Application of Biostatistics in Clinical Trials

Shubha Rani, Ph.D.

Technical Director &

Head - Biometrics & Data Management

Synchron Research Services Pvt. Ltd.

Ahmedabad 380 054, India

drshubha@synchronresearch.com

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What Statistics Means to Different People?

- Spending their time compiling tables of numbers - as actuaries
- A type of accountant - a caretaker and manipulator of figures

- The physicist Ernest Lord Rutherford -

"if your experiment needs statistics, you ought to have done a better experiment"

Why Statistics is Used in Clinical Trial

- If the same treatment is given to the same subject twice the outcomes will not be identical.
- If a formulation is compared with placebo, there will be some response for placebo also.
- Patients may respond very differently to exactly the same dose of a drug
- It is fairly unusual to find that an individual's pulse rate or blood pressure is exactly the same when the measurement is repeated, even if only a few minutes later

Why Statistics is Used in Clinical Trial

There is some variation which can not be avoided.

These variations can confuse the interpretation of data and overshadow important underlying real effects.

⇓

gives rise to uncertainty

⇓

Problem in drawing meaningful conclusions directly from the experiments

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However, Timely and appropriate use of statistical techniques has proven to be a great help in making wise decisions in the presence of uncertainty

Why Statistics is Used in Clinical Trial

- Test whether the new treatments / new diagnostics / new vaccine works or not?
- Ideally clinical trial should include all patients.
  - Is it practically possible? No
- We test the new treatments / new diagnostics / new vaccine on a representative sample of the population

Statistics allows us to draw conclusions about the likely effect on the population using data from the sample

BUT ALWAYS REMEMBER...

Statistics can never ***PROVE*** or ***DISPROVE*** a hypothesis, it only suggests to ***accept or reject the hypothesis*** based on the available evidences

Statistics can be a very useful tool

to make decisions,

but it should not be used as only yardstick

Emergence of Statistics in Clinical Trial

- The use of statistics to support discovery and testing of new medicines has grown exponentially since the Kefauver-Harris Amendments, which became effective in 1962.
- The Kefauver-Harris Amendments required drug sponsors to prove a product's safety and efficacy in controlled clinical trials in order to market the product.
- Statistics, as a discipline, has broadened its scope significantly over the past 47 years.

Emergence of Statistics in Clinical Trial

- Today it has become a necessity to improve the quality of any experiment by including statistical inputs.
- Statistical design and analysis are essential tools for clinical trials in order to properly develop drugs.
- In many countries, the FDA has a well established statistical group.

Various Phases of Clinical Trial

- Phase 1
  - First introduction of investigational new drug in humans usually performed in healthy volunteers
  - Used to determine absorption, metabolism, distribution, elimination in humans
- Phase 2
  - Early controlled clinical trials, dose response
  - Preliminary efficacy of drug in patients
  - Determine common short term side effects

Various Phases of Clinical Trial

- Phase 3
  - Pivotal information on safety and efficacy
  - Further information on dose
  - Adequate and well -controlled trials
  - Basis for extrapolating results to general population and product labeling

- Phase 4 - post-marketing

Different Statistical Skills for Different Phases of Clinical Trial

- Despite common statistical principles, different phases of clinical testing focus on different statistical skill sets.
- For early proof-of-concept and dose-ranging efforts, study designs could be more flexible and the goal is to learn as efficiently and effectively as possible.
- The purpose of this phase of development is primarily to generate information to aid internal decisions, the developers are free to use innovative approaches as long as they can successfully defend the decisions that become the basis for later development.

Different Statistical Skills for Different Phases of Clinical Trial

- Statistical approaches for the confirmatory phase need to be carefully pre-planned, pre-specified.
- We need to decide *a priori* study designs, primary endpoints, primary analysis population, success criteria, handling of missing data, multiple comparisons, plus many others.
- ICH E9 (1998) gives a very detailed description of all aspects of trial design and analysis. When adaptation is planned, the rule needs to be clearly specified in advance. When interim analysis is anticipated, a sponsor's access to the interim results needs to be tightly controlled.

What Statistics Can Answer

- What exactly do we want the statistics to assess
- Assess the weight of evidence that a treatment works (or doesn't)
- Test to see how likely it is that this effect would have been seen by chance
- Give an estimate (and likely range) of the treatment effect

Why statistics is used at all

In God we trust. All others must bring data.

