Clinical Trial

Designs

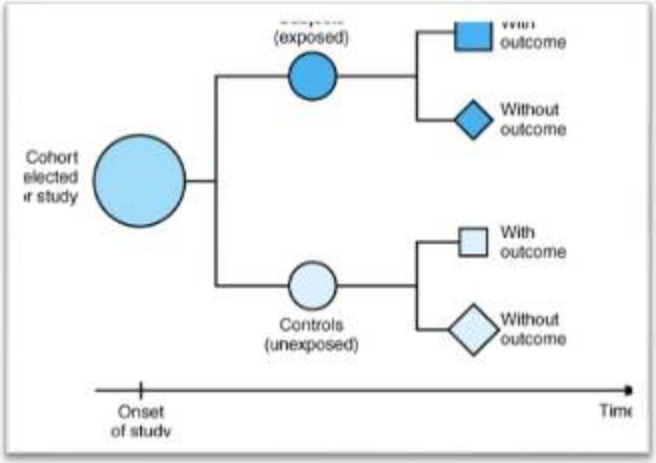
Module 3 Topic 4

Topics

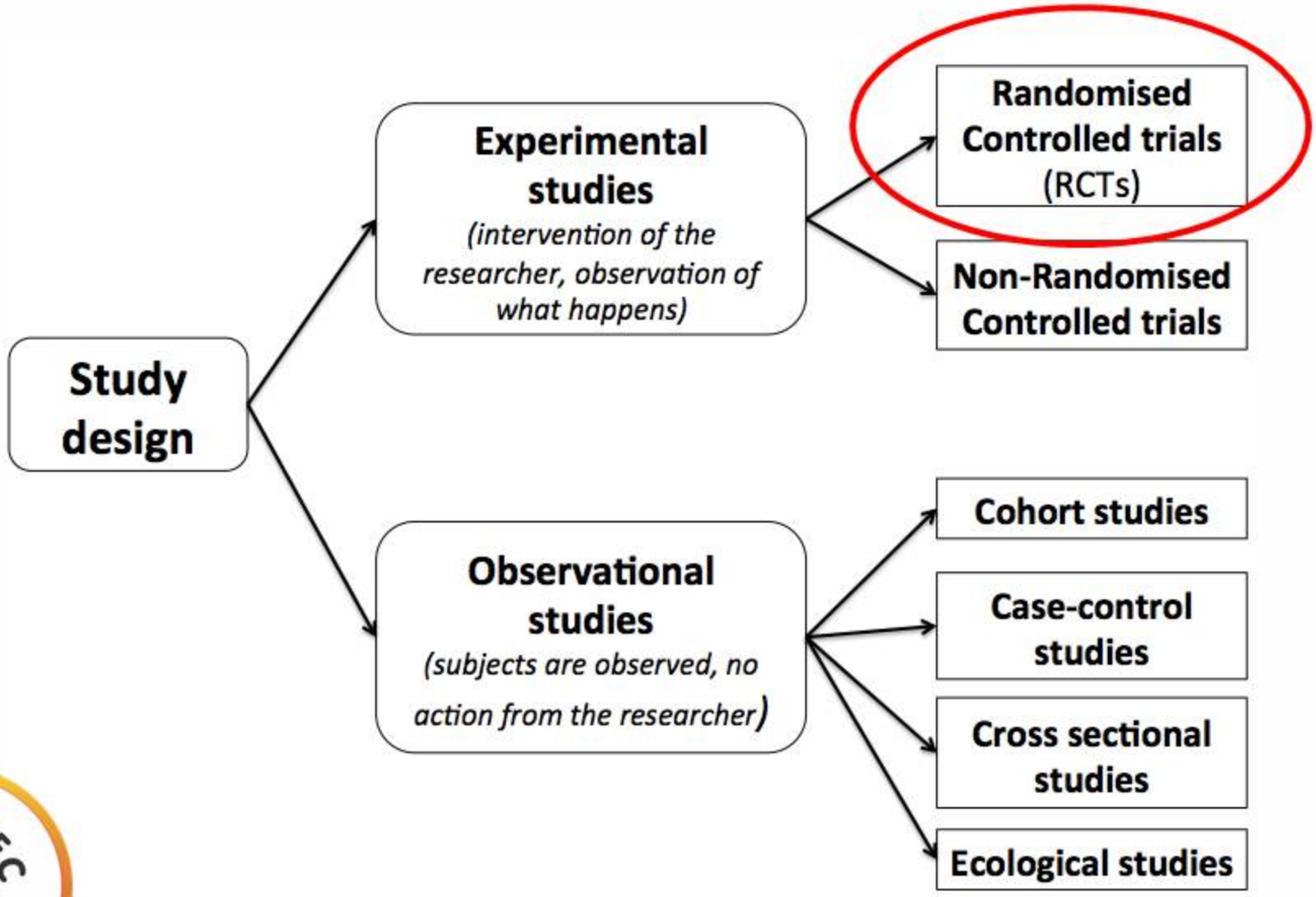
- Clinical Trial Designs
- Introduction to trial designs
- Bias in Research
- Randomization
- Blinding of Trials
- Controls in Clinical Research
- Role of placebos
- Biomarkers / endpoints

Clinical Trial Designs

Experimental design originated in agricultural research and influenced laboratory and industrial research before being applied to trials of pharmaceuticals in humans. Experimental design is characterized by control of the experimental process to reduce experimental error; and replication of the experiment to estimate variability in the response and randomization.




