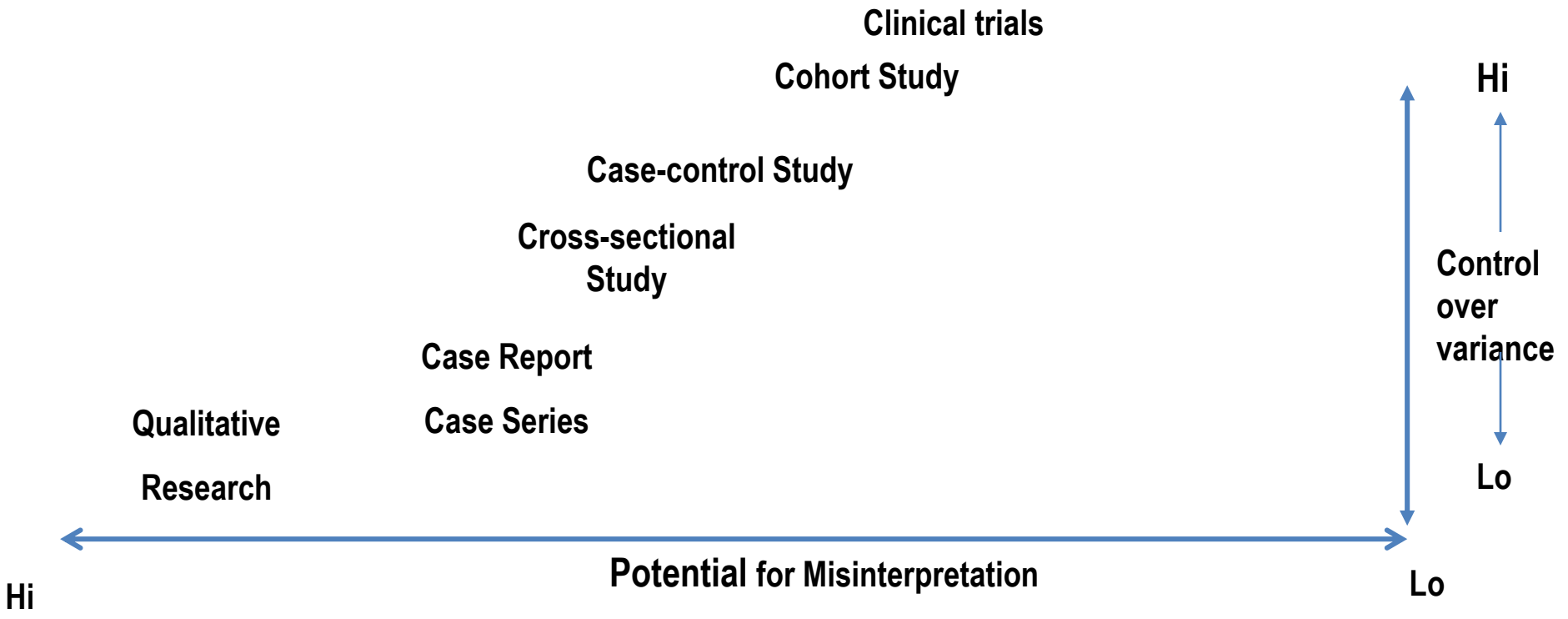
Methodologies for a RCT

AIMS

- Questions RCTs might answer
- Main strengths and weaknesses
- How to conduct them
- Different types of RCTs
- Randomization
- Blinding

Logic in Research



An unplanned trial 1510-1590

- Ambroise Pare, the surgeon (1510-1590)
- Boiling oil finished
- He used a mixture of Yolk of egg, oil of rose, and turpentine
- *The day after* the results were amazing
- He decided to never cauterize again

A planned trial, James Lind 1747

- Scurvy killed thousands seaman each year

I took 12 patients in the scurvy on board the Salisbury at sea. The cases were as similar as I could have them ... they lay together in one place and had one diet common to them all. Two of these were ordered a quart of cider per day.... Two others took 25 gutts of elixir vitriol.... Two others took two spoonfuls of vinegar.... Two were put under a course of sea water.... Two others had two oranges and one lemon given them each day.... Two others took the bigness of nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of 6 days fit for duty.... The other ... was appointed nurse to the rest of the sick.

