PBIO 504

Clinical Trials and Randomized Controlled Trials

Experimental Studies in Epidemiology

Defined:

A study design in which the investigator actively controls who is exposed and who is not. Subjects are randomly assigned to various treatment groups and followed to observe outcomes.

In epidemiology , it is called:

Intervention Studies or

Randomized Controlled Trials

- Conducted much like the controlled experiments in scientific research
- The unit of analysis is the individual
- Clinical Trial: randomized controlled trial in a clinical setting

Experimental Studies in Epidemiology

- Identify clinical and public health approaches to solving public health problems
- Provide the strong evidence for causality and temporality
- Useful to evaluate the efficacy of prophylactic and therapeutic interventions
- Test the efficacy of new drugs or medical devices

Quasi-Experimental Studies
Community Trials

- Designed to test community interventions (behavioral change at the population level or any other educational interventions)

- The unit of observation in community trials is a group of people (e.g. school, neighborhood)

- Goal is to test if the intervention is successful in practice

Natural Experiment

- Some times in nature, unplanned events produce a natural experiment

- Exposure levels considered risk factor for a certain condition differ among a population in such a manner that it is relatively unchanged by other factors like a planned experiment

Experimental Studies

Between-group design (preferred):

comparison made between outcomes observed in *two or more groups* of subjects receiving different levels of the intervention

Within-group design:

comparing the outcomes observed in a *single group* of subjects before and after the intervention

Random Assignment

- Random assignment makes groups *similar*
- Chance alone determines group assignment

  For Community Experiments:

- Groups are randomly assigned the intervention

Non-Randomized Study

- Sample of convenience
- Unmeasured confounding cannot be controlled for
- Can only adjust for measured confounding variables in the analyses

Randomized Clinical Trials

Advantages

- Strong evidence for causality and temporality
- Averages out unconscious bias due to unknown factors
- Groups are similar due to randomization
- Minimizes selection bias, recall bias, or interviewer bias
- Interference with doctor-patient relationship (prevents conscious bias resulting from physician or participant selection)

Disadvantages

- Limited generalizability due to enrollment of volunteers, eligibility criteria, and loss to follow-up
- Ethical issues
- Expensive to conduct
- Side effects and adverse events can harm patients
- For certain health conditions it may be unethical to randomize and interfere with the doctor-patient relationship

Blinding (or Masking)

Blind with respect to the exposure assignment in order to prevent bias that could influence any aspect of assignment, assessment, compliance.

- A **single-blind** controlled study blinds the participants so that they are not aware as to who received the active treatment.

- A **double-blind** study blinds both the participants and investigators (or those who perform the outcome assessment) so that neither know who is receiving the active treatment.

- A **triple-blind study** involves blinding the participants and all those involved with the outcome assessment, and those analyzing the data.

Masking/Blinding

- Minimize potential bias from a *placebo effect* (Patients may get better or worse based only on their expectation that the assigned pill is going to have an effect or not. Also the observer may expect improvement/worsening if not knowing the treatment assignment)

- For drug studies, the pills/treatments for the different groups should have the same size, color, shape

- It may not always be possible to mask, depending on the type of intervention (e.g. side effects would reveal the treatment, or for surgery intervention placebo is unethical)

Clinical Trial

“ a clinical trial is a *planned experiment* designed to assess the efficacy of a treatment *in man* by comparing the outcomes in a group of patients treated with the *test treatment* with those observed in a *comparable group* of patients receiving a *control treatment*, where both patients in both groups are enrolled, treated and followed over the *same time period*.” Meinert, 1986

