Research designs

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EQUATOR – OUCAGS training course
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Outline

1. **Introduction to research design**
   - Introducing some key concepts
2. **Major research designs**
   - Advantages & disadvantages
3. **Exercise**

Short Break

4. **Protocol preparation**
5. **Measurement (O in PICO)**
6. **Key Messages: pitfalls to avoid**

Objectives of the day

- **To understand the key issues to consider when designing a research study**
- **To understand the features of main design options**
  - Including key differences between observational and experimental studies
- **To be aware of the strengths and weakness of alternative designs**
  - Overall and for a specific research question

Types of research

- **Pre-clinical**
  - Laboratory studies, e.g. developing and testing assays
  - Animal studies
- **Clinical**
  - Evaluating therapies (interventions)
  - Diagnosis
  - Prognosis
- **Epidemiological**
  - Surveys
  - Aetiological studies
  - Ecological studies

Key points

- **The study question must be precisely identified (PICO)**
- **Design should match the research question**
- **Analysis should match the design**

"The question being asked determines the appropriate research architecture, strategy, and tactics to be used"

Sackett & Wennberg. Choosing the best research design for each question. *BMJ* 1997;315:1636.

- **Planning is vital – trial protocol**
- **Methodological input is valuable/essential at each stage of research**

Some sources

EPIDEMIOLOGY SERIES

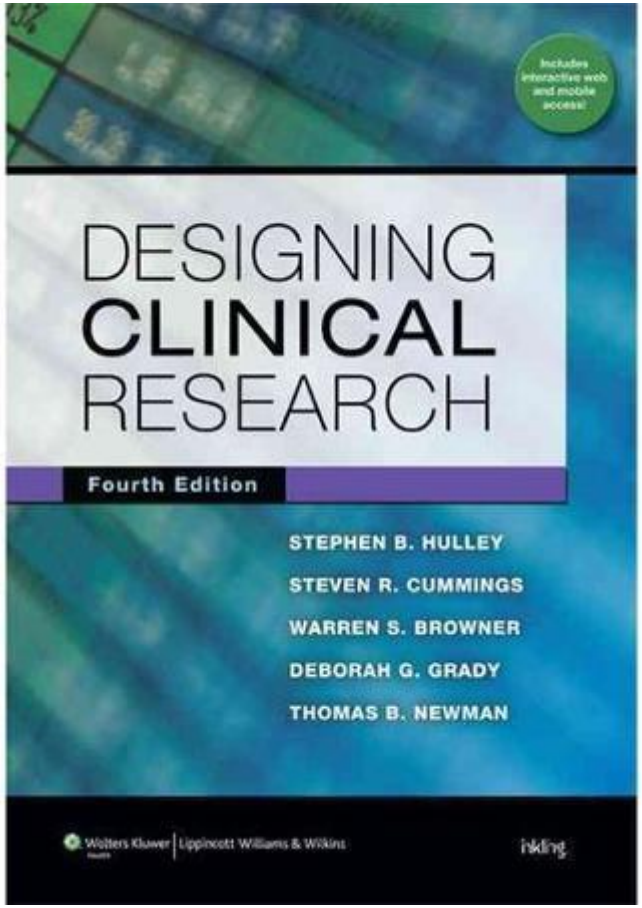
Epidemiology series

An overview of clinical research: the lay of the land

David A Grimes, Kenneth F Schulz

11 Articles in *Lancet* in 2002 and 5 more in 2005

Some sources



Aims of research

- **Clinical research studies have various aims:**
  - To quantify
  - To compare
  - To predict
  - To assess association
  - To explore aetiology

Different questions require different study designs to be answered.

Aims of research

- **A Research Project may have more than one objective** (primary and secondary)
- **The main answer you want to get will define the study design**
- **Every single aspect of the study will be related to the design**

Sampling

- **Research is conducted a sample of individuals**
- **The sample should be representative of a population**
  - e.g. Patients with asthma
- **Selecting the participants**
  - Inclusion criteria – describes the target group
  - Exclusion criteria – reasons for excluding some (few?) participants
    - e.g. pregnant, age, comorbidity
- **Degree of selectivity affects inferences about the population (generalisability)**

Sampling

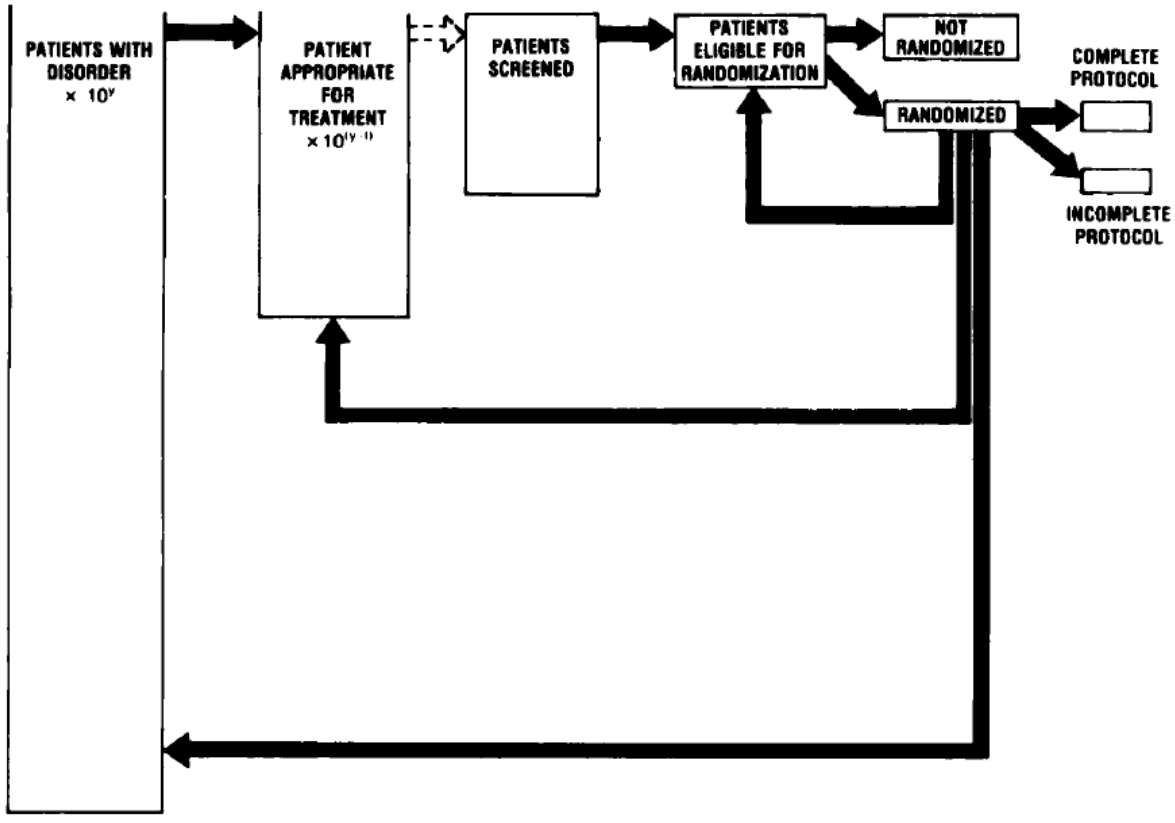


Figure 1. Hypothetical selection process of patients entered into a clinical trial (read left to right) and generalization of results from randomized patients to other patients (read right to left). Multiplication of area of first two boxes by 10^y and $10^{(y-1)}$ for patients with disorder and the subset of patients appropriate for treatment indicates order of magnitude of respective cohorts