Designing of Clinical Trials

The best time to contemplate the quality of evidence from a clinical trial is before it begins. Conceptualizing and designing good clinical trials is never an accident but results from careful planning.

Steven piantadosi Clinical Trials: a Methodologic Perspective

Designing of Clinical Trials

- Formulation of the problem
- Method selection
  - Design selection
  - Analysis of the data

Formulating The Problem

- What is the question
- What is the treatment
- What are the response variables
- What is the population
- What is the design
- What is the necessary sample size

What Is The Question?

- Each clinical trial must have a primary question.
- The primary question, as well as any secondary or subsidiary questions, should be carefully selected, clearly defined, and stated in advance.
- All clinically important outcomes should be considered.
- Patients may live but with nasty disfiguring painful side effects

What Is The Treatment

- Dose of treatment
- Frequency of administration
- Time of initiation
- Duration of treatment
- Logistics of blinding in drug studies
- Determine the availability of the treatment
  - If not licensed, special approval

What Are The Response Variables

Outcomes measured during the course of the trial

For example:

- Symptomatic relief
- A lab measurement
- Total mortality
- Death from a specific cause
- Incidence of a disease
- A complication or specific adverse effect of diseases

What Are The Response Variables

- In general, a single response variable identified for the primary question
- Primary response variable must be capable of being assessed in all participants, and should be measured the same way.
- Response variables should be capable of unbiased assessment

What Is The Population

- Target population
- The groups should be similar at the start of the trial
  - Homogeneous in age, body weight etc.
  - Possible to adjust for baseline
  - Sex
  - Ethnic group
- Aside from the experimental intervention, the groups should be treated equally?
  - Some sort of treatment protocol
  - Measure important co-interventions

Design of Experiment

- Designing an experiment means deciding how the measurements should be taken to answer a particular question in a valid, efficient and economical way
- Identify the sources of variation that can be considered important and choose a design that will allow to measure the extent of the contribution of these sources to total variation

Possible Results of Design

Decision \ Truth	No Better	Better
No Better	a	B
Better	C	d

a and *d* are correct decisions.

B = declare the treatment is worthless when it has promise. (usually called the 'type II error')

C = declare the treatment has promise when it's worthless. (usually called the 'type I error')

Goal of Designs

Enable the treatment comparison be obtained in a manner …

- That is ethically acceptable
- That allows one to make an **unbiased** or fair evaluation
- That is the most "efficient" possible

Fundamental Points of Study Design

Control group: A control group be used against which the new intervention can be compared.

- Simple Control: The control group receives no treatment.
- Placebo Control: The control group receives a treatment that is identical in outward appearance, but has no effect. Sugar pills, saline injections.
- Existing Treatment: The control group receives a different treatment, often the current standard treatment.

Fundamental Points of Study Design

Randomization:

- The preferred way of assigning participants to control and treatment groups.
- Eliminates assignment bias
- Ensures comparable study groups
- Allows for use of valid statistical tests
- Requires a predetermined ratio of allocation (usually equal allocation)

*Day of week & visit number (e.g., even gets A and odd gets B) are NOT random assignments

Fundamental Points of Study Design

Replication:

- Apply each treatment to more than one experimental unit within the experiment.
- Reduce chance variation and measure variability.

Blinding

- Blinding is the masking of the treatment assignment among particular individuals.
- This process helps to control the potential for bias because individuals tend to change their behaviors based on treatment information.

Unblinded / Open Label

- May be simpler to execute
- Better reflects actual clinical practice
- Introduces bias

Single Blind

Patient is blinded to treatment but investigator is not.

- Puts investigators at ease
- Easier to administer
- May introduce investigator bias

Double Blind

Patient and investigator are blinded to treatment.

