BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024

Tamil Nadu, India.

Programme: M.Sc. Statistics

Course Title: Survival Analysis and Clinical Trials

Course Code: 23ST04DEC

Unit-V

Design of Clinical Trials

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UNIT – V

Design of Clinical Trials

Clinical Trial Design

Clinical trial design is an important aspect of interventional trials that serves to optimize, ergonomise and economize the clinical trial conduct. The purpose of the clinical trial is assessment of efficacy, safety, or risk benefit ratio. Goal may be superiority, non-inferiority, or equivalence.

There are several types of clinical trial designs. These may be classified as follows:

1. Regarding the presence (or absence) of a control group as comparator to the investigational treatment:
    - Uncontrolled trials
    - Controlled trials
2. According to the method used to allocate participants to a treatment or control group, we will have:
    - Non-randomized trials
    - Randomized trials
3. Based on participants' or investigators' awareness of the treatment group to which participants have been allocated, we will have:
    - Open-label studies
    - Blind studies
4. Based on the significance of the result expected to be found between treatment and control groups:
    - Superiority trials
    - Bioequivalence trials
    - Non-inferiority trials
5. Based on the treatment structure:
    - Parallel trials
    - Cross-over trials
    - Sequential trials

Based on the presence or absence of a control group:

Uncontrolled Trials:

In this type of trial, the efficacy or toxicity of a medication is compared in a group of patients without a control group. Results obtained can be compared with those obtained in previous studies or with results published by other investigators. Uncontrolled trials are typical in Phases I and II to investigate tolerated dosing intervals or pharmacokinetic characteristics of a new drug.

Controlled Trials:

In these trials, the study group is compared with a control group, which may receive placebo or another effective treatment. Both groups are studied simultaneously. This type of trial is the most common in phase III.

Based on the method used for participant allocation:

Non-Randomized Clinical Trials:

In this type of trials, it is the investigator who allocates participants to the different treatment groups or arms, or to control.

Randomized Controlled Clinical Trials:

In these trials, participants are randomly allocated to treatment groups or arms, or to control. The process of randomly allocating a participant to either the treatment arms or to control is called randomization. In order to do this, different tools can be used, such as closed envelopes, computer-generated sequences, random numbers, etc. Randomization prevents participants from decoding the sequence and learning what group they were assigned to, and it prevents investigators from allocating patients to the different groups in a biased way.

Based on participants' or investigators' awareness of the group assigned:

Open-Label Studies:

Trials in which investigators are aware of what group patients were allocated to. In this type of studies, the use of subjective variables by investigators may involuntarily condition results based on the information that the investigator has regarding the patient’s treatment.

Blind Studies:

This is a method used in clinical trials to reduce the risk of bias, which may be intentional or not, when trial participants and/or investigators are aware of which participants are receiving treatment (or placebo).

- **Single-Blind Study:** In this case, participants do not know to which group they have been assigned, but investigators do.
- **Double-Blind Study:** Neither the research team nor the participants are aware of which group patients were assigned to, so no one knows what treatment the patient is receiving.

Based on the significance of the result expected to be found between groups:

Superiority Trials:

Studies intended to show that the investigational drug is better than the control.

Equivalence Trials:

Studies intended to show that the final result is similar (neither worse nor better) than the control.

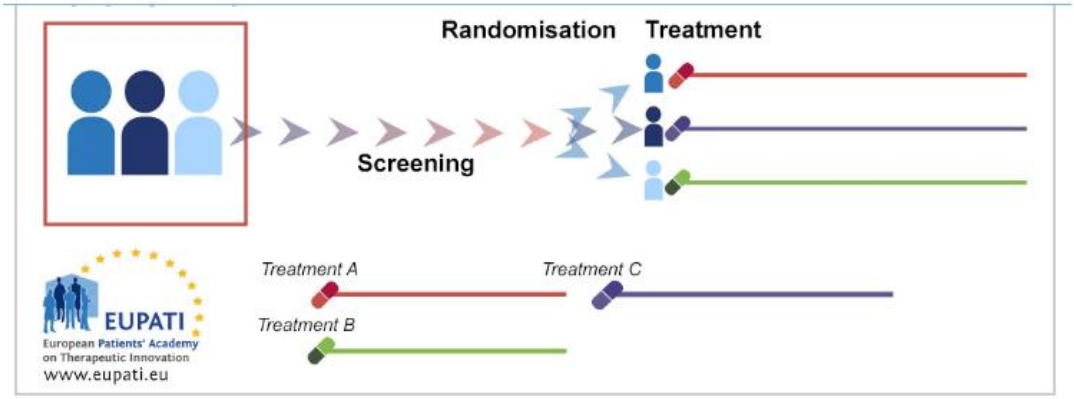
Non-Inferiority Trials:

Studies intended to show that the investigational drug is not worse than the control.

Based on the structure of the treatment:

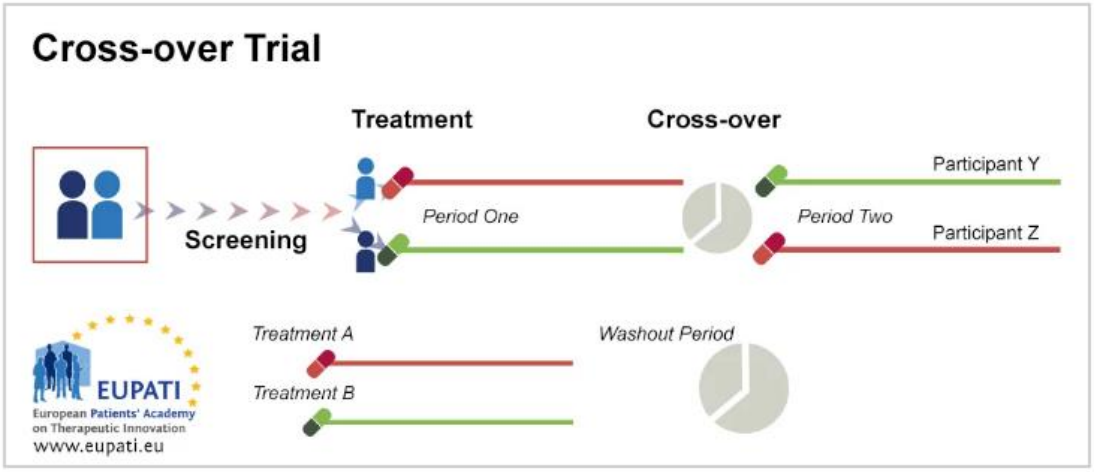
Parallel group trial design

In this type of design, each group of patients receives only one treatment. It is used for comparative trials.



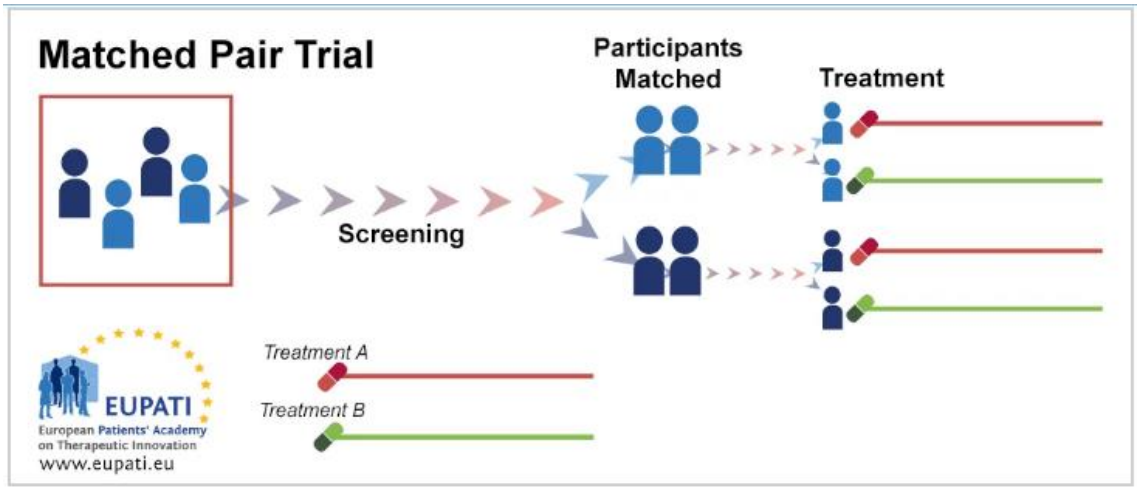
Cross-over trial design

Each patient consecutively receives each of the study treatments. Cross-over designs may raise an ethical issue when a patient that was improving with one treatment is switched over to the other.