Systematic reviews and meta-analyses of RCTs*
Randomized controlled trials
Cohort studies
Case-control studies
Cross-sectional studies, surveys
Case reports, case studies
Mechanistic studies
Editorials, expert opinion
Higher
Quality of evidence
Lower
Lower
Risk of bias
Higher


Study design
Experimental studies
(intervention of the researcher, observation of what happens)
Randomised Controlled trials (RCTs)
Non-Randomised Controlled trials
Observational studies
(subjects are observed, no action from the researcher)
Cohort studies
Case-control studies
Cross sectional studies
Ecological studies

Research Question

Research Design

Testable Hypothesis

Intervention

Endpoints

Data

Analysis

Evolution of Designs

- Experimental design started mainly in agricultural research and influenced laboratory and industrial research before finally reaching pharmaceuticals trials in humans.
- The roots of clinical design steams from classical experimental design with additional features of not able to control many sources of variability through design as laboratory experiment.
- Lengthy periods for patient accrual and follow-up, have been the bane of clinical research, innovative designs have helped in cut down on both.

Objectives of Experimental Design

- Minimize possibility of bias
- Reduce sampling variability
- Increase precision of estimates
- Enable treatment comparisons

"Tools":

Randomization	Stratification	Controls
Blinding	Sample size	Power
Replication	Covariates	Type I error

Advantages of Proper Design

- Good trial design and conduct is more important than selecting the correct statistical analysis.
- Skillful statistical analysis CANNOT overcome basic design flaws.
- Two major shortcomings of poorly design trial:
  - Inaccuracy (bias)
  - Imprecision (large variability) in estimating treatment effect

Advantages of Proper Design

- Piantadosi (2005)
  - Allows investigators to satisfy ethical constraints
  - Permits efficient use of scarce resources
  - Isolates the treatment effect of interest from confounders
  - Controls precision
  - Reduces selection bias and observer bias
  - Minimizes and quantifies random error or uncertainty
  - Simplifies and validates the analysis
  - Increases the external validity of the trial

Clinical Trial Objectives

- Estimate the magnitude of treatment effects or estimate differences in treatment effects.

- Clinical trial design should accomplish the following (Piantadosi 2005):
  - Quantify and reduce errors due to chance
  - Reduce or eliminate bias
  - Yield clinically relevant estimates of effects and precision
  - Be simple in design and analysis
  - Provide a high degree of credibility, reproducibility, and external validity
  - Influence future clinical practice

Replicated Controlled Clinical Trial

Controlled Clinical Trial

Observational Study

Database Analysis

Case Series

Case Report

Uncontrolled Observation Studies

Case Report

1. Only demonstrates that a clinical event of interest is possible.
2. There is no control of treatment assignment, endpoint ascertainment, or confounders.
3. No control group for the sake of comparison.
4. Report is descriptive in nature; NO formal statistical analysis.

Case Series

- Carries a little more weight than case report, but cannot prove efficacy of a treatment.

Observational Studies

- **Case-control study (retrospective study) -** comparisons are made between individuals who have a particular disease or condition (the cases) and individuals who do not have the disease (the controls).
- **Cohort study -** investigation in which a group of individuals (the cohort) is identified and followed prospectively, perhaps for many years, and their subsequent medical history recorded.
- **Database analysis -** similar to a case series, but may have a control group, depending on the data source. Databases are best used to study patterns with exploratory statistical analyses.

Terminology

- "Experimental Unit" is randomized to the treatment regimen and receives the treatment directly.
- "Observational Unit" has measurement taken on it.
- In clinical studies these two terms are one in the same namely the patient (except is community intervention trial).
- Factors - variables that are controlled and varied during the course of the experiment. Ex. treatment

Terminology

- One-way design - only one factor (most clinical trials)
- Two-way design - two factor studies (ex. oncology trial where various combinations of doses of two chemotherapeutic agents comprise the treatment.)
- Parallel design - patients are randomized to a treatment and remain on the treatment throughout the course of the trial.
- Randomization - use to remove systematic error (bias) and to justify Type I error probabilities in experiments.

Terminology

- Selection bias - this occurs when a physician decides treatment assignment and systematically selects a certain type of patient for a particular treatment.
- Confounding - the effect of other relevant factors on the outcomes that may be incorrectly attributed to the difference between study groups.
- Example: study assigns 10 patients to A and 10 to B with one-week follow-up. Group A assigned treatment at beginning of the month while B is given control at the end of the month. Can 5 pats be assigned to each treatment at a time?

Terminology

- Internal validity - if the observed difference in outcome between the study groups is real and not due to bias, chance, or confounding.
- Randomized placebo-controlled, double-blinded clinical trials have high levels of internal validity.
- External validity - with human trials refers to how well study results can be generalized to the population.

