BIOSTATISTICS COURSE #5

CLINICAL TRIALS

OCTOBER 2025

SUMMARY OF THE COURSE #5

INTRODUCTION

01

INTRODUCTION

SCIENTIFIC METHOD

02

SCIENTIFIC METHOD
DEFINITION

- **Empirical** method for acquiring knowledge in science fields

- Emerged in the **17th century**

- Involves careful **observations** with rigorous **skepticism**

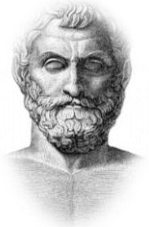
- Can be biased by **cognitive assumptions**

- Formulation and test of **hypotheses** is key

SCIENTIFIC METHOD
BRIEF HISTORY

- **Ancient Egypt** : Edwin Smith papyrus (~1600 BCE) : Egyptian medical textbook with first signs of **empirical** methodology : examination, diagnosis, treatment and prognosis

- **Classical antiquity** :



THALES (626/623 – 548/545 BCE) : first philosopher to use **natural explanat**ions.

ARISTOTLE (384 – 322 BCE) : founder of **Modern Science** with the Aristotelianism movement : deductive logic, analytic inductive method.

SCIENTIFIC METHOD
BRIEF HISTORY

- Middle Ages :

Ibn AL-HAYTHAM (965 - 1040) : Persian mathematician, astronomer and physicist considered as the father of **modern optics**

Roger BACON (1219/1220 – 1292) : English scientist and polymath and founder of **modern scientific method**.

SCIENTIFIC METHOD
BRIEF HISTORY

- Renaissance :

Francis BACON (1561 – 1626) : English philosopher, father of **empiricism** (evidence finding through experiments).

René DESCARTES (1596 – 1650) : father of modern philosophy and **rationalism** (“*reason has precedence over other ways of acquiring knowledge : faith, sensory experience or tradition*”)

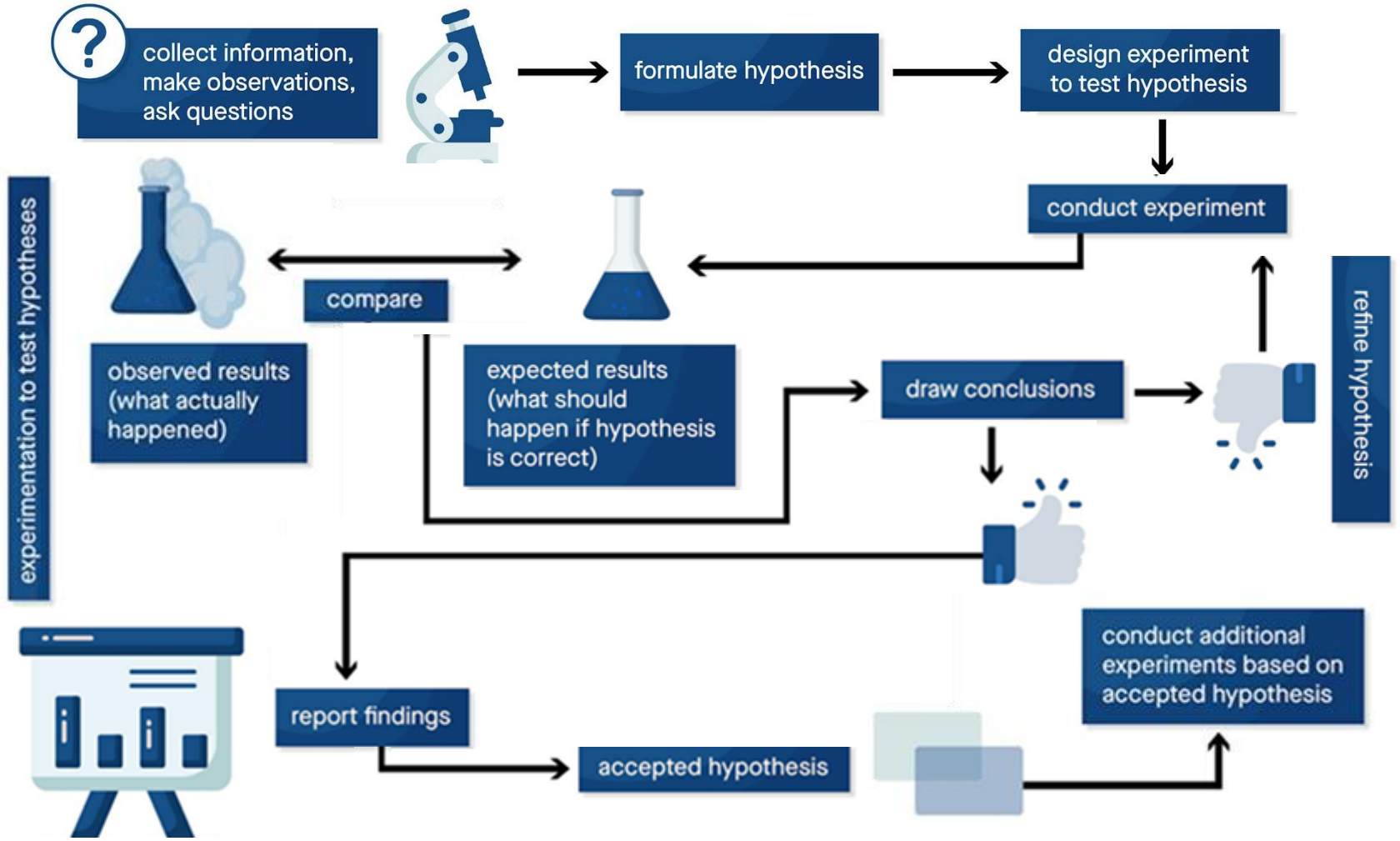
SCIENTIFIC METHOD
BRIEF HISTORY

- Scientific Revolution / Age of Enlightenment :

Galileo GALILEI (1564 – 1642) : Italian astronomer, physicist and engineer, father of **observational astronomy** and **modern science**

Isaac NEWTON (1642 – 1726/1727) : English mathematician, physicist and astronomer, founder of **modern scientific method**.

SCIENTIFIC METHOD
WORKFLOW



CLINICAL TRIALS

03

CLINICAL TRIALS
DEFINITION

- **Prospective** biomedical or behavioral research study on human participants designed to answer specific question about biomedical or behavioral interventions

- **Application domains** : treatments (vaccines, drugs, chirurgy…), dietary supplements, medical devices

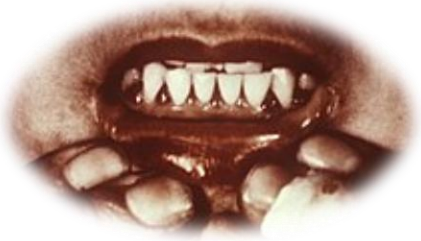
- Strictly **controlled**, **monitored** and **evaluated** by international (FDA in the USA, EMEA in Europe) and national health authorities (ANSM in France).