Matched pair trial design

Patients are arranged in pairs, one being allocated to the investigational group and the other to the control group. Results are analyzed as they are obtained and added to previous data. The size of the sample (the number of patients to be included) is not predetermined but depends on accumulated results.



Stratification

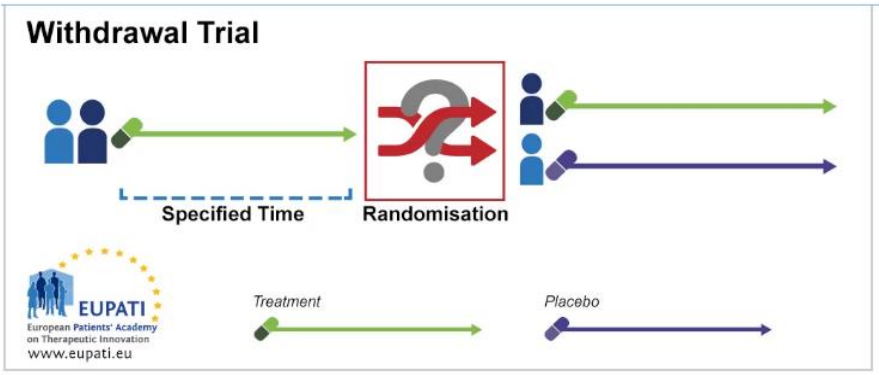
Stratification also allows for comparison between similar study participants who undergo different study procedures. All study participants are grouped according to one or more factors (for example, age, gender, lifestyle factors, concomitant medication) before being randomised. This ensures balanced allocation within each combination.

Cluster sampling

Randomised trials can also use cluster sampling. In cluster sampling, suitable geographical areas are found (for instance, city, region, etc.). A number of these geographical areas are then randomly chosen. For each of these chosen geographical areas, a proportionate subsample from the members of the study sample in that area are chosen, and these subsamples are then combined into a sample group.

Withdrawal trials

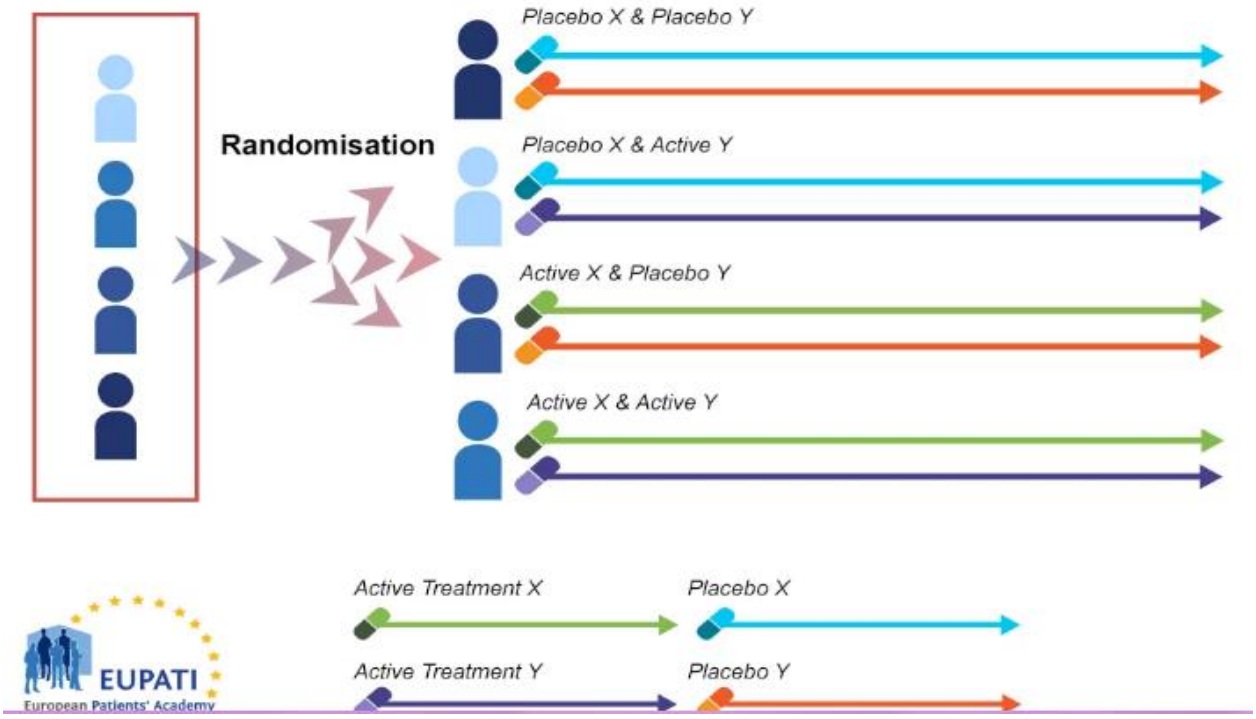
In a withdrawal trial, the participant receives a test treatment for a specified time and are then randomised to continue either with the test treatment or a placebo (withdrawal of active therapy).