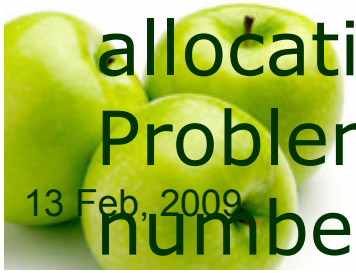
- Reduces risk of bias
- Requires outside personnel to monitor safety and treatment allocation
- May be very difficult to accomplish in studies of some treatments

Basic Study Designs

- Randomized control studies
- Nonrandomized concurrent control studies
- Nonrandomized Historical controls
- Cross-over designs
- Factorial design
- Adaptive designs

Simple Randomization

- Eligible, consenting patients are assigned treatment in a random fashion regardless of their characteristics.
- For equal allocation design, every patient has an equal chance of receiving any treatment.
- The less equal the allocation, the lower the statistical power becomes.
- With large numbers of patients, random allocation yields groups almost equal in size. Problems can arise in studies with small numbers of patients.



Blocked Randomization

1. A block size is chosen.
2. Within this block size, equal allocation of treatment is provided.
3. Treatments are randomized within blocks, and/or the blocks are randomized.

In our multicenter trials, we usually block within each center.

Blocked Randomization—Example

- Within a block size of 4 patients, possible blocks would include:
  AABB ABBA ABAB BABA BAAB BBAA
- The first 12 patients may be:
  BABA ABBA BABA
- If study was discontinued after 10 patients were enrolled, you would have equal allocation:
  B A B A A B B A B A

Blocked Randomization

Used to ensure:

- A fairly equal distribution of treatments (across trial, within each center)
- A fairly equal distribution of treatments in case the trial ends early (also at time of DSMBs)
- That there is no temporal problem in case of slow enrollment

Stratification

- For the stratification variable, predetermine the proportion of patients who will be enrolled from each strata
- Use block randomization within each strata.
- This process ensures a balance among key characteristics that are expected to affect the outcome of the study.

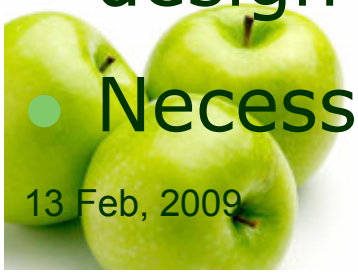
Stratification—Example

- If in a trial of comparing treatments A & B, the sample size was calculated to be 10,000 patients.
- Investigators wish to ensure that the study population should have 20% female.
- Therefore, the study will be designed as follows:

	Males	Females	Total
A	4000	1000	5000
B	4000	1000	5000
Total	8000	2000	10,000

Group Allocation Design

- Uses groups of individuals as the randomized sampling units
- Allows mass intervention
- Avoids contamination
- Differing response rates across sampling units can affect ability to detect differences
- Requires more patients than an individual design
- Necessitates cluster sampling methods



Nonrandomized—Concurrent Controls

- Overcomes physicians' ethical concerns regarding randomization
- Overcomes patients' fears about random treatment allocation
- Allows for selection of patients to receive the treatment and then matches on controls
- Reduces cost
- May result in incomparable treatment groups

Nonrandomized—Historical Controls

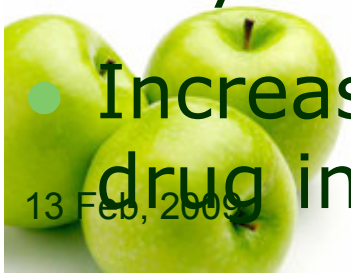
- Requires that controls be comparable in key characteristics to the current treatment group
- Allows all new subjects to receive the intervention
- Reduces both cost and the number of patients needed to treat
- May be more representative of the population of interest

Nonrandomized—Historical Controls

- Encourages patient participation
- Likely to introduce biases
  - Control data may vary widely
  - Patient management may have changed
  - Methods for selecting patients may have changed
  - Diagnostic criteria may have shifted
  - Control data may have been collected non-uniformly

Factorial Design

- Studies two or more types of treatments simultaneously
- Randomizes patients to both treatments
- Performs two experiments in one, using fewer patients than would be necessary for two separate studies
- Adds complexity to the study
- May negatively affect recruitment
- Increases potential for adverse events doe to drug interaction



