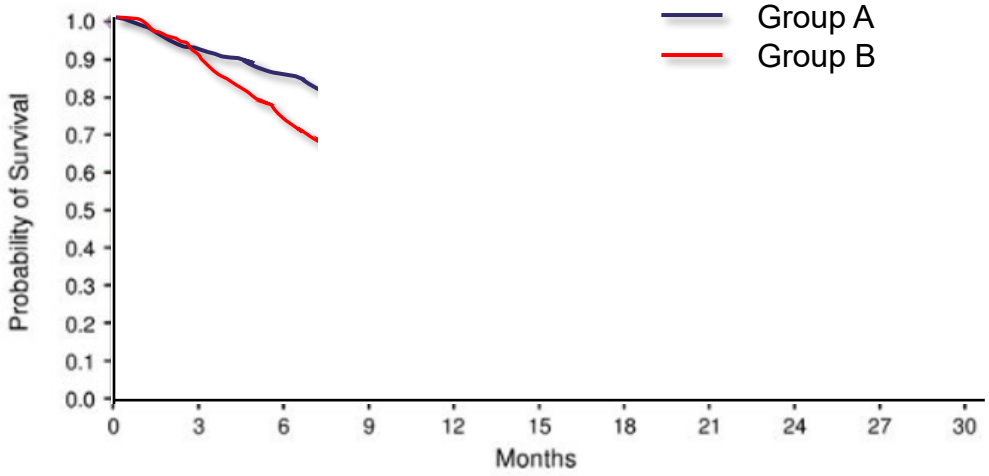
DMC Decision

- No safety concerns

Recommendation

- Continue trial

Second Meeting



What the DMC saw

- OS Kaplan-Meier
- Still Masked

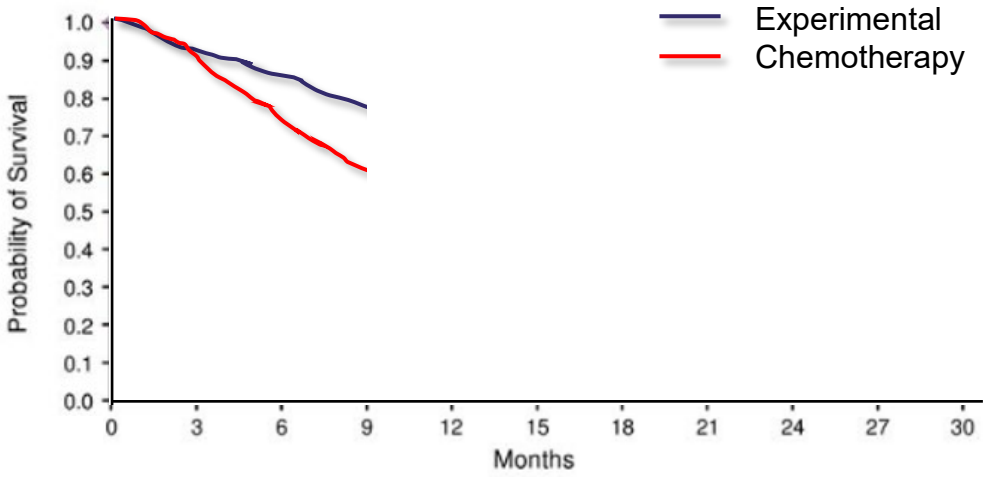
DMC Decision

- No safety concerns
- Due to difference in OS asked to be unmasked

Recommendation

- Continue trial

Third Meeting



What the DMC saw

- OS Kaplan-Meier
- Unmasked

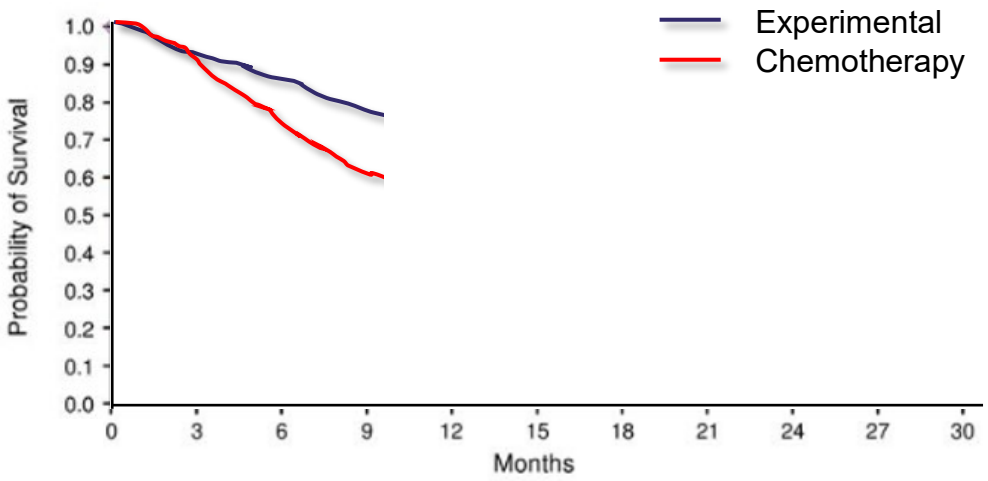
DMC Decision

- No safety concerns
- Asked to see hazard ratio in one month

Recommendation

- Continue trial

Fourth Meeting



What the DMC saw

- OS Kaplan-Meier
- Hazard ratio is 0.4 (95% CI 0.2-0.7)

