

Introduction of Clinical Trial

Book Reference

- **Clinical Trials; A Practical Guide to Design, Analysis, and Reporting**
- **Duolao Wang and Ameet Bakhai, Editors**

Chapter 1 (Randomized Clinical Trials)

- **Definition:** Randomized clinical trials are scientific investigations that examine and evaluate the **safety** and **efficacy** of new drugs or therapeutic procedures using **human subjects**.
- The results that these studies generate are considered to be the most valued data in the era of **Evidence-Based Medicine (EBM)**.
- Understanding the principles behind clinical trials enables an appreciation of the **validity** and **reliability** of their results.

Key Assumption in Clinical Trial

- **Blindness:** patients and trial personnel are deliberately kept unaware of which patient is on the new drug. This minimizes bias in the later evaluation so that the initial blind random allocation of patients to one or other treatment group is preserved throughout the trial.
- **Ethic:** Clinical trials must be designed in an ethical manner so that patients are not denied the benefit of usual treatments. Patients must give their voluntary **consent** that they appreciate the purpose of the trial. Several key guidelines regarding the ethics, conduct, and reporting of clinical trials have been constructed to ensure that a patient's rights and safety are not compromised by participating in clinical trials
- **Random Allocation:** It is crucial to **randomize** patients to minimize **systematic bias** or **confounding** at the start of the study

Different Phase of Clinical Trials

- **Phase I:**
- Test the effects of a new drug in **healthy** volunteers or patients **unresponsive** to usual therapies.
- look at how the drug is handled in the human body (pharmacokinetics/pharmacodynamics),
- Particularly with respect to the immediate **short-term safety** of **higher doses**.

Different Phase of Clinical Trials

- **Phase 2:**
- Examine **dose–response curves** in patients and what benefits might be seen in a small group of patients with a particular disease.

Different Phase of Clinical Trials

- **Phase 3:**
- A new drug is tested in a controlled fashion in a large patient population against a **placebo** or **standard** therapy.
- This is a key phase, where a drug will either make or break its reputation with respect to **safety** and **efficacy** before **marketing begins**.
- A positive study in Phase III is often known as a **landmark** study for a drug, through which it might gain a license to be prescribed for a specific disease.

Different Phase of Clinical Trials

- **Phase 4:**
- Called a **post marketing** study as the drug has already been granted regulatory approval/license.
- These studies are crucial for gathering additional safety information from a larger group of patients in order to understand the long-term safety of the drug and appreciate drug interactions.

Clinical Trial Classified by Design

- **Parallel-Group Trial:** Patients are randomized to the new treatment or to the standard treatment and followed-up to determine the effect of each treatment in parallel groups.
- **Crossover Trial:** Randomize patients to different sequences of treatments, but all patients eventually get all treatments in varying order, the patient is his/her own control
- **Factorial Trial:** Assign patients to more than one treatment-comparison group. These are randomized in one trial at the same time, while drug A is being tested against placebo, patients are re-randomized to drug B or placebo, making four possible treatment combinations in total
- **Cluster Randomized Trial:** Larger groups (eg, patients of a single practitioner or hospital) are randomized instead of individual patients

Clinical Trial Classified by Number of centers

- Clinical trials can also be classified as **single-center** or **multicenter** studies according to the number of sites involved.
- **Single-Center** studies are mainly used for Phase I and II studies
- **Multicenter** studies can be carried out at any stage of clinical development .
- **Multicenter studies are necessary for two major reasons:**
- Evaluate a new medication or procedure more efficiently in terms of accruing sufficient subjects over a shorter period of time
- Provide a better basis for the subsequent generalization of the trial's findings, the effects of the treatment are evaluated in many types of centers

Classifications (Study Designed to Prove)

- **Superiority studies:** Study aims to show that a new drug is more effective than the comparative treatment (placebo or current best treatment). Most clinical trials belong to this category.
- **Equivalence studies:** Designed to prove that two drugs have the same clinical benefit. Hence, the trial should demonstrate that the effect of the new drug differs from the effect of the current treatment by a margin that is clinically unimportant.
- **Noninferiority studies:** Study aims to show that the effect of a new treatment cannot be said to be significantly weaker than that of the current treatment. In the latter two trials the new treatment might still turn out to be more effective than the comparative treatment, but this is not the prior assumption of the trials.