During a withdrawal trial, after the first specified period of time has elapsed, participants are randomised into two groups, one of which receives a placebo instead of continuing to receive the active treatment.

Factorial design

Factorial clinical trials test the effect of more than one treatment. This allows assessment of potential interactions among the treatments.

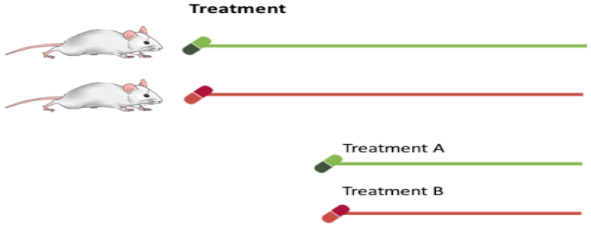


An example of a trial using a 2×2 factorial design.

Parallel vs. Crossover Study

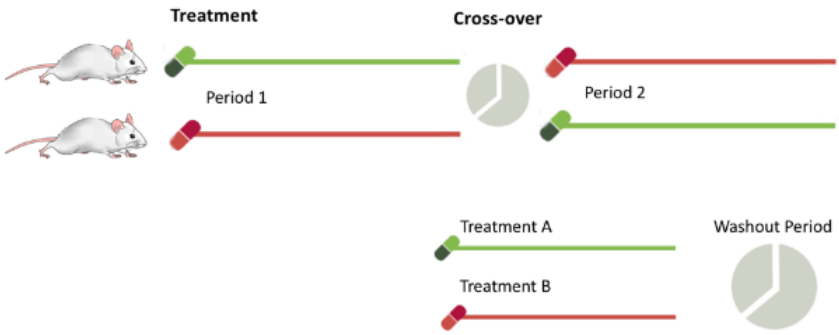
Parallel Study

A parallel study is also referred to as "between patient" or "non-crossover" study. It is defined as a type of clinical study, in which two separate treatment arms, A and B, are given so that one group receives only treatment arm A while another group receives only treatment arm B. The two treatment groups of a parallel study can either be composed of two completely separate treatments (i.e. different drugs), or simply different doses of the same drug. A major characteristic of a parallel study is randomization, which ensures accuracy of the results and lower risk of being biased. Generally, a placebo or active control are used as control groups in parallel studies.



Crossover Study

A crossover study, also known as a crossover trial, is a longitudinal study where subjects receive an array of different treatments or exposures. In a crossover study, all subjects should receive the same number of treatments and should be involved in the same number of periods, which is the so-called "balance" required in practically all crossover designs. Unlike the parallel study, at first one treatment group of a crossover study receives treatment A and subsequently followed by treatment arm B while the other group receives treatment B followed by treatment arm A. Actually, in most of the crossover studies, each subject receives all treatments. Many important crossover studies are controlled experiments, although it can be observational studies. Crossover studies are common in many scientific disciplines, including medicine.