CLINICAL TRIALS
BRIEF HISTORY

Medical experiments exists from Antiquity but without any **control group**

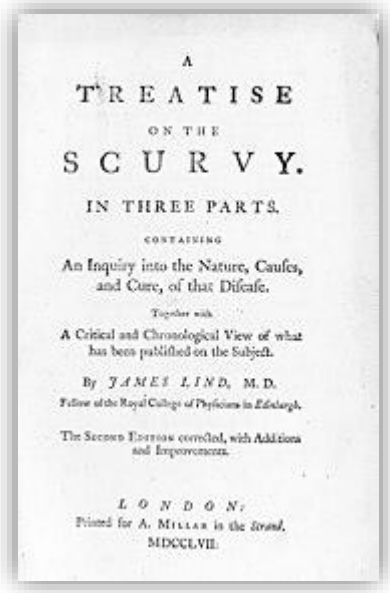
The **first clinical trial** was managed in 1747 by **James LIND** (1716 – 1794) : study of effect of various dietary supplements on **scorbutic** sailors during 2 months on a boat.

Scurvy : deficiency disease very common during long sailing travels.
Symptoms : weakness, fatigue, decreased red blood cells, skin bleeding, poor wound healing and death from infection



CLINICAL TRIALS
BRIEF HISTORY

Assumption to test : **citrus fruit** consumption is protective from **scurvy** (**vitamin-C** effect) : John WOODALL (1570 – 1643), surgeon of British East India Company


A
TREATISE
ON THE
SCURVY.
IN THREE PARTS.
CONTAINING
An Inquiry into the Nature, Causes, and Cure, of that Disease.
Together with
A Critical and Chronological View of what has been published on the Subject.
By JAMES LIND, M. D.
Fellow of the Royal College of Physicians in Edinburgh.
The Second Edition corrected, with Additions and Improvements.
LONDON:
Printed for A. MILLAR in the Strand.
MDCCLVII.

12 sailors divided into **6 groups of 2** with different **supplements** :

1. Cider
2. Sulfuric acid
3. Vinegar
4. Seawater (control group)
5. Oranges + lemon
6. Spicy paste + barley water

Only patients in **group 5** quickly recovered from scurvy.

CLINICAL TRIALS
BRIEF HISTORY

John HAYGARTH (1740 – 1827) : English physician who demonstrated the importance of **control group** for the correct identification of **placebo effect** in smallpox studies.

Ronald A. FISHER (1890 – 1962) : English statistician who proved the benefits of **randomization**, **replication** and **blocks** in clinical trials

Austin BRADFORD HILL (1897 – 1991) : English epidemiologist who pioneered the **randomized clinical trials** (first proved link between cigarette smoking and lung cancer)

CLINICAL TRIALS
BIAS

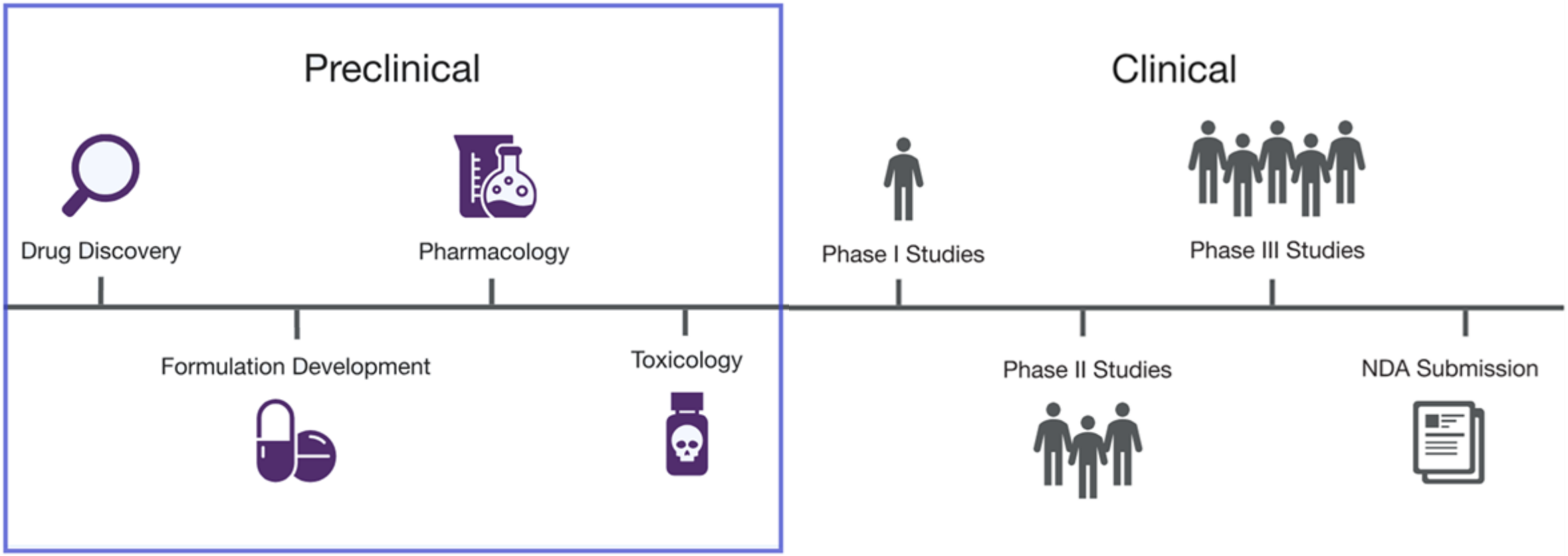
- **Selection bias :** systematic differences between **baseline characteristics** of the groups that are compared. **Randomization** helps to control it.

- **Performance bias** : systematic differences between groups in the care that is provided, or in exposure **to factors other than the interventions of interest. Blinding of treatment allocation** helps to control it.

- **Attrition bias** : systematic differences between groups in **withdrawals** from a study (missing values).