47 year wasted

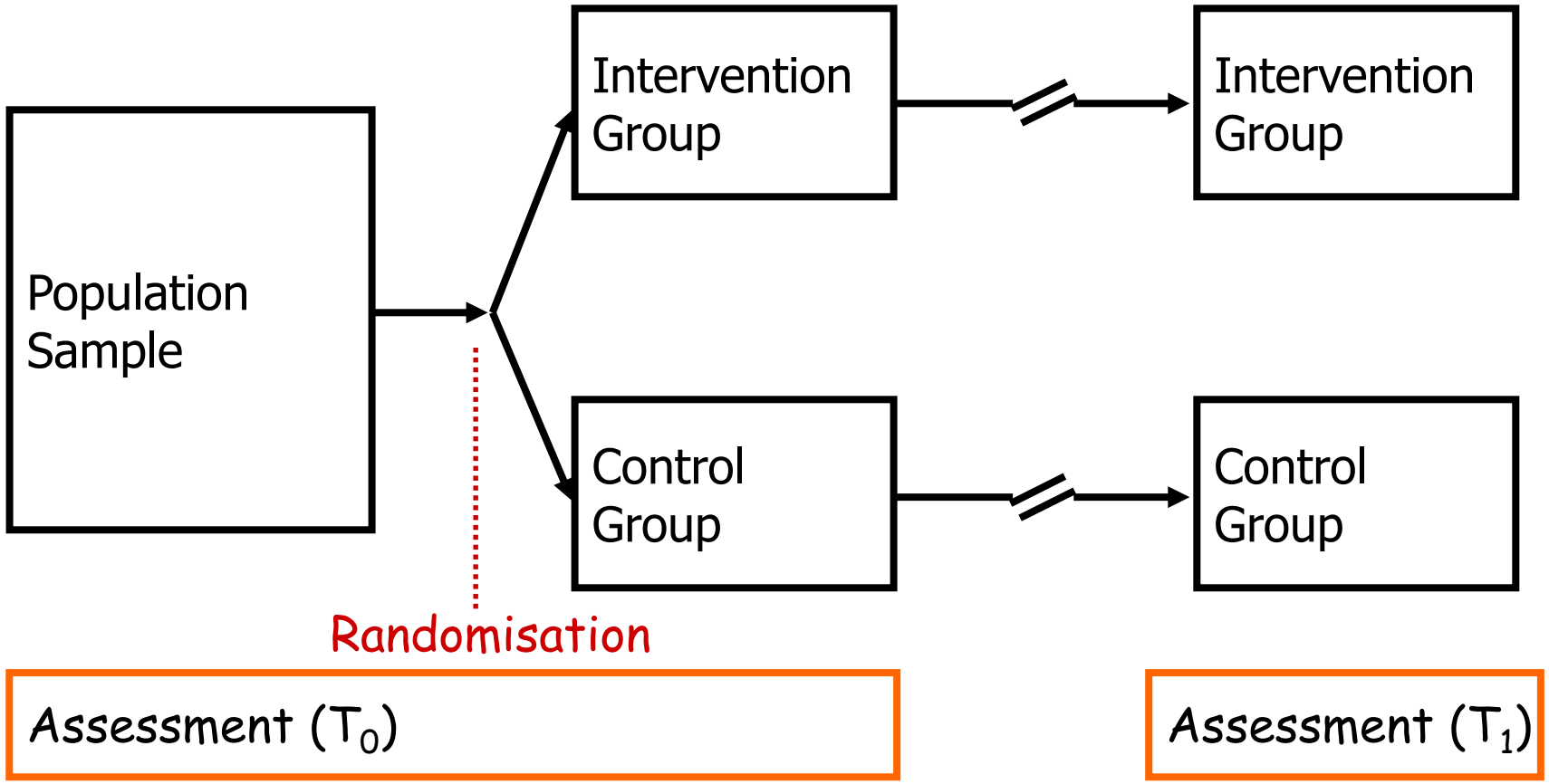
- His explanation of dietary cause for scurvy was not accepted
- It took 47 years for British Admiralty to let him repeat the experiment
- 1795: lemon juice standard part of british seaman’s diet