Advantages of Parallel and Crossover Study

There are certain characteristics that allow for differentiation between parallel and crossover studies. The advantage of a parallel design is that it provides the best way to assess the effect of a drug on survival, if that is the critical endpoint in its evaluation. For instance, if there are any concerns about carryover effects, a parallel study is considered more appropriate. Similarly, if the disease being studied has a possible chance of progression during the time in which the study occurs, parallel study might also be more beneficial. However, crossover study has two advantages over parallel study. First, the influence of confounding covariates is decreased because each crossover subject serves as its own control. Second, optimal crossover studies are statistically efficient and thus require fewer subjects than do non-crossover designs.

<u>Cross-Sectional Study Vs Longitudinal Study</u>

Cross-Sectional Study:

Cross-sectional study is defined as an observational study where data is collected as a whole to study a population at a single point in time to examine the relationship between variables of interest.

1. In an observational study, a researcher records information about the participants without changing anything or manipulating the natural environment in which they exist.

2. The most important feature of a cross-sectional study is that it can compare different samples at one given point in time. For example, a researcher wants to understand the relationship between joggers and level of cholesterol, he/she might want to

choose two age groups of daily joggers, one group is below 30 but more than 20 and the other, above 30 but below 40 and compare these to cholesterol levels amongst non-joggers in the same age categories.

3. The researcher at this point in time can create subsets for gender, but cannot consider past cholesterol levels as this would be outside the given parameters for cross-sectional studies.

4. Cross-sectional studies allow the study of many variables at a given time. Researchers can look at age, gender, income etc in relation to jogging and cholesterol at a very little or no additional cost involved.

5. However, there is one downside to cross-sectional study, this type of study is not able to provide a definitive relation between cause and effect relation (a cause and effect relationship is one where one action (cause) makes another event happen (effect), for example, without an alarm, you might oversleep.)

6. This is majorly because cross-sectional study offers a snapshot of a single moment in time, this study doesn't consider what happens before or after. Therefore in this example stated above it is difficult to know if the daily joggers had low cholesterol levels before taking up jogging or if the activity helped them to reduce cholesterol levels that were previously high.

Longitudinal Study

Longitudinal study, like the cross-sectional study, is also an observational study, in which data is gathered from the same sample repeatedly over an extended period of time. Longitudinal study can last from a few years to even decades depending on what kind of information needs to be obtained.

1. The benefit of conducting longitudinal study is that researchers can make notes of the changes, make observations and detect any changes in the characteristics of their participants. One of the important aspects here is that longitudinal study extends beyond a single frame in time. As a result, they can establish a proper sequence of the events occurred.

2. Continuing with the example, in longitudinal study a researcher wishes to look at the changes in cholesterol level in women above the age of 30 but below 40 years who have jogged regularly over the last 10 years. In longitudinal study setup, it would be possible to account for cholesterol levels at the start of the jogging regime, therefore longitudinal studies are more likely to suggest a cause-and-effect relationship.

3. Overall, research should drive the design, however, sometimes as the research progresses it helps determine which of the design is more appropriate. Cross-sectional studies can be done more quickly as compared to longitudinal studies. That's why a researcher may start off with cross-sectional study and if needed follow it up with longitudinal studies.

Differences between Cross-Sectional Study and Longitudinal Study

Cross-sectional and longitudinal study both are types of observational study, where the participants are observed in their natural environment. There are no alteration or changes in the environment in which the participants exist.

Despite this marked similarity, there are distinctive differences between both these forms of study. Let us analyze the differences between cross-sectional study and longitudinal study.