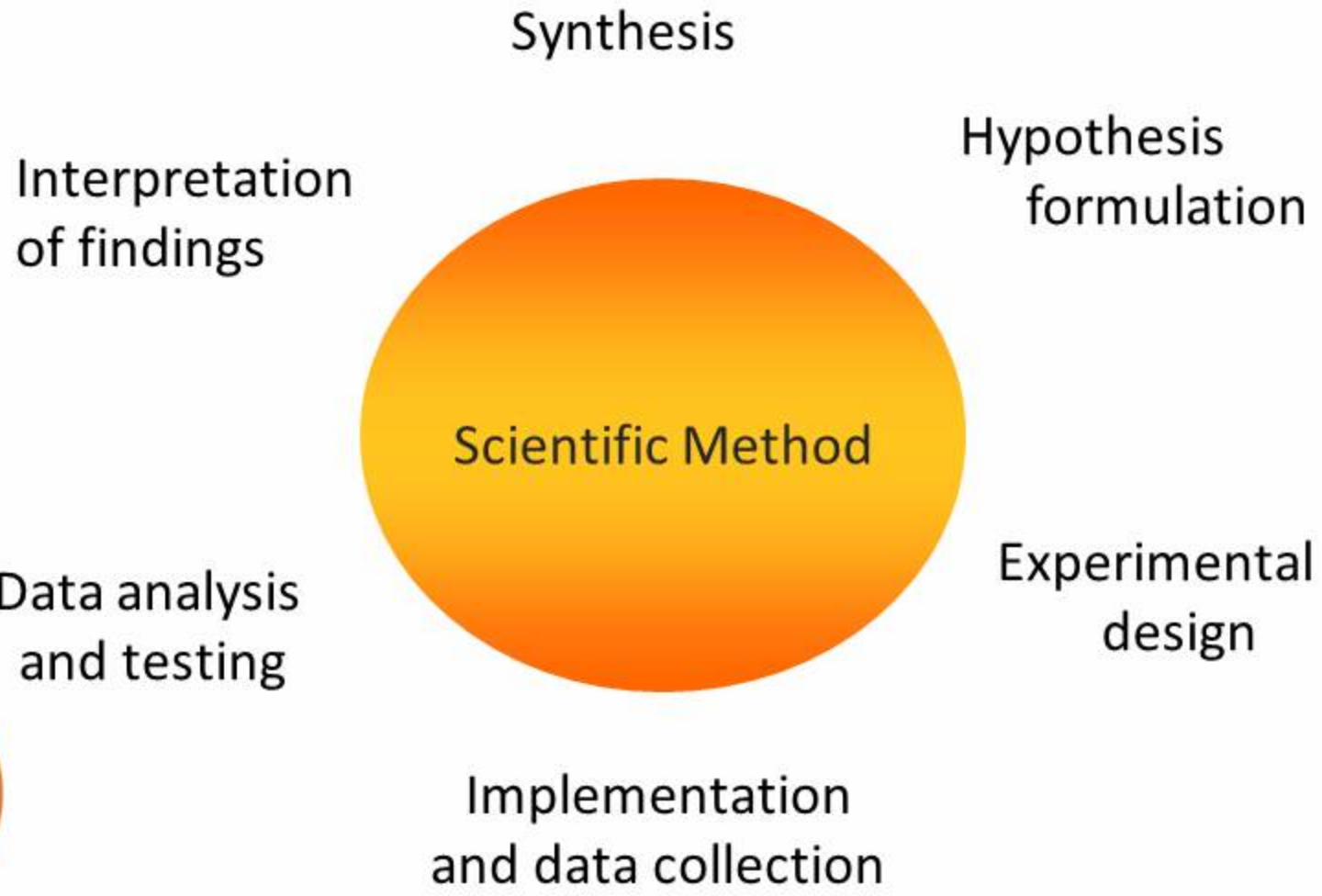
Terminology

- Blocking and Stratification - used to control unwanted variation.
- Example: Clinical trial comparing treatments A and B in patients between ages of 18 and 65. Suppose the younger patient tend to be healthier. There would be a need to stratify with respect to age.

Age	Treat A	Treat B
18 - 30	12	13
31 - 50	23	23
51 - 65	6	7

Note: not necessary to have same number of patients per age stratum but we want a balance in the number on each treatment within each age group. This is accomplished by blocking within the age strata.

Research Cycle



Requirements

1. Pertinent questions are asked
2. Appropriate methods are used to investigate and obtain information
3. Information is evaluated critically and objectively
4. Analytical evaluation leads to application of probability laws (statistics)
5. Logical conclusions are drawn

Stages of a Clinical Trial

1. **Design Stage**
   - Research question
   - Experimental design
   - Funding

2. **Planning Stage**
   - Write protocol
   - Forms development
   - Data management plan
   - Resource centers
     (e.g. Data coordinating center)

3. **Implementation Stage**
   - Patient accrual
   - Treatment
   - Follow-up

4. **Analysis Stage**
   - Statistical analysis

5. **Interpretation Stage**
   - Publication of results
   - Reporting

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Design Stage (Purpose)

- Establish rationale for the trial
- Aims and objectives
- Identify patient population
- Specify proposed treatment
- Specific research hypotheses

Planning Stage (Design)

- Eligibility criteria
- Informed consent
- Patient selection and entry
- Detailed description of treatments
- Endpoints used to evaluate treatments
- Allocation of patients to treatments
- Select analysis methods
- Calculate sample size
- Masking/blinding
- Early stopping rules
- Monitoring and interim analyses
- Forms and data handling
- Organizational structure and responsibilities
- Stratification

Implementation Stage (Conduct)

- Patient accrual by the site
- Randomization
- Follow-up
- General adherence to design
- Unforeseeable problems

Analysis Stage

- Test hypotheses
- Make inferences
- Investigate prognostic value of variables
- Summarize accrual and treatment numbers
- Assess adequacy of design
- Evaluate toxicities

Interpretation Stage

- Ensure proper interpretation of results
- Gauge reasonableness of conclusions

Research Questions

Patient safety and well-being must be balanced relative to the scientific question.