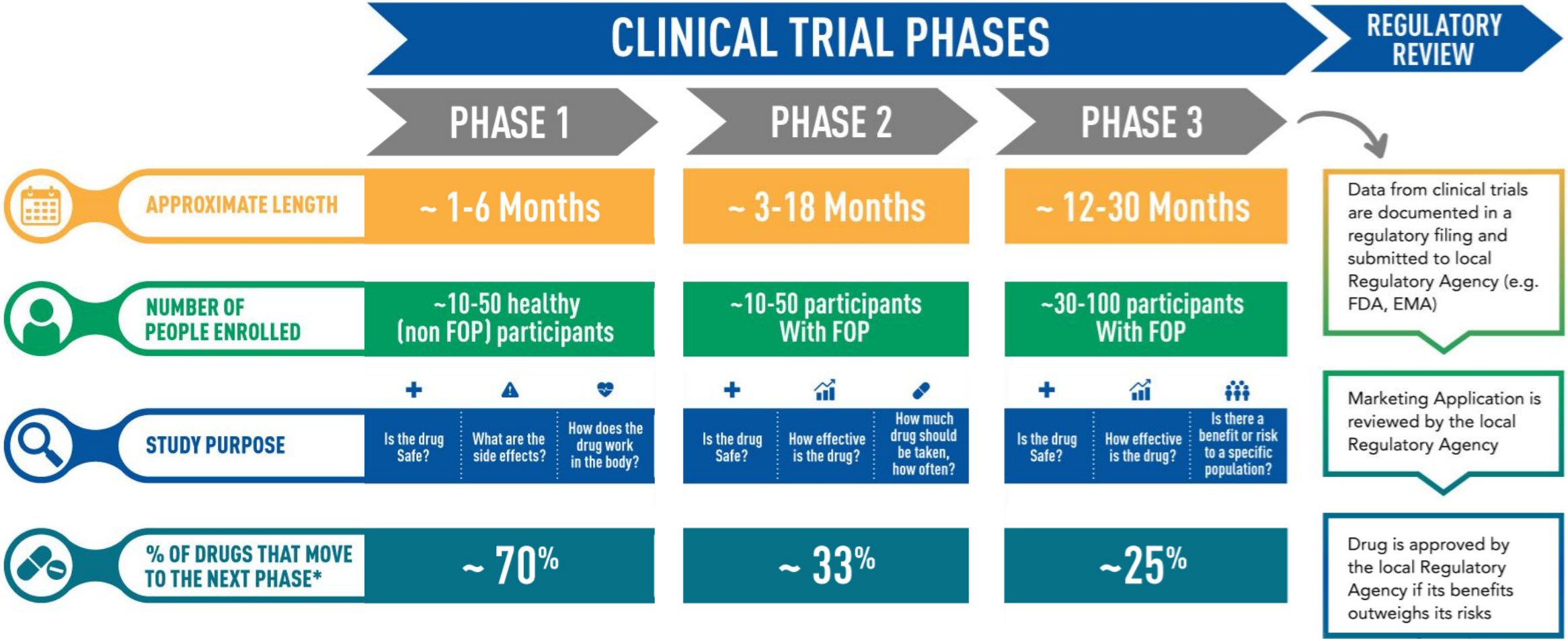
- **Reporting bias** : systematic differences between reported and **unreported** findings.