Cross-sectional study	Longitudinal study
Cross-sectional studies are quick to conduct as compared to longitudinal studies.	Longitudinal studies may vary from a few years to even decades.
A cross-sectional study is conducted at a given point in time.	A longitudinal study requires a researcher to revisit participants of the study at proper intervals.
Cross-sectional study is conducted with different samples.	Longitudinal study is conducted with the same sample over the years.
Cross-sectional studies cannot pin down cause-and-effect relationship.	Longitudinal study can justify cause-and-effect relationship.
Multiple variables can be studied at a single point in time.	Only one variable is considered to conduct the study.
Cross-sectional study is comparatively cheaper.	Since the study goes on for years longitudinal study tends to get expensive.

Phases of clinical trials

Clinical drug development often consists of five phases ((Phase 0 to IV). Clinical trials happen in these phases to answer different questions and each phase builds on the results of previous phases.

Phase	Study goal	Dose
Phase 0	Pharmacokinetics, particularly oral bioavailability and half-life of the drug	Small, sub therapeutic
Phase I	Dose-ranging on healthy volunteers for safety	Often sub therapeutic, but with ascending doses
Phase II	Testing the drug on participants to assess efficacy and side effects	Therapeutic dose
Phase III	Testing the drug on participants to assess efficacy, effectiveness, and safety	Therapeutic dose
Phase IV	Post marketing surveillance in public	Therapeutic dose

The phase of the study and clinical trial designs

Drug development is ideally a strategical, step-wise procedure in which researchers use information from previous studies to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational medicine or treatment or device in the early stages of development and to plan an appropriate development based on this profile.

The initial phase of trials provides an early evaluation of short-term safety and tolerability and may provide pharmacodynamic and pharmacokinetic information required to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials.

Phase 0 trials and clinical trial designs

Phase 0 is a designation for optional exploratory trials to conduct in accordance with the **United States Food and Drug Administration's (USFDA)**.

- These studies are also known as human micro-dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies.
- Phase 0 studies generally use only a few small doses of a new drug in a few people.
- These studies give no data on safety or efficacy, as the dose is too low to cause any therapeutic effect.

Researchers use Phase 0 trials to

- Determine drug pharmacokinetics.
- Pharmacologically significant doses of the drug.
- Understand the drug mechanism of action.
- They help in making go/no-go decisions on relevant human models instead of relying completely on animal data.

An example of these studies includes the studies that test whether the drug reaches the tumor, in case of cancer clinical trials, how the drug acts in the human body, and how cancer cells in the human body respond to the drug.

Distinctive features of phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (like 10 to 15) to gather preliminary data.

The ideal requirements for evaluation of a new drug under phase 0 investigations can be

- Pharmacodynamic activity of the drug.
- The broad therapeutic window of a drug.
- The drug candidate should be non-toxic at a dose level and should expose for a short duration, that is, about a week, on a limited number of volunteers (like 10 to 15).

Phase I trials and clinical trial designs

The primary aims of phase I clinical trials are to determine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) of a compound, and early measurement of drug activity.

Designs used in Phase I trials

- **Single ascending dose (Phase Ia):** These are the studies in which a small group of subjects receives a single dose of the compound in a clinical setting, usually a Clinical Research Unit (CR0U). Perform close safety monitoring and usually PK assessments for a predetermined time. Subjects are usually randomly assigned to treatment using computer-generated randomization codes to minimize the effect of bias.
- **Multiple ascending doses (Phase Ib):** These studies elucidate the PK and PD of multiple doses of the compound.

Phase II trials and clinical trial designs

Phase II trials usually start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients. An important goal for this phase is to determine the dose and regimen for phase III trials.

Initial therapeutic exploratory studies may use a variety of clinical study designs, including concurrent controls and comparisons with baseline status. Subsequent trials are usually randomized and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication.

- Early studies in this phase usually utilize the dose-escalation designs to give an early estimate of dose-response and later studies may confirm the dose-response relationship for the indication in question by using recognized parallel dose-response designs.
- Researchers may perform confirmatory dose-response studies in phase II or leave for phase III.
- Doses in phase II are usually but not always less than the highest doses used in phase I.

Phase II studies sometimes consist of **Phase IIa** and **Phase IIb**. However, there is no formal definition for these two sub-categories, but

- Phase IIa studies are usually pilot studies designed to demonstrate clinical efficacy or biological activity (also known as **proof of concept' studies**)
- Phase IIb studies determine the optimal dose at which the drug shows biological activity with minimal side-effects (**definite dose-finding** studies).

