

Introduction to study design

Doug Altman

**EQUATOR Network, Centre for Statistics in Medicine,
NDORMS, University of Oxford**

**EQUATOR – OUCAGS training course
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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



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**



Some sources

EPIDEMIOLOGY SERIES

Epidemiology series

An overview of clinical research: the lay of the land

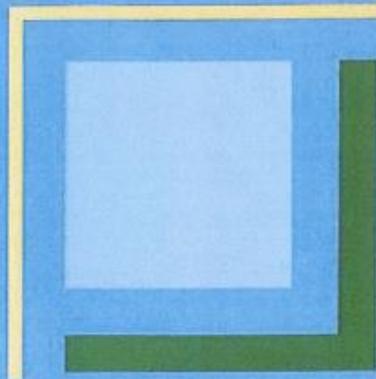
David A Grimes, Kenneth F Schulz

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



Designing Clinical Research

SECOND
EDITION



Stephen B. Hulley
Steven R. Cummings
Warren S. Browner
Deborah Grady
Norman Hearst
Thomas B. Newman

 LIPPINCOTT WILLIAMS & WILKINS



Aims of research

- **Clinical research studies have various aims:**
 - To quantify (e.g. prevalence of a disease in community)
 - To compare (which intervention is better?)
 - To predict (who gets cancer?)
 - To assess association
 - To explore aetiology (exposure causing outcome)
 - ...



Sampling

- **Research is conducted on a sample of individuals**
- **The sample should be representative of a population**
 - e.g. Patients with asthma; liver transplant recipients; ...
- **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)**



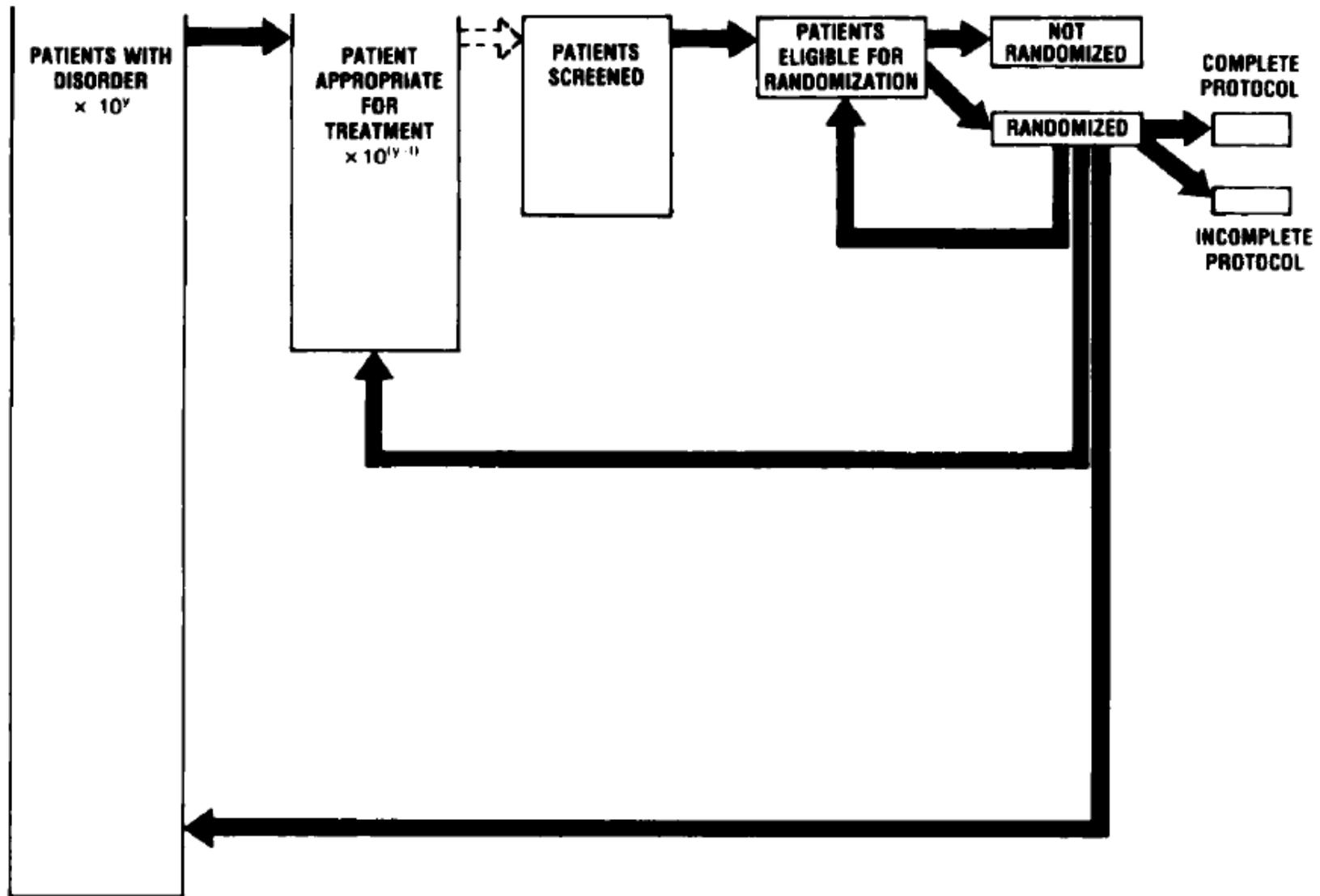


Figure 1. Hypothetical selection process of patients entered into a clinical trial (read left to right) and generalization of results from randomized patients to other patients (read right to left). Multiplication of area of first two boxes by 10^y and 10^{y-1} for patients with disorder and the subset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

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



Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Parasitaemia with a density of ≥ 500 parasites/ μ l (any species)	Use of FA in the last four weeks
Gestational age 17–34 weeks	Gestational age ≤ 16 wk or ≥ 35 weeks
Willingness to provide blood samples and participate in HIV counselling and testing	History of an allergy to sulfa containing drugs or other unknown drugs
Haemoglobin > 7 g/dl	Haemoglobin ≤ 7 g/dl
Available for the follow up period of four weeks	An intake of sulfa containing drugs or 4-aminoquinolones in the previous month
Informed consent	A urine test positive for sulfa compounds
Aged 15–45 years	Sickle cell disease
	Concomitant diseases needing treatment with cotrimoxazole or other sulfa-containing drugs
	Severe malaria or any other serious medical condition requiring hospitalisation or additional treatment ^a

^aDanger signs or signs of severe malaria in adults are as follows. Clinical: prostration, impaired consciousness, respiratory distress, multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, or hemoglobinuria; laboratory: severe anaemia (Hb < 7 g/dl), hypoglycemia, acidosis, hyperlactataemia, hyperparasitaemia, or renal impairment [41].