Ellenberg, *Stat Med* 1994

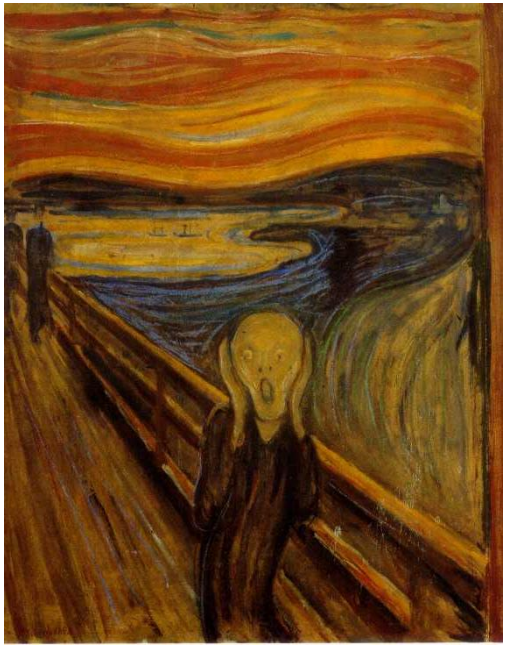
Types of study design

Descriptive vs Analytical

Observational vs Interventional

Cross-sectional vs Longitudinal

Prospective vs Retrospective



Descriptive vs Analytical

- **Descriptive**
  - Merely observational
  - No comparison group
  - Describe symptoms, a condition, a series of cases

- **Analytical**
  - Observational or interventional
  - Cross-sectional or longitudinal
  - Prospective or retrospective

Observational vs Interventional

- **Observational studies**
  - Do not involve any intervention or experiment
  - Cross-sectional or longitudinal
  - Prospective or retrospective

- **Interventional (experimental) studies**
  - Entail manipulation of the study factor (intervention/exposure) and allocation (with or without randomization) of subjects to treatment groups (active/exposed or control).
  - Longitudinal **AND** Prospective

Cross-sectional vs Longitudinal
Prospective vs Retrospective

Longitudinal

Prospective

Types of clinical research
(an incomplete list)

- **Observational studies**
  (Descriptive)
  - Case reports
  - Surveys

  (Analytical)
  - Cohort studies
  - Cross-sectional studies
  - Case-control studies
- **Experimental studies**
  - Randomised trials (RCTs)
  - Non-randomised studies
- **Qualitative research**
- **Research synthesis (systematic reviews)**

Types of clinical research
(an incomplete list)

- **Observational studies**
  (Descriptive)
  - Case reports
  - Surveys

  (Analytical)
  - **Cohort studies**
  - **Cross-sectional studies**
  - **Case-control studies**
- **Experimental studies**
  - **Randomised trials (RCTs)**
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- **Qualitative research**
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Summary of designs

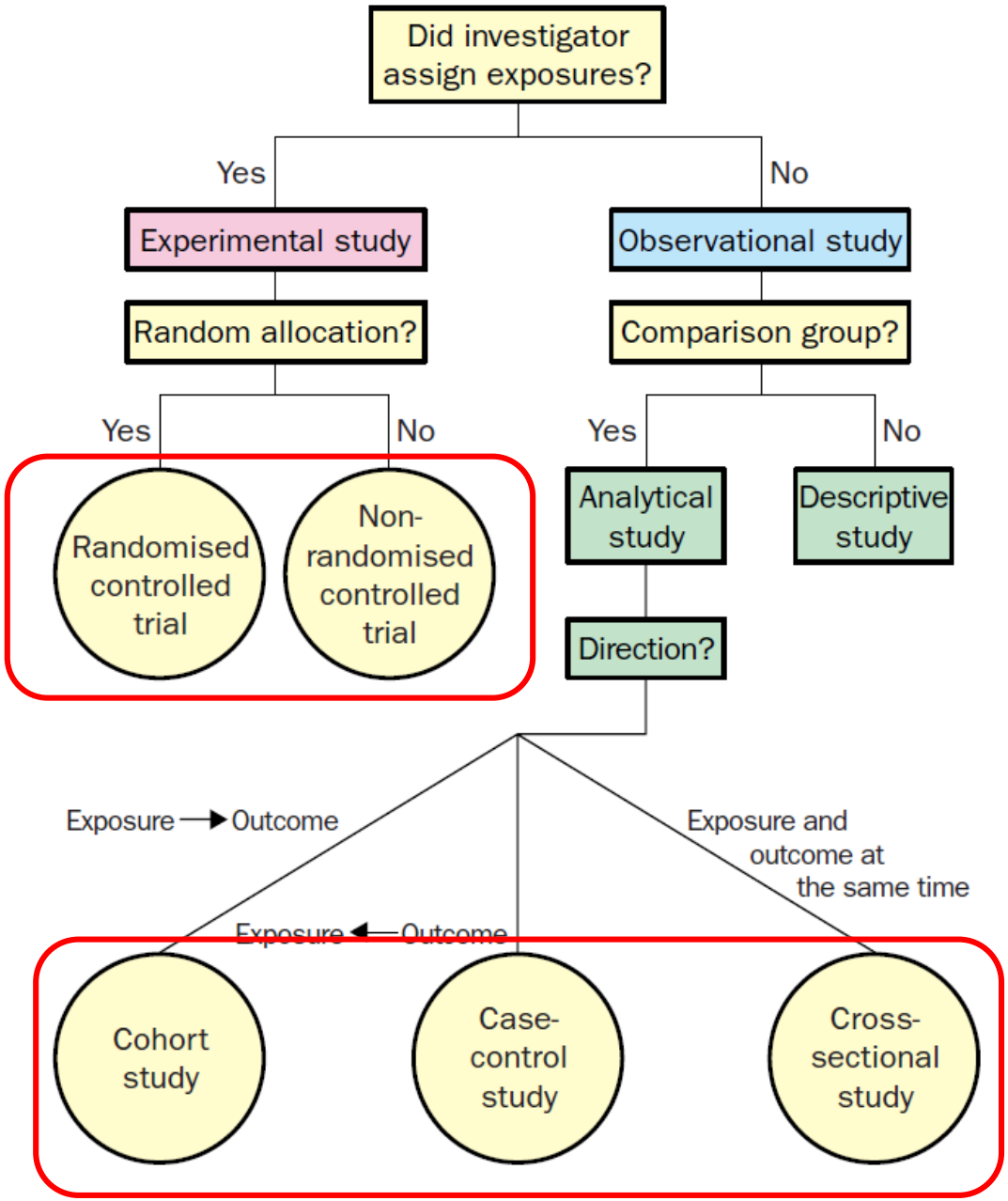


Figure 1: **Algorithm for classification of types of clinical research**

Schulz & Grimes, *Lancet* 2002

equator network

Cause and effect studies

- **Studies of aetiology**
  - RCT usually not possible
- **Studies of interventions**
  - RCT usually possible

Types of clinical research

- **Some research designs are more suitable for answering a given research question than others**

- **It is important to choose an appropriate research design!**

  (e.g. RCTs are best for comparing effectiveness of different interventions)

- **Each approach has advantages and limitations**

  (observational studies are more appropriate to test the association of depression and suicide.)