CLINICAL TRIALS
PHASES

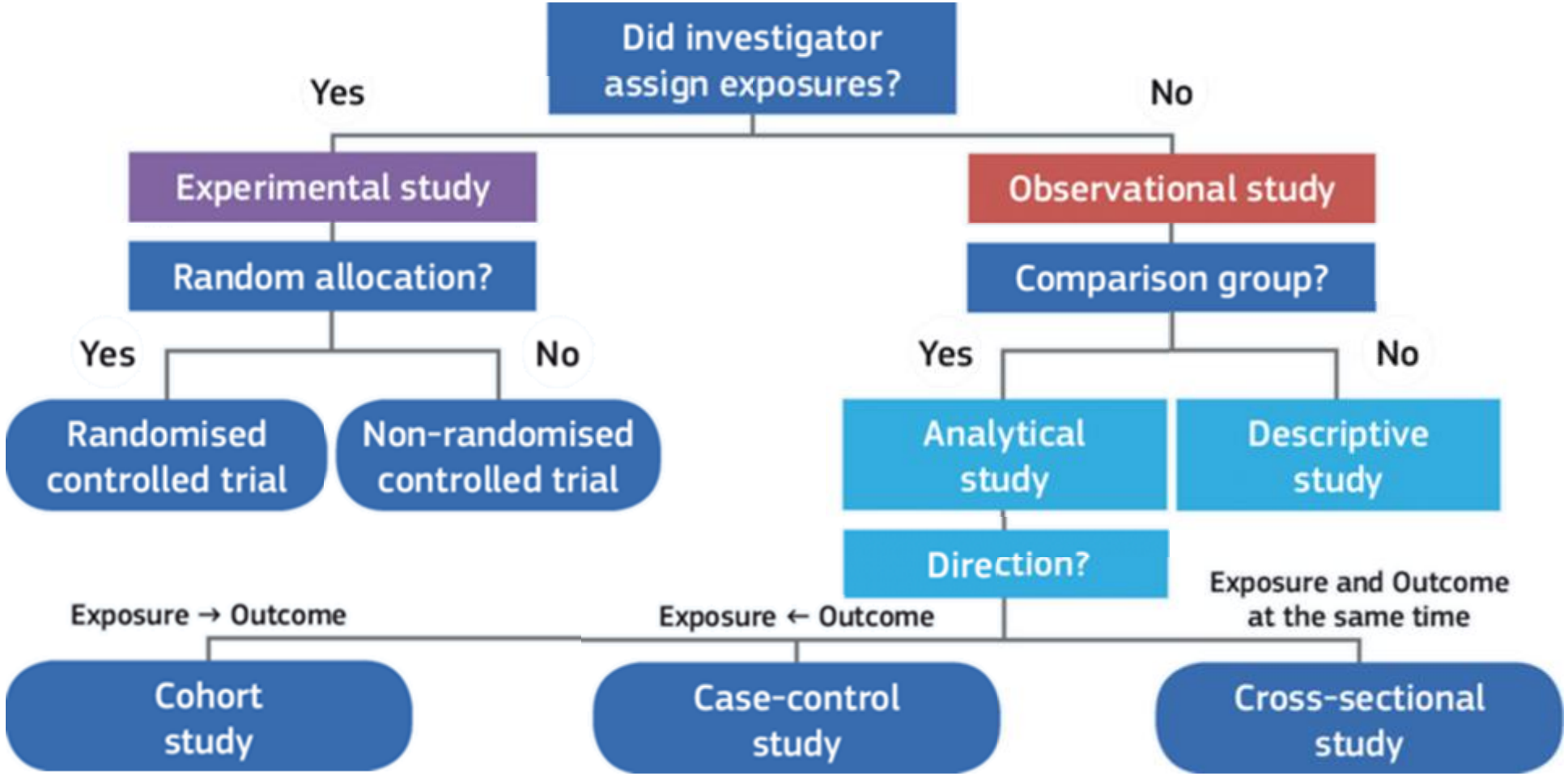


Many years + many costs + many drugs evaluated

CLINICAL TRIALS
PHASES



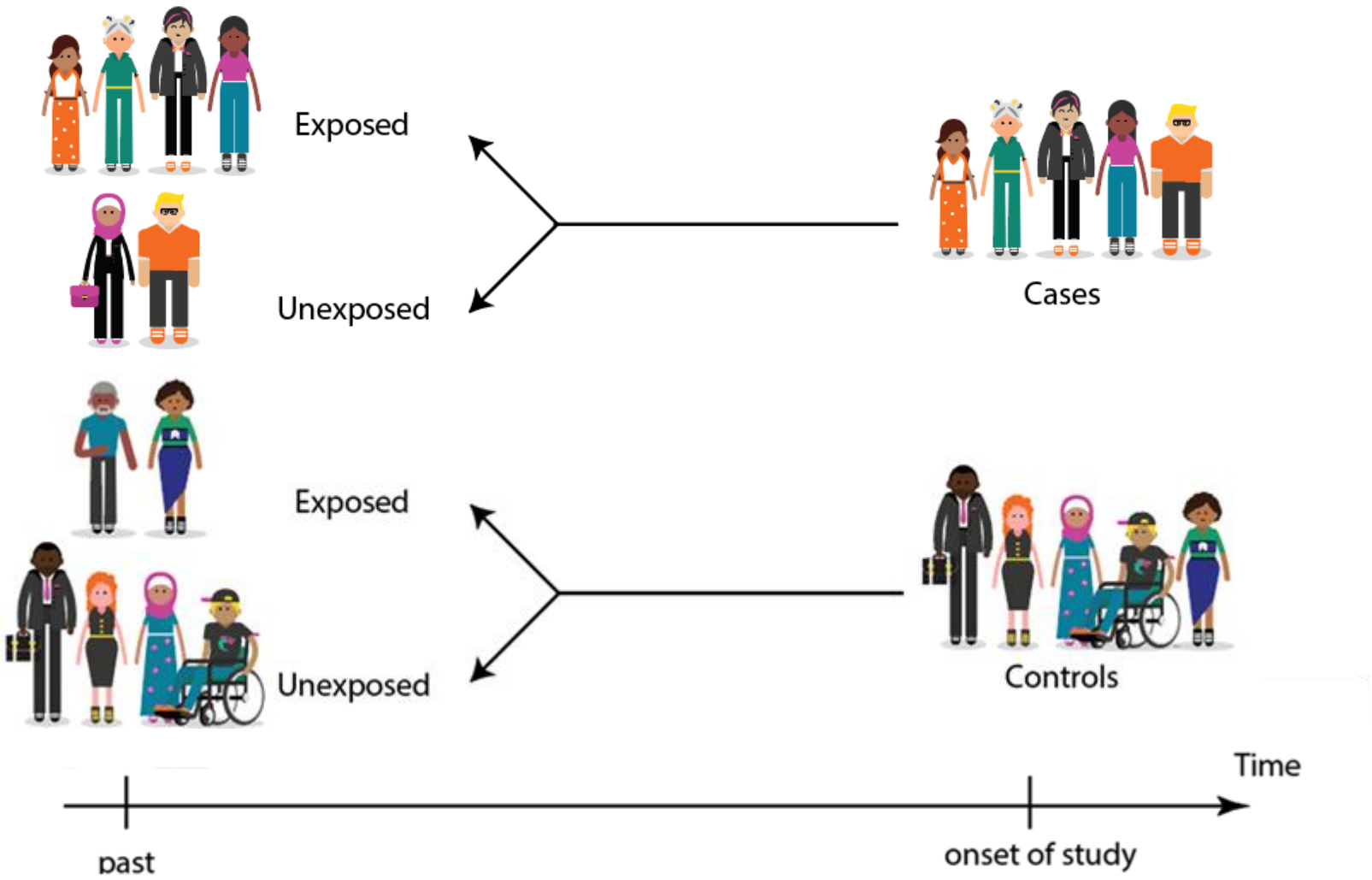
CLINICAL TRIALS
5 TYPES



CLINICAL TRIALS
COHORT STUDY : EXPOSURE → OUTCOME

CLINICAL TRIALS

CASE-CONTROL STUDY : EXPOSURE ← OUTCOME

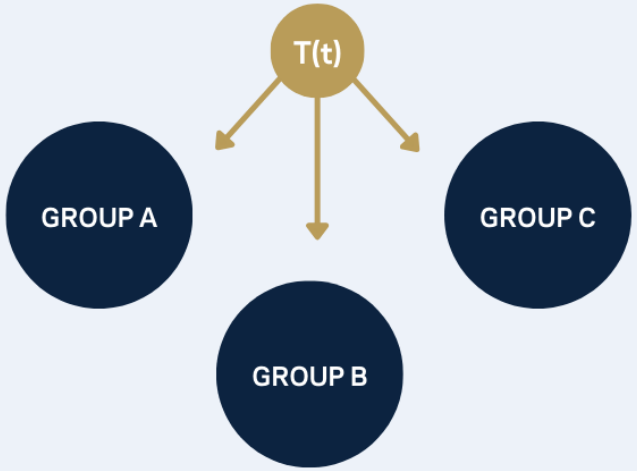


CLINICAL TRIALS

CROSS-SECTIONAL STUDY : EXPOSURE ↔ OUTCOME

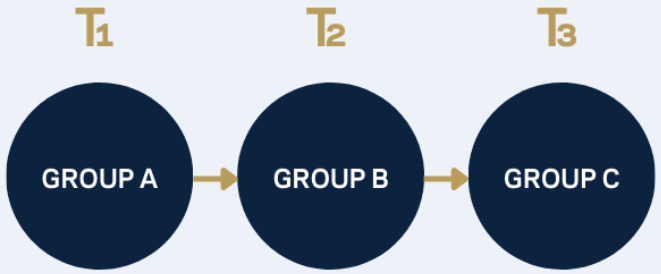
CROSS-SECTIONAL STUDY

Comparing **different groups** at the same time



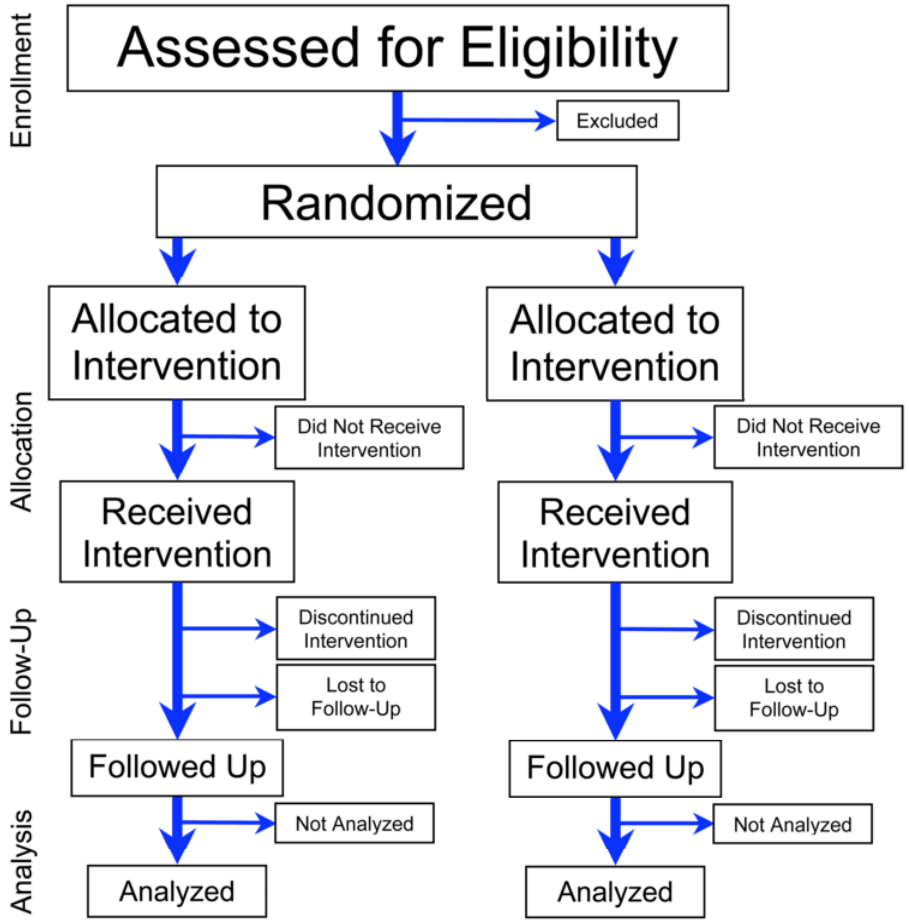