Randomised Controlled Trials (RCTs)

- A planned intervention study in which each member of a study population has the same chance of receiving one or more experimental or control treatments
- Randomisation is the *only* unique feature of RCTs

- The randomized trial is considered the ideal design for evaluating both the effectiveness and the side effects of new forms of intervention.

Randomised control Trial



Why RCT?

Two way for testing hypothesis

- Observentional
- Interventional

Example ; high speed

Who is in control?

- Every experiment should have a "**control group**."
- People in control group are treated exactly the same way as the other people in the experiment, except they do not get the "**active treatment**."
- A "**placebo group**" is a special kind of control group.

Control Groups

- What is the control group for?
  - Time
  - Attention
  - 'Placebo Effect'
- Inappropriate control group may threaten results

Question?

- Why shouldn’t we just give the new treatment to people and see if it works?

Coincidence

- The question is if we administer a drug and patient gets improved; Is one the cause of the other?
- "Results can always be improved by omitting controls"
  - Professor Hugo Muensch of Harvard University

Simultaneous nonrandomised controls

- Story of sea captain with anti-nausea pills

> the captain reported the results enthusiastically. "Practically every one of the controls was ill, and not one of the subjects had any trouble. Really wonderful stuff." A skeptic asked how he had chosen the controls and the subjects. "Oh, I gave the stuff to my seamen and used the passengers as controls."[10]

Randomization

- Randomisation in effect means tossing a coin to decide the assignment of a patient