Exploratory or Confirmatory Clinical Trial

- **Exploratory** :The trial is the first to compare a specific treatment.
- An exploratory study might also seek to identify key issues rather than to confirm or challenge existing results regarding the treatment effect.
- For example, it might look at the impact of a new drug in a specific subset of patients who have additional diseases to the main disease of interest, such as diabetic patients with heart disease.
- **Confirmatory**: Further trial trying to confirm a previous observation and evaluating a specific treatment, the data can also be used to explore further hypotheses, ie, subgroup effects that have to be confirmed by later research.
- **Note**: On occasions, a study can have both confirmatory and exploratory aspects.

Source of Error in Clinical Trial

- **Bias/Systematic Errors:**
 - Why this happened?
 - Selection Bias, Noncompliance or Missing data
- **Confounding:**
 - What Should do?
 - Randomization, Multivariate Statistical Analysis
- **Random Error/ Sampling Error**
 - What Should do?
 - Very Large Sample OR Meta Analysis

Source of Error in Clinical Trial

- **Bias/Systematic Errors:** These are associated with the design, conduct, analysis, and reporting of the results of a clinical trial.
- Bias can also make the trial-derived estimate of a treatment effect deviate from its true value.
- The most common types of bias in clinical trials are those related to **subject selection** and **outcome measurement**.

Source of Error in Clinical Trial (Bias)

- For example, if the investigator is aware of which treatment a patient is receiving, it could affect the way that he/she collects information on the outcome during the trial, or he/she might recruit patients in a way that could favor the new treatment, resulting in a **selection bias**.
- In addition, exclusion of subjects from statistical analysis because of **noncompliance or missing data** could bias an estimate of the true benefit of a treatment, particularly if more patients were removed from analysis in one group than the other. Much of the advanced design strategies seek to reduce these systematic errors.

Source of Error in Clinical Trial

- **Confounding:** represents the distortion of the true relationship between treatment and outcome by another factor, eg: age, Sex, the severity of disease.
- Confounding occurs when an extra factor is associated with both the outcome of interest and treatment group assignment.
- Confounding can both obscure an existing treatment difference and create an apparent difference that does not exist.
- If we divided patients into treatment groups based on inherent differences (such as mean age) at the start of a trial then we would be very likely to find the benefit of the new treatment to be influenced by those pre-existing differences.

Source of Error in Clinical Trial

- **Randomization** in conjunction with a **large sample size** is the most effective way to restrict such **confounding**, by evenly distributing both known and unknown confounding factors between treatment groups.
- If, before the study begins, we know which factors may confound the trial then we can use randomization techniques that force a balance of these factors (**stratified randomization**).
- In the analysis stage of a trial, we might be able to restrict confounding using special statistical techniques such as **stratified analysis** and **Multivariate Analysis** (MANOVA, ANCOVA, Regression (Linear, Logistic, Cox, Poisson,...))

Source of Error in Clinical Trial

- **Random error:**
- Even if a trial has an ideal design and is conducted to minimize bias and confounding, the observed treatment effect could still be due to **random error** or **chance**.
- The **random error** can result from **sampling, biologic, or measurement variation** in outcome variables.
- Since the patients in a clinical trial are only a sample of all possible available patients, the sample might yet show a chance false result compared to the overall population.

Source of Error in Clinical Trial (**Random error**)

- This is known as a ***sampling error***.
- Sampling errors can be **reduced** by choosing a **very large group** of patients or by using special analytic techniques that combine the results of several smaller studies, called a **meta-analysis**.
- Other causes of random error are described elsewhere.

Source of Error in Clinical Trial

- **How to deal with Random error?**
- Statistical analyses deal with random error by providing an estimate of how likely the measured treatment effect reflects the true effect.
- Statistical testing or inference involves an assessment of the probability of obtaining the observed treatment difference assuming that there is no difference between treatments.
- This probability is often called the *P*-value or false-positive rate. If the *P*-value is less than a specified critical value (eg, 5%), the observed difference is considered to be statistically significant.
- The smaller the *P*-value, the stronger the evidence is for a true difference between treatments.
- Statistical estimates summarize the treatment differences for an outcome in the form of point estimates (eg, means or proportions) and measures of precision (eg, confidence intervals [CIs])

Source of Error in Clinical Trial

- **Random error:**
- **Note:** Testing several different hypotheses with the same trial (eg, comparing treatments with respect to different outcomes or for several smaller subpopulations within the trial population) will increase the chance of observing a statistically significant difference purely due to chance.
- Even looking at the difference between treatments at many time points (**interim analyses**) throughout the length of the trial could lead to a spurious result due to multiple testing.
- Therefore, the aim should always be to plan a trial in such a way that the occurrence of any such errors is minimal.

