Statistical Overview for Clinical Trials
Basics of Design and Analysis of Controlled Clinical Trials

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Disclaimer

The views expressed in this presentation do not necessarily represent those of the U.S. Food and Drug Administration.
Common Study Designs

• Case-Control Study
  – Retrospective Observational Study

• Cohort Study
  – Prospective Observational Study
    • e.g. Natural History Studies

• Controlled Clinical Trial (focus of this portion of the presentation)
  – Prospective Experimental Study
  – Best design to study causality
  – Utilized for design of adequate and well-controlled trials
STUDY OBJECTIVE

• What do you want to show with this trial?
• What is the population of interest?
• What trial design will be used?
• What are the specific study hypotheses?
What do you want to show with this trial?

Efficacy

• New drug is more efficacious than current standard therapy - active controlled *superiority* trial

• New drug is more efficacious than placebo treatment - placebo controlled *superiority* trial

• New drug is not worse (in terms of efficacy), by a pre-specified and clinically relevant amount, than the current therapy - active controlled *non-inferiority* trial
  – Note that there are no placebo controlled *non-inferiority* trials!
What do you want to show with this trial?

Efficacy

• New drug is neither worse nor better than an existing drug or device (generic drug criterion) - *equivalence* trial

• Combination of a new drug and an existing drug (or two existing drugs) is better than no treatment and better than each component drug alone - *combination* trial
What do you want to show with this trial?

Efficacy

• That a new drug is more efficacious than past medical practice or experience - *historically controlled* trial

• That a group of patients do better when being treated with this drug than they did prior to treatment – “*baseline controlled* trial”
  
  – Utilized primarily in “Ultra-Orphan” Disease Trials
What do you want to show with this trial?

Safety

• That new drug is as safe (regarding specific endpoint) as current therapy or placebo
  – More difficult to determine design parameters for safety studies (may need quantitative safety review)
  – Ideally, study should assess efficacy and safety simultaneously (risk/benefit analyses)
Study Objective/Research Question

Study Population of Interest and Design
What is the population of interest? 

Study Sample

- All people who have the target disease
- A subset of the general population
  - Only patients in a certain age group
  - Only patients who have a certain severity of the disease
  - Only patients with (or without) certain other diseases
  - Only patients who are taking (or are not taking) certain other medications
What is the population of interest?  
Study Sample

- Ideal situation - randomly select patients from the population of interest (NOT Ethical!)
- Real World - we attempt to match population of interest as closely as possible (through Inclusion/Exclusion Criteria)
  - Demographics
  - Severity or progression of disease/condition
  - Other factors that may determine how well the new drug or control will work
What trial design will be used? Parallel Group Design

Baseline

Randomization

New Drug

Control Drug
What trial design will be used?

Dose Response Design

Baseline

Randomization

New Drug: Low Dose

New Drug: Medium Dose

New Drug: High Dose

Control Drug
What trial design will be used? Cross-Over Design

Baseline

Randomization

New Drug

Control Drug

Washout Period

New Drug

Control Drug
What trial design will be used? Cross-Over Design

• Efficient
  – Power a trial with less patients
• Inadvisable if the condition of interest is non-chronic or degenerative
  – Patient may never revert back to baseline and the progression of the disease may not be constant
• Must have adequate washout
  – Avoid carry-over treatment effect (“AB vs. BA”)
• Greater propensity for dropout
  – Handling missing data is more of a challenge
What trial design will be used?

• There are many other types of trial designs which we won’t go into detail e.g. various dose finding/escalation, various other dose response, factorial (for combination trials), randomized withdrawal, randomized add-on, group sequential adaptive, seamless adaptive, N of 1, enrichment, etc.

• Note that Study Duration MUST be Appropriate!
What are the specific study hypotheses?