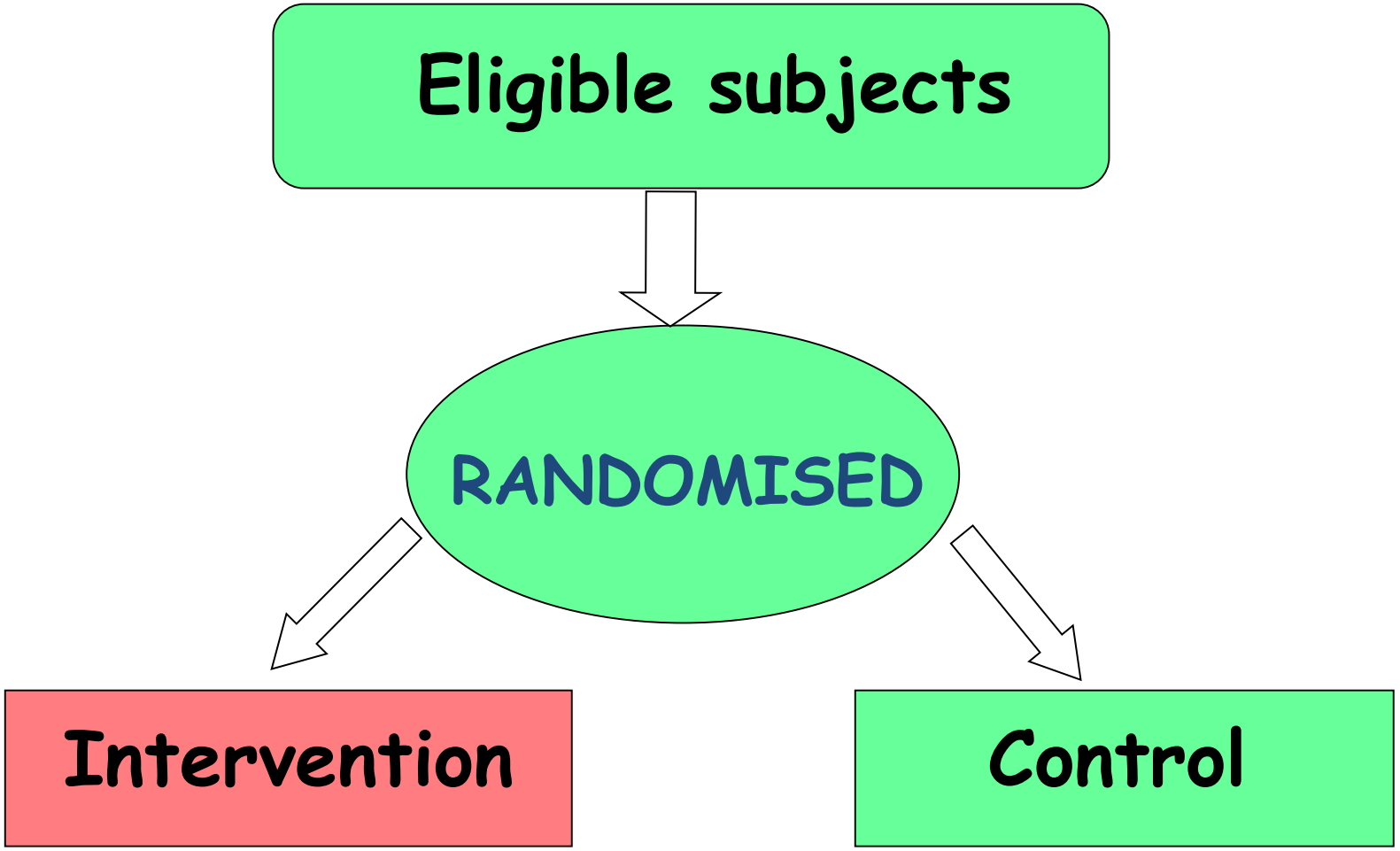
What do we achieve by randomization

- Equal chances for any subject to enter either the treatment or control group
- Comparable groups
- Balanced distribution of confounders even for confounders that we don't know