Clinical Trials

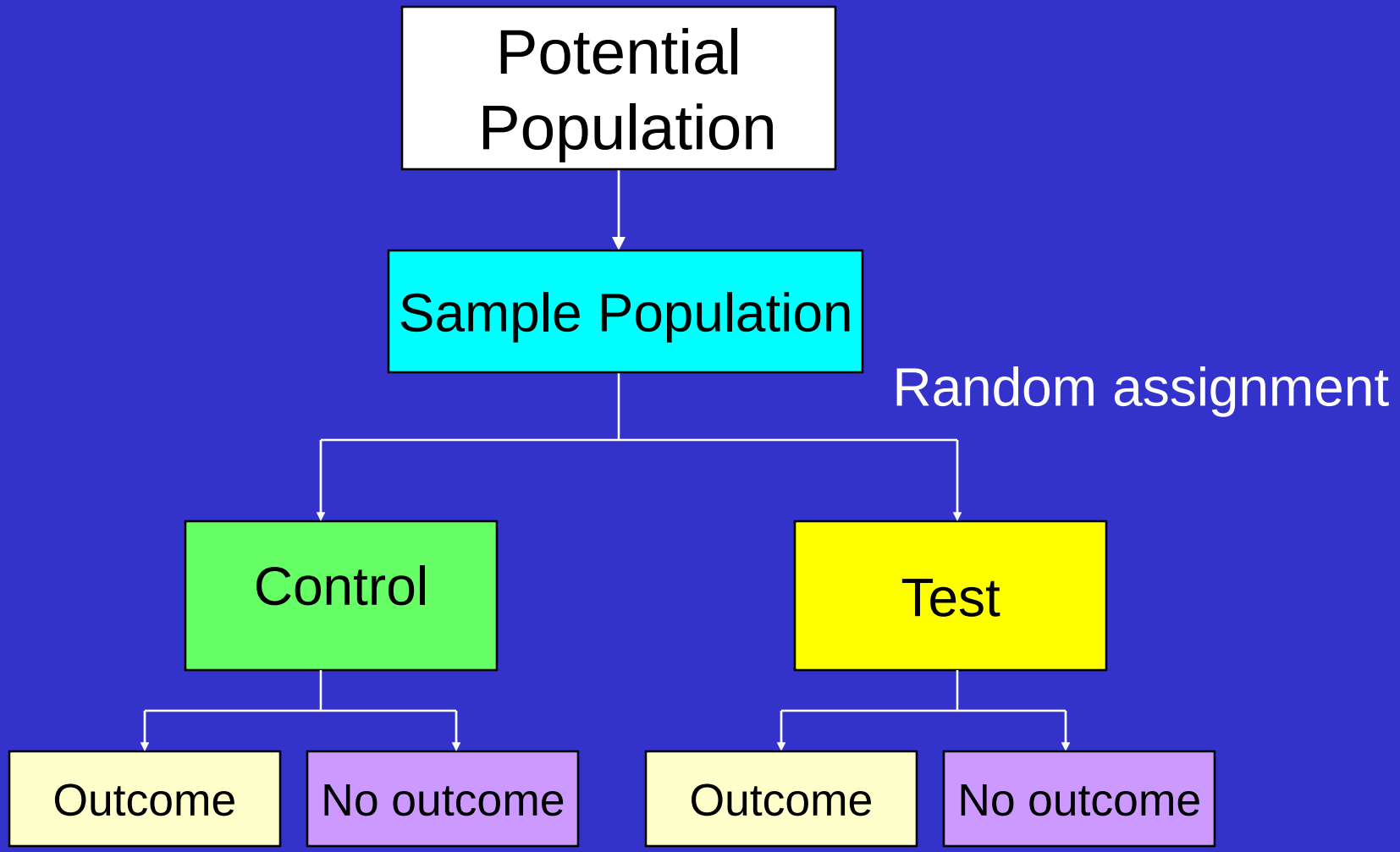
- Similar to Cohort Studies
- Groups enrolled at baseline
- Random assignment to the *test* and the *comparison* intervention
- Follow-up for a specific outcome

Types of Trials

- Treatment trials testing
  - drugs
  - surgery
  - procedures

- Trials of preventive procedures
- Trials of diagnostic or screening tests
- Trials of health care delivery
- Trials of health care policy

Design of Randomized Trials



Intervention Trial Example

A randomized trial was carried out among British civil servants to measure in middle-aged men the health effects of smoking cessation.