• Primary Null Hypothesis - what you hope to disprove

• Primary Alternative Hypothesis - the desired outcome
Study Objective/Research Question

Study Population of Interest and Design

Endpoint and Measurement of Outcome
Choice of Endpoints

• The primary goal in choosing endpoint(s) is to select definitive and appropriate measures of the condition being studied

  – Should be clinically relevant
  – Should coincide with current medical practice
  – Should be measurable/interpretable
Choice of Endpoints

- Numeric, Categorical, Ordinal
- Single vs. Composite
- Objective or subjective
- Ease of measurement
- Measurement Sensitivity and Specificity (must know the variability of what is being measured)
- Time Frame - Is the study long enough to observe important changes in the endpoints? (as stated previously, study duration must be appropriate)
Measurement of Outcome

• Assessment - Determine the results (outcome of endpoint) of the investigation on study patients

• Measurement schemes to assess endpoints
  – Recording the presence or absence of a disease
  – Calculating the relative change in an endpoint
  – Grading criteria on a pre-specified scale
  – Using global criteria rather than specific parameters as endpoints
Case Report Forms

• Did the study accurately capture what it meant to measure (reliability and validity)?

• Are the questions asked in a leading or biased manner?

• Are the answers in a form that will be straightforward to analyze?

• Are the answers which were on the case report forms the values that were analyzed?
Control Group

• The drug, device, or test procedure administered in a clinical trial that serves as a standard against which experimental group are evaluated

• For non-life-threatening diseases, the control group can be a placebo

• For life-threatening diseases, the control group cannot be a placebo (due to ethical reasons) and is often the standard care for the disease
Treatment Assignment - Randomization

• Randomization attempts to assign individuals to groups (or vise-versa) without bias
  – Protects Against Selection Bias
  – Balances Treatment Groups
    • With respect to factors known or suspected to influence outcome
    • With respect to factors which are not known to affect outcome (“Magic”)

• Consequently response differences between study groups can only be attributed to the difference in the treatments themselves

• Insures the validity of results from Statistical Testing (i.e. claims of Causality are justified)
Treatment Assignment - Randomization

• Randomization may not fully eliminate the possibility that the groups may differ according to some factors that affect response to therapy (confounding variables)
  – Known prognostic/confounding factors must be measured and may need to be adjusted for in the analysis
  – Study design can control for confounding
Bias

• Bias is a (sometimes unconscious) preference of one treatment/study group over another
  – Two major classes of Bias in Clinical Research:
    • Selection Bias
    • Information/Observation Bias

• The best way to minimize bias is to institute study blinding/masking
Blinding/Masking

• Double-Blind: Neither the patient nor the investigator (nor the sponsor!) know group assignment (test or control); note that Double-Blind should really be called “Triple-Blind”

• Single-Blind: The patient does not know group assignment

• Open-Label: Group assignment known by patient, investigator, sponsor, etc.
Study Objective/Research Question

Study Population of Interest and Design

Endpoint and Measurement of Outcome

Test Drug

Control Drug

Statistical Comparisons
Statistical Analysis

• Compare group results using appropriate statistical methods
  – Test the primary hypothesis to draw conclusions regarding populations based on the sample studied
  – Measure the size of the differences between the groups or the strengths of the relationships between variables (through estimation techniques)

• Remove the effect of confounding variables if necessary
Who(+) do you analyze?

• Considerations for a Particular Analysis
  –(1) Analysis Set determination
    • Defining different sets of patients to be studied in order to minimize bias and avoid inflation of Type I Error
  –(2) Amount of Time Followed
    • Up to point of last contact/lost to follow-up, end of study/prior to follow-up, discontinuation, etc.
  –(3) Treatment Group determination
    • Randomized treatment or Actual treatment received
Who(+) do you analyze?

- Determinations made for a given consideration dependent on:
  - Type of Study
    - ‘Adequate and Well Controlled’ (21 CFR 314.126) or not
    - Blinding/Masking strategy
  - Type of Analysis
    - Efficacy Analysis
      - Type of Efficacy Analysis (superiority, non-inferiority, equivalence, etc.)
    - Safety Analysis
Who(+) do you analyze?

Efficacy Analysis

• Intention-to-Treat (ITT) Principle: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment. (ICH E9)
Who(+) do you analyze?  

Efficacy Analysis

• Consequently, the Traditional Approach

  **ITT Analysis**

  – (1) Analysis Set - **All Randomized patients (ITT)**
  – (2) Time Followed - **Until point of last contact/lost to follow-up**
  – (3) Treatment Group - **Randomized treatment**

  • (Note: Always the case for any type of Efficacy Analysis)
Who(+) do you analyze?  
Efficacy Analysis

• **Full Analysis Set (FAS):** The set of subjects that is as close as possible to the ideal implied by the Intention-to-Treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects. (ICH E9)
  
  – Typically the basis for all Efficacy Analyses (potential exception: non-inferiority and/or equivalence studies)
Who(+) do you analyze?