Main elements of research

- **Clear/precise question(s)**

- **Research Design**
  - Who to study? How large the sample? (P and C)
  - What interventions/exposures to investigate? (I)
  - What outcome to measure? (O)
  - When to measure? (t)

Many difficult decisions, so we need a <u>protocol</u>!

Key concepts

- **Study sample**

  (adequate sample size will confer power and the appropriate selection of participants will give external validity to the study)

- **Preventing bias**

  (making sure that the assessments are reliable and that potential confounders are taken into account will allow the hypothesis to be tested)

Designing and implementing a research project

- **Which designs might we use to see whether compression stockings reduce the risk of deep vein thrombosis (DVT) among travellers?**

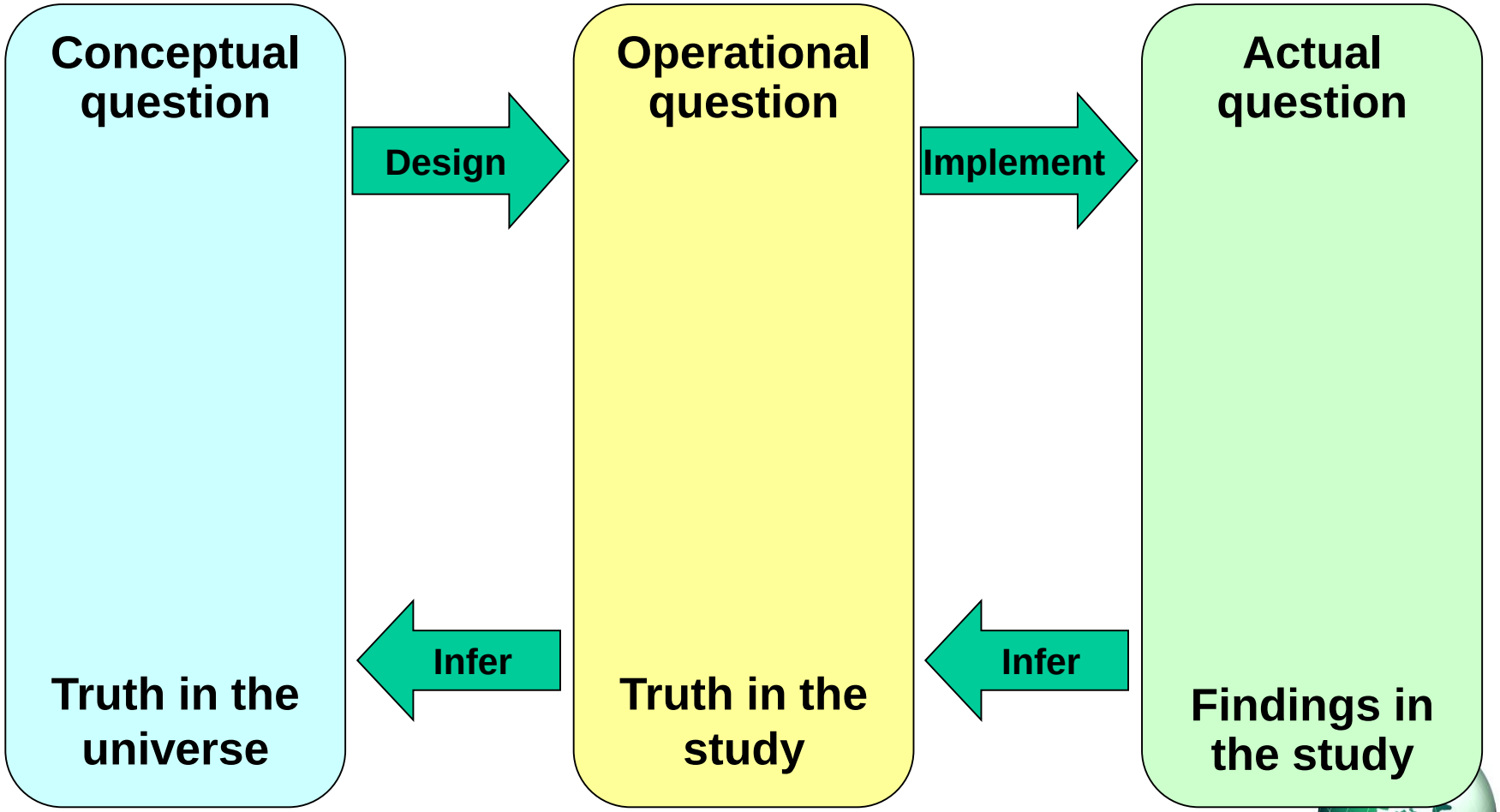
Designing and implementing a research project

- The ideal study
- The planned study
- What actually happens

e.g. Participants

- Target population: all travellers
- Intended sample: everyone invited to participate
- Actual sample: those who agree to participate

The research cycle (Hulley et al)



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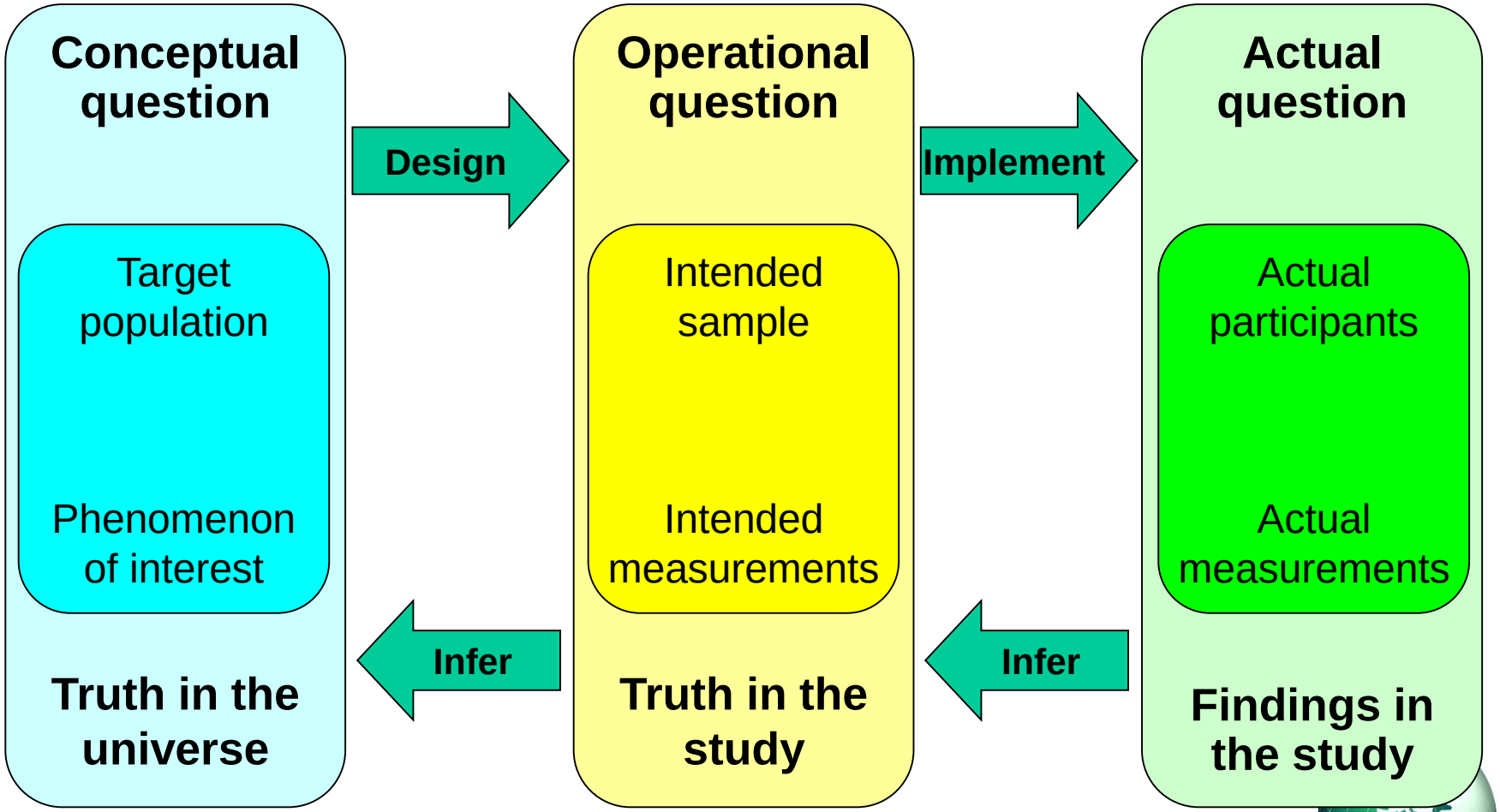