LONGITUDINAL STUDY

Comparing the **same group** over a period of time

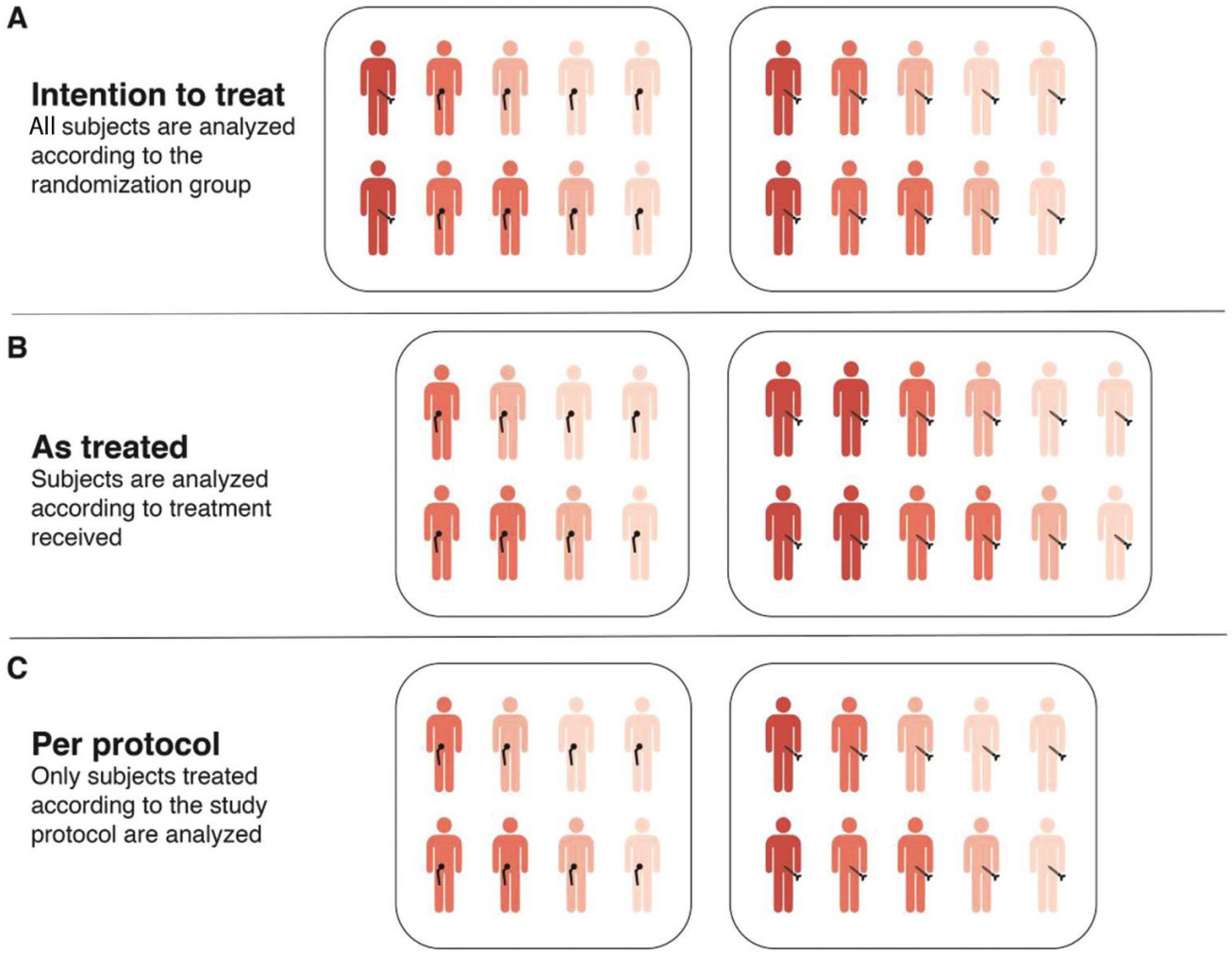


CLINICAL TRIALS
RANDOMIZED CLINICAL TRIAL (RCT)

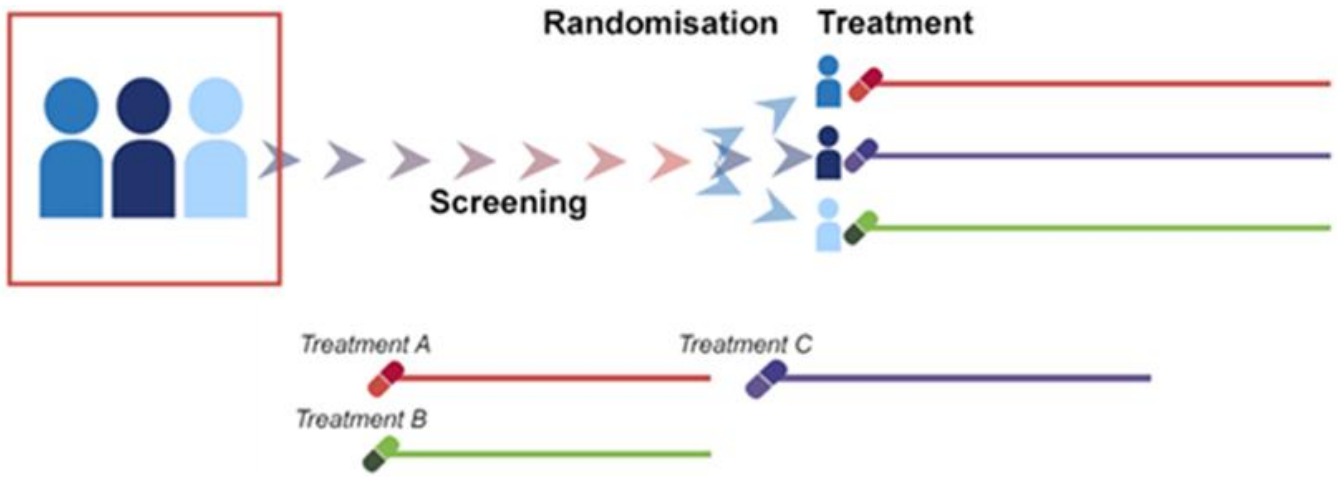
- Clinical trial with the **highest level of evidence** (Gold Standard in medical research)
- Often with **two-parallel groups** studied during the same period of time (longitudinal study)
- Patients are allocated randomly to a group, in order to have **balanced groups** (same characteristics)
- Often **two groups**
  - **Controlled** : placebo or standard of care
  - **New treatment**