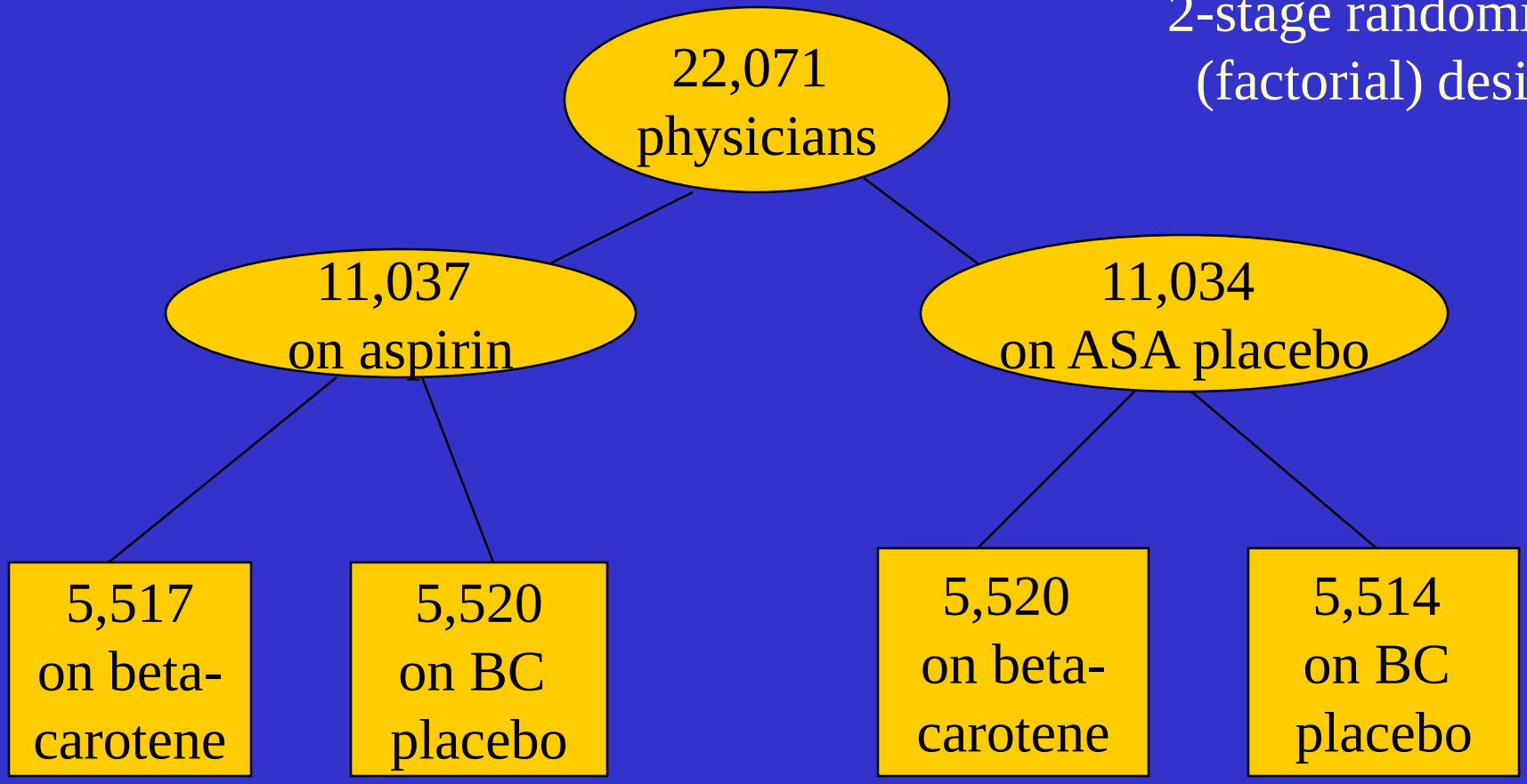
A total of 1,445 male cigarette smokers (40-59 yrs old) were randomly allocated to intervention (n=714) or normal care (n=731).

