The Role of a Clinical Statistician in Drug Development

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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”

Phase I

- 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

Scheduled timepoint	Summary statistics of plasma concentrations							
	n	Mean	Geometric mean	%Coefficient of Variation	SD	Min	Median	Max
Pre-dose	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
0.5 hour	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1 hour	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
1.5 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
2 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
3 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
4 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
6 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
8 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
12 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
24 hours	xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

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

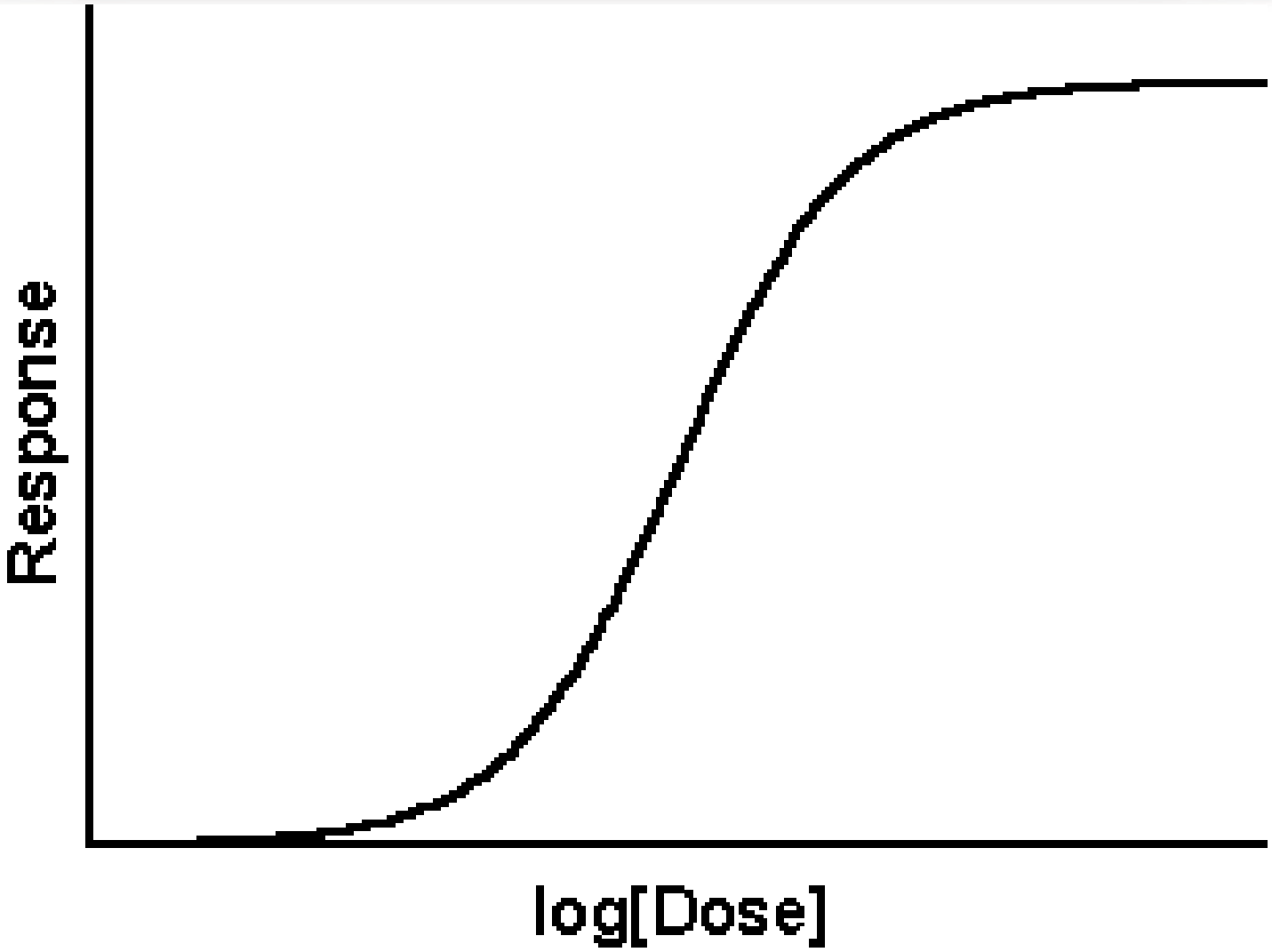
Phase II role of statistician

- 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
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Phase III role of statistician