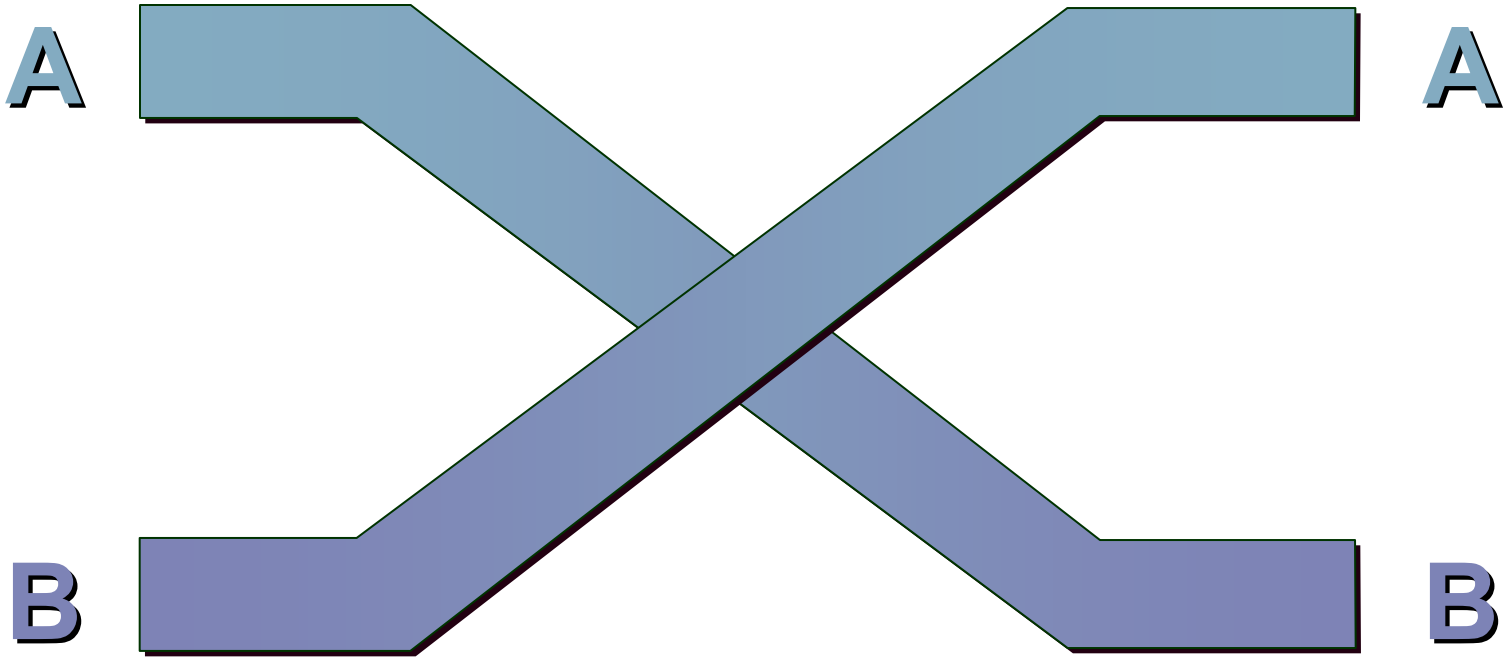
Factorial Design

	A	No A
B	A & B	No A & B
No B	A & No B	No A & No B

Crossover Design

- Each subject is his/her own control.
- Design reduces variability and sample size.
- Design must assume that the treatment effect does not carry over to the second period.
- Fatal endpoints cannot be used (no crossover!).

Crossover Design



Adaptive designs

- Suitable for rapidly evaluated outcomes
- Minimizes numbers of subjects when clear differences between treatments

Analysis of The Data

- Different types of analysis are appropriate depending on design and the sort of outcome measure.

- One should be careful in
  - Choosing the appropriate test
  - Interpreting the results correctly

Designing of Clinical Trials

No one can guarantee that the results of any piece of research will prove useful, but at least it should not be doomed from the start to prove nothing

FINAL WORDS

- The design of clinical trial is vital and mistakes can be very costly!
- Statistics helps in looking at the strength of the evidence for a given hypothesis in the light of the given data observed in the trial.
- Calculations are based on formulas, but the application of the appropriate formulas and the interpretation of the results is an art rather than a science
- Significance is not evidence of absence of effect, merely absence of evidence of an effect.

"To call in the statistician after the experiment is done may be no more than asking him to perform a post mortem examination: he may be able to say what the experiment died of."

Sir R.A. Fisher

Indian Statistical Congress, Sankhya, c. 1938