Primary question:

- Usually only one or two
- Most important question to be answered
- Stated clearly before trial is conducted
- Leads to primary hypothesis stated in the context of a primary response or outcome variable

Research Questions

Secondary questions:

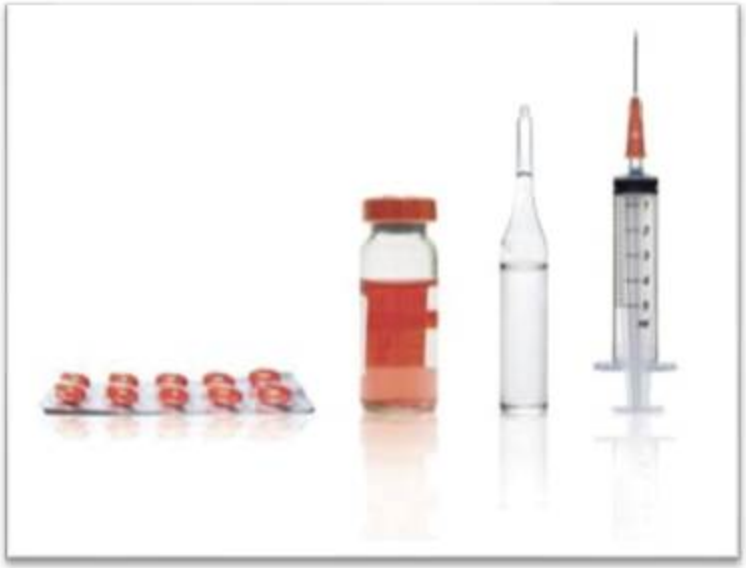
- Often more than one but usually not more than three
- May address additional response variables
- May address subgroups of subjects

Research Questions

- Adverse effects often are the subject of secondary questions. Usually these relate to shorter-term events and sub-lethal events.
- Exploratory questions can sometimes be addressed using a small cohort of study subjects for detailed investigations
- The simpler the research question, the more easily the trial can be designed, conducted, analysed, and interpreted.
- Large simple trials involve less stringent eligibility and easy assessment, and have better ability to address small effects and sub-group questions.

Intervention

- Must be well defined
- Must have favourable benefit-to-toxicity ratio
- The treatment to the control group also must be well described



Study Population

Intimately tied to the research question.

- The study population is "the subset of the population having the condition or characteristics of interest defined by the eligibility criteria (inclusion/exclusion)". This is the population to which an inference is desired to be made.
- Eligibility criteria, together with the characteristics of the subjects that actually are enrolled, define the study sample, and the population to which the inference may truly be valid [external validity].

Subjects

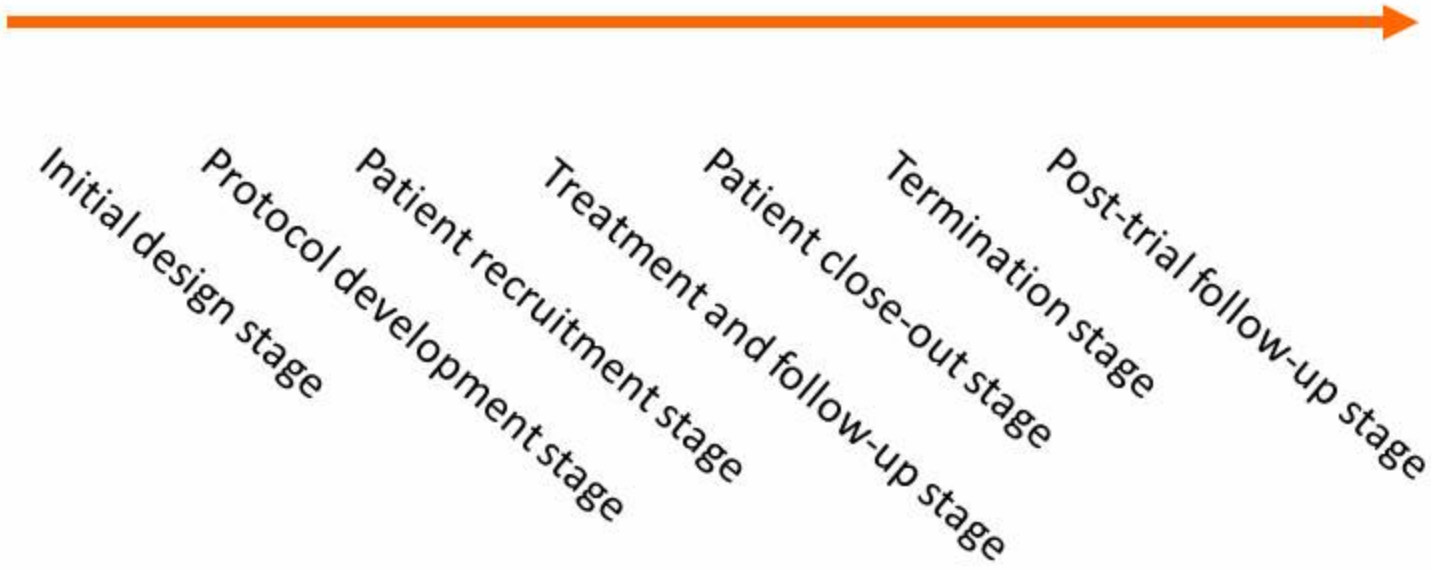
- Should have the potential to benefit from the intervention
- Should be selected (via eligibility) so that the intervention will produce a measurable effect of reasonably high magnitude if successful.
- Who are likely to be harmed should be deemed ineligible before being enrolled rather than being removed from the study later.