DOI: 10.1371/journal.pctr.0010028.t001

Ouma et al, *PLoS Clin Trials* 2006



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



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What are these?

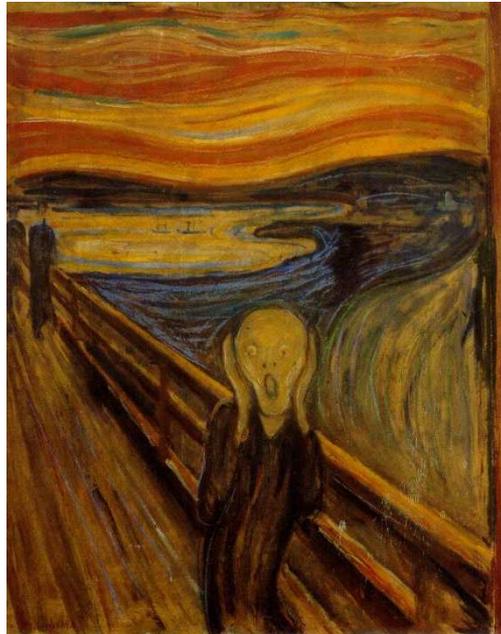
- **A case study**
- **A case-control study**
- **An n-of-1 trial**
- **A case series**
- **A cohort study**
- **A cross-sectional study**

- **What is the difference between a prospective and a retrospective study?**



Types of study design

Descriptive vs Analytical (Inferential)
Observational vs Interventional
Cross-sectional vs Longitudinal
Prospective vs Retrospective



Observational vs Interventional

- **Observational studies**
 - do not involve any intervention or experiment
- **Interventional (experimental) studies**
 - entail manipulation of the study factor (exposure) and randomization of subjects to treatment (exposure) groups



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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TITLE: “Oral ibuprofen and ductus arteriosus closure in full-term neonates: a prospective case-control study”

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Types of clinical research

(an incomplete list)

- **Observational studies**

- Case reports
- Surveys
- Cohort studies
- Cross-sectional studies
- Case-control studies

- **Experimental studies**

- Randomised trials (RCTs)
- Non-randomised studies

- **Qualitative research**

- **Research synthesis (systematic reviews)**



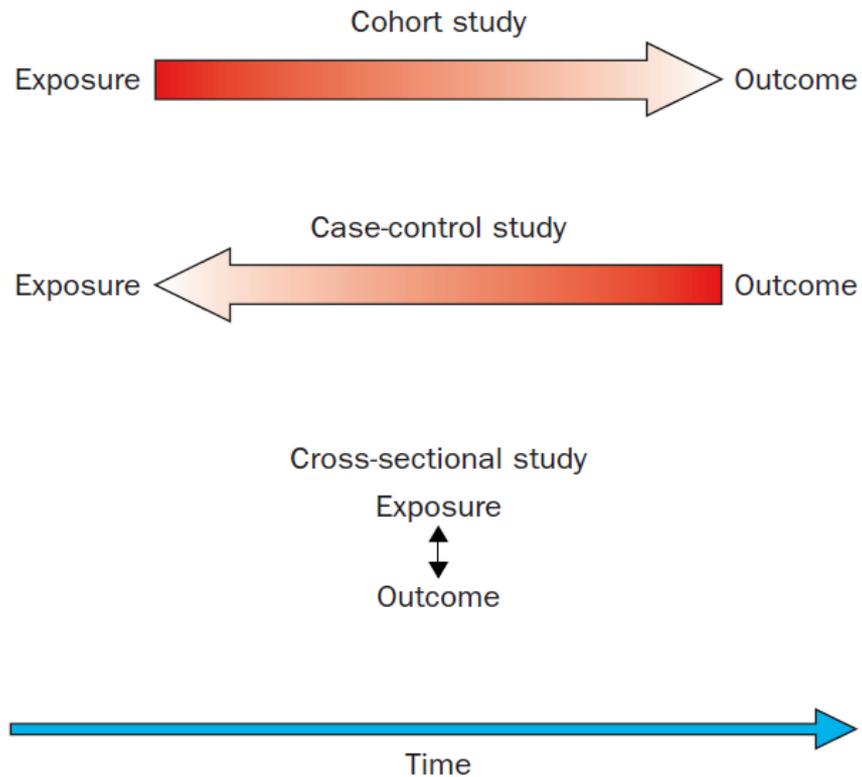


Figure 2: **Schematic diagram showing temporal direction of three study designs**



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]

Types of studies by research focus

(another incomplete list)

- **Treatment evaluations (nonrandomised cohort studies, RCTs)**
 - Benefits, harms
- **Disease aetiology (case-control)**
- **Prognosis (cohort)**
- **Diagnostic studies (case-control)**
- **Experiences, views (Qualitative studies)**
- **Quality improvement studies**
- **Economic evaluations**



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



Types of clinical research

- **Some research designs are more suitable for answering a given research question than others - important to choose an appropriate research design!**
 - e.g. RCT – best for comparing effectiveness of different interventions
- **Each approach has advantages and limitations**



Main elements of research

- **Clear/precise question(s)**
- **Research Design**
 - Who to study
 - What to measure and when
 - What interventions to make, and when (if any)
 - How large a sample
 - Many difficult decisions, so we need a **protocol**