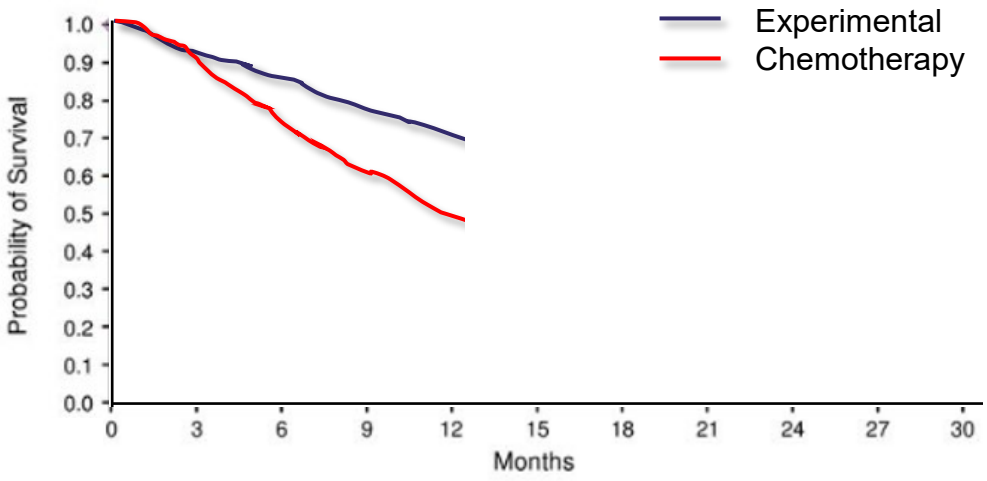
DMC Decision

- No safety concerns
- Meet in a couple months for potential ethical concerns

Recommendation

- No recommendation

Fifth Meeting



What the DMC saw

- OS Kaplan-Meier
- Hazard ratio is ~0.4
- P-value is less than 0.0001
- Crosses O'Brien-Fleming Boundary using the 1/3 planned events

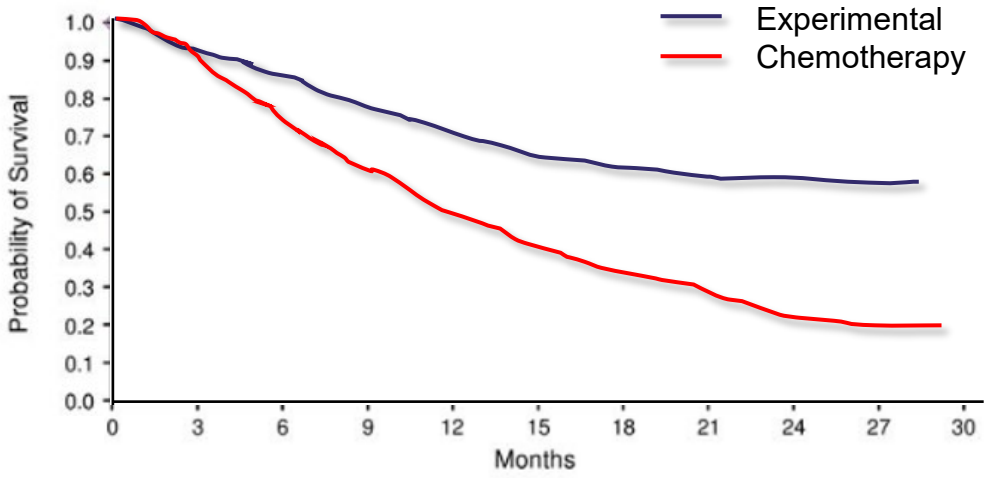
DMC Decision

- No concerns regarding safety or potentially unblinding trial

Recommendation

- Limited group in sponsor meet with the DMC to discuss unblinded data

Final Study Data



- Sponsor Executives met with DMC
- Sponsor decided to unblind the study and offer Experimental therapy to all subjects
- DMC was able to use O'Brien-Fleming framework planned for IA to benefit subjects in the trial without putting the trial results at risk

Example 2 - Hepatitis Trial

- Phase 3 trial investigating a drug for Hepatitis C
- 2 active treatment arms (high dose and low dose) versus placebo
- Open label trial
- DMC will meet every 3 months to review safety
- No interim analysis for efficacy

Safety Concern- Ad Hoc Meeting #1

- After the first DMC safety review, there is one event from a very serious but rare side effect
- DMC schedules ad hoc meeting before 2nd meeting
- Event is in the high dose group
- After discussion with sponsor, DMC decides to recommend continuing study

Safety Concern - Ad Hoc Meeting #2

- Month later a different subject in high dose arm had the same serious but rare side effect
- DMC schedules a second ad hoc meeting
- DMC decides to recommend stopping the high dose arm
- DMC discusses the recommendation with the sponsor executives and steering committee after closed session

Member of the Steering Committee Arrested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French Doctor Sentenced in Manhattan Federal Court for Insider Trading Scheme

- Member of the Steering Committee gave information regarding DMC review to a hedge fund manager
- Both pled guilty and had to pay multiple million dollar fines (hedge fund manager got jail time as well)

Why I Enjoy the Work

- Get to work on:
  - Trials in a variety of disease/therapeutic areas
  - Innovative trials that are making a difference
- Unique challenging work including:
  - Investigating potential safety issues
  - Identifying effective data displays for emerging issues
- Learn from DMC members who are leaders in their fields
- Play an important role in ensuring patient safety
- Often the first person to know if a trial will be successful

Thank You