Subjects

- Should be at low risk of experiencing competing events or causes of toxicity, to ensure that subjects remain in the study and are evaluated rather than becoming dropouts.

- Should be considered likely to adhere to the protocol (patient compliance).

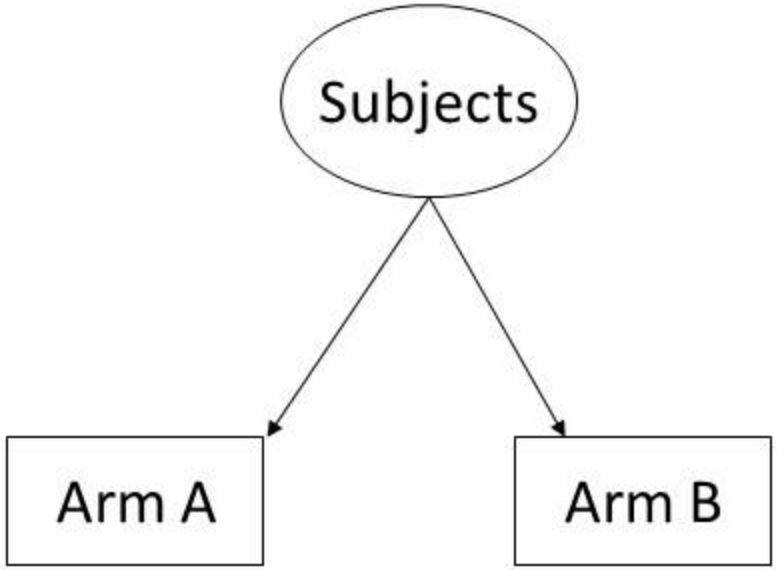
Meinert's Clinical Trial Stages



Basic study designs

- Randomized controlled trials (RCT)
- Nonrandomized concurrent control studies
- Studies using historical controls
- Cross-over (change-over) designs

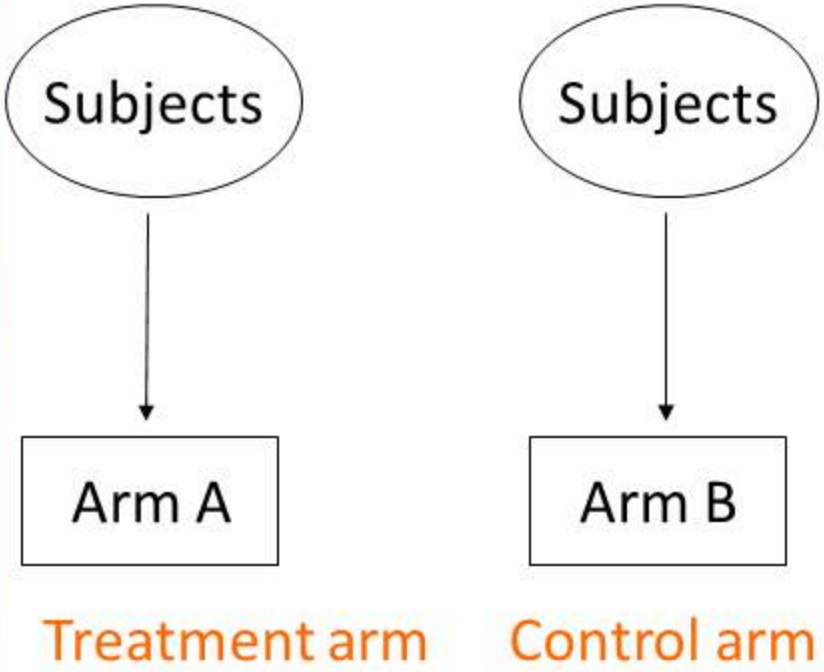
Randomized controlled trials (RCT)



1. Simple and easy to implement
2. Universally accepted
3. Applicable to acute conditions
4. Analysis less complicated & interpretation straightforward

