



# Experimental studies

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# Types of clinical studies (1)

## I. Observational studies:

- *Case series*
- *Case-control*
- *Cross-sectional* (only 1 time observation)
- *Cohort* (prospective)
- *Retrospective cohort studies*

Note: Observational studies are not discussed in this session

# Types of clinical studies (2)

## II. Experimental studies (= Clinical Trial, CT):

### A. With control:

- Parallel
- *Cross-over*
- *Latin- square*
- Factorial

# Types of clinical studies (3)

B. Without control:

- Time-series
- Before and after

III. Meta analysis

# Experimental studies (Clinical trials)

# Important elements in planning an experimental study (1)

- The rationale and the objective(s) of the study
- Design of study: parallel, cross-over, etc.
- Subject population
- Sample size determination
- Selection criteria
- Outcome measures (primary and secondary)
- Study procedure

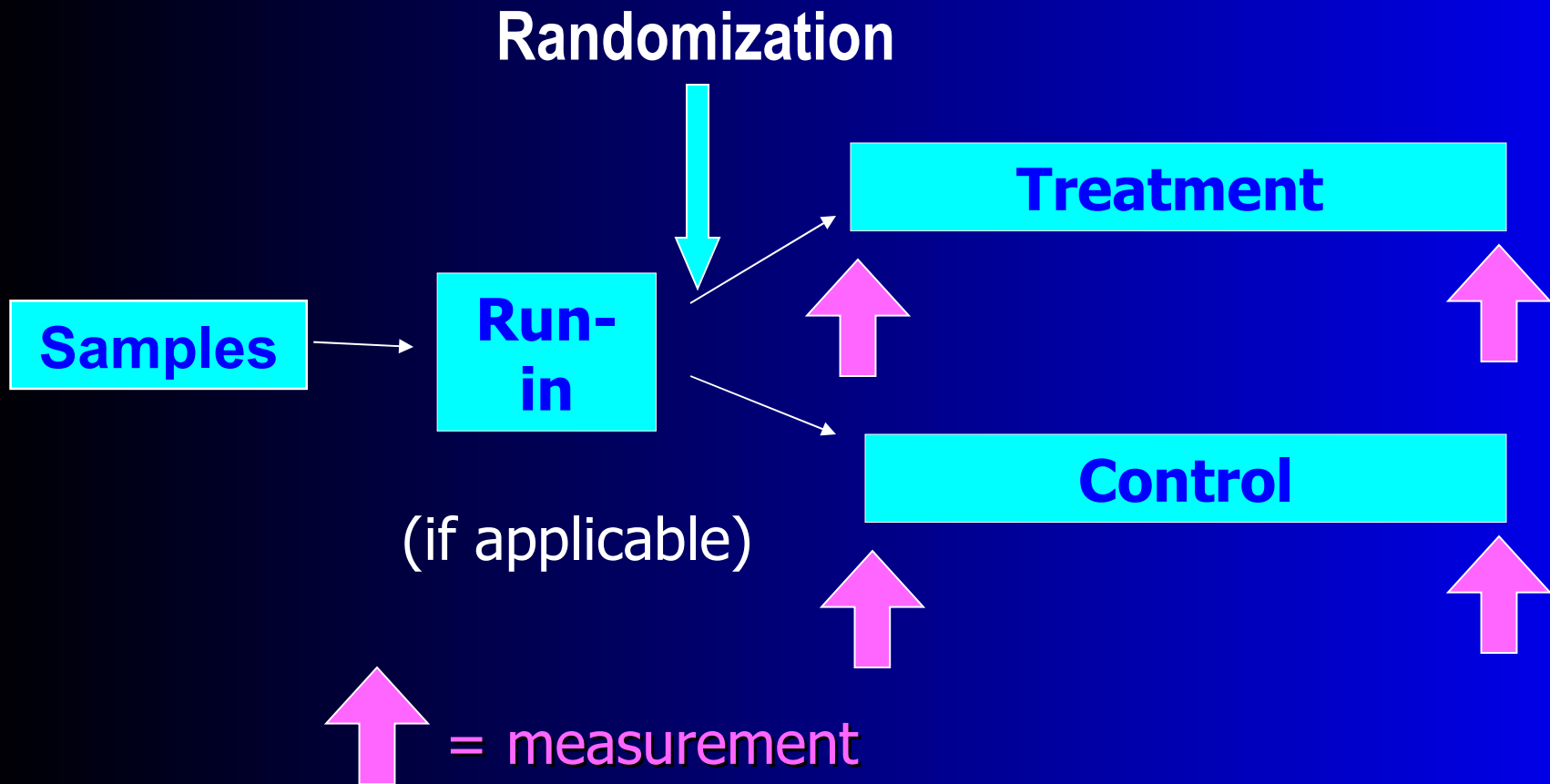
# Important elements in planning an experimental study (2)

- Randomization
- Blinding
- Control drug
- Managing dropouts
- Analysis: per protocol (PP) or intent-to-treat (ITT)
- Ethical aspects: ethical approval and informed consent
- Statistical analysis

# Study design: Parallel (1)

- Most commonly used
- Applicable for both acute and chronic diseases
- Applicable for 2 groups or more
- Randomization is mandatory
- Blinding is also of paramount importance, except it is technically impossible to implement

# Study design: Parallel (2)



# Study design: Parallel (3)

The advantages conducting of randomized, controlled trial:

- Bias is minimized because randomization and blinding
- More conclusive results are obtained because the confounding factors are controlled.