Observational studies

- **General advantages:**

  Usually comprises a bigger number of individuals than experimental studies (easier to recruit and follow)

  Can examine a wider range of exposures

  Examine causal factors (etiology)

- **Main options:**
  - Cohort
  - Case-control
  - Cross-sectional

Observational studies

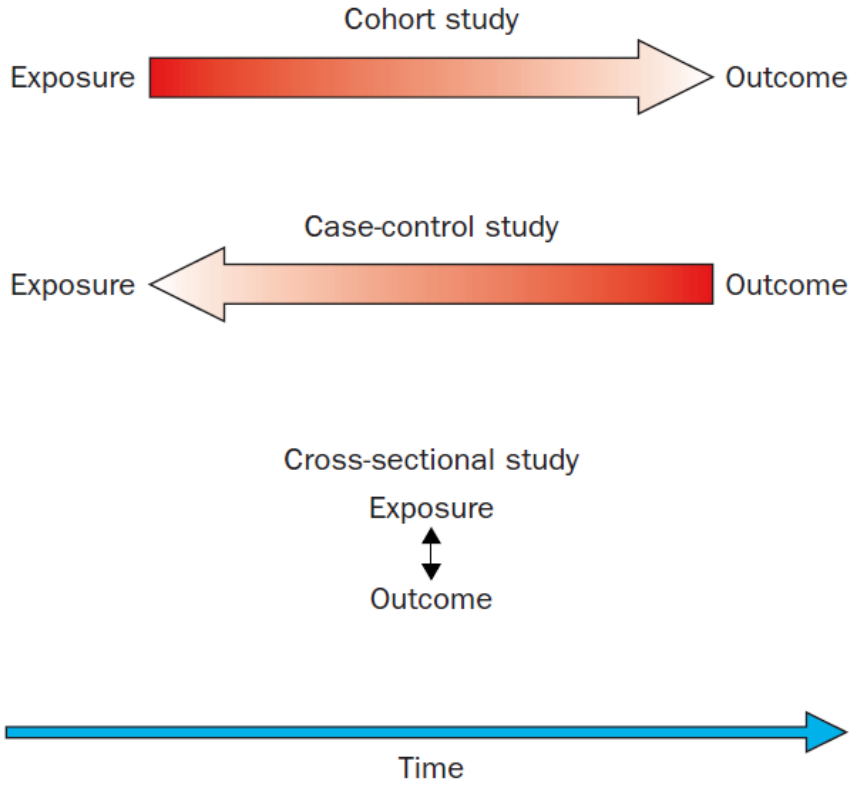


Figure 2: **Schematic diagram showing temporal direction of three study designs**

Observational studies

In **cohort studies**, the investigators follow people over time. They obtain information about people and their exposures at baseline, let time pass, and then assess the occurrence of outcomes. Investigators commonly make contrasts between individuals who are exposed and not exposed or among groups of individuals with different categories of exposure. Investigators may assess several different outcomes, and examine exposure and outcome variables at multiple points during follow-up.

In **case-control studies**, investigators compare exposures between people with a particular disease outcome (cases) and people without that outcome (controls). Investigators aim to collect cases and controls that are representative of an underlying cohort or a cross-section of a population. That population can be defined geographically, but also more loosely as the catchment area of health care facilities. The case sample may be 100% or a large fraction of available cases, while the control sample usually is only a small fraction of the people who do not have the pertinent outcome. Controls represent the cohort or population of people from which the cases arose.

In **cross-sectional studies**, investigators assess all individuals in a sample at the same point in time, often to examine the prevalence of exposures, risk factors or disease. Some cross-sectional studies are analytical and aim to quantify potential causal associations between exposures and disease. Such studies may be analysed like a cohort study by comparing disease prevalence between exposure groups. They may also be analysed like a case-control study by comparing the odds of exposure between groups with and without disease. A difficulty that can occur in any design but is particularly clear in cross-sectional studies is to establish that an exposure preceded the disease, although the time order of exposure and outcome may sometimes be clear.

[Vandenbroucke et al, *Epidemiology* 2007]

Common bias in observational studies

Selection bias

- In a cohort study, are participants in the exposed and unexposed groups similar in all important respects except for the exposure?
- In a case-control study, are cases and controls similar in all important respects except for the disease in question?

Information bias

- In a cohort study, is information about outcome obtained in the same way for those exposed and unexposed?
- In a case-control study, is information about exposure gathered in the same way for cases and controls?

Confounding

- Could the results be accounted for by the presence of a factor associated with both the exposure and the outcome e.g. age, smoking, sexual behaviour, diet)?