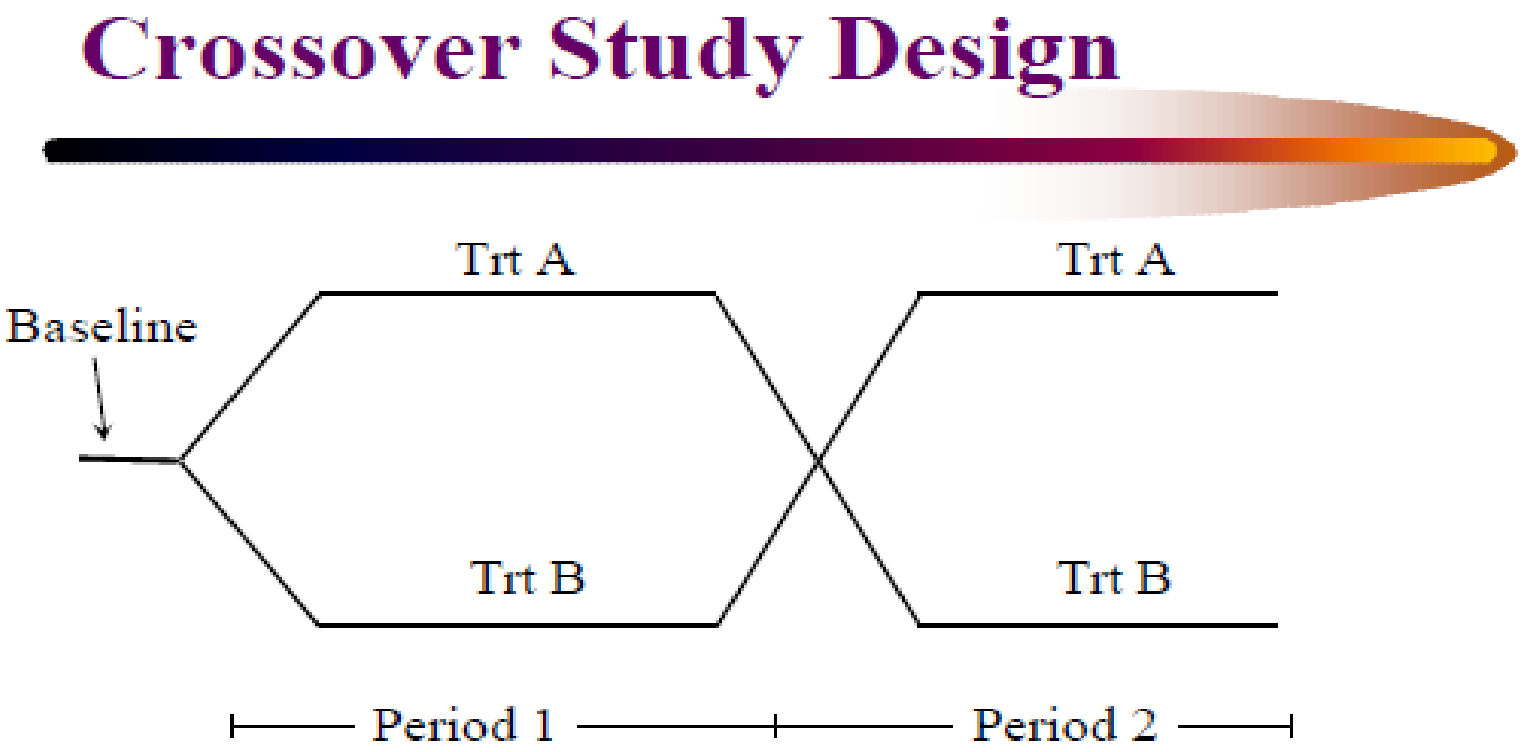
Clinical trial designs

- ❖RCT with Parallel (concurrent) controls
- ❖RCT with sequentional controls
- Self control (before- after study)
- Cross- over

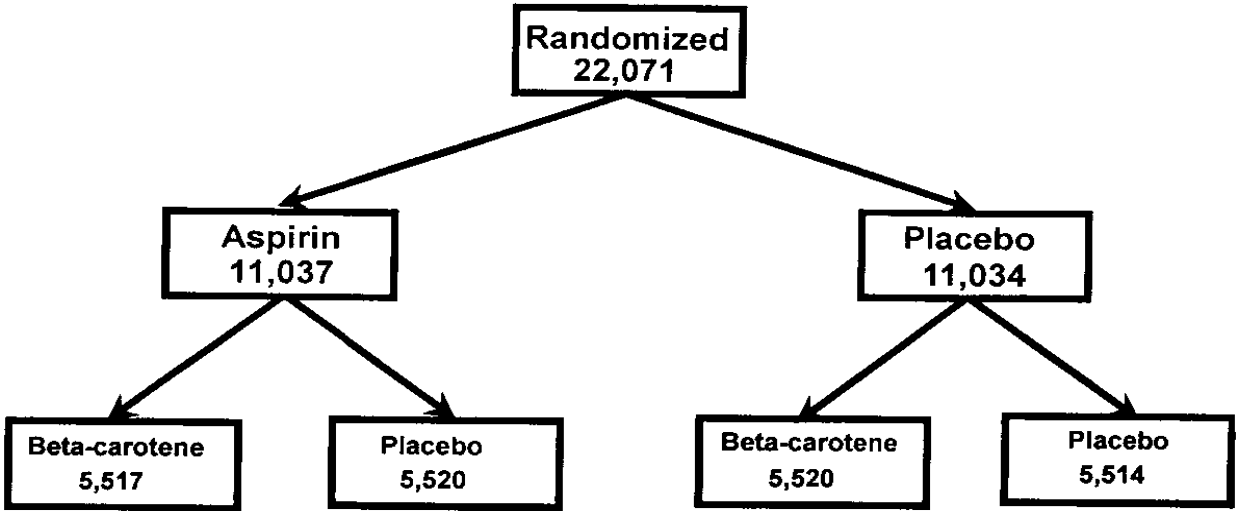
Parallel-group Randomised Controlled Trial



