The Role of a Clinical Statistician in Drug Development

By: Jackie Reisner
Types of studies within clinical development

- Phase I
- Phase II
- Phase III
- Phase IV
Phase I

- First Human Dose (FHD)
- Young healthy individuals
  - Usually males
  - Although sometimes patients (e.g. oncology drugs)
- Usually 12-24 patients
- Trials usually not sized based on statistics
  - Unless bioequivalence study
Phase I

- Assay drug and metabolites in biological fluids
- Define pharmacokinetics (PK)
  - mechanisms of absorption and distribution
  - chemical changes of the substance in the body (e.g. by metabolic enzymes)
  - effects and routes of excretion of the metabolites of the drug.
  - In summary “what the body does to the drug”
Define pharmacodynamics (PD)

- biochemical and physiological effects of drugs on the body
- or on microorganisms or parasites within or on the body
- mechanisms of drug action
- the relationship between drug concentration and effect
- In summary “what the drug does to the body”
Phase I

- Intense observation, usually hospitalized
- Identify and monitor target organ toxicity
  - Target organ based on toxicology results, other drugs in class
Phase I

- Types of Phase 1 Studies
  - Single dose, dose escalation
  - Multiple dose
  - Drug-drug interactions
    - May be conducted during Phase I, II or III
- Special Populations
  - Elderly, Pediatric, Hepatically Impaired, Renally Impaired
  - Usually performed during Phase III
- Bioequivalence/Bioavailability
Phase I role of statistician

- Work with PK/PD scientists to write the protocol
- Create the analysis plan
- Analyze the results using SAS (other software?)
  do you mostly write your own code, create your own tables?
- Work with PK/PD scientists to write a clinical study report
Phase I methodology

- Descriptive statistics
- PK/PD modeling of dose response
- Analysis of variance
- Mixed effects model
- Crossover studies
- Power/Sample Size calculation
### Phase I example

#### Summary statistics of plasma concentrations

<table>
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<th>Scheduled timepoint</th>
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<th>Mean</th>
<th>Geometric mean</th>
<th>%Coefficient of Variation</th>
<th>SD</th>
<th>Min</th>
<th>Median</th>
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Phase II

- Small trials (typically 100-300 patients) in patients with the disease
- Determine optimal efficacious dose (Phase IIA)
- Determine how well the drug works ~ efficacy (Phase IIB)
- Evaluate safety in patients
Phase II

- Some designed as case series, demonstrating a drug's safety and activity in a selected group of patients.
- Randomized clinical trials
  - some patients receive the drug/device and others receive placebo/standard treatment
  - far fewer patients than randomized Phase III trials
Phase II

- Powered for primary objective
  - Underpowered for secondary objectives
  - Underpowered for subset analyses

- Secondary objectives
  - Exploratory in anticipation of larger Phase III trials
  - Exploratory subset analyses
Phase II role of statistician

- Assist in design of the study
- Review literature
- Methods of analysis
- Conduct simulation analyses to help with complex designs (e.g. adaptive designs)
- Sample size
- Meet with cross-functional team, including medical and statistical consultants
- Meet with regulatory agency as appropriate
Phase II role of statistician

- Write the statistical analysis plan (SAP)
- Design tables/listings/graphs for summarizing data
- Help/prepare analysis programs
- Perform interim analysis
- Determine patients evaluability
- Analyze data, draw conclusions from analysis and write up results
Phase II methodology

- Descriptive statistics
- PK/PD modeling of dose response
- Analysis of variance
- Mixed effects model
- Crossover studies
- Power/Sample Size calculation
Phase II example
Phase III

- Large clinical trials (300-3000) in patients with the disease
- Multi-center trials
- Typically randomized, double-blind and placebo or active comparator controlled
- 2 or more trials
- Pivotal trials in registration dossier
- Most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions
Phase III

- Less homogeneous patient population than Phase II
- Relax inclusion/exclusion criteria to match treatment population
- Confirmatory of efficacy
  - Subset analyses of efficacy
Phase III

- Determine safety
- Concomitant medications
- Comorbid conditions
- Powered for efficacy
- Powered for specific safety issues
  - Subset analyses – age, race, gender
Phase III role of statistician

- Assist in design of the study
- Review literature
- Methods of analysis
- Conduct simulation analyses to help with complex designs (e.g. adaptive designs)
- Sample size
- Meet with cross-functional team, including medical and statistical consultants
- Meet with regulatory agency as appropriate
Phase III role of statistician

- Write the statistical analysis plan (SAP)
- Design tables/listings/graphs for summarizing data
- Help/prepare analysis programs
- Perform interim analysis
- Determine patients evaluability
- Analyze data, draw conclusions from analysis and write up results
Phase III methodology

- Categorical Analysis
- Logistic regression
- Relative Risk
- Mixed effects model
- Repeated measures
- Multiple Comparison
- Meta-Analysis
- Outliers
- Missing data
- Survival analysis
- Power/Sample Size calculation
Phase III example
Non-Statistical skills – Influence

- Demonstrate your value:
- Become an indispensable member of the team by offering ideas of innovative designs, analyses, data summarization methods, and data presentation
- Educate and learn!
Non-Statistical skills – relationship building

- Don’t assume your cross-functional teammates understand even the very basic concepts
- Don’t bombard them with statistical technical terminology
- Don’t make them feel stupid!

- TEACH THEM!
Non-Statistical skills - communication

- Teachers always learn. Always assume others know something you don’t.
- Never say “It can’t be done.” Suggest an alternative way. This will start a dialogue in search of the best solution.
- Don’t raise problems and walk away. Offer a solution.
- Never say “This is unclear.” Say, “I am not sure I understand. Can you explain it again to me?”
Non-Statistical skills - leadership

- Be a teacher: listen and offer your ideas (remember: they know you’re smart even if they tell statistician’s jokes)
- Be creative: offer doable solutions that will make everyone look good (“the way we have always done it” may be safe but ineffective)
- Be proactive: think ahead and prepare for the expected
- Have fun!
About me

- 7 years at mid-size Pharma company
  - NDA submission
  - FDA interactions
  - Spent almost entire time on one compound studying multiple diseases

- 3 years at large Pharma company
  - NDA submission
  - Spent almost entire time on one compound studying one disease

- 7 years at large contract research organization
  - Many different study designs
  - Many different phases of development
  - Many different therapeutic areas