Efficacy Analysis

(1) Analysis Set

• All Randomized (ITT; always qualifies as a FAS)

• All Randomized + other baseline conditions [modifies ITT (mITT); may qualify as a FAS]

• All Randomized + other baseline conditions + further post-baseline conditions [further modifies ITT (mITT); usually does NOT qualify as a FAS]

(2) Time Followed

• Up to point of last contact/lost to follow-up

• Up to end of study/prior to follow-up

• Up to discontinuation time point prior to end of study

• Usually some combination of the previous bullets
Who (+) do you analyze?

Efficacy Analysis

- **Per Protocol (PP) Set (valid cases, efficacy sample, evaluable subjects sample):** The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. (ICH E9)
  - Typically the basis for Sensitivity Analysis (potential exception: non-inferiority and/or equivalence studies)
  - **Per Protocol Analysis** self-evident
Who(+) do you analyze?

Safety Analysis

• Common Approach consistent with “As-Treated Principle”

Safety Analysis
– (1) Analysis Set - All patients who receive study treatment at least once during the trial (Safety)
– (2) Time Followed - only while on treatment (with possible additional time for monitoring)
– (3) Treatment Group – Actual treatment received
When do you analyze?

• At the end of the study
• All patients reach primary assessment
• All data is in-house and cleaned (i.e. “Database Lock”)
• Before data unblinding (if blinded study)
When do you analyze?

Exceptions:

• Study Interim:
  – Conducted by Independent Data Monitoring Committees (IDMC) or Data Safety Monitoring Boards (DSMB)
    • Long study duration
    • Concerns of safety
    • Interim Analyses for Efficacy
    • Interim Analyses for Futility
    • Sample Size Re-Estimation
    • Study Adaptation
  – Note that sponsors should **ALWAYS** remain blinded to the data in these circumstances
    • IDMC/DSMB Charter
How do you analyze?

• Beyond the scope of this presentation
  – Needs a Formal Education in Statistics
“Data Dredging”

If you torture any data set long enough, it will confess to something!
Study Objective/Research Question

Study Population of Interest and Design

Endpoint and Measurement of Outcome

Test Drug

Control Drug

Statistical Comparisons

Interpretation
Interpretation

• Give clinical meaning to the results - need medical reviewer to aid in the interpretation of study results

• Draw conclusions about the meaning of any differences (or lack of) between treatment groups in study

• Generalizability to overall patient population - not always appropriate
Significant Results

Statistical Significance

• The statistical analysis of a study leads to a decision to reject or fail to reject the null hypothesis
  – Note: Failing to reject the null hypothesis is NOT the same as accepting the null hypothesis
Significant Results

Clinical Significance (more important than statistical significance)

• The amount of difference or relationship between treatments that assures that the results are clinically meaningful
Study Objective/Research Question

Study Population of Interest and Design

Endpoint and Measurement of Outcome

Test Drug

Control Drug

Statistical Comparisons

Interpretation

Extrapolation
Extrapolation

Make decisions about the meaning of the study to persons or to situations beyond those that were involved in the study.
Extrapolation

• Extrapolation of Population
  – If the conclusions of a trial are to be generalized to a larger population of patients, as is usually the case, an assumption that patients under study can be regarded as a random sample from the larger population is crucial. However, there are almost always differences between the study patients and the target population. Trials are designed to use patients most likely to respond to treatment and least likely to have issues.
Extrapolation

• Extrapolation of Dose
  – It is sometimes assumed that a higher dose will produce a greater treatment effect, or that a lower dose will produce fewer side effects. However, neither of these assumptions is always correct. Drug efficacy or safety should never be extrapolated beyond the range of doses which was studied. For the range of doses to be complete, trials during the development of a drug should evaluate doses ranging from the minimally effective dose to the maximally tolerated dose.
Extrapolation

• Extrapolation of Time
  – Drugs are studied for a very limited amount of time, often not much more than a year, but will sometimes be used for a lifetime. Does the drug effect change over time? Can a patient build up a tolerance, or can they build up a toxicity level with prolonged use? Will unexpected adverse events appear?
  – Post-Market Studies are key for informing this type of extrapolation
References

E9

E10
Thank You for Your Attention!