Designing and implementing a research project

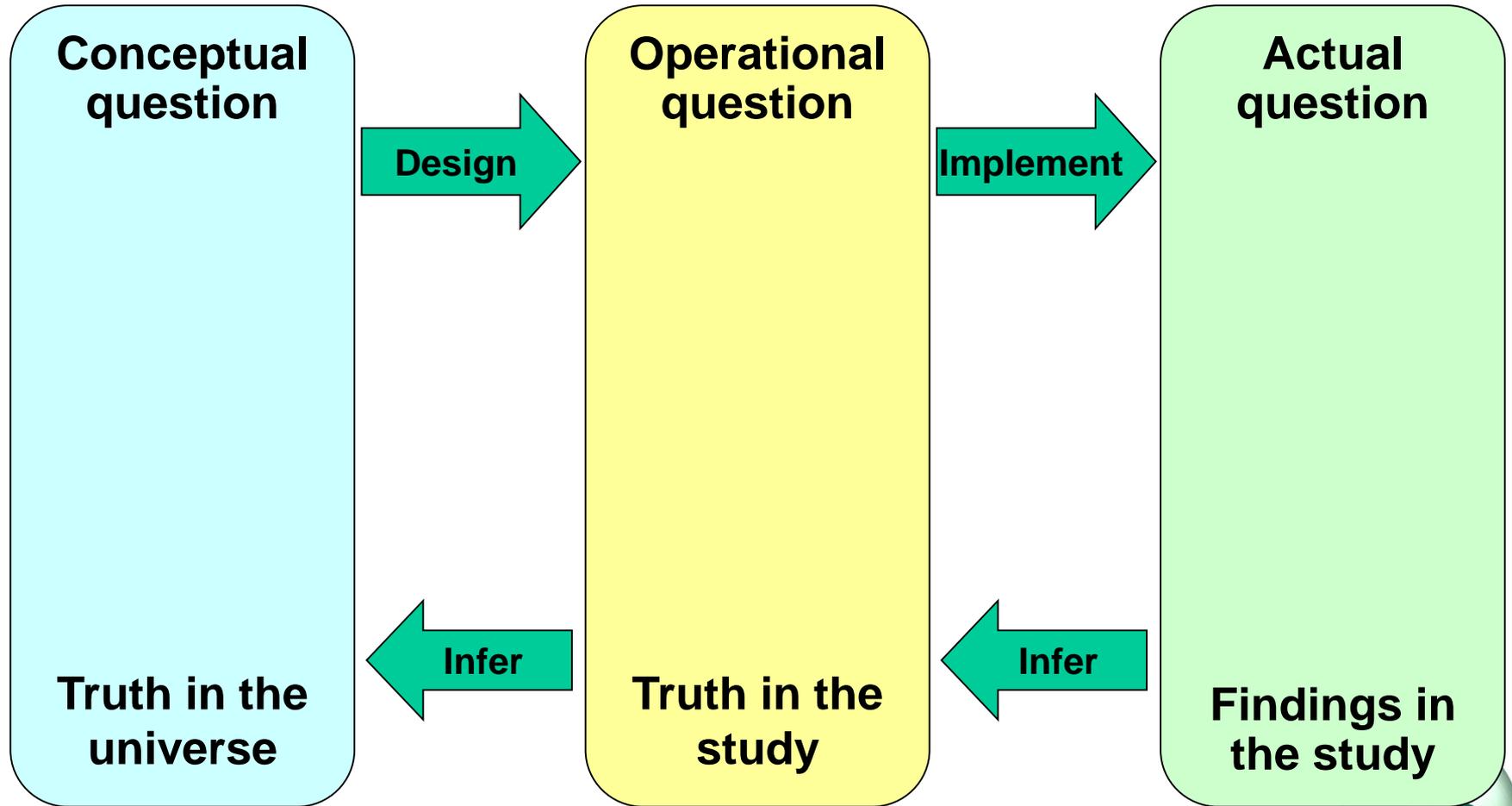
- **The ideal study**
- **The planned study**
- **What actually happens**