Trial designs in Phase II studies

Some phase II trials are designed as case series to demonstrate drug safety and activity in a selected group of participants. Other phases II trials are designed as randomized controlled trials, where some patients receive the drug/device, and others receive a placebo or the standard

treatment. Randomized phase II trials generally have fewer patients than randomized phase III trials.

Adaptive trial designs

The adaptive clinical trial design is a new design that helps to reduce the costs of phase II testing by providing an earlier determination of futility and prediction of phase III success, reducing overall phase II and III trial participant sizes, and shortening overall drug development time.

Phase III trials and clinical trial designs

Phase III usually is considered, to begin with, the initiation of studies in which the primary objective is to demonstrate or confirm the therapeutic benefit of a treatment/drug/device, etc.

- Studies usually in phase III are designed to confirm the preliminary evidence accumulated in phase II that a drug is safe and effective for use in the intended indication and recipient population.
- These studies intend to provide an adequate basis for obtaining regulatory and marketing approval.
- Studies in phase III may also further explore the dose-response relationship, or explore the drug's use in wide populations, in different stages of the disease, or combined with another drug.
- For drugs for long period administration, trials involving extended exposure to the drug are ordinarily conducted in phase III, although researchers may start in phase II.
- These studies carried out in phase III complete the information needed to support adequate instructions for use of the drug.
- This stage of drug assessment is conducted in a larger and often more diverse target population to demonstrate and/or confirm the efficacy and to identify and estimate the incidence of common adverse reactions.

Trial designs in Phase III studies

Comparative efficacy trials (referred to as "superiority" or "placebo-controlled trials") that compare the intervention of interest with either standard therapy or placebo are common Phase III designs.

Phase IV trials and clinical trial designs

Phase IV trials are conducted generally after the drug approval. Therapeutic use studies go beyond the prior demonstration of the drugís safety, efficacy, and dose definition. These studies are also called pharmacovigilance studies.

These studies are not considered necessary for approval but are often important for optimizing the drug's use.

Commonly conducted studies include

- Additional drug-drug interaction,
- Dose-response or safety studies, and
- Studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.

These studies help to detect any rare or long-term adverse effects over a much larger patient population and longer period than was possible during the Phase I-III clinical trials.

Clinical trial designs in Phase IV studies

- Pharmacovigilance studies can include observational or intervention studies. Common designs in these phase include case-control studies, cohort studies (cohort event monitoring), and spontaneous (passive) reporting schemes.
- In some circumstances, RCTs might also be possible.

Bioavailability and bioequivalence studies

These are studies to measure bioavailability and/or establish bioequivalence of a compound which are important elements in support of regulatory submissions.

- For orally administered compounds, bioavailability studies elucidate the drug release process from the oral dosage form and move to the site of action within the body.
- Bioavailability data may provide an estimate of the fraction of drug absorbed, as well as its subsequent distribution and elimination.
- This can either be absolute bioavailability (the compound is compared to IV administration, assumed to be 100% bioavailable) or relative bioavailability such as the compound is compared to another formulation or non-intravenous route of administration.
- Researchers also perform bioequivalence studies for generic drugs which contain the same active ingredients as the original formulation, which is no longer under patent protection.
- Bioavailability and bioequivalence studies usually have a small number of subjects in phase I.

Clinical trial designs in bioavailability and bioequivalence studies

- The common design in these studies include randomized, two-period, two-sequence, single dose cross-over design, parallel design and replicate designs.
- Pharmacokinetics and Pharmacodynamics of the study designs make an important role.

The Role of a Clinical Trial Statistical Analysis

In the majority of Phase 2 and Phase 3 clinical trials, the statistical analysis serves two major roles:

1. Demonstrating compound efficacy
2. Demonstrating compound safety

Trial statistical analyses are complex in and of themselves. But when you start to consider the impact of a heterogenous population, they become even more complicated.