Cross over studies



Factorial design, example of Aspirin and Beta-carotene study



- The aspirin part of study was terminated, because of obvious results in 44% reduction of myocardial infarction
- Beta-carotene continued for 12 years and showed no effect in reducing cancer or heart disease

Non-compliance (dropouts)

- Overt: people stop participating
- Covert: stopping without admitting
- Tests can be done e.g. urine test for metabolites

The net effect of non-compliance

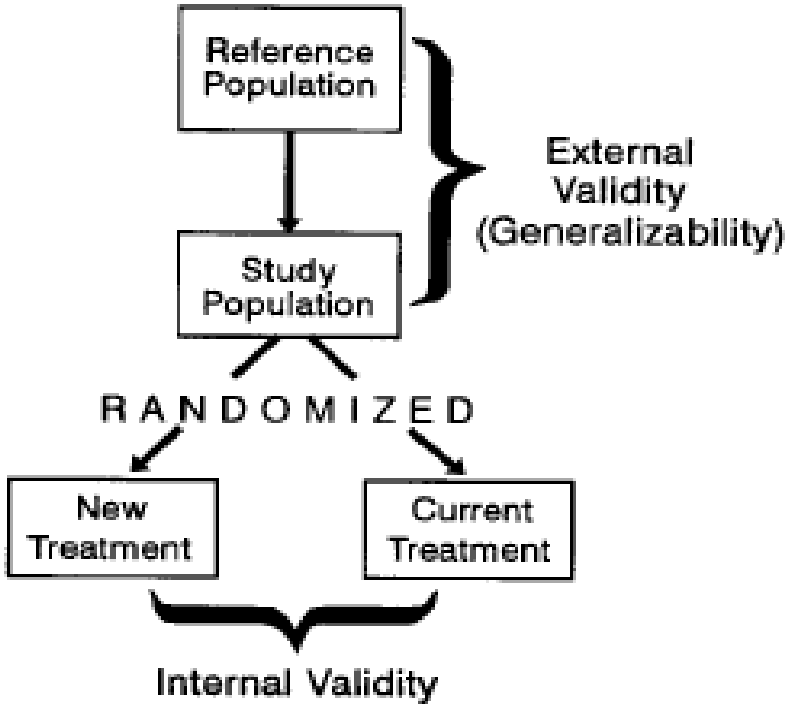
- Reducing observed differences
- Underestimation
- Example of clofibrate and placebo to reduce cholestrol

	No. of Patients	Mortality (%)
Clofibrate	1,065	18.2
Placebo	2,695	19.4

	No. of Patients	Mortality (%)
Clofibrate		
Poor complier (<80%)	357	24.6
Good complier (≥80%)	708	15.0
Placebo	2,695	19.4

Internal and external Validity

Are basic concerns in conduct of any trial



Whether the study is well done and findings are valid

Phases in testing new drugs

- Phase I: clinical pharmacologic studies, small studies of 20-80 look at toxic and pharmacologic effects
- Phase II: clinical investigation of 100-200 patients for efficacy and relative safety
- Phase III: large scale randomised controlled trials for effectiveness and relative safety; often multi-centre
- Phase IV: post marketing surveillance for possible late adverse effects such as carcinogenesis and teratogenesis

What Randomisation is NOT

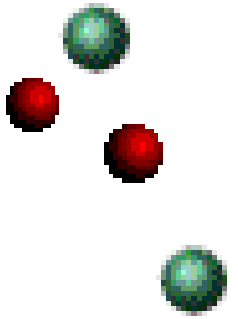
- Randomisation is often confused with random SAMPLING.
- Random sampling is used to obtain a sample of people so we can INFER the results to the wider population. It is used to maximise external or ecological validity.