e.g. Participants

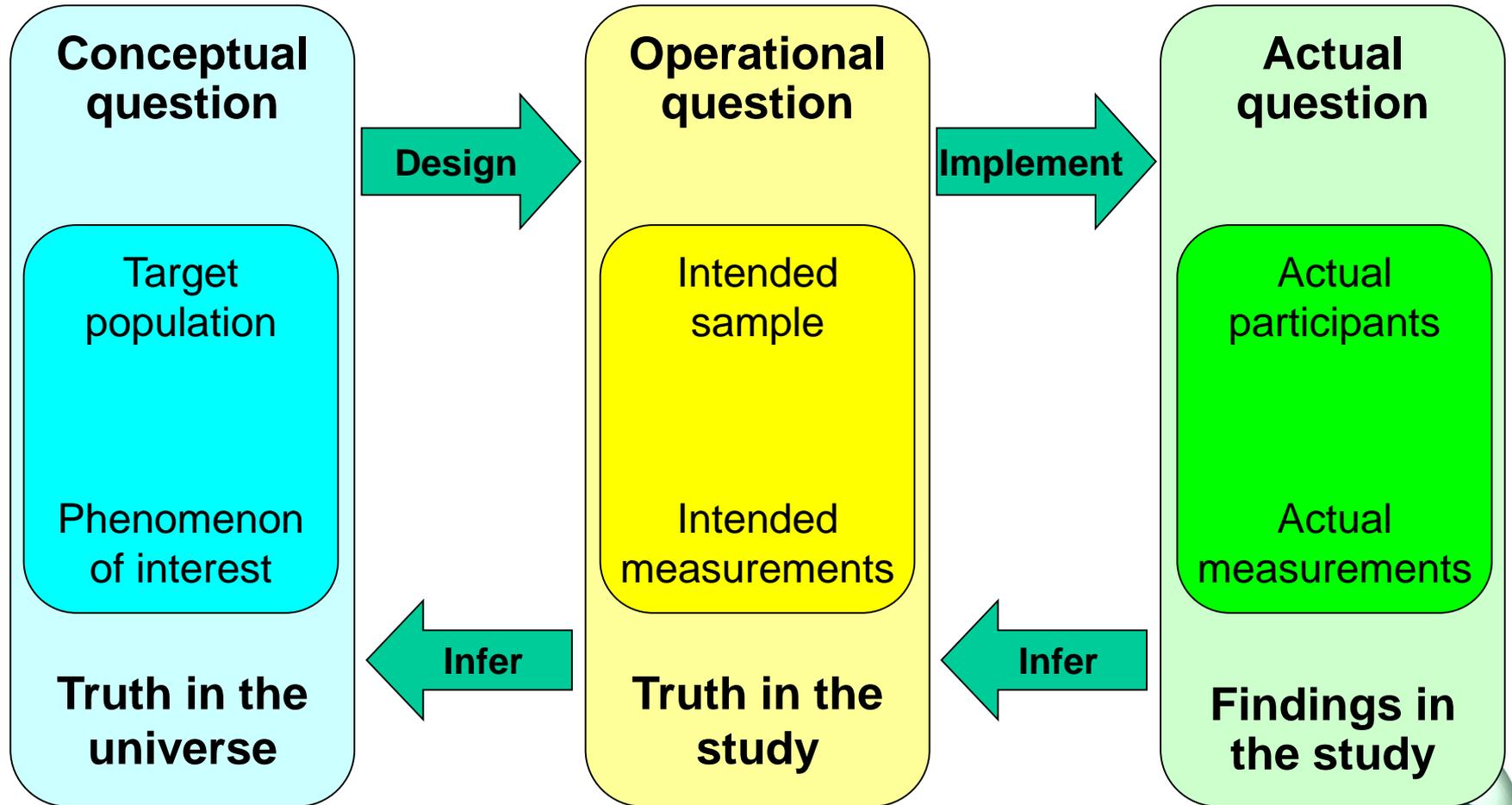
- **Target population: all travellers**
- **Intended sample: everyone invited to participate**
- **Actual sample: those who agree to participate**



The research cycle (after Hulley et al)



The research cycle (after Hulley et al)

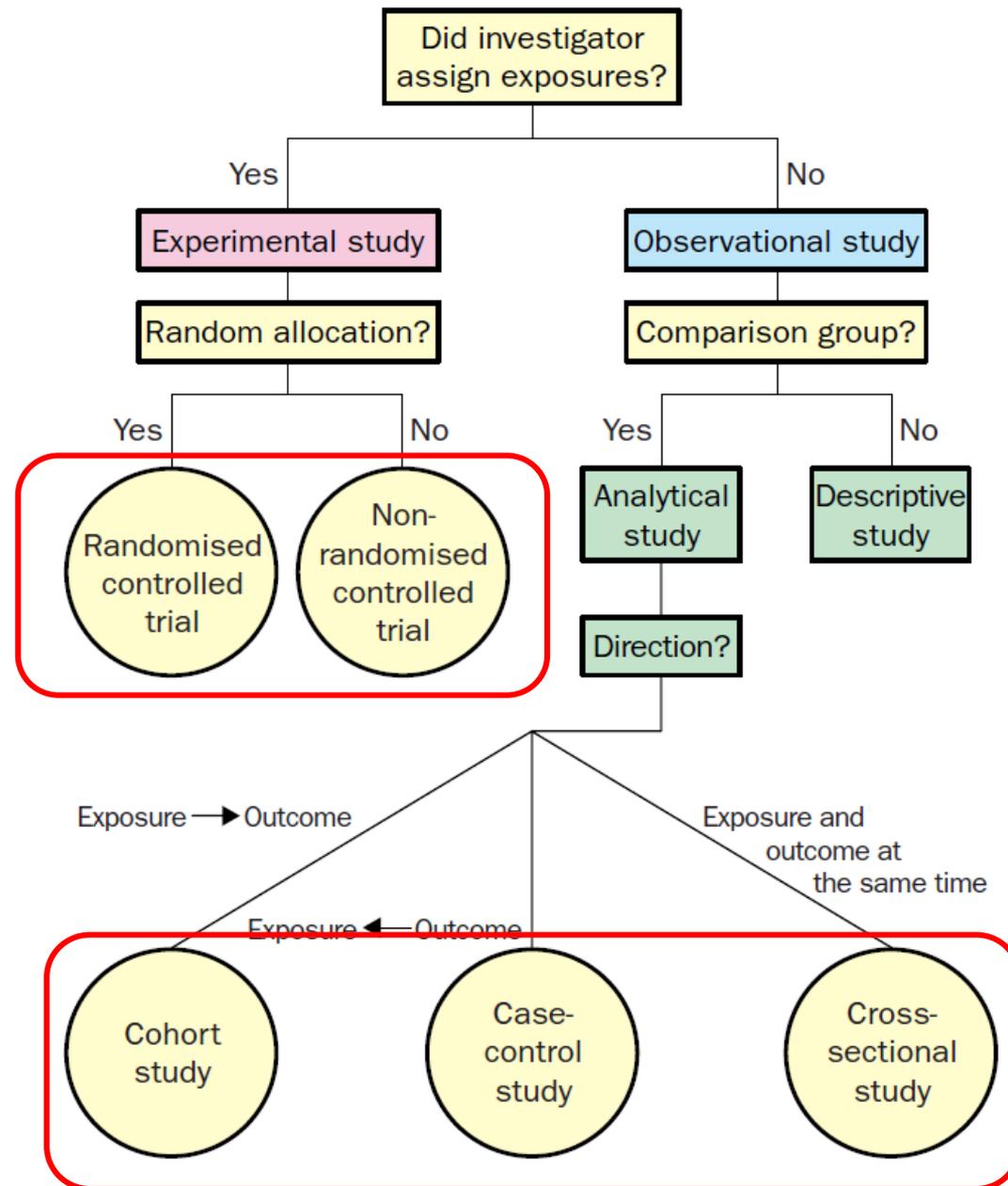


Experimental studies

- **Nonrandomised studies**
 - Cheap (especially if retrospective)
 - Based in clinical practice – representative sample of patients
 - Open to bias – who gets which treatment and why?
 - Assume treatment groups are not comparable
- **Randomised trials**
 - Expensive and slow
 - Less representative patients
 - Randomisation removes biased allocation



Summary of designs



Schulz & Grimes,
Lancet 2002

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



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—e.g. age, smoking, sexual behaviour, diet—associated with both the exposure and the outcome (but not directly involved in the causal pathway)?