E.g.:

Various observational studies proved that beta-carotene reduced the risk of cancer. Four clinical trials, in contrast, showed the contrary results (Marshall, 1999)

# Study design: Parallel (4)

- May be faster and less expensive: This is especially true for fast-responding diseases  
E.g.: to find out the efficacy of cholesterol-lowering drugs, it is practically impossible to use observational studies.

# Study design: Parallel (5)

The disadvantages:

- Could be complex and expensive
- Sometimes it is time consuming
- Often confronted with ethical problems because it exposes research subjects to risks and inconveniences

E.g.: liver biopsy, endoscopic procedure, bone marrow puncture, etc.

# Study design: Cross-over (1)

- Each subject serves as control for his or her own.
- Advantages:
  - Eliminates inter-individual variations and therefore dramatically reduces the sample size down to 25% of that of the parallel design
  - Suitable for chronic and stable diseases

# Study design: Cross-over (2)

- Disadvantages:
  - Unsuitable for diseases which can be quickly cured or requiring only 1 x treatment (e.g. acute non-specific diarrhea, acute gonococcal urethritis, avian flu)
  - There are possibilities for carry over effect and order effect
  - Larger possibility for drop out
  - Requires sufficient wash out period
  - Cannot be done in subjects with low compliance
  - Difficulty to obtain  $SD_{diff}$  value

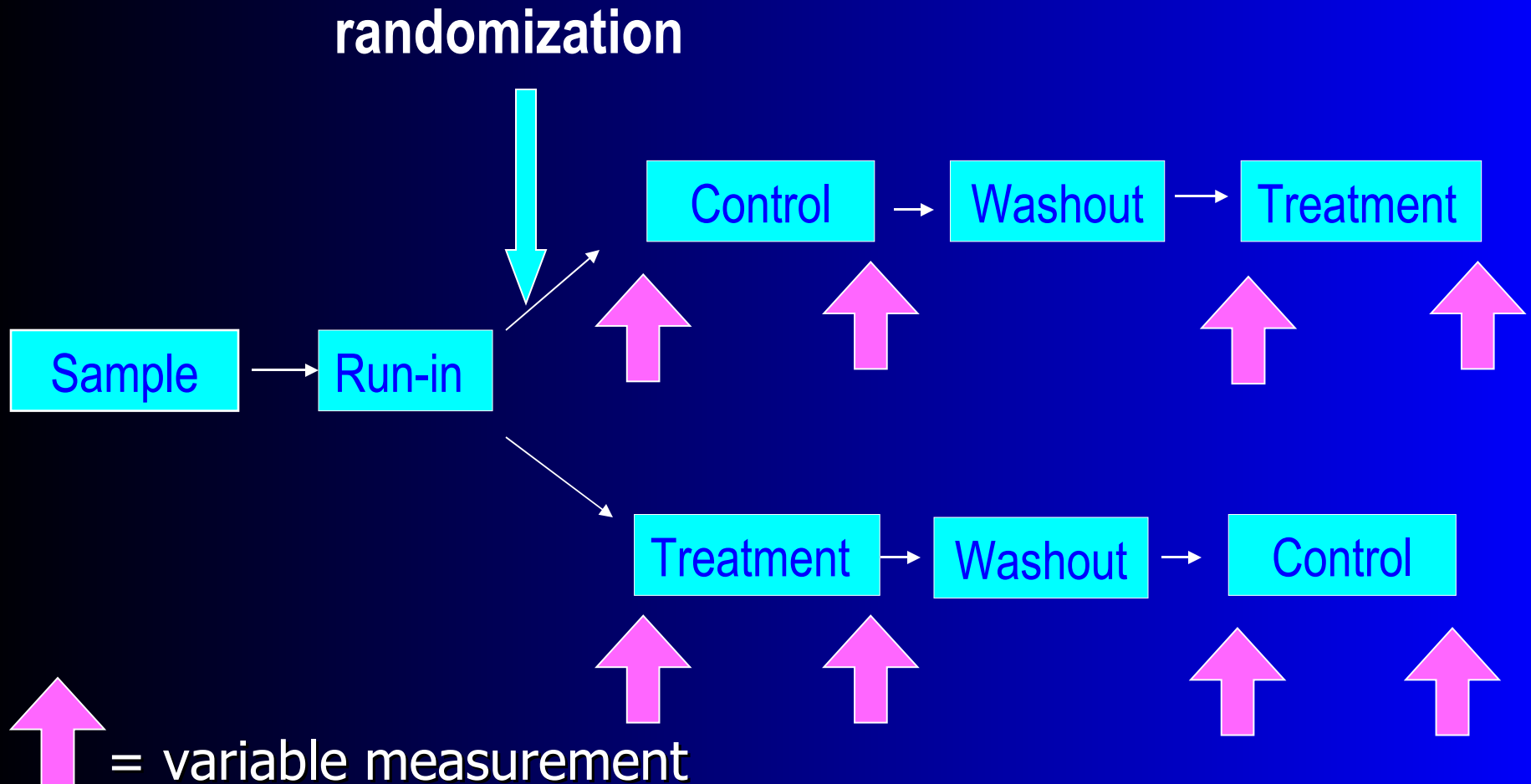
# Study design: Cross-over (3)