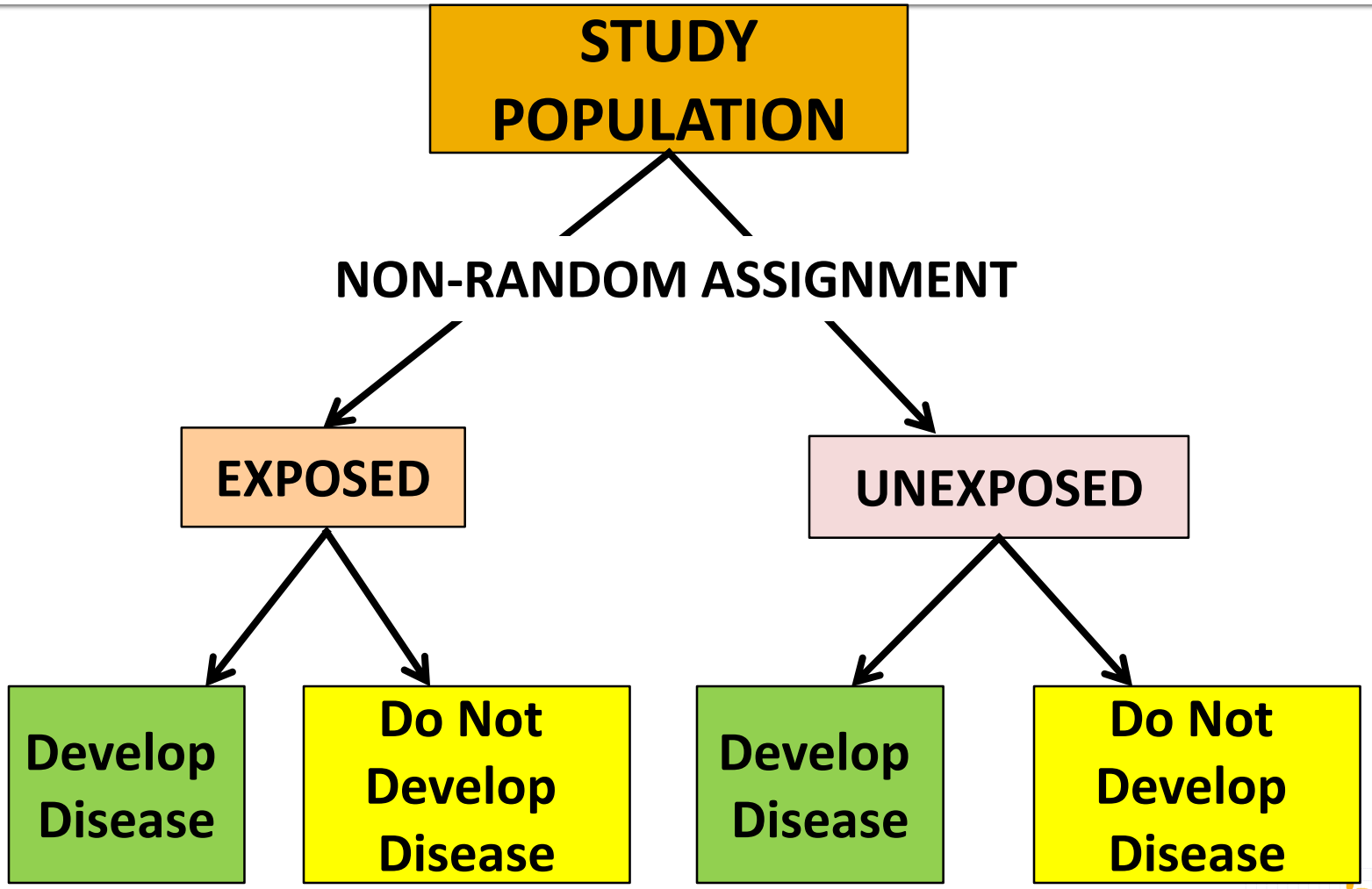
Cross-sectional studies

- **No follow-up** (all information is collected just once)
- Commonly **quicker and cheaper** than longitudinal studies
- Very useful to **estimate prevalence** of a disease
- Usually allow much **bigger samples** (if not entire populations)
- Can be used to assess associations and **generate hypothesis**
- **Temporal relation between exposure and outcome cannot be assessed!**

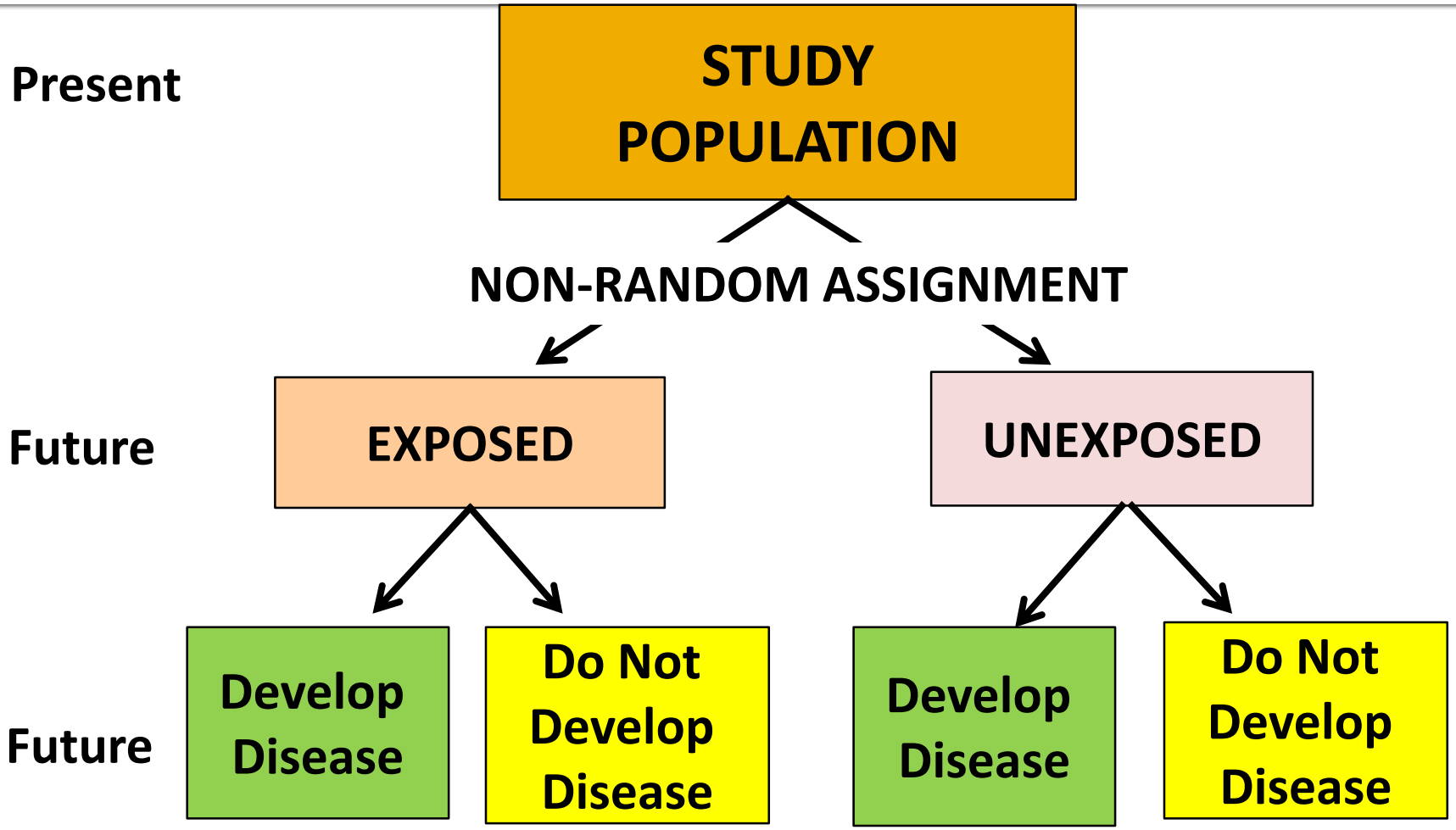
Cohort studies

- **May be descriptive (what happens to this group of people?)**
  - e.g. prognostic study
- **Often they compare subgroups**
  - Look at effects of exposure on outcome
  - Exposure can be a medical treatment