Those in the intervention group got advice and support for smoking cessation.

Both groups were followed for more than 20 years.

Physicians Health Study (1982-) effects of aspirin + beta-carotene on cardiovascular disease and cancer

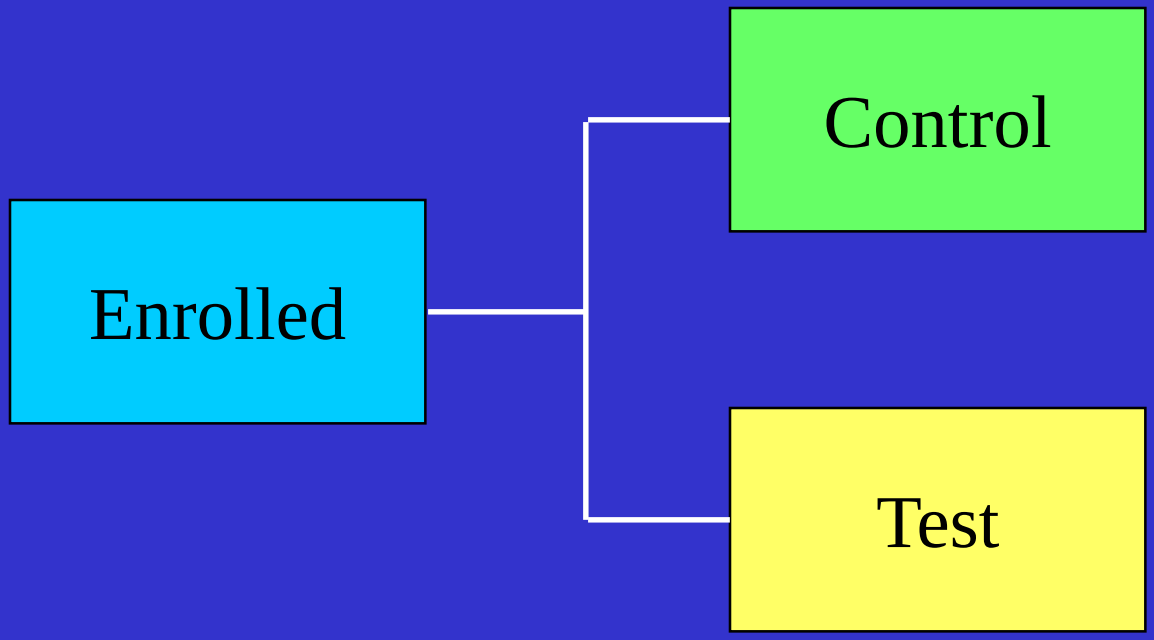
2-stage randomized (factorial) design



Randomization

Randomization is when patients are assigned to one of two or more interventions using an explicit method that assures the assignment will be random, or by chance (similar to flipping a coin).

Simple Randomization



Randomization

Usually results in comparable groups on *measured & unmeasured* variables that might affect the outcome differentially.

Controls confounding

Reduces selection bias (see next slides)

Selection Bias

- Often seen in hospital-based studies, in which the available cases differ on some characteristic from all other cases, or if the controls have an increased probability of being admitted to that hospital based on a certain characteristic (e.g. a host factor or disease agent of interest).

- This can lead to over-estimating or under-estimating the association between the disease and the main risk factor.

Examples of Selection Bias

- Patients with advanced disease may elect more extensive surgery

- Patients with family history may elect to be screened more often and earlier

- Physicians may not enter frail patients into a trial (or the other way around, they may only enter "worse" patients into the trial).