Cause and effect studies

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



Observational studies

- **Observational studies can examine a wider range of exposures than experimental studies**
 - e.g. an experimental study could not examine the affect of smoking during pregnancy on birth outcomes
 - Examine causal factors (aetiology)
- **Main options:**
 - Cohort
 - Case-control
 - Cross-sectional
 - ... with several variants



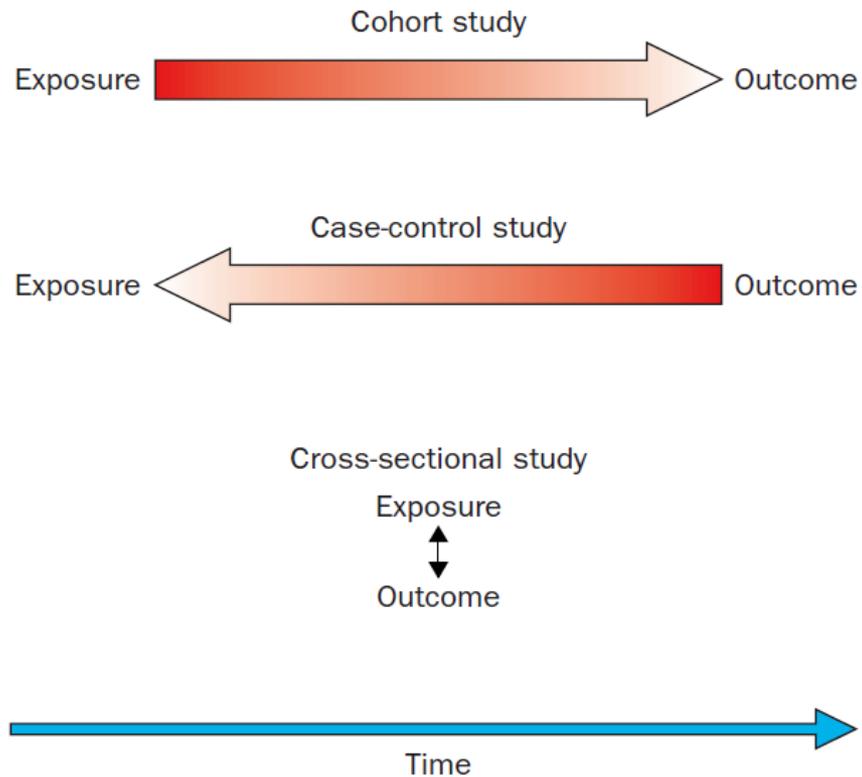


Figure 2: **Schematic diagram showing temporal direction of three study designs**