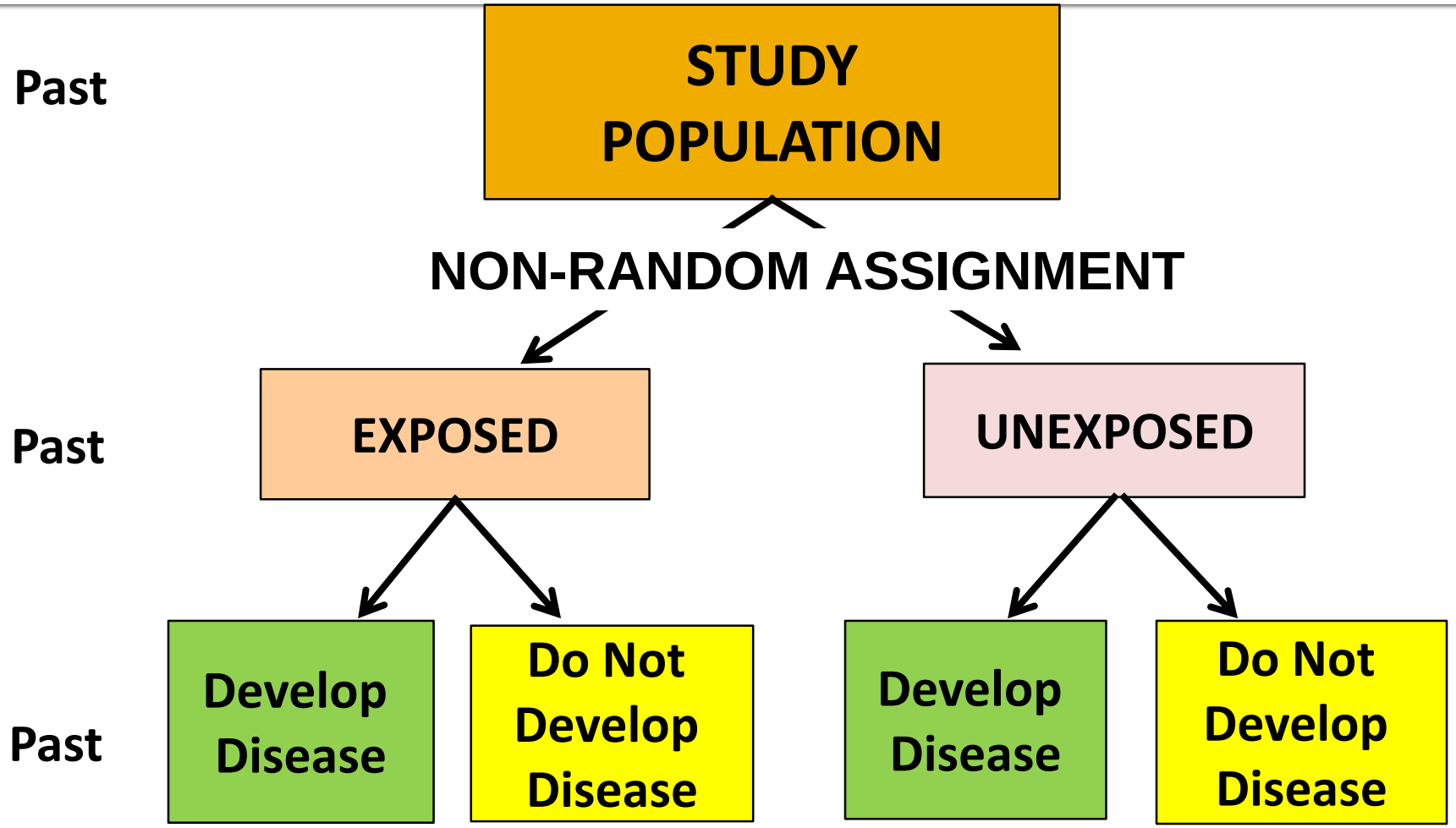
Cohort Study Design



Prospective Cohort Study Design



Retrospective Cohort Study Design



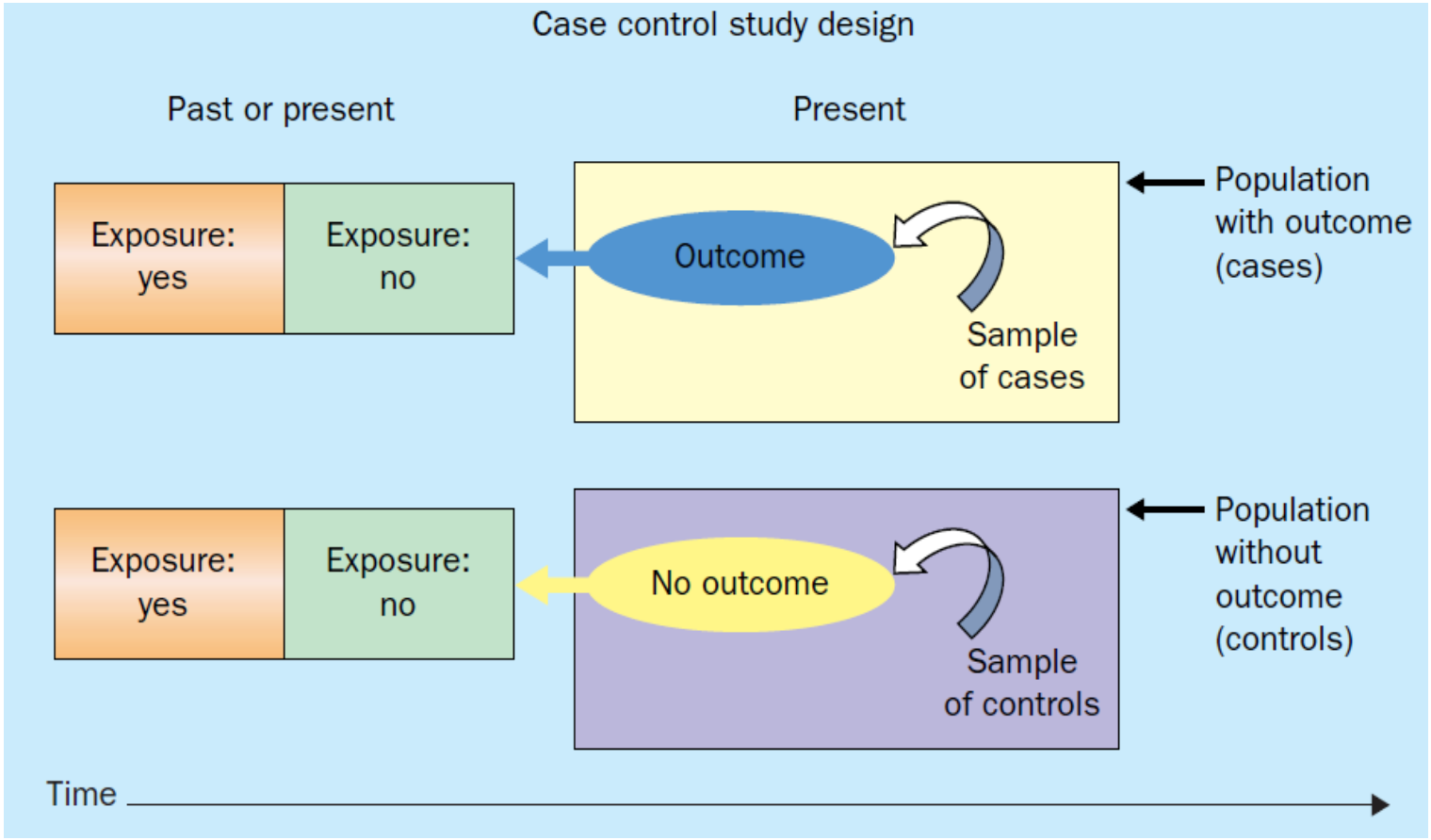
Advantages and disadvantages of cohort studies