CHARM program

- To design and analyze a clinical trial, needs to ask several questions.
- **What** are the objectives and endpoints of the study?
- **What** patient population or disease is the drug meant to treat?
- **What** criteria should be used to select patients eligible for the study?
- **How** large should the sample size be so that the study will have enough power to detect a clinically significant benefit?
- **How** sure can be about the observed treatment benefits and that they will reflect a genuine treatment difference with minimal influence of systematic errors, confounding, or chance?

CHARM Program (Example)

- **What are the objectives and endpoints of the study?**
- Candesartan in Heart failure – Assessment of Reduction in Mortality and Morbidity
- The main objective of the CHARM program was to determine whether the use of candesartan could reduce mortality and morbidity in a broad population of patients with symptomatic heart failure.
- To test these hypotheses, the primary endpoint was defined as the time from randomization to death from any cause in the total CHARM population.
- In each component trial, the primary endpoint was the time to the first occurrence of cardiovascular death or emergency hospitalization for the management of CHF (chronic heart failure).

CHARM Program (Candesartan in Heart Failure)

- **What patient population or disease is the drug meant to treat?**
- Patients with chronic heart failure (CHF) are at high risk of cardiovascular death and recurrent hospital admissions.
- The three patient populations enrolled (all with heart failure) were distinct but complementary, so that the effects of candesartan could be evaluated across a broad spectrum of patients with heart failure.
- The CHARM study population consisted of symptomatic heart failure patients (New York Heart Association class II–IV) aged ≥ 18 years, except those with recent major events or a very poor prognosis (such as patients with myocardial infarction, stroke, or open heart surgery in the previous 4 weeks, and any noncardiac disease judged likely to limit 2-year survival) [14–17].
- Due to the principle of not harming patients, the study also excluded patients who presented with contraindications to treatment with candesartan.
- All patients gave their written informed consent before being enrolled.

CHARM Program (Candesartan in Heart Failure)

- **What criteria should be used to select patients eligible for the study?**
- Patients were allocated depending on their left ventricular ejection fraction (strength of their heart function) and background use of angiotensin-converting enzyme (ACE) inhibitors at presentation.
- Patients who had preserved left ventricular function (left ventricular ejection fraction $\geq 40\%$) were randomly allocated to either candesartan or placebo in the 'CHARM-Preserved' trial.
- Patients who had left ventricular ejection fraction $< 40\%$ were split into a further two trials, depending on whether they had a known intolerance of ACE (angiotensin-converting enzyme) inhibitors ('CHARM-Alternative' trial) or were already on an ACE inhibitor ('CHARMAdded' trial). They were then randomized to candesartan versus placebo.

CHARM Program (Candesartan in Heart Failure)

- **How large should the sample size be so that the study will have enough power to detect a clinically significant benefit?**
- The sample size calculation was used to minimize random error. We call this process *power* calculation. The study needed sufficient ‘power’ to be able to say something definitive about the effect of the treatment (relating to the primary endpoints) so it was important to include a sufficient number of patients.
- In the CHARM program, the overall study was designed to address the question of all-cause mortality. The investigators assumed an annual overall mortality in the placebo group of 8%. On that basis, the program of investigation had >85% power to detect a 14% reduction in mortality at a significance level of 0.05, based on the log-rank test.
- Each component trial independently estimated its respective sample size based on the anticipated event rate for the combined outcome of cardiovascular death or admission to hospital for CHF (chronic heart failure).

CHARM Program (Candesartan in Heart Failure)

- How sure can be about the observed treatment benefits and that they will reflect a genuine treatment difference with minimal influence of systematic errors, confounding, or chance?
- Patients were **randomly** assigned in a **double-blind** fashion.
- Patients were followed-up for outcomes (at least two years) if possible.
- All deaths and first CHF hospital admissions were adjudicated by an endpoint committee.
- In the CHARM program, the assignment code of randomly assigned patients was held at an independent statistical center and an independent **data and safety monitoring board** (DSMB) was established to over see the safety of patients enrolled in the trial and to monitor trial progress.

CHARM Program (Candesartan in Heart Failure)

- It had access to all data through the independent statistical center. Predefined stopping rules for **efficacy** or **safety** concentrated on mortality from the overall trial program data and safety monitoring board (DSMB).
- A pharmaceutical company that has heavily invested in a trial has a considerable interest in ensuring that the conduct of the trial does not jeopardize the likelihood of a positive outcome of the trial, eg, that the drug of interest is safe and efficacious.
- The use of an independent statistical center and a DSMB makes the whole process more transparent as these groups have patient safety as their primary concern.