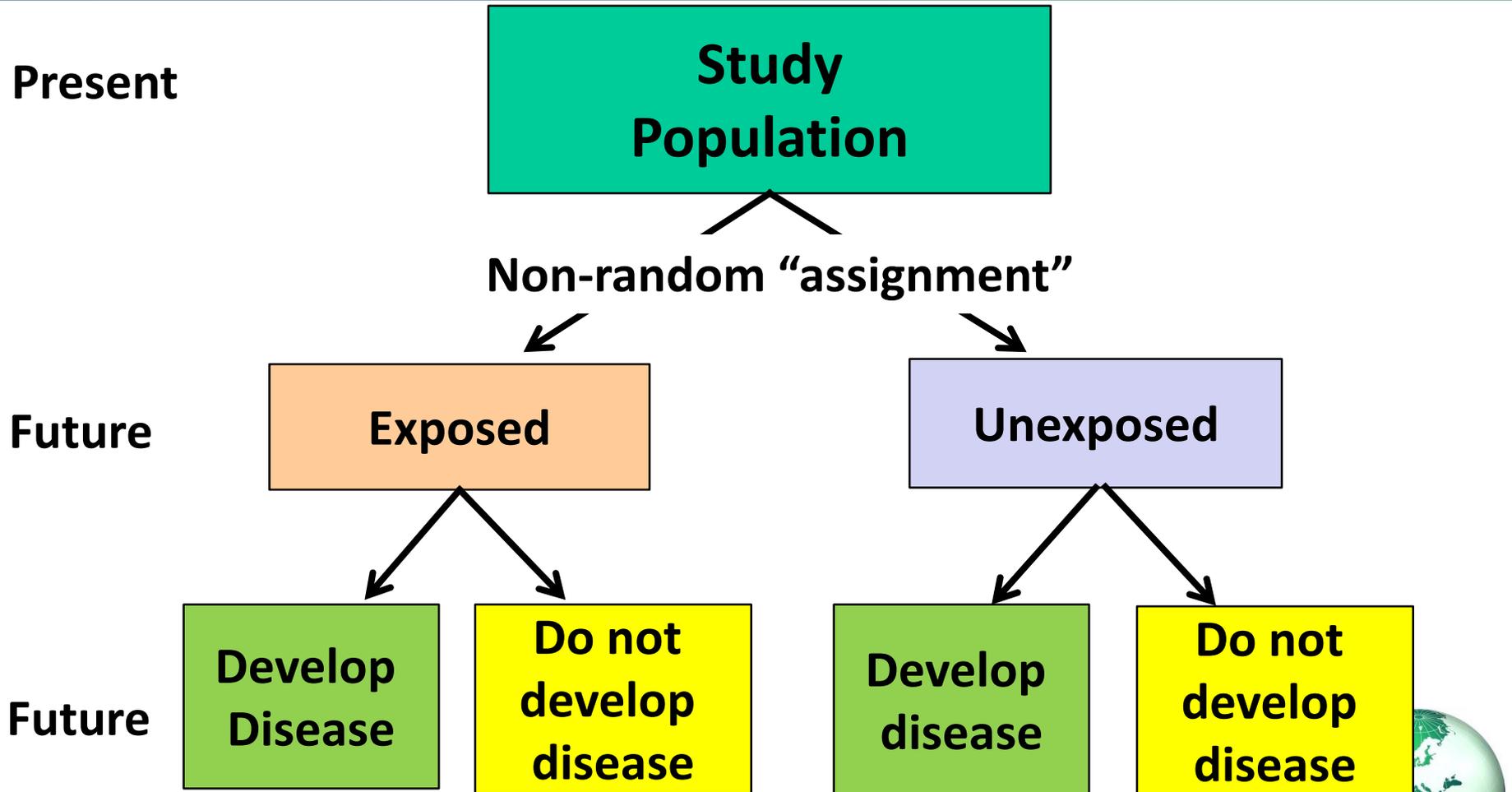


Cohort studies

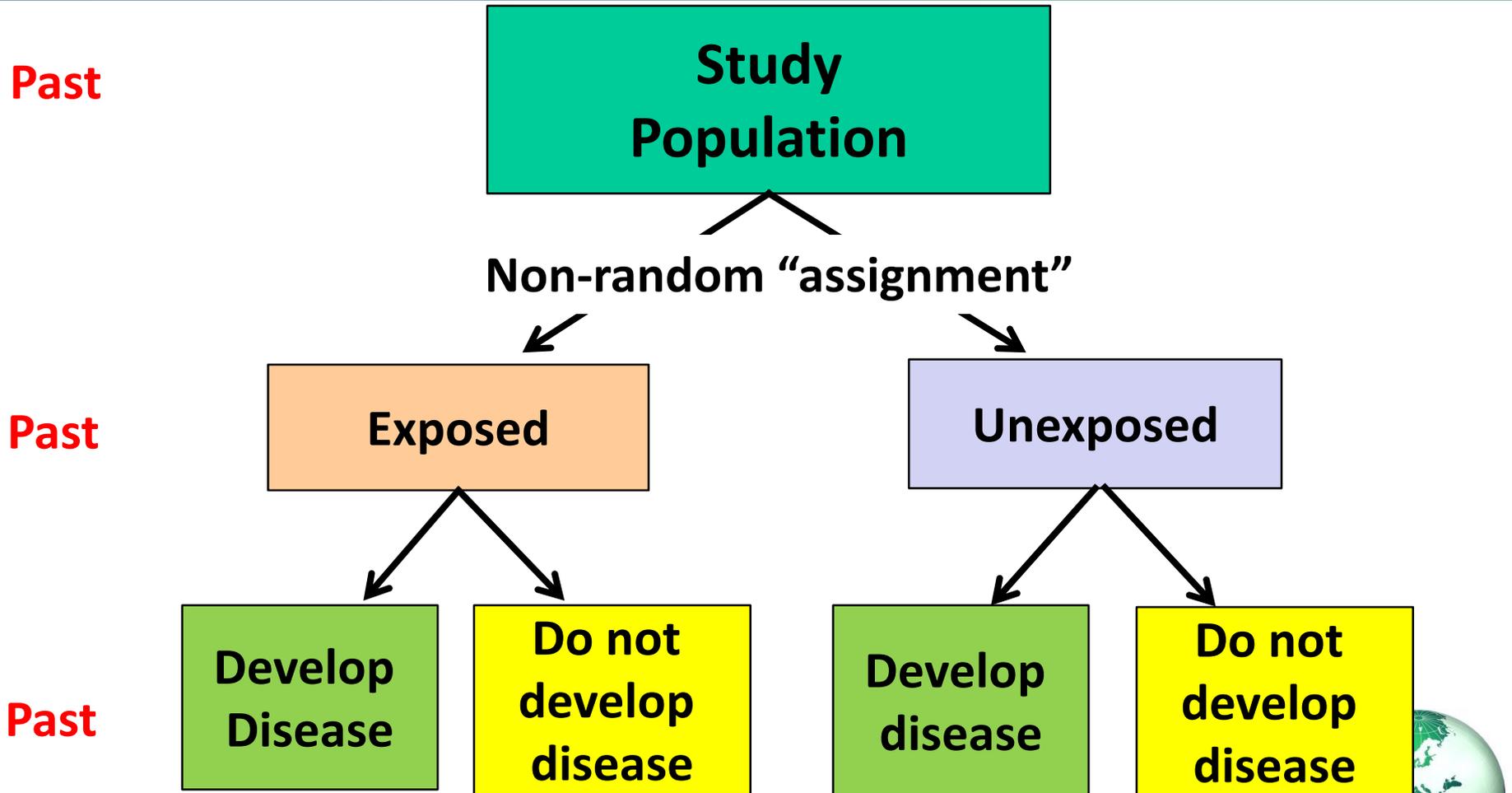
- **May be descriptive – what happens to this group of people**
 - e.g. prognostic study
- **Often they compare subgroups**
 - Look at effects of exposure on outcome
 - Exposure can be a medical treatment