Random Allocation Methods

Randomisation is main allocation method in scientific experiments
First proposed by Fisher (1935)
'The Design of Experiments'

Two Properties :

1. **Unbiased allocation**
2. **Balances covariates, known and unknown**



What do we achieve by randomization

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Randomised Trials

- The ONLY distinguishing feature of a RCT is that 2 or more groups are formed by random allocation.
- All other things, blinding, theoretical justification for intervention, baseline tests may be important but are not sufficient for a study to be a RCT.

Random Allocation

- It has no effect on the external validity of a study or its generalisability.

- It is about INTERNAL validity the study results are correct for the sample chosen for the trial.

Comparable Groups

- It has been known for centuries to properly evaluate something we need to compare groups that are similar and then expose one group to a treatment.
- In this way we can compare treatment effects.
- Without similar groups we cannot be sure any effects we see are treatment related.

Allocation Concealment

- Were the practitioner and the client both unaware of the next allocated treatment?
- Leads to recruitment bias or performance bias
- Safeguard the assignment sequence *before* and *until* allocation

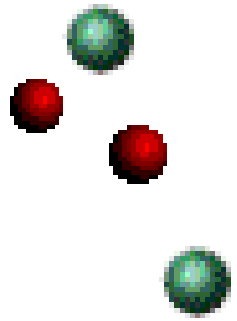
Allocation Methods Overview

Fixed Methods:

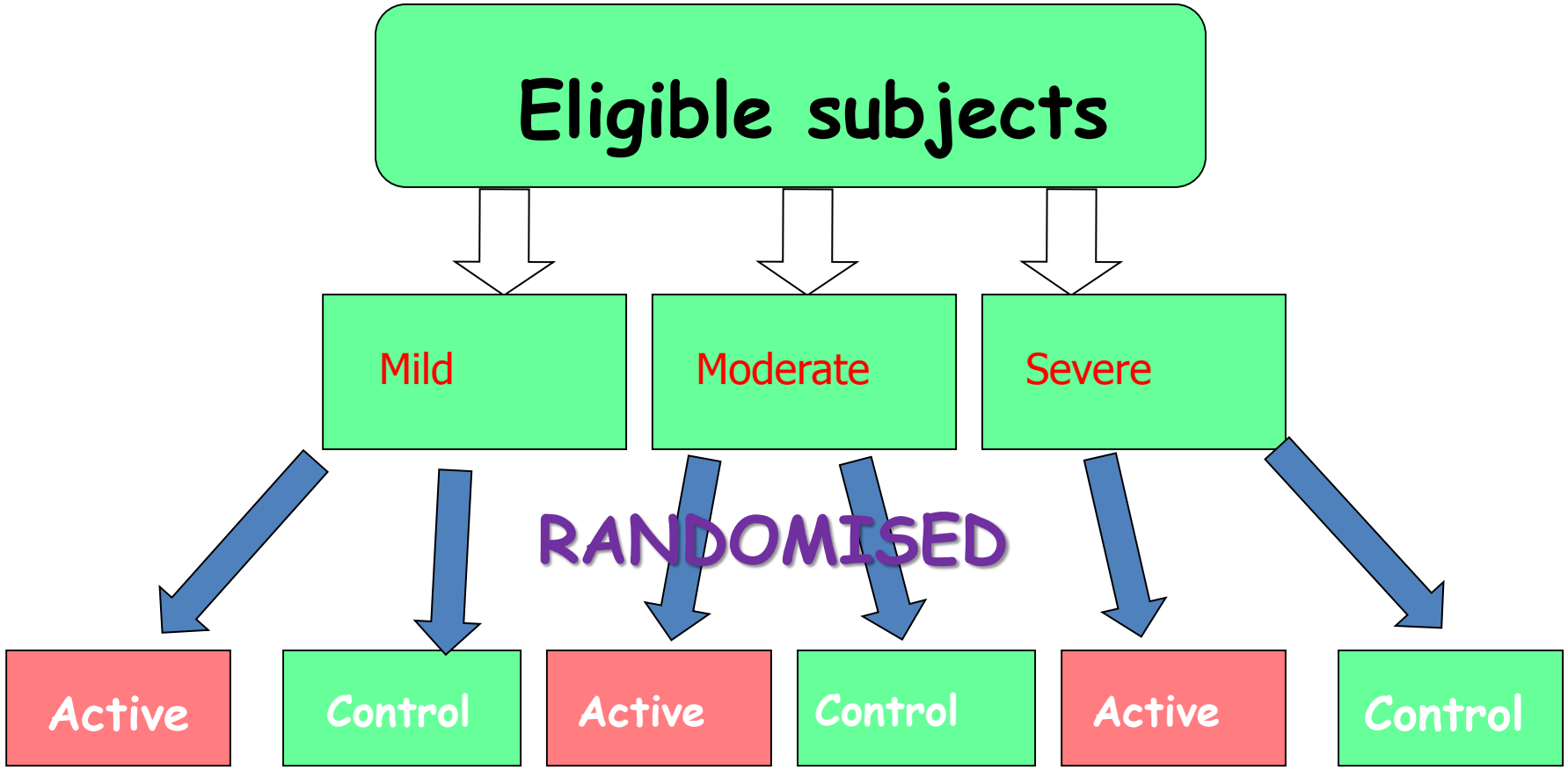
- Simple randomisation
- Stratification
  - paired
  - Blocking
- Minimisation