Variance & Bias in Clinical Trial Data

People are, by nature, heterogenous. Everyone is different; different ages, gender, medical history, psychology. This is true also for patients participating in clinical trials. The variability of these characteristics creates variability, or noise, in clinical trial data. Noise can also be related to other factors; for example unequal distribution of patients with specific characteristics between treatment groups.

Noise in clinical trial data makes it difficult to detect true differences between treatment groups (e.g. between drug treatment and placebo treatment); yet, evaluating experimental therapies in heterogeneous patient populations is necessary to represent the general population. So, statisticians need ways to minimize these differences and biases while still being able to prove efficacy and safety for a generalized population.

The Clinical Trial Statistical Analysis Process

1. Decide on Hypothesis

Like all scientific research, a clinical trial starts with a hypothesis.

There are generally two positions trials can take about a compound: superiority or equivalence (non-inferiority).

This statistical analysis discussion is focused on a superiority trial, in which the statistics must demonstrate drug superiority over a placebo (or competitor).

2. Calculate Study Power & Required Sample Size

The statistical analysis starts by defining the sample size, which is based on the study power to be achieved. Study power is related to the probability of detecting the different between study groups assuming a difference exists, or the likelihood of avoiding a Type II (false negative) error. Study power needs to be at least 80-90 percent to be adequate for clinical research.

Depending on the study design, statisticians will help clinical trial teams figure out if the sample size required is realistic or not.

As outlined by the FDA's guidance, E9 Statistical Principles for Clinical Trials, the following should be specified when determining sample size:

- Primary efficacy endpoints (variable)

- The test statistic
- The null hypothesis (no difference in treatments)
- The alternative hypothesis at chosen dose
- The probability of Type I error (conventionally 5 percent or less)
- The probability of Type II error (conventionally 10-20 percent)
- Approach to dealing with treatment withdrawals and protocol violations

3. Develop a Statistical Analysis Plan (SAP)

As soon as the study protocol design is outlined, the statistical analysis strategy is discussed and defined. Here are critical elements of an SAP:

- Clinical trial summary, including objectives, endpoints, design and sample size.
- Dataset description, including study variables and data transfer.
- Data analysis considerations, including adjustments for covariates.
- Statistical issues, including outlier detection and handling of dropouts or missing data.
- Study population characteristics, including subject disposition and measurements of treatment compliance.
- Statistical analysis approach descriptions.

The study design, study power and statistical analysis plan are all set before the study starts. This is to remove potential bias that could occur if these parameters were adjusted while the clinical trial is ongoing.

4. Collect Data & Run Study

Next, the research begins, starting with pre-trial patient data. Again, it's important to capture important patient information before the trial begins to prevent any bias (resulting from treatment interference).

For example, if you plan to use a covariate for body mass index (BMI) in an osteoarthritis (OA) study, you need to identify that in the SAP and collect patient BMI before the trial begins.

5. Conduct Statistical Analysis & Report Outcomes

Once you have your results, it's time for the clinical trial statistical analysis.

Statistical analyses in clinical trials are typically based on estimating confidence intervals, hypotheses and drawing conclusions based on observed data. In this type of analysis for a superiority trial, there are generally four statistical methods:

1. **ANOVA**: Used to determine how one factor impacts a response variable.

2. **ANCOVA**: Includes one or more covariates, which can help statisticians better understand how a factor impacts a response variable after accounting for some relevant, unchanging characteristics.
3. **MANOVA**: Identical to an ANOVA, except it uses two or more response variables.
4. **MANCOVA**: identical to a MANOVA, except it also includes one or more covariates.

More often than not, clinical trials will analyze data using an ANCOVA, which helps with variance reductions in a concrete way. ANCOVA normalizes data related to innate patient traits (like age or BMI) and creates cleaner, more precise understanding of true treatment effect.

As the FDA says, "Sponsors can use ANCOVA to adjust for differences between treatment groups in relevant baseline variables to improve the power of significance tests and the precision of estimates of treatment effect."

On clinical trial statistical analysis and covariates, these industry guidance's:

- FDA's E9 Statistical Principles for Clinical Trials
- EMA's ICH E9 Statistical Principles for Clinical Trials
- FDA's Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
- EMA's Adjustment for Baseline Covariates in Clinical Trials

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