Randomization

- Reproducible method, one where future assignments cannot be predicted
- Examples:
  - Table of random numbers
  - Computer generated random numbers

  Not Recommended:
  - alternative numbers, choosing odd/even ID numbers because treatment for a particular patient can be predicted
  - coin toss because cannot prevent or show lack of bias in audit

Stratified Randomization

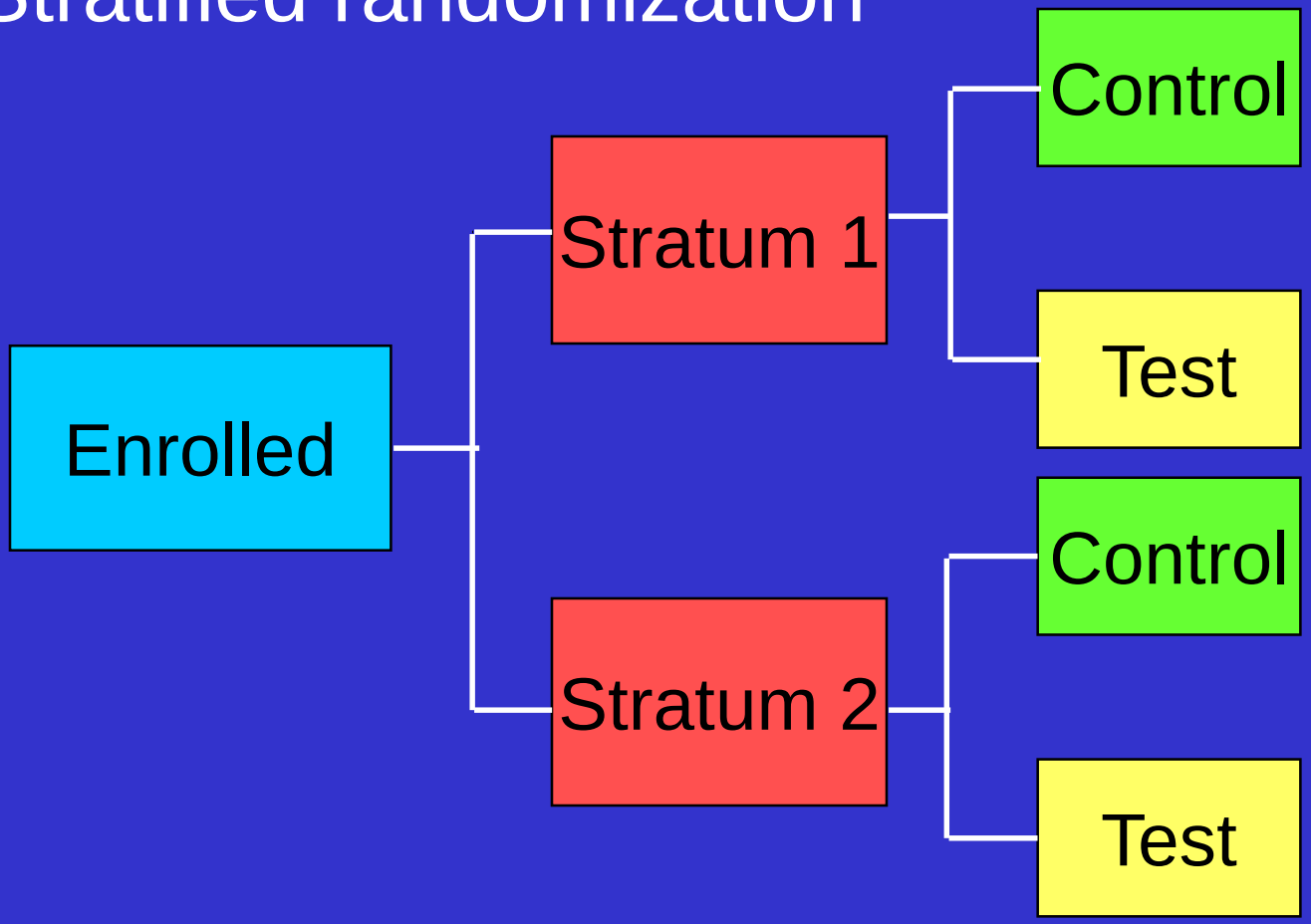
Stratified randomization is a two-stage procedure in which patients who enter a clinical trial are first grouped into strata according to clinical features that may influence outcome risk. Within each stratum, patients are then assigned to a treatment according to separate **randomization** schedules.*