- Random treatment assignment
- Study conducted during one time period

Nonrandomized concurrent control studies

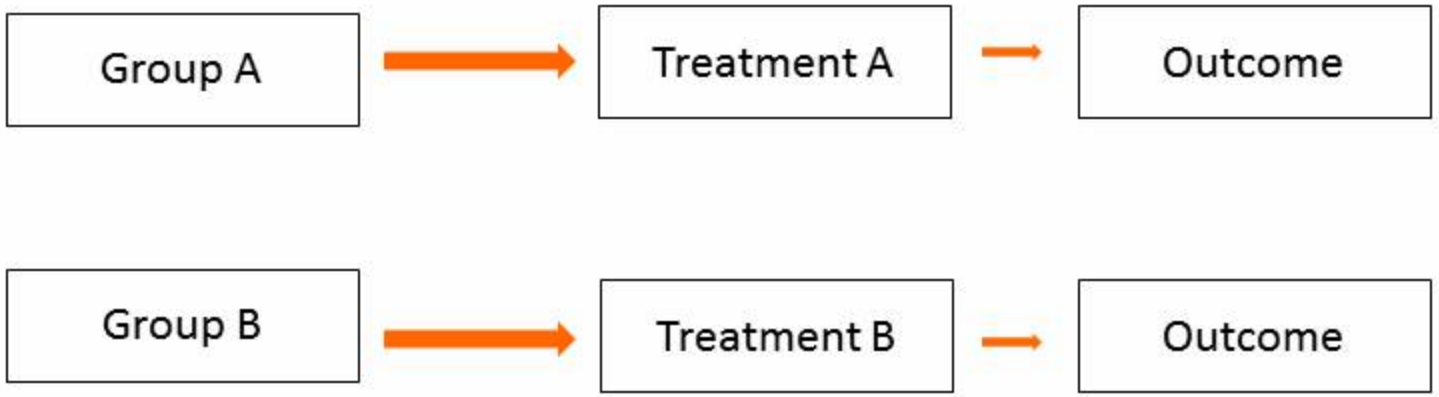


Ex. Survival results of results of patients treated at two sites, one using new surgical procedure and the other using traditional medical care.

- Non-random treatment assignment
- Studies conducted during same time periods

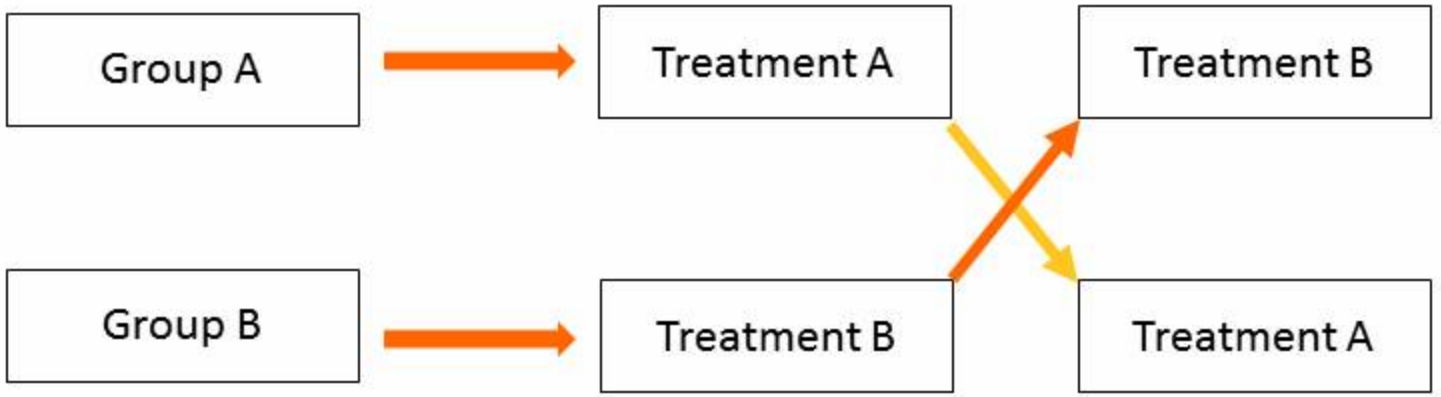
Parallel design

Each subject receives:



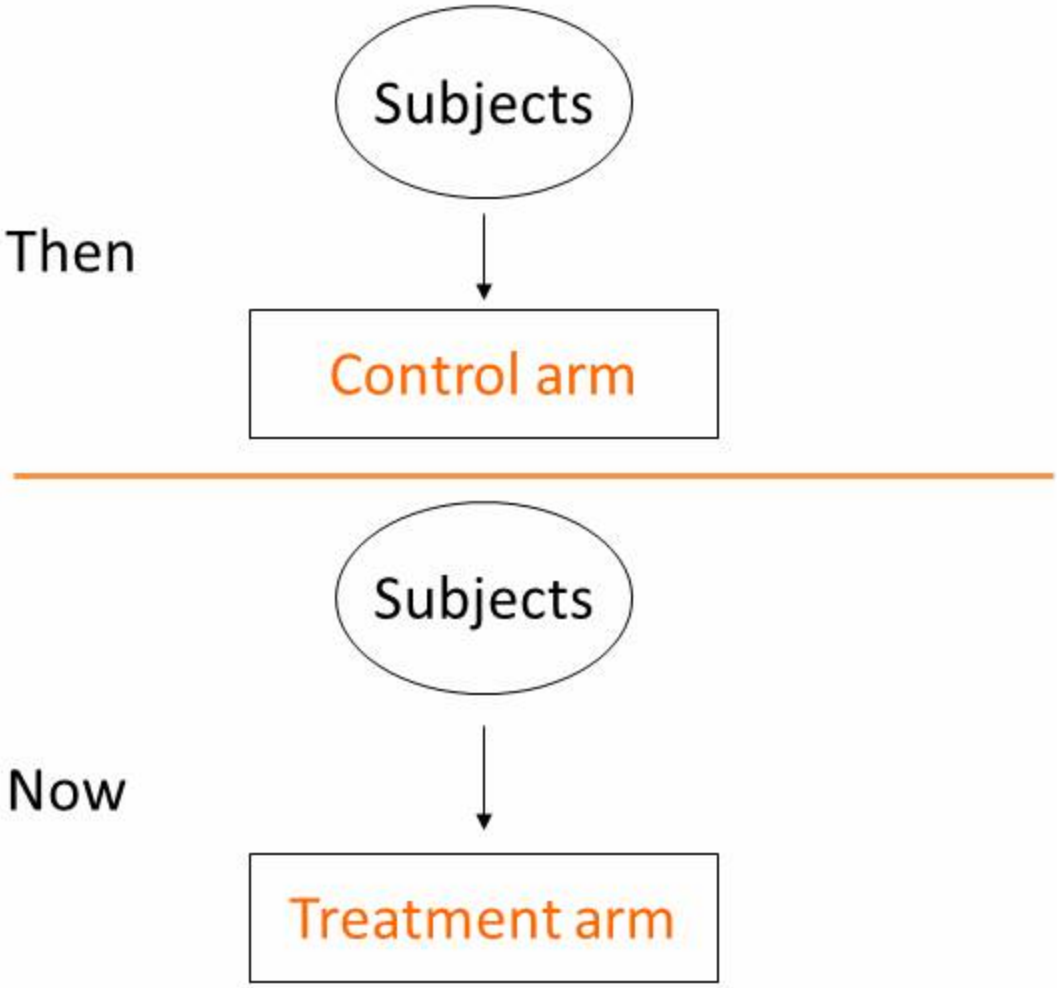
Cross-over (change-over) designs

Each subject receives:



Two-period cross-over

Studies using historical controls



Studies conducted during different time periods

Special Design Issues

- "Active Control" studies are designed to demonstrate the equivalence of two treatments or non inferiority of new treatment.
- A comparative trial with an active control can be used to demonstrate the superiority of a new treatment over the standard or to demonstrate the equivalence (non inferiority) of the new treatment.
- Superiority trials are concerned essentially only with the relative effect of treatment.
- Non inferiority trials must address both the relative and absolute effects of treatment.

Parameter

- A well-defined characteristic of an individual subject (experimental unit) or group of subjects that is unknown and unknowable in truth, but which may be measured, observed, or estimated (albeit with random error).

Random Error

- Also known as variability, random variation, or “noise in the system”. The heterogeneity in the human population leads to relatively large random variation in clinical trials.

Observation

A measured or observed value of a parameter for an individual subject (experimental unit).

Observed value = True value + Random error

(Unbiased) Estimate of a parameter

A function of observations that, on average, equals the true parameter value. (Example: Mean)

Bias

Systematic error.

In the absence of random error, bias is the difference between the “true” value of a parameter and the value actually observed or estimated after adjusting for causes other than sampling variability.

Observed value = True value + Systematic error + Random error

(Biased) Estimate of a parameter

A function of observations that, on average, equals the true parameter value plus the bias.

Treatment effect (compared to a control treatment)

Treatment effect = True value for treatment group
- True value for control group

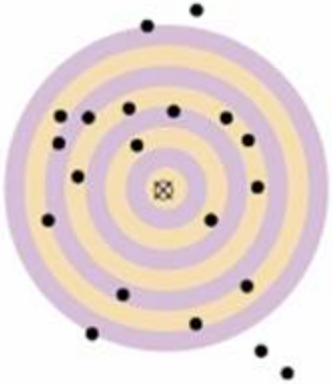
If the true value for one group is estimated with a bias, the estimate of the treatment effect will be biased.

Random Error vs. Bias

- Random error has no preferred direction, so we expect that averaging over a large number of observations will yield a net effect of zero.
- The estimate may be imprecise, but not inaccurate (minimized with large sample sizes).
- Bias has a net direction and magnitude so that averaging over a large number of observations does not eliminate its effect.
- Bias can be large enough to invalidate any conclusions.
- In human studies, bias can be difficult to detect and the suspicion of bias can render judgment that a study is invalid.

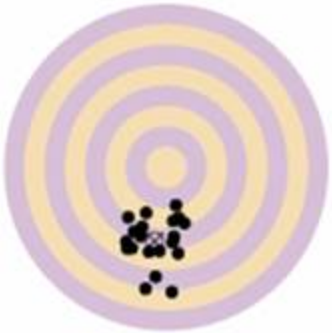
Random Error vs. Bias

- Random error corresponds to imprecision and bias to inaccuracy.



Large variation, but unbiased

Accuracy & Imprecision



Small variation, but biased

Inaccuracy & Precision

Small variation, and unbiased

Accuracy & Precision

Review of Hypothesis Testing

- Null hypothesis – reflects the lack of an effect.
- Alternative hypothesis – reflects the presence of an effect (supporting the research hypothesis).
- The investigator needs to have sufficient evidence, based on the data collected in a study, to reject the null hypothesis in favour of the alternative hypothesis.

Clinical Biases

- If a bias is small relative to the random error, then we do not expect it to be a large component of the total error.
- A strong bias can yield a point estimate that is very distant from the true value.
- Investigators seldom know the direction and magnitude of bias, so adjustments to the estimators are not possible.

Common Types of Bias

- Selection Bias
- Procedure Selection Bias
- Post-Entry Exclusion Bias
- Bias due to selective loss of data
- Assessment Bias

Common Sources of Bias

- Assessment method (trained observer / self reporting)
- Measurement techniques or devices
- Improper assignment of subjects to treatments
- Classification of subjects

Selection Bias

- Selecting a sample that is not representative of the population because of the method used to select the sample.
- In the study cohort this can diminish the external validity of the study findings.
- Randomized controls increase internal validity of a study.
- Randomization can also provide external validity for treatment group differences.
- Selection bias should affect all randomized groups equally, so in taking differences between treatment groups, the bias is removed via subtraction.