Examples:

Comparative trial on drug efficacy for:

- Chronic asthma
- Rheumatoid arthritis
- Hypercholesterolemia
- Hypertension

# Study design: Cross-over (4)



# Study design: Latin square (1)

Similar to cross-over design, but more than 2 groups are involved here.

Advantages:

- Reduces sample size

Disadvantages:

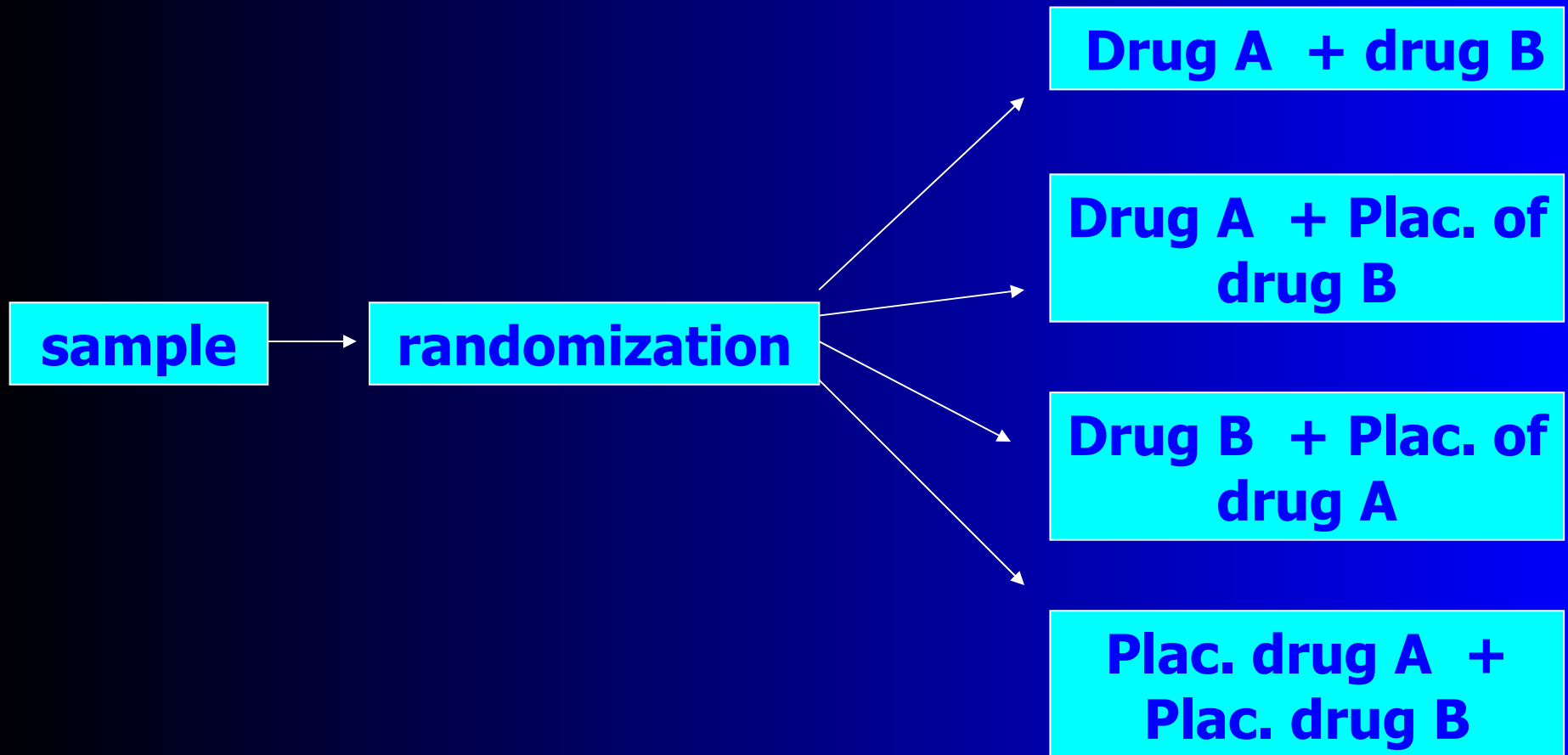
- Not applicable to quickly cured or immediately fatal diseases
- Requires highly cooperative subjects
- Requires long time for conducting the study