Adaptive Methods:

- Urn randomisation
- Biased Coin
- Play-the-winner



Stratified Parallel-group Randomised Controlled Trial



Non randomized trials

- Uncontrolled trial
- Historical controls
- Psude randomization

Blinding

- Safeguards the assignment sequence *after* allocation
  - Users
  - Practitioners/Clinicians
  - Assessors
- Not always possible
- Financial burden
- (often requires more staff)

Figure 1: **The authors: double blinded versus single blinded**

Single Blind Studies

- single blind studies are usually done to blind the patient to the treatment given. Health care providers and assessors

  usually know the actual treatment given

- justification is usually that double-blind is "impractical" because of need to adjust medication, medication affecting laboratory values, potential side effects, etc.

- a single blind study should be used only when it would be

  unacceptable ethically to give an appropriate placebo treatment to a patient, and in such a case, the assessor (not the patient) should be the one blinded to the treatment

Double Blind Studies

- When both the subjects and the investigators are kept from knowing who is assigned to which treatment, the experiment is called “double blind"

- Serve as a standard by which all studies are judged, since it minimizes both **potential** patient biases and **potential** assessor biases

- Should be used whenever possible, which is **whenever** it is ethically permissible to blind a patient

Double Blinding:always feasible??

Situations when double blinding might not be possible

- it might not be ethically permissible to blind a patient. As an example, it is unlikely that sham surgery would be considered ethical in a study
- it might not be possible to blind a patient. For example, it would be hard to blind a patient to the therapy given in an exercise study
- it might not be possible to blind a patient while comparing utility of different invasive procedures

Triple Blinding

- Patients
- Researcher
- Assesor

Allocation v. Blinding

- Allocation concealment refers to the process of recruitment and assignment to groups and *occurs before and during the enrollment process*
- Blinding refers to the knowledge of practitioners, staff, patients, etc. to the actual assignment *(i.e. it occurs during and after enrollment)*

- Double blinding prevents ascertainment bias and protects randomization after allocation and during study
- Allocation concealment prevents selection bias and protects randomization during selection

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A N Y
QUESTIONS?