- Attempts to assure comparability of groups on important prognostic variables known to affect outcome
- Better to use a small number of strata
- Examples of strata:
  - demographics: age, sex
  - baseline lab: blood glucose
  - physiological variables: hypertension
  - clinical characteristics: previous MI

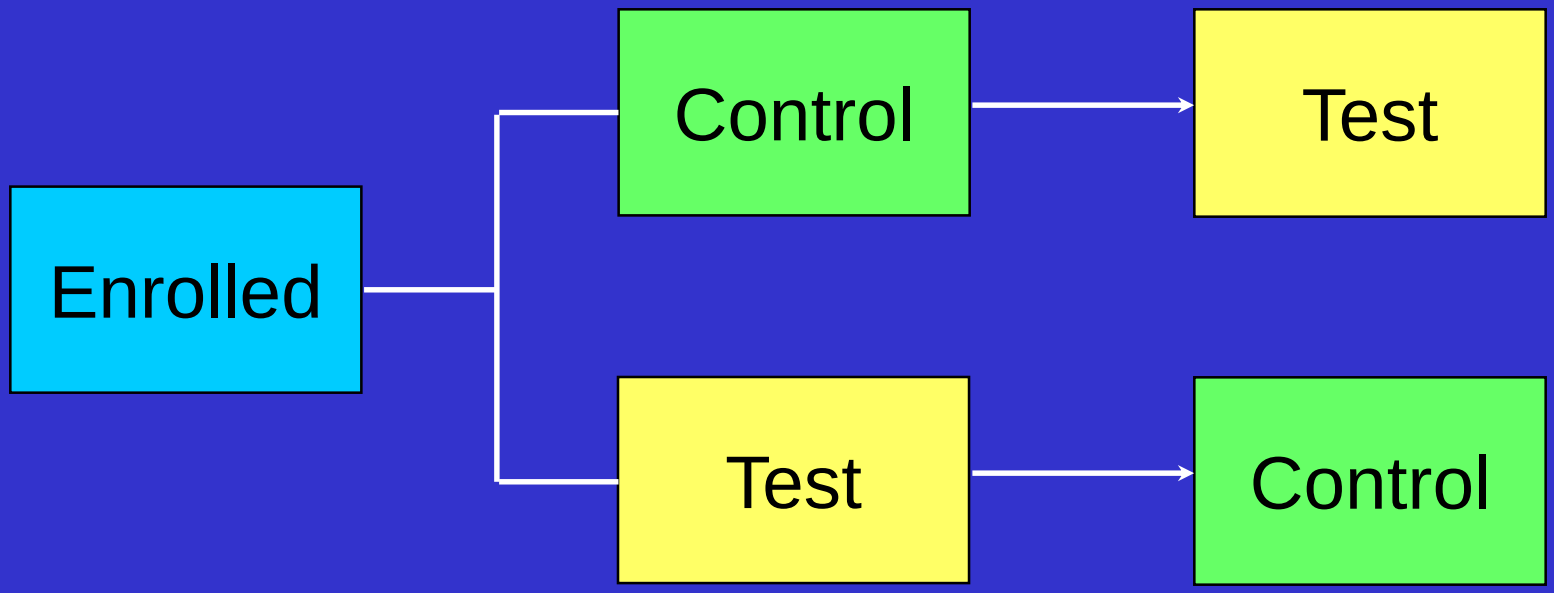
*Reference :Simon R. Restricted randomization designs in clinical trials. Biometrics 1979; 35: 503–512.