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

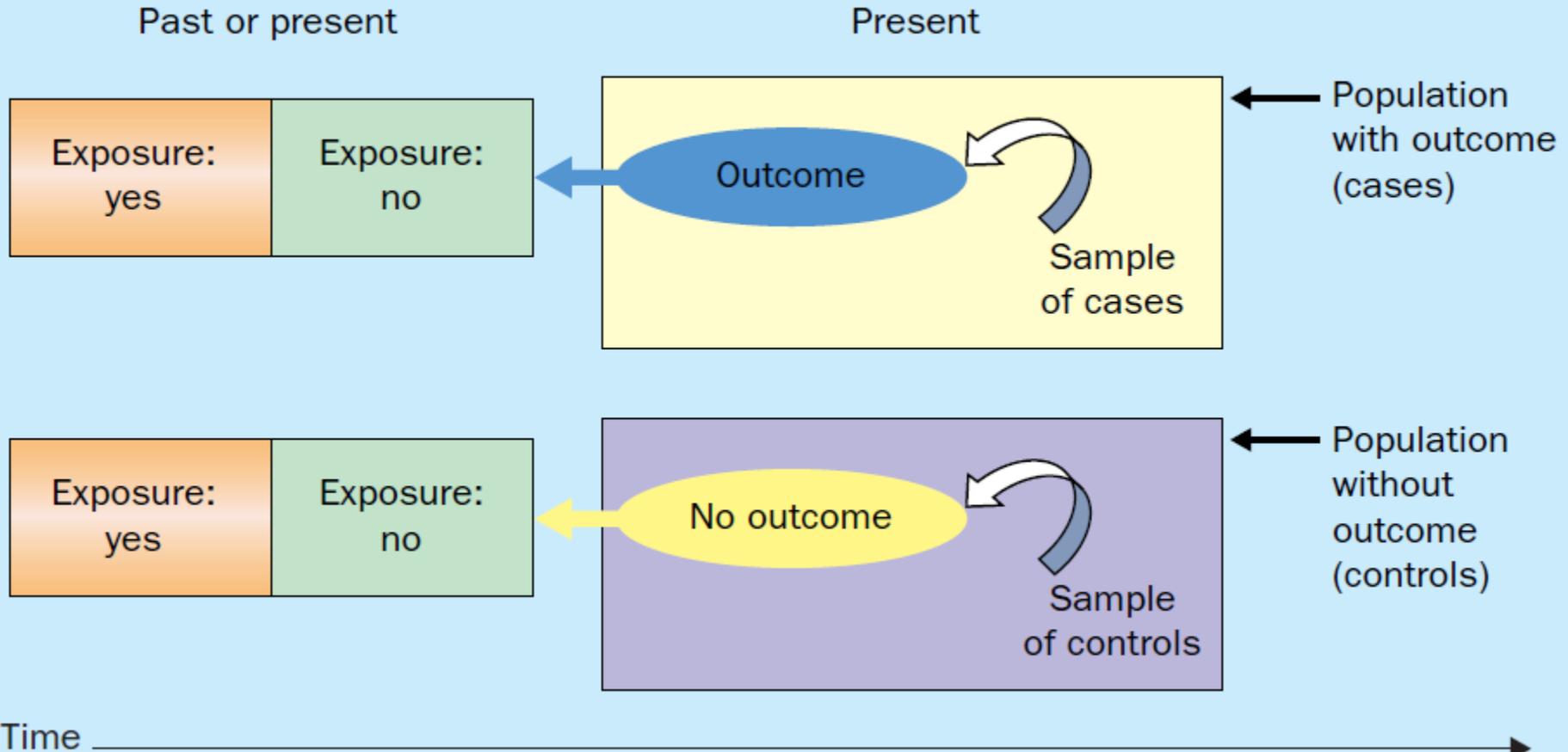
Disadvantages

- Requires a large sample size
- Long latency period
 - Delayed results
- Lost to follow-up
- Ethical considerations
- Resource intensive
- High cost