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CHARM Program (Candesartan in Heart Failure)

- At predefined time points the existing data are therefore analyzed by the independent statistical center and the results are discussed with the DSMB.
- The DSMB has to make sure that the new drug that patients are taking is not harmful. If, during the course of the trial, such evidence is found then the trial has to stop (**stopping for safety**).
- This idea can also be turned around: if there is major evidence for a beneficial effect of the new treatment before the planned end of the trial then the trial also has to stop. This is called **stopping for efficacy** because there is evidence of conclusive benefit of the treatment.
- Monitoring trial results is ethically challenging and has to balance individual ethics with the long-term interest in obtaining sufficient data.

Conduct of the Trial(Candesartan in Heart Failure)

- The CHARM component trials recruited patients from 618 sites in 26 countries, with use of uniform procedures and management, and coordination via a single central unit. Between March 1999 and March 2001, 7,599 patients were randomly assigned in a double-blind fashion to candesartan or matching placebo, stratified by site and component trial, with randomization provided through telephone to the central unit.
- The initial dose used was either 4 or 8 mg of the study drug. The dose was increased or decreased in response to the patient's clinical status, and algorithms were provided as guidelines for the management of hypotension or kidney dysfunction.
- After the titration, visits were scheduled every 4 months, with a minimum planned duration of 2 years.

Final Data analysis

- **Intention-to-treat** analysis means that outcomes of patients who were randomized but who subsequently discontinued or changed treatment are taken into account as if they had finished the trial This is a pragmatic realization of the view that at the time of treatment start, we will never be sure whether a patient will continue with that treatment.
- Hence, the intention-to-treat analysis reflects the general policy of using/prescribing the treatment in a given situation.
- All analyses in the CHARM program were done by intention-to-treat, and P -values were two-sided.
- All time-to-event endpoints were analyzed with the log-rank test, stratified by three sub studies and displayed on Kaplan–Meier plots by treatment.

Final Data analysis

- The estimated hazard ratio from the Cox proportional hazards model was used to assess the size of treatment effect (candesartan against placebo).
- In addition, a covariate-adjusted Cox regression model was fitted with the prespecified 33 baseline covariates to adjust the hazard ratio for other factors that might affect prognosis.
- Prespecified subgroup analyses were done, each using a test for heterogeneity to assess for possible interactions between treatment and selected baseline variables.

Final data analysis

- Statistical analyses are usually prespecified in the trial protocol and should be performed as planned to ensure credibility and to deal with the issue of multiple testing.
- The principal statistical test for the primary endpoint analysis that was prespecified in the sample size calculation should be applied.
- This means that it is imperative to plan a trial with care and to use current evidence that is as rigorous as possible in order to avoid as much bias as possible at the planning stage.
- Subgroup analysis can be performed, but it has to be recognized that a significant effect seen in a subgroup is not definitive evidence of a differential effect within subgroups of patients, unless the trial was powered initially to assess this.

Trial Reporting

- The eventual results of the CHARM program were published in four reports, which followed the CONSORT (Consolidated Standards of Reporting Trials) statement and guidelines of reporting.
- A trial profile was provided to describe the flow of participants through each stage of the randomized controlled trial (enrollment, randomization, treatment allocation, follow-up, and analysis of a clinical trial).
- The baseline characteristics of patients (including demographic information, heart disease risk factors, medical history, and medical treatment) were displayed in an appropriate format for each component trial as well as the overall program.

Trial Reporting

- The results with respect to the prespecified primary endpoints and relevant secondary endpoints were provided in appropriate tables and figures.
- Results on the effects of candesartan on cardiovascular death or CHF hospitalization in different populations of patients with heart disease (CHARM-Preserved, -Added, and -Alternative) were reported in three separate articles.

Conclusion

- **Randomized** clinical trials are a major investment in terms of patient and personnel involvement, and the funding needed to undertake the trial for the progress of medical care.
- We have provided a short overview on the various types of clinical trials, and the main types of errors that can arise and can seriously compromise our ability to draw valid conclusions from clinical trials.
- Many of the concepts mentioned in this chapter deal with **minimizing bias** and **maximizing precision**.
- An appropriate design requires a clear definition of **the primary** and **secondary** hypotheses in terms of measured outcomes and an explicit definition of the study population in order to avoid **systematic errors**.

Conclusion

- Statistical analyses deal with **random errors** due to **sampling** or **random variation** in the outcome variables.
- Interpretation of these statistical measures of treatment effect and comparisons should consider the potential contribution of **bias** or **confounding**.
- Finally, it is ethically imperative that a trial is conducted and monitored in such a way as to minimize harm to patients, while looking to answer the initial questions posed by the trial of whether the new treatment is better, worse, or similar to the comparison group.