Stratified Randomization

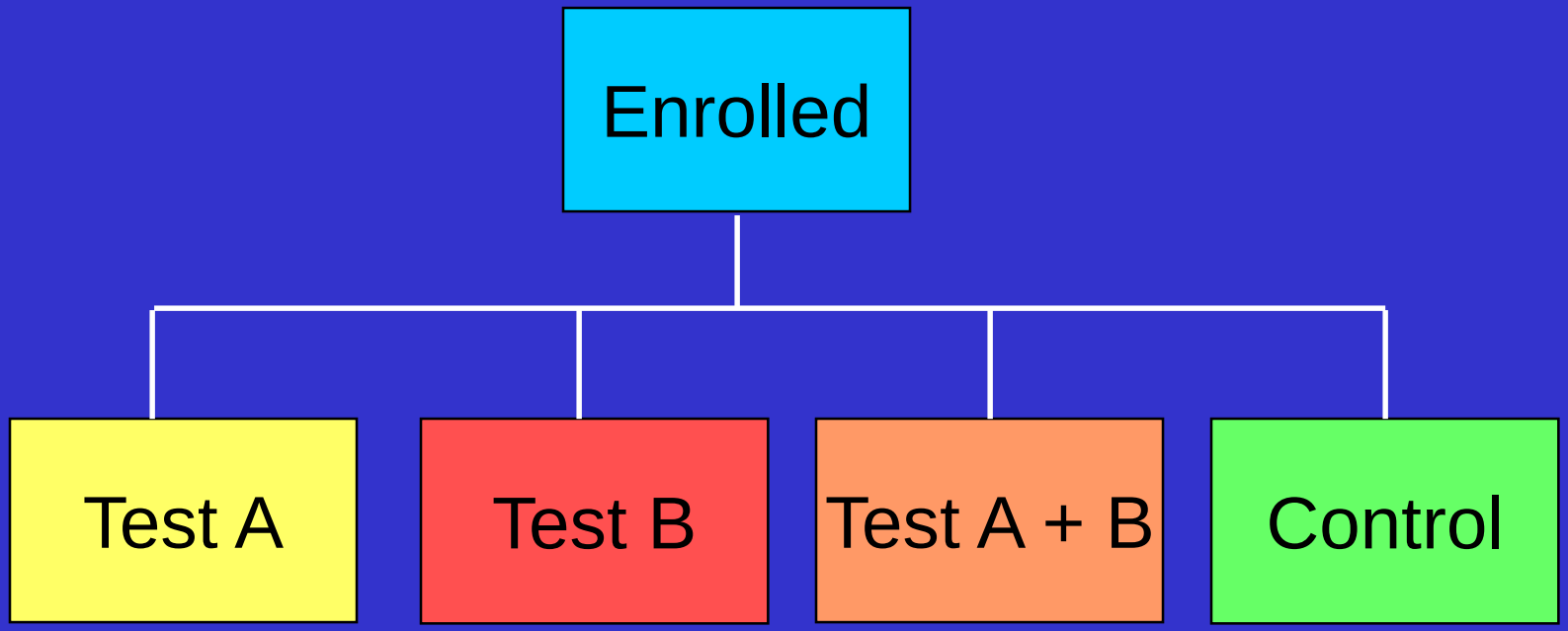
- Stratified randomization



Crossover Trials



Factorial Design



Outcome Measures

- **Primary outcome** -- used to demonstrate the efficacy of the intervention, and to calculate the required sample size
- **Secondary outcomes** -- used to show efficacy for other health effects, besides the primary outcome
- **Safety outcomes** -- adverse events, side effects