- **Advantages**
  - Can measure incidence and risks
  - Good for rare exposures
  - Clear temporal relationship between exposure and outcome
  - Less subject to selection bias
- **Disadvantages**
  - Requires a large sample size
  - Latency period
  - Lost to follow-up
  - Ethical considerations
  - Resource intensive
    - High cost
    - Timely

Cohort study
Example of Inclusion Criteria

- **Women's Health Study**
  - ≥ 45 years
  - No history of coronary heart disease, cerebrovascular disease, cancer, or other major chronic illness
  - No history of side effects to any of study medications
  - Were not taking any of following meds more than once per week: aspirin, NSAIDs, supplements of vitamin A, E, or beta-carotene
  - Were not taking anticoagulants or corticosteroids

Case-control study



Advantages and disadvantages of case-control studies

Advantages

- **Suitable for rare diseases**
- **Can explore several exposures**
- **Low cost**
- **Rapid**
- **Can cope with long latency**
- **Small sample size**
- **No ethical problems**
- **No losses to follow-up**

Disadvantages

- **Not suitable for rare exposures**
- **Cannot explore multiple outcomes**
- **Temporal relationship difficult to establish**
- **Cannot calculate the risk**
- **Subject to bias**
  - Selection of controls
  - Recall bias
  - …

Summary

- **Cohort studies are better but harder to carry out and provide true measure of risk**
- **Case-control studies are rapid and easy to carry out, but only provide estimates of risks**
- **Prefer cohort to case-control when feasible**
- **Observational studies give evidence on interventions**
  - but how trustworthy?

Randomised controlled trial

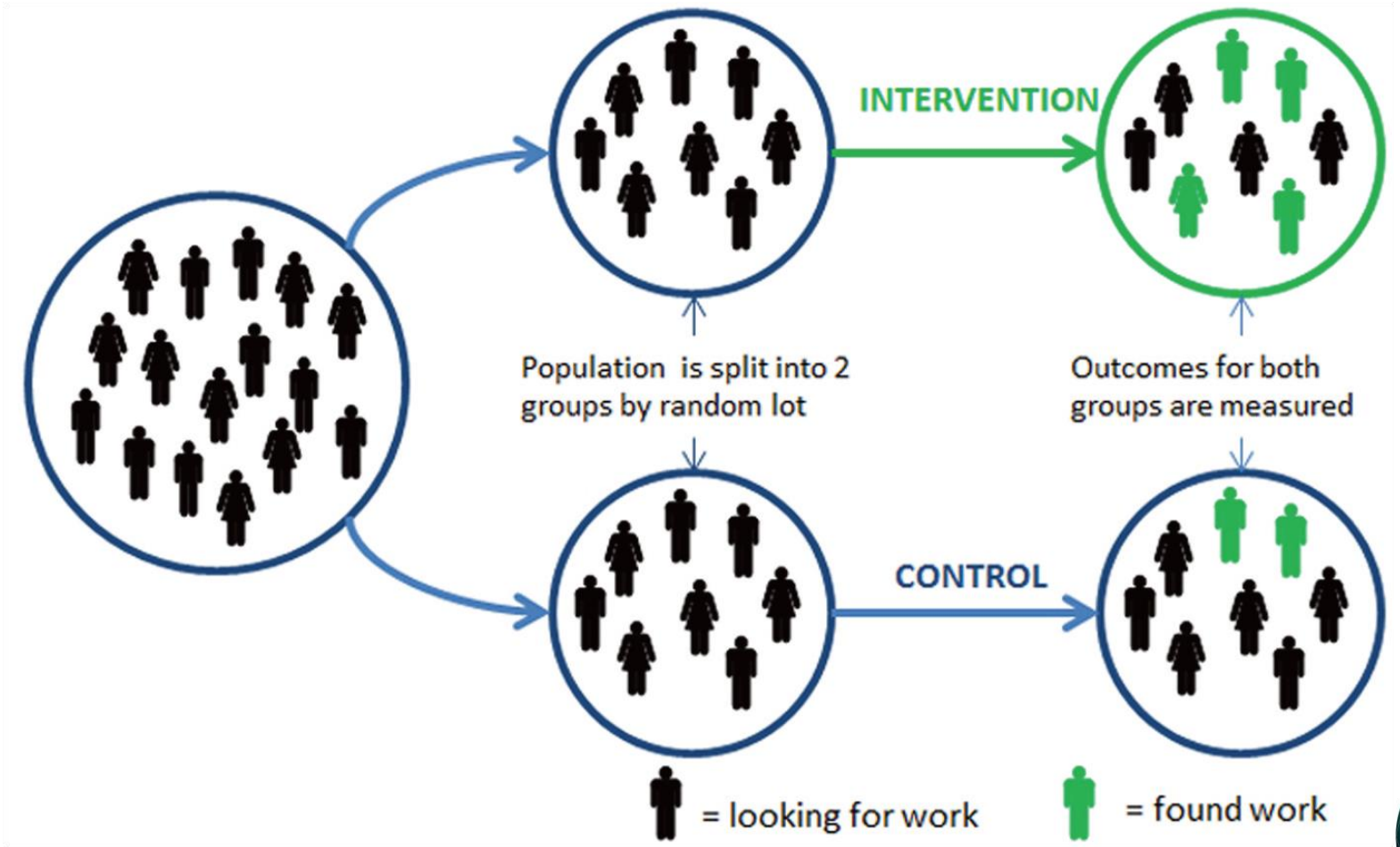
- **We wish to compare groups of subjects who differ only with respect to their treatment**

- **If the outcome differs in the treatment groups we may reasonably assume that this is because of differences in treatment**

  ....but only if the trial was performed properly

- **Bias can enter a trial at several stages**
  - design, execution, analysis, interpretation

Randomised controlled trial



Main strategies for avoiding bias

- **Random allocation**
  - Concealed
- **Blinding**
- **Minimising loss to follow up**
- **Analysis strategy – intention to treat**

Random allocation (randomisation)

- **What do we mean by random allocation?**
  - each participant has a known chance, normally an equal chance, of receiving each treatment, **but the treatment to be received cannot be predicted**
- **Is the only reliable way to avoid selection biases**
- **Two separate components:**
  - method of **generating** the random sequence
  - mechanism for **allocating** the treatments to participants

Allocation concealment

- **The person entering patients should not know in advance which treatment the next person will get**
  - 'concealed allocation'
  - Avoids selection bias
- **Allocation concealment is always possible**
- **Good methods**
  - **Centralised 24 hour telephone hotline (e.g. group assignment by an independent central office)**
  - **Pre-numbered/coded identical bottles or containers administered serially to participants by Pharmacy**
- **Acceptable method**
  - Sequentially numbered, opaque, sealed envelopes

What does randomisation achieve?

