

Introduction to Clinical Trials

A clinical trial is defined as a prospective study comparing the effect or value of an intervention against a control in subjects. The core components of clinical trials are the population, intervention, control and outcome. The great majority of clinical trials are concerned with the evaluation of drug therapy, but intervention could be anything.

The steps in creating a clinical trial:

1. Research question
2. Design the trial (protocol)
3. Enrollment/Data collection and check
4. Conduct the trial
5. Data freeze
6. Data analysis
7. Interpret results

Clinical Equipoise

The genuine uncertainty within the scientific and medical community as to which of the two interventions is superior.

FINER Criteria

- Feasible (is it possible?)
- Interesting
- Novel (is it new?)
- Ethical - always the most important
- Relevant (does it matter now?)

Belmont Principles

Relevant to the ethics of research involving human subjects:

1. Respect of persons - informed consent
2. Beneficence - to do no harm
3. Justice - Fairness among those chosen for the study

Possible Objectives of the Intervention

The new experimental intervention being tested usually has one of the following primary objectives:

- Cure a disease
- Reduce disease symptoms
- Prevent disease worsening
- Prolong survival time (terminal disease) or prevent disease (vaccine)
- etc.

Types of Intervention Studies

- Pharmaceutical products
 - Synthetic drugs
- Biologics
 - Products made from human or animal cell/tissue such as vaccines or blood replacement products
- Medical Devices
 - Pacemaker, cardiac stents, etc
- Other (education, exercise, therapy, etc)

Case-Control Experiments

Blinding ensures patients and/or investigators and/or analysts don't know which treatment is assigned to whom. It is not always possible to blind a study.

- Single-blind: One group does not know treatment assignment
- Double-blind: Two groups do not know treatment assignment (usually the subject and investigator)
- Open-label: Patient and investigators know the treatment

Placebo Control

A **placebo** is made of something that shouldn't have an effect on the body and is useful in determining if an intervention is "better than nothing". A placebo control theoretically has no physical effect on the disease, but it may have a psychological effect.

Active Control

Sometimes it is best to compare a new product to the currently marketed treatment or "standard of care". This would be preferable in control groups for terminal diseases, where it would be unethical to give a placebo.

Randomization

Allocation of the subject to one the interventions by chance. Yields the highest probability that treatments have a balanced distribution on measured and unmeasured covariates related to the outcome.

Non-Compliance in Clinical Trials

Some individuals never receive treatment to which they were randomized, stop treatment, or fail to consistently take treatment. We must consider how we approach this in our analysis:

- Intention to treat: Compare randomized groups regardless of compliance (usual primary approach)
- Modified intention to treat: Exclude patients who were randomized but not eligible or did not have any post-baseline data
- Per-protocol: Compare only individuals who took the medication and/or are compliant with the assigned treatment and were eligible

Study Designs

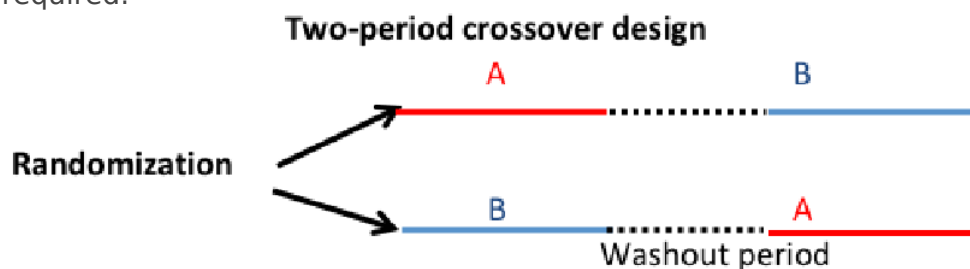
Parallel Group Design

Most common design and the main focus of this course. Multiple treatment groups and subjects are randomized to exactly 1 treatment



Crossover Design

Each patient is randomized to a random sequence of treatment that will be administered sequentially. The objective remains to compare treatment A vs B. Typically less individuals are required.



Factorial Design

Often researchers are interested in studying the effect of two or more interventions applied alone or in combination.

Ex. 2x2 factorial design in which two interventions in A and B are evaluated

(left is A, top is B)	-	+
-	Control	B only
+	A only	A and B

Study Protocol

Every trial has a written protocol, documenting all information concerning the purpose, the design, conduct of the trial and data analysis. This promotes good faith by stating what data is collected and for what purpose, and facilitates communication with relevant ethics committee or regulatory bodies and the sponsor.

Investigators are expected to summarize the study design, regularly provide updates on recruitment and submit results.

1. Administrative information
 - Title, trial registration, protocol version, funding, roles and responsibilities
2. Introduction
 - Background
 - Research hypotheses
 - Study design
3. Methods
 - Settings and recruitment
 - Eligibility criteria
 - Treatment/interventions
 - Primary outcome
 - Timeline
 - Sample size considerations
 - Treatment allocation, randomization and blinding
 - Data collection and data management
 - Statistical analysis plan
 - Data monitoring and auditing
 - Ethics, ethics approval, protocol amendments, consent, confidentiality, declaration of interests, access to data, post-trial care and dissemination policy

Every clinical trial regardless of the sponsor must be registered at clinicaltrials.gov

Key Players in Regulatory Approval

- Patients
 - Informed consent required for all study participants
- Sponsor

- Pharmaceutical industry, government agencies, research institutions, health maintenance organizations, or insurance companies
- Investigators
 - Study team, including statisticians and clinical coordinators
- Regulatory agency
 - FDA in US, EMEA in EU

Clinical Research for Drug and Device Trials

The average time a pharmaceutical company

spends to get a drug on the market is 15 years; 6.5 years in pre-clinicals and discovery, 7 years in clinical trials, 1.5 years review time at FDA.

Pharmacokinetics how the drug flows through body and how it is excreted

Pharmacodynamics how drug affects the body

1. Sponsor and submit IND application to FDA
2. Phase 1: First time in humans
 - Goal: Assess the safety and determine the metabolism of the drug in humans - usually no interest in efficacy
 - Sample size: 20-80 healthy volunteers, unless the treatment is for a life-threatening disease
 - Typically exposed to increasing doses to determine maximum tolerated dose (MTD)
 - There are concerns about exploitation for participants who underestimate the risk vs reward
3. Phase 2: Exploratory
 - Goal: to investigate short term safety and efficacy of the drug in patients with the disease that the drug is intended to treat
 - Sample size: 50 - 300 patients
 - Focus on dose-response relationship, usually case-control with a placebo for non-serious diseases and active-control for serious diseases
4. Phase 3: Pivotal, Confirmatory
 - Goal: Confirm the efficacy of the new drug while assessing safety. Final stage before drug is licensed
 - Sample size: based heavily on statistics, sample must be large enough to detect clinically relevant effect
 - Patients are randomized to usually one dose of experimental product vs one control
5. Phase 4: Post-license monitoring
 - Focus: Establish long-term efficacy and safety of the drug after the drug has been licensed
 - Sample size: Similar to phase 3
 - Evaluated long period of time in a large number of patients, the difference from phase 3 is these trials tend not to be placebo controlled.

FDA usually requires at least 2 adequate well controlled trials conducted in humans to demonstrate substantial evidence of effectiveness and safety. Exceptions are made for serious or immediately life-threatening disease with no therapy available, approval can be granted based on several Phase 2 trials or surrogate outcomes.

The "International Conference on Harmonisation" (ICH) is a conference of professionals from Europe, Japan, and US to determine guidelines related to the conduct and design of pharmaceutical/biotech clinical trials.

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