Procedure Selection Bias

- Likely result when patients or investigators decide on treatment assignment, can lead to extremely large biases.
- The investigator may consciously or subconsciously assign particular treatments to specific types of patients.
- Randomization is the primary design feature that removes this bias.

Post-Entry Exclusion Bias

- Can occur when the exclusion criteria for subjects are modified after examination of some or all of the data.
- Some enrolled subjects may be re-categorized as ineligible and removed from the study.
- Unethical practice.

Bias due to selective loss of data

- Related to post-entry exclusion bias.
- Data from selected subjects are eliminated from the statistical analyses.
- Protocol violations may cause an investigator to request an analysis using only the data with patients who adhered to the protocol.
- Statisticians prefer that intention-to-treat analyses be performed as the main statistical analysis.

Statistical Biases

- Statistical bias for a point estimator is defined as the difference between the parameter to be estimated and the mathematical expectation of the estimator.
- Not accounting for important prognostic factors can bias estimated treatment effects.
- Statistical biases can be corrected BUT design flaws lead to biases that CANNOT be corrected!!!

Minimizing Bias

- Randomization
  - Unrestricted
  - Restricted
- Blinding
  - Double-blinded
  - Single-blinded
  - Open-label
- Compliance
  - High proportion of subjects
  - Unaffected by treatment
  - Uniform across strata

Controls

The control group plays an essential role in clinical studies and serves as standard or baseline for ascertaining the effectiveness of the study drug. By comparing the data obtained from the experimental group with that of the control group, one *can nullify the external factors (factors other than the study drug) that may be affecting the overall condition of the participants.* For example, in a study involving a drug for asthma patients, by having a control group the researchers can be assured that the improvements in the condition of the participants is caused by the drug and not by factors like change in weather and/or season.

Types of Controls

- Placebo concurrent control
- No treatment concurrent control
- Dose response concurrent control
- Active positive control
- External control (including historical control)
- Multiple control groups

Control

Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment. The control group experience tells us what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective.

ICH E10

Placebo

In a placebo-controlled trial, subjects are randomly assigned to a test treatment or to an identical-appearing treatment that does not contain the test drug. Such trials are almost always double-blind. The name of the control suggests that its purpose is to control for "placebo" effect (improvement in a subject resulting from thinking that he or she is taking a drug), but that is not its only or major benefit.

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Placebo and the DoH

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

Placebo and the DoH (Contd)

- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option.

Biomarkers

The term “biomarker”, a portmanteau of “biological marker”, refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly.

- Surrogate biomarker: A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint, e.g. Blood glucose, tumour size.
- Non-surrogate biomarkers: adjunct to clinical measures, provide added value

Classification of Biomarkers

- Many ways to classify biomarkers:
- Clinical Use
  - Diagnostic biomarkers
  - Staging biomarkers
  - Monitoring biomarkers
  - Pharmacodynamic
- Nature of Biomarker
  - Physiologic Biomarkers
  - Chemical biomarkers
  - Genetic biomarkers

Essential Properties

- Association
  - The biomarker must be associated with the disease or disorder. (Blood glucose and diabetes mellitus)
- Specificity
  - The biomarker should not be associated with other diseases, or related to a small number of diseases (Blood glucose is a good biomarker while ESR is not)
- Kinetic relation
  - Biomarker level should rise and fall with changes in the disease trajectory.

There are very few true biomarkers

End Point

In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumour.

National Cancer Institute

- End point is the finishing line of the trial.
- In most trials the end points are clear cut, but in some diseases there could be multiple end points.

Types of End Points

- A quantitative (or continuous or numerical) measurement representing a specific measure or count (e.g., quality of life, blood pressure, or heart rate). These endpoints can be summarized by means and medians

(Wang et al., 2006f)

- A binary clinical outcome indicating whether an event has occurred (e.g., death from any cause, the occurrence of disease signs or symptoms, the relief of symptoms). The proportions, odds ratios and risk ratios can be used to compare these endpoints

(Wang et al., 2006d)

Types of End Points

- The time to occurrence of an event of interest or survival time (e.g., the time from randomization of patient to death). Kaplan-Meier plot is often used to compare the survival experience graphically and Cox model is frequently used to estimate the treatment effect

(Cox, 1984; Wang et al., 2006b)

- The use of healthcare resources (e.g. the number of hospital admissions)

Types of End Points

- Primary endpoints measure outcomes that will answer the primary (or most important) question being asked by a trial. In a trial whether a new treatment is better at preventing disease-related death than the standard therapy, the primary endpoint would be based on the occurrence of disease-related deaths during the duration of the trial.
- Secondary endpoints ask other relevant questions about the same study; for example, whether there is also a reduction in disease measures other than death, or whether the new treatment reduces the overall cost of treating patients.

Composite End Points

- Many studies include multiple outcomes as part of a composite endpoint. Exploratory clinical investigations or early-phase studies are more likely to have multiple outcomes, with some of these being developed during the study.

Composite End Points

- An example of a clinical trial with a composite endpoint of multiple outcomes is the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study. This study looked at the effects of clopidogrel in patients with acute coronary syndromes without ST-segment elevation. In this trial, the primary endpoint was a composite of the following clinical outcomes:
  - Death from cardiovascular causes;
  - Stroke; and
  - Nonfatal myocardial infarction.

Trial Success

A good trial design itself does not ensure success, but success is virtually impossible unless the trial design is good.