CLINICAL TRIALS
RANDOMIZED CLINICAL TRIAL – THREE POPULATIONS

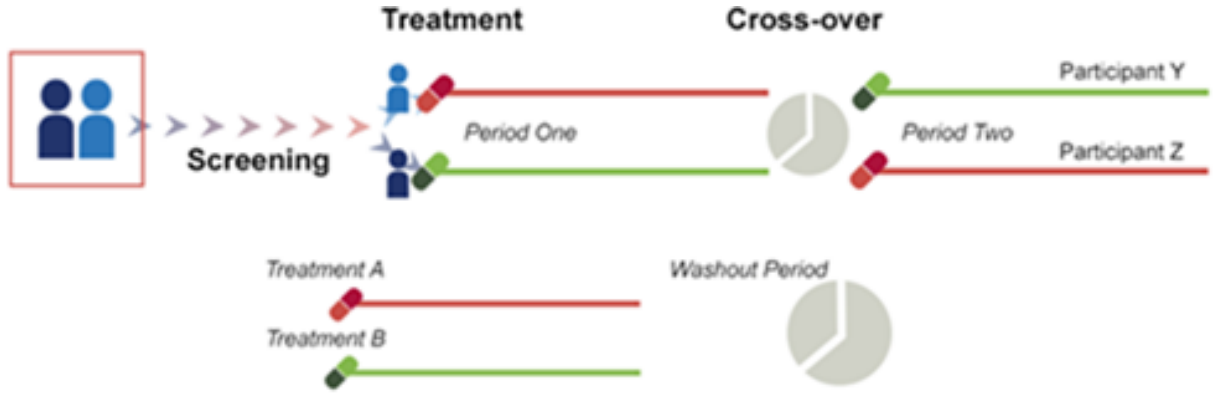


CLINICAL TRIALS
RANDOMIZED CLINICAL TRIAL – PARALLEL TRIAL



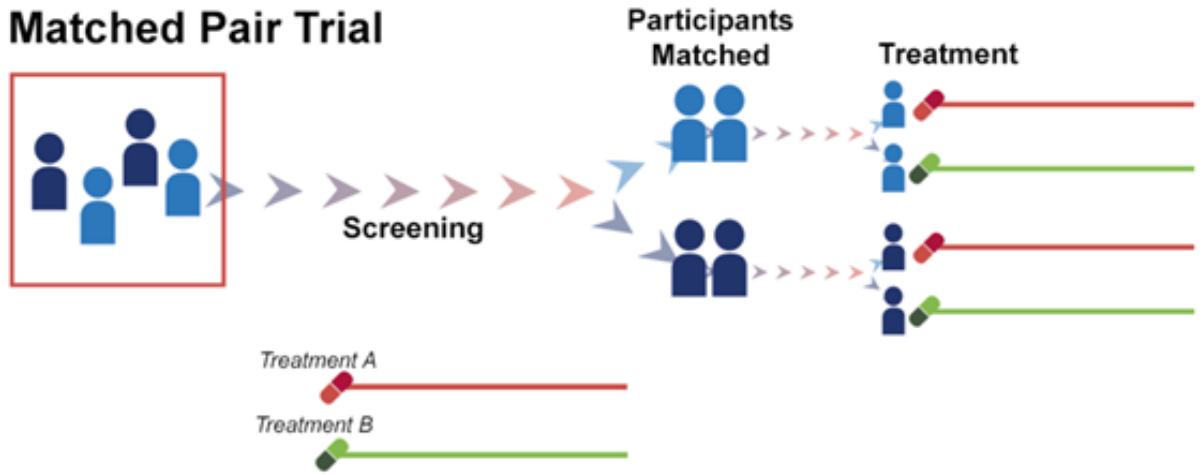
Advantages	Disadvantages
Can be applied to almost **any disease**.	In **multiple treatment groups** statistics may become challenging.
Any number of groups can be run simultaneously.	
Groups can be in **separate locations**.	

CLINICAL TRIALS
RANDOMIZED CLINICAL TRIAL – CROSS-OVER TRIAL



Advantages	Disadvantages
Low variance due to participant and control being the same.	Requires a **long-term illness** as treatments are applied one after the other.
Can include **several treatments.**	Carry over effects need to be avoided (**washout period must be sufficiently long**).
Groups can be in **separate locations**.	

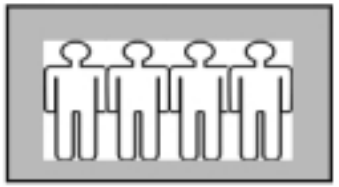
CLINICAL TRIALS
RANDOMIZED CLINICAL TRIAL – MATCHED-PAIR TRIAL



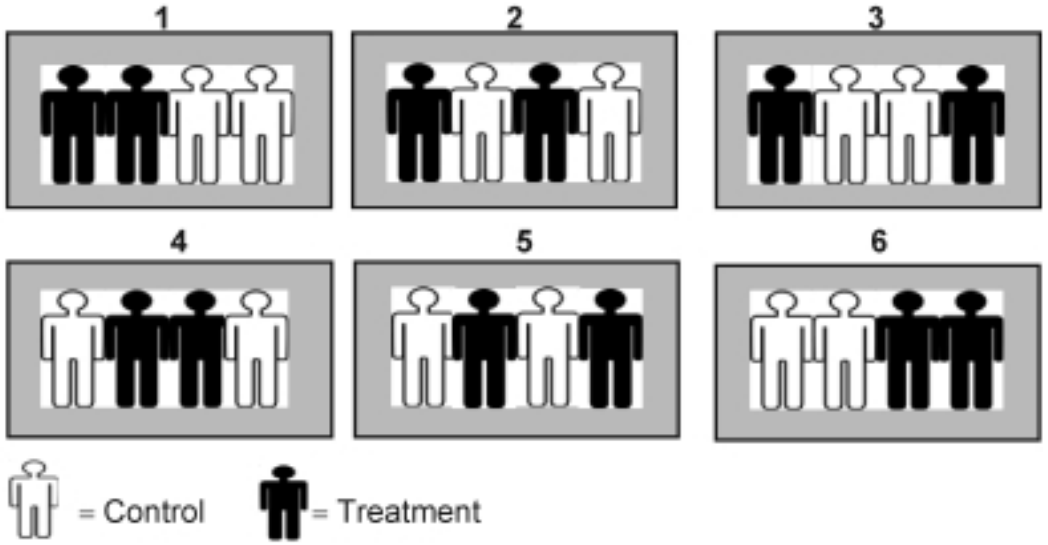
Advantages	Disadvantages
Less variability found in results, and it can be applied to most diseases.	Based on **similarity within the selected groups**, the researcher needs **awareness of factors** that could influence results (confounding variables).