Example of Trial Outcomes

efficacy study of a new anti-diabetic medication

Primary Outcome

- Blood sugar control

Secondary Outcomes

- weight control
- glaucoma
- microvascular changes
- cardiovascular function
- atherosclerosis

Safety outcomes: side effects, adverse events

RCT Performance

- **Efficacy:** the extent to which the intervention produces a beneficial result under ideal conditions
- **Effectiveness:** the extent which the intervention produces a beneficial result when deployed in the population
- **Efficiency:** the extent to which the resources used to provide the intervention can be minimized (i.e. not wasted)

Early Stopping Rules

- Most clinical trials have a Data and Safety Monitoring Committee, independent of the investigator, to decide if a trial should be stopped early.
- Early stopping might be due to an unacceptably high rate of adverse events or side effects, or because a benefit of the intervention is so clear that it would be unethical to continue to withhold the intervention from those who might benefit from it.

Sample Size Calculations

Important because:

- If sample size too large:
  - costly
  - may expose too many patients to inferior intervention
- If sample size too small:
  - may be unable to detect important effect
  - no difference will not establish no effect

Sample Size Modifications

- Usually need to increase calculated sample size because of:

  - dropouts
  - non-compliance
  - treatment crossovers
  - ineligible patients

Basic Principles of Analysis

The initial comparison of treatment groups should:

- Include ALL patients assigned to treatment groups
- Should be done by the ORIGINAL treatment assignment
- Should include ALL recorded events for outcomes

The **"Intention to Treat" Principle**

Example of Intention to Treat Analysis

Randomly assigned to:	Coughing stopped		
	Yes	No	
Cough medicine	30	125	155
Control	28	126	154

Relative Risk = (30/155) / (28/154) = 1.06 and 95% CI=0.6-1.9, so we would conclude cough medicine does not help

BUT--Treatment Assigned is Different from Treatment Received

What if the cough medicine tasted terrible?

-- and people had stopped taking it

Example of
Analysis by Treatment Received

Treatment Taken	Coughing stopped: Yes	Coughing stopped: No	
Cough medicine	30	90	120
Control	28	161	189

Relative Risk = (30/120) / (28/189) = 1.69, and 95% CI: (1.3 - 4.7), so we'd conclude cough medicine was efficacious! But was it really?

Always Want to Use Intention to Treat Analysis

The reason for randomization is to avoid confounding and selection bias. By selecting which patients to analyze, we lose the advantage of randomization!

But we also need to account for ineligible patients, treatment cross-overs, non-compliers, and missing data – we should think about this while determining sample size!

Another Example: Intention to Treat Analysis

- The Coronary Drug Project was carried out to evaluate the efficacy of using a drug, CX, in older adults to lower mortality from atherosclerosis.

- The mortality rate after 5 years of follow-up of 1,103 people randomized to receive CX was 20.0%, compared to 20.9% mortality in the control group of 2,789 people randomized to the placebo.

- This difference was not statistically significant (p=0.15).

Analysis of Same Data Set by Adherence to Treatment

- Good adherence to using CX was defined as taking 80% or more of the prescribed pills.
- Good adherers had a mortality rate of 15.0% in 5 years
- Poor adherers had 24.6% mortality.
- The p-value for this difference is 0.00011
- Isn’t it sensible to accept this finding as evidence for the efficacy of CX in the people who might actually use it as directed?

What about adherence among those in the placebo group?

- The 5-year mortality rates in the placebo group were 15.1% for good adherers, compared to 28.3% for poor adherers ($p<0.0001$)
- These results show the serious difficulty, if not the impossibility, of evaluating treatment efficacy in subgroups determined by patient behaviors after randomization!

Advantages and Disadvantages of Randomized Clinical Trials

PLUSES

- Direct control of confounding
- Causality
- Temporality
- No selection bias

MINUSES

- Ethical issues
- High costs
- Losses to follow-up
- Non-compliance
- Operational problems
- Side effects
- Early termination