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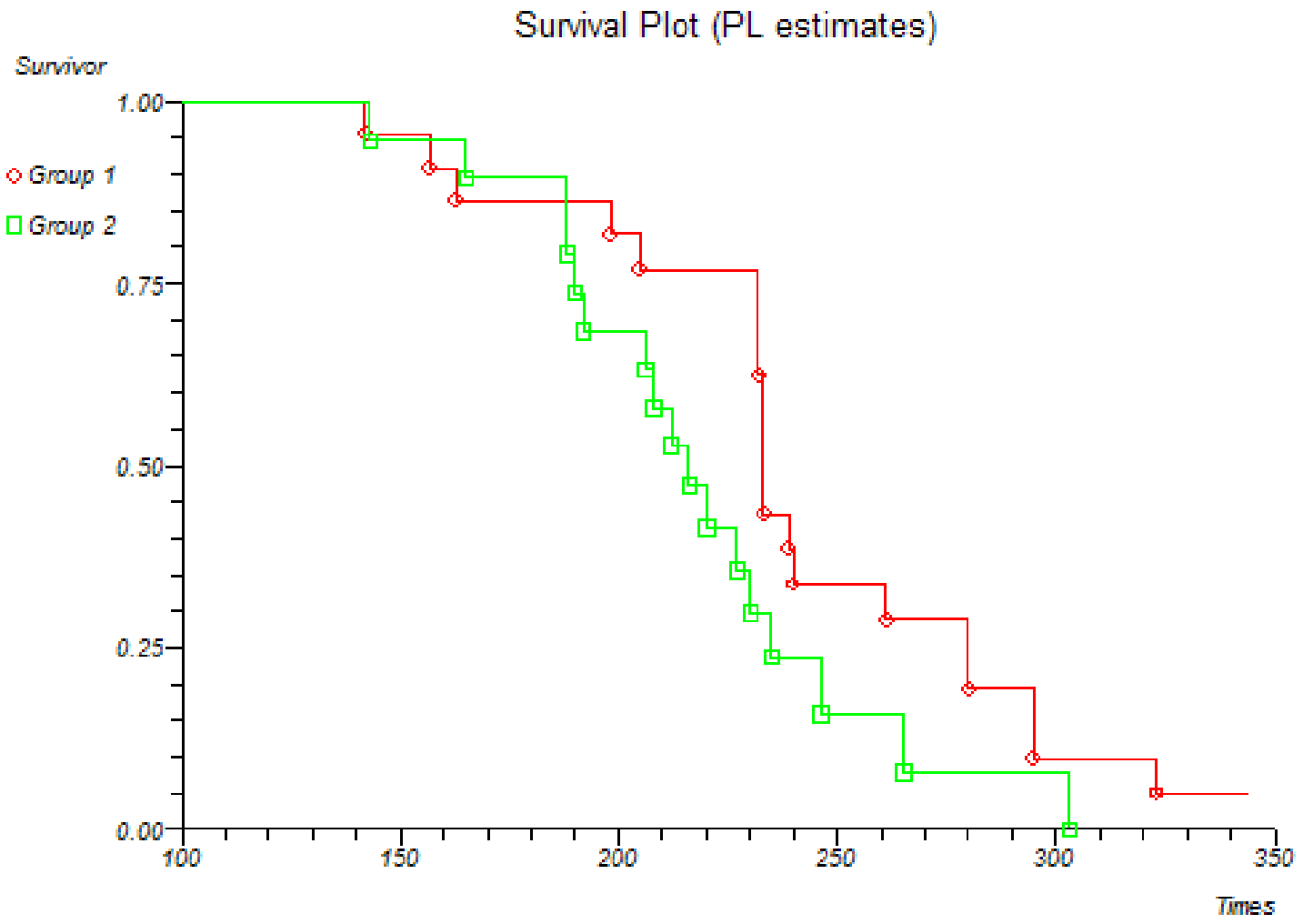
Phase III methodology

- 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