CLINICAL TRIALS
BLOCK RANDOMIZATION

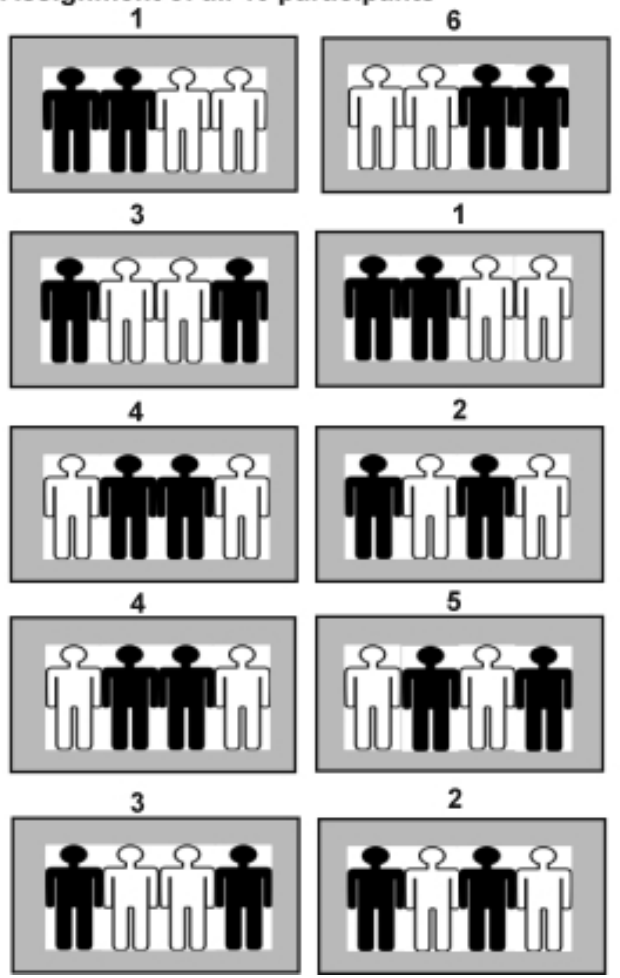
A) Block size



B) Possible balanced combinations (ie, 2 to control group, 2 to treatment group)



C) Random selection of blocks (ie, 1, 3, 4, 4, 3, 6, 1, 2, 5, 2)
Assignment of all 40 participants



CLINICAL TRIALS
PYRAMID OF EVIDENCE

CLINICAL TRIALS
CLINICAL TRIAL WORKFLOW

CLINICAL DOCUMENTS

04

CLINICAL DOCUMENTS
GOOD CLINICAL PRACTICE

- In 1945, the world discovered Nazi's concentration camps and inhuman "*medical*" **experiments** performed there.**The Doctors' trial** in Nuremberg in 1947 condemned Nazi doctors to long prison (10 years to life imprisonment) or death sentences

- International medical community decided to **standardize medical trials**, particularly the "***ethical***" side.

- The **Declaration of Helsinki** in 1964 stated **Good Clinical Practices** (GCP), an international quality standard for clinical trials on humans.

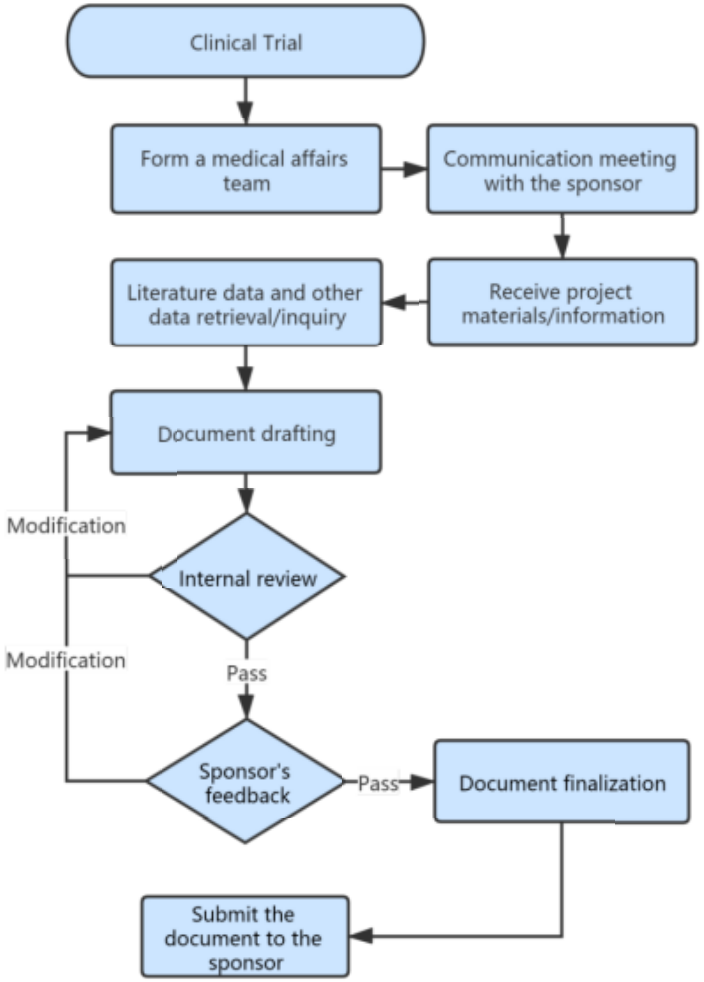
- GCP aims to **protect human rights for the subjects and volunteers** in a clinical trial.

CLINICAL DOCUMENTS
CLINICAL TRIAL PROTOCOL

- **First document** to write before launching the trial
- Describes the **objectives**, **design**, **methodology**, **statistical considerations** and **aspects** related to the organization of a trial
- Provide the **background** and **rationale** for conducting a study, highlighting **specific research questions** that are addressed, and taking into consideration ethical issues
- Mandatory for ethics approval by local **Ethics Committees** or **Institutional Review Boards**.
- Must meet a standard that adheres to the principles of **Good Clinical Practice**

CLINICAL DOCUMENTS
CLINICAL TRIAL PROTOCOL STRUCTURE

1. Title page : general information of the trial
2. Background information : prior knowledge
3. Objectives / Purposes of the trial
4. Study Design
5. Selection / Exclusion of subjects
6. Treatments
7. Assessment of Efficacy / Safety
8. Adverse Events
9. Discontinuation of the Study
10. Statistical methodology
11. Quality Control and Assurance
12. Ethics
13. Data handling and recording
14. Publication policy
15. Project timetable / flowchart
16. References
17. Supplements / Appendices



CLINICAL DOCUMENTS
CLINICAL TRIAL PROTOCOL REVIEW

20-30 minutes

CLINICAL DOCUMENTS
STATISTICAL ANALYSIS PLAN

- Complementary document (**appendix** of protocol)