- **Ensures that allocation to the comparison groups is unbiased with respect to prognosis**
  - it is not determined by the investigators, the clinicians, or the study participants

- **Tends to produce comparable groups**
  - known and unknown prognostic factors and other characteristics of the participants at the time of randomisation will be, on average, evenly balanced between the groups

- **Provides a theoretical foundation by which a treatment effect can be estimated and a hypothesis tested**

When randomisation works properly

Characteristic	Vitamin Group (n = 141)	Placebo Group (n = 142)
Mean age ± SD, *y*	28.9 ± 6.4	29.8 ± 5.6
Smokers, *n (%)*	22 (15.6)	14 (9.9)
Mean body mass index ± SD, kg/m^2	25.3 ± 6.0	25.6 ± 5.6
Mean blood pressure ± SD, *mm Hg*		
Systolic	112 ± 15	110 ± 12
Diastolic	67 ± 11	68 ± 10
Parity, *n (%)*		
0	91 (65)	87 (61)
1	39 (28)	42 (30)
2	9 (6)	8 (6)
>2	2 (1)	5 (4)
Coexisting disease, *n (%)*		
Essential hypertension	10 (7)	7 (5)
Lupus or antiphospholipid syndrome	4 (3)	1 (1)
Diabetes	2 (1)	3 (2)

To randomise or not to randomise?

- **Non-randomised studies**
  - Cheap (if retrospective)
  - Based in clinical practice – representative sample of patients
  - **Open to bias – who gets which treatment and why?**
  - **Assume treatment groups are <u>not</u> comparable**

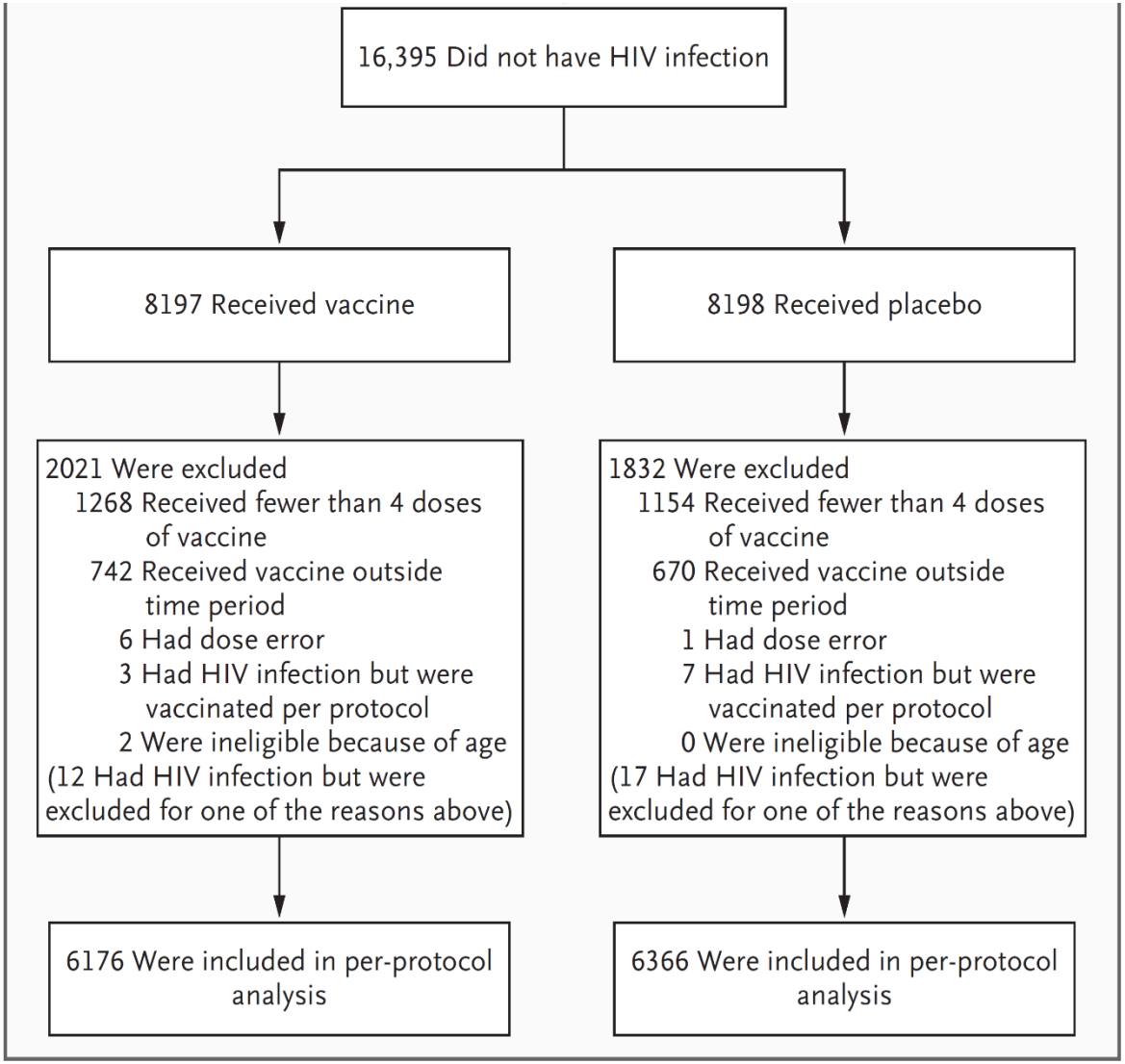
- **Randomised trials**
  - Expensive and slow
  - Less representative patients
  - **Randomisation removes biased allocation**

Blinding

- **Knowledge of the treatment received may influence its apparent effect**
- **Blinding (masking) keeps the assignments unknown after allocation**
- **Helps to minimise**
  - "Performance bias"
    - unequal provision of care apart from treatment under evaluation
  - "Detection bias"
    - biased outcome assessment
- **Blinding is not always possible**

Losses to follow-up and analysis

Rerks-Ngarm
N Engl J Med
2009



Disadvantages of RCTs

- **Prospective – can be long and expensive**
- **Not suitable for very rare diseases or rare outcomes**
- **Ethical constraints**
- **Generalisability – many trials exclude many groups such as the very young, very old, pregnant women, with comorbidity, etc**

An Abstract

"Management of patent ductus arteriosus (PDA) in full-term neonates remains controversial. We evaluated the effects of oral ibuprofen on PDA closure in 51 full-term neonates. All neonates were >3-days-old and had a gestational age > or = 37 weeks. Patients with ductal-dependent congenital heart disease or severe pulmonary artery hypertension (gradient >40 mmHg) were excluded. Patients were randomly assigned to the treatment group (n = 30) or the control group (n = 21). The treated group received ibuprofen suspension (initially 10 mg/kg, then two 5-mg/kg doses 24 h apart), and control neonates received a placebo."

[Amoozgar et al, *Pediatr Cardiol* 2009]

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