# Study design: Latin square (2)

Patient	Period			
	I	II	III	IV
Group 1	A	B	C	D
Group 2	B	D	A	C
Group 3	C	A	D	B
Group 4	D	C	B	A

Note: A,B,C,D = treatments

# Study design: Factorial (1)



# Study design: Factorial (2)

## Advantages:

- Highly efficient because it can answer 2 research questions without adding trial subjects
- Example: studying aspirin effect on myocardial infarction + beta carotene effect on cancer

## Disadvantage:

- If interaction occurs between the drugs being tested → interpretation of result becomes difficult

# CT without control

- Potentially produces in very misleading results
- Often used for promotional purposes (not scientific)
- Example: Publication on psychotropic drugs (Foulds, 1958):
  - Those without control: success rate 85% (n=52)
  - Those with control: success rate only 25% (n=20)

# CT with historical control

- Generally fails to produce valid result
- Associated with many weaknesses which give chance for bias in the study implementation (e.g. selection criteria, outcome measure, severity of disease, inclination to drop the non-responsive subjects, etc.)
- There is also inclination to exaggerate the superiority of the new drug

# Study design: Before and after

- Compares one variable before and after an intervention on each subject in a group
- No control group
- Bias may likely occur because subjects change their behaviour because they are enrolled in a study (Hawthorn's effect)
- Example: Comparing triglyceride serum level before and after intervention in a group of subject

# Subject selection (1)

- Determine the target population:  
i.e. the general population.  
E.g.: patients with psoriasis
- Determine the accessible population:  
this is part of the target population which is accessible by the investigator in terms of place and time.  
E.g.: patients with psoriasis who visit the out-patient clinic in Ciptomangunkusumo Hospital

# Subject selection (2)

Types of sampling:

- Probability sampling:
  - Simple random sampling
  - Systematic sampling
  - Stratified random sampling
  - Cluster sampling

Note: probability sampling is applied in epidemiological studies

# Subject selection (3)

- Non-probability sampling:
  - Consecutive sampling: all subjects who meet the selection criteria are enrolled (this one is commonly applied in CT)
  - Convenience sampling: does not use any system → does not represent the population
  - Judgmental sampling: subjects are chosen base on the investigator's subjective consideration.

# Subject selection (4)

- Establish the inclusion and exclusion criteria:
  - Inclusion criteria:
    - Do not be too strict or too lenient
  - Exclusion criteria:
    - Applied to subjects who already met the inclusion criteria but have to be excluded due to a particular reason before they take the trial drug, e.g. because of pregnancy

# Measuring the outcome variables

- Measurements include:
  - Demographic data: age, body weight, gender, etc.
  - Clinical data
  - Laboratory data

# Sample size determination

- Sample size should be determined for each primary research objectives
- Various rules are available for this purpose
- Too small sample → false negative or false positive results
- Too large sample → too sensitive, time and fund wasting, ethical problems

# Randomization

- What is the difference between random sampling and random allocation?
- Types of randomization allocation:
  - Simple randomization
  - Block randomization
  - Stratified randomization

# Blinding

- Open trial
- Single blind
- Double blind
- Double dummy method: when is it used?

# During the intervention

- Pilot study: when is it required?
- Interim analysis
- Dropout handling:
  - Find out the reason of dropout
  - At what stage does it occur?
  - Intent-to-treat or per protocol analysis?

# Dropouts

- Dropouts are the patients who have entered the Clinical Trial but do not complete the trial due to various reasons
- Whenever possible find the reason for dropout
- Depending on the reason the patient may or may not be replaced
- If the reasons for dropout are adverse event or inefficacy of treatment → these patients must be included in analysis (as failure)

# Measuring the outcomes

- Determine the variables to be measured
- Determine 1 primary outcome and  $\geq 1$  secondary outcome(s)
- Use the primary outcome for sample size estimation
- If possible, try to measure the true/clinical outcome or established surrogate outcomes.
- Determine the scale of measurement: categorical, ordinal, or numerical

# Choosing a statistical test

The choice of a statistical test depends on:

- Measurement scale: categorical, ordinal, or numerical
- Distribution of data: is it normally distributed?
- Sample size
- Number of group

**Thank you**