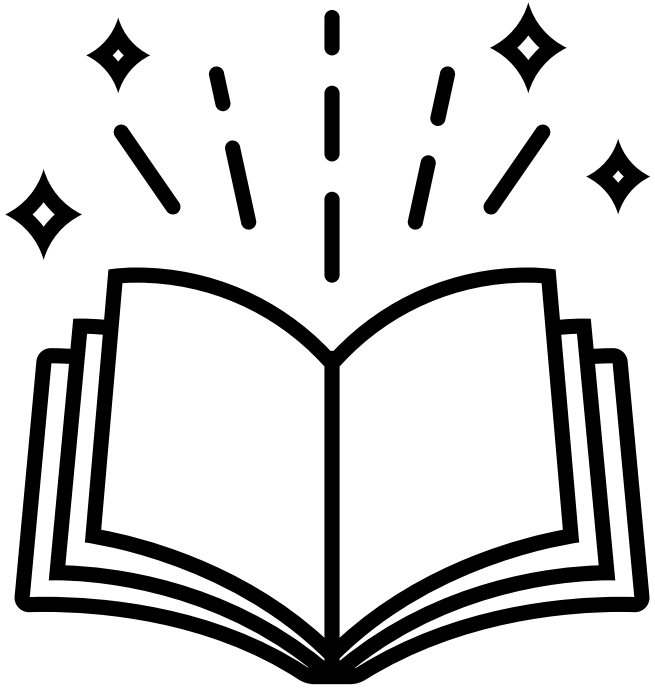
- Details the scope of planned analysis :

  - **Primary** and **secondary endpoints**
  - Analysis **methods**
  - Pre-defined **comparisons** and **significance levels**
  - **Exploratory** analyses

- **Mandatory** for regulatory agencies

- Also provide the **sample size calculation** method used if applicable

CLINICAL DOCUMENTS
STATISTICAL ANALYSIS PLAN REVIEW



20-30 minutes

CLINICAL DOCUMENTS
CLINICAL STUDY REPORT

- Most important **document**
- Summarizes study's data and **outcomes** with tables, figures, listings…
- Provides a **detailed description** of the study's **design** and **methodology**
- Part of the "***package***" sent to Health Authorities at the end of a trial with protocol, SAP, data.
- Statistical analyzes are often **validated by independent statisticians**
- Should respect **ICH** (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) **guidelines**

SCIENTIFIC PUBLICATIONS

05

SCIENTIFIC PUBLICATIONS
BRIEF HISTORY

- « *Journal des sçavans* » (France) : first scientific journal
  First edition : 5th January 1665

- Publication of the first estimation of the speed of light by **Ole RØMER** in 1676

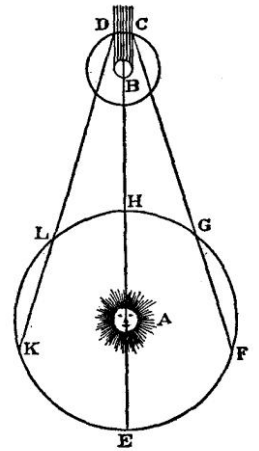
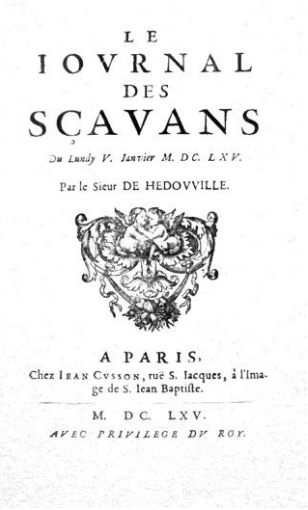
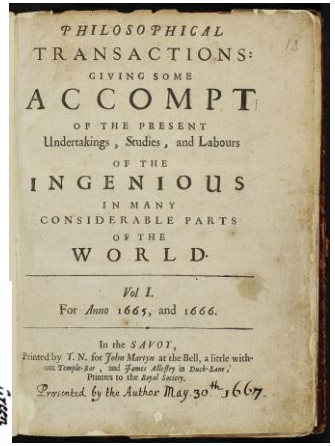


FIG. 70.


LE
IOVRNAL
DES
SCAVANS
Du Lundy V. Ianvier M. DC. LXV.
Par le Sieur DE HEDOVVILLE.
A PARIS,
Chez IEAN CVSSON, rué S. Iacques, à l'Image de S. Iean Baptiste.
M. DC. LXV.
AVEC PRIVILEGE DV ROY.

- « *Philosophical Transactions of the Royal Society* » (United Kingdom) : second scientific journal. First edition : 6th March 1665


PHILOSOPHICAL
TRANSACTIONS:
GIVING SOME
ACCOMPT
OF THE PRESENT
Undertakings, Studies, and Labours
OF THE
INGENIOUS
IN MANY
CONSIDERABLE PARTS
OF THE
WORLD.
Vol I.
For Anno 1665, and 1666.
In the SAVOY,
Printed by T. N. for John Martyn at the Bell, a little without Temple-Bar, and James Allestry in Duck-Lane;
Printers to the Royal Society.
Prosented by the Author May 30th 1667

- Publication du premier article scientifique d'Isaac NEWTON en 1672 : "*New theory about light and colors*".

SCIENTIFIC PUBLICATIONS
OVERVIEW

- Allows to submit results of clinical trials to **independent reviewers**

- Two types of journals : **specialized** or **generalist** journal

- Several publication formats :
  - **Review article**
  - **Letter**
  - **Research note**
  - **Data papers**

- Ranked according to "***impact factor***" (yearly mean number of citations of articles published in a journal)

SCIENTIFIC PUBLICATIONS
STRUCTURE

1. **Title** : Summary of the content of article in one short sentence

2. **Abstract** : Summary of the article in 5 to 10 sentences structured in 4 parts :

    - **Background/Objectives**: include the hypothesis
    - **Methods**: Briefly explain the type of study, sample/population size and description, the design, and any particular techniques for data collection and analysis
    - **Results**: Essential data, including statistically significant data (use # & %)
    - **Conclusions**: Summarize interpretations of results and explain if hypothesis was supported or rejected

SCIENTIFIC PUBLICATIONS
STRUCTURE

3. Introduction : explain the context and the background of the work

4. Material & methods :
   - Outline the design of experiment
   - Describe materials or subjects
   - Describe data collected and methods used for collection
   - Describe statistical analysis

5. Results :
   - Describe study sample demographics
   - Present the data

SCIENTIFIC PUBLICATIONS
STRUCTURE

6. Discussion :
    - Relate major findings to your hypothesis
    - Include a focused review of literature in relation to results
    - Interpret the results
    - Discuss possible limitations of study
    - Suggest future work that could be done

7. References : links to the studies / works in the literature cited as reference in the text of the article

SCIENTIFIC PUBLICATIONS
ARTICLE REVIEW

20-30 minutes

QUESTIONS

06

THANK YOU FOR YOUR ATTENTION

OCTOBER 2025