Case-control study

Case control study design



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

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



Non-randomised intervention study

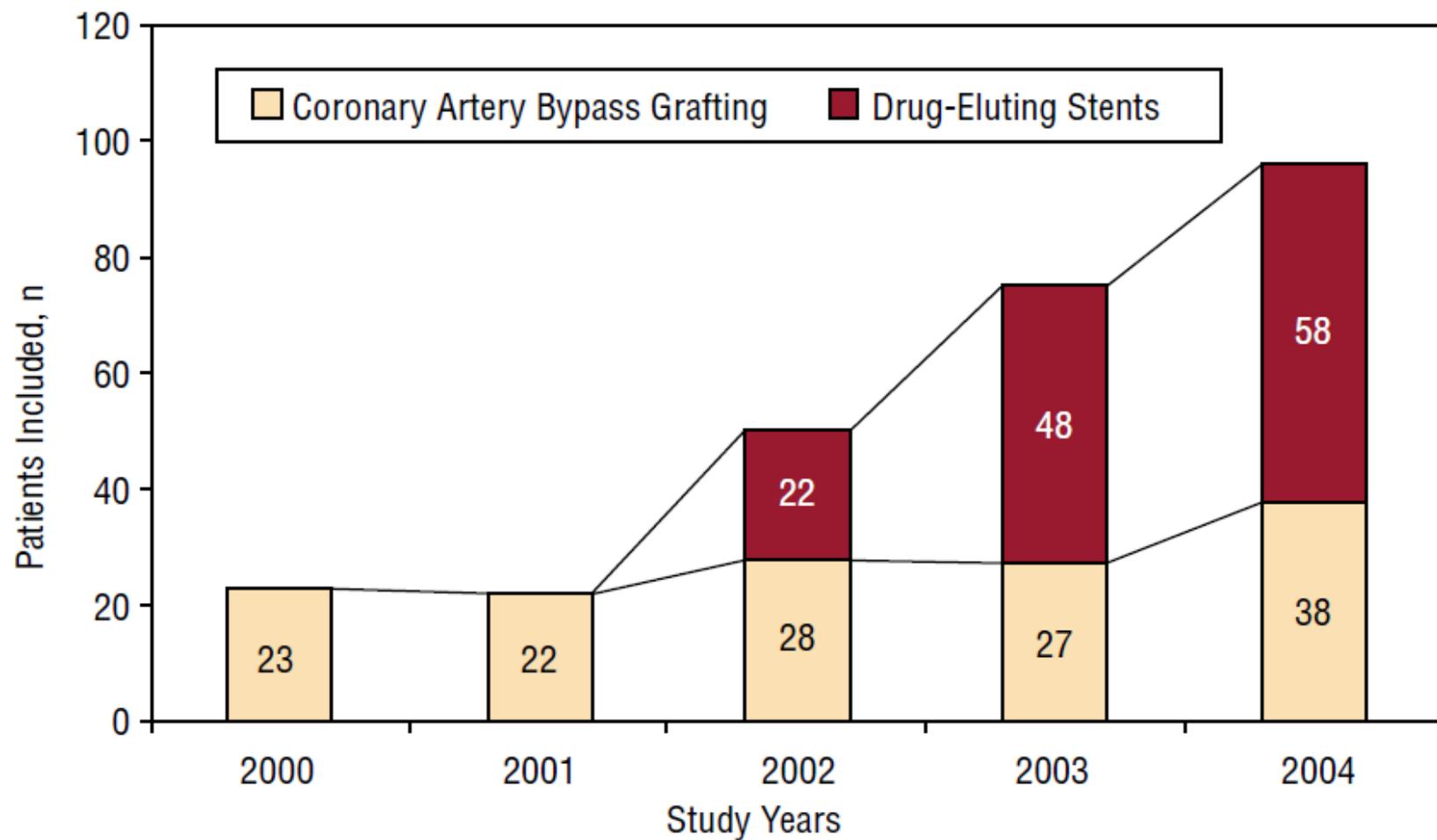
ORIGINAL ARTICLE

Comparison of Medium-Term Outcomes Obtained With Drug-Eluting Stents and Coronary Artery Bypass Grafts in an Unselected Population of Diabetic Patients With Multivessel Coronary Disease. Propensity Score Analysis

Antonio J. Domínguez-Franco^{a,b}, Manuel F. Jiménez-Navarro^a, José M. Hernández-García^a, Juan H. Alonso-Briales^a, Antonio L. Linde-Estrella^a, Olga Pérez-González^b, Inés Leruite-Martín^a, Eduardo Olalla-Mercadé,^a and Eduardo de Teresa-Galván^a

270 consecutive diabetic patients with multivessel disease (≥ 2 vessels with a $>70\%$ de novo stenosis involving the proximal left anterior descending coronary artery) who underwent either coronary artery bypass grafting (CABG; $n=142$) or implantation of a drug eluting stent (DES; rapamycin or paclitaxel; $n=128$).





492 Rev Esp Cardiol. 2009;62(5):491-500

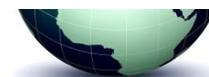


TABLE 1. Patient Characteristics at Baseline

	CABG Group (n=142)	DES Group (n=128)	<i>P</i>
Age, mean (SD), y	65.3 (8)	67.5 (7)	.05
Women, %	34.5	37.5	.6
High blood pressure, %	59.2	71.1	.04
Active smokers, %	43.7	39.1	.44
Dyslipidemia, %	49.3	43	.29
IDDM, %	32.4	39.8	.2
Kidney failure (creatinine clearance rate <60 mL/min), %	22.5	26.6	.44
Previous myocardial infarction, %	28.9	49.2	.001
Previous stroke, %	12	12.5	.89
Peripheral vascular disease, %	8.5	13.3	.2
Acute coronary syndrome, %	78.2	85.2	.14
LVEF<45%, %	32.4	28.1	.44
Three vessel disease, %	81	57.8	<.001
Left main stem, %	37.3	7.8	<.001
Chronic occlusion, %	47.2	36.7	.08
SYNTAX score	25.9 (7)	18.5 (6)	<.001
EuroSCORE	4.2 (2.9)	4.6 (2.7)	.21

CABG indicates coronary artery bypass grafting; DES, drug-eluting stent.; IDDM, insulin dependent diabetes mellitus; LVEF, left ventricular ejection fraction.

^aAfter adjusting for propensity score.

Data are expressed as mean (standard deviation) or percentages.



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



Main design strategies to avoid bias

- **Random allocation to interventions**
- **Concealed allocation**
- **Blinding**



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 (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**



	Placebo (n=88)	Apremilast			Total (N=352)
		10 mg (n=89)	20 mg (n=87)	30 mg (n=88)	
Age (years)	44.1 (13.7)	44.4 (13.9)	44.6 (12.6)	44.1 (14.7)	44.3 (13.7)
Male	53 (60%)	63 (71%)	55 (63%)	50 (57%)	221 (63%)
Race					
White	83 (94%)	82 (92%)	82 (94%)	80 (91%)	327 (93%)
Black	1 (1%)	2 (2%)	1 (1%)	2 (2%)	6 (2%)
Asian	4 (5%)	3 (3%)	2 (2%)	4 (5%)	13 (4%)
Other	0	2 (2%)	2 (2%)	2 (2%)	6 (2%)
Hispanic or Latino	7 (8%)	7 (8%)	5 (6%)	4 (5%)	23 (7%)
Height (cm)	171.2 (8.6)	171.5 (10.2)	171.7 (9.6)	171.2 (10.7)	171.5 (9.6)
Weight (kg)	90.4 (21.5)	95.9 (23.2)	89.9 (20.2)	91.4 (23.1)	92.0 (22.0)
Body-mass index (kg/m ²)	30.8 (6.7)	32.5 (7.4)	30.4 (6.1)	31.1 (7.7)	31.2 (7.1)
Total PASI score	18.1 (5.7)	18.1 (6.3)	18.5 (7.3)	19.1 (7.1)	18.5 (6.6)
Body surface area (%)	21.0 (11.2)	21.3 (11.4)	20.7 (12.4)	25.0 (15.3)	22.0 (12.7)
History of psoriatic arthritis	17 (19%)	20 (23%)	16 (18%)	21 (24%)	74 (21%)
Plaque psoriasis history (years)	19.6 (11.6)	18.0 (12.4)	19.2 (12.1)	19.2 (12.0)	19.0 (12.0)
Previous systemic therapy for psoriasis	39 (44%)	47 (53%)	43 (49%)	47 (53%)	176 (50%)

Data are mean (SD) or n (%). PASI=psoriasis area and severity index.

Table 1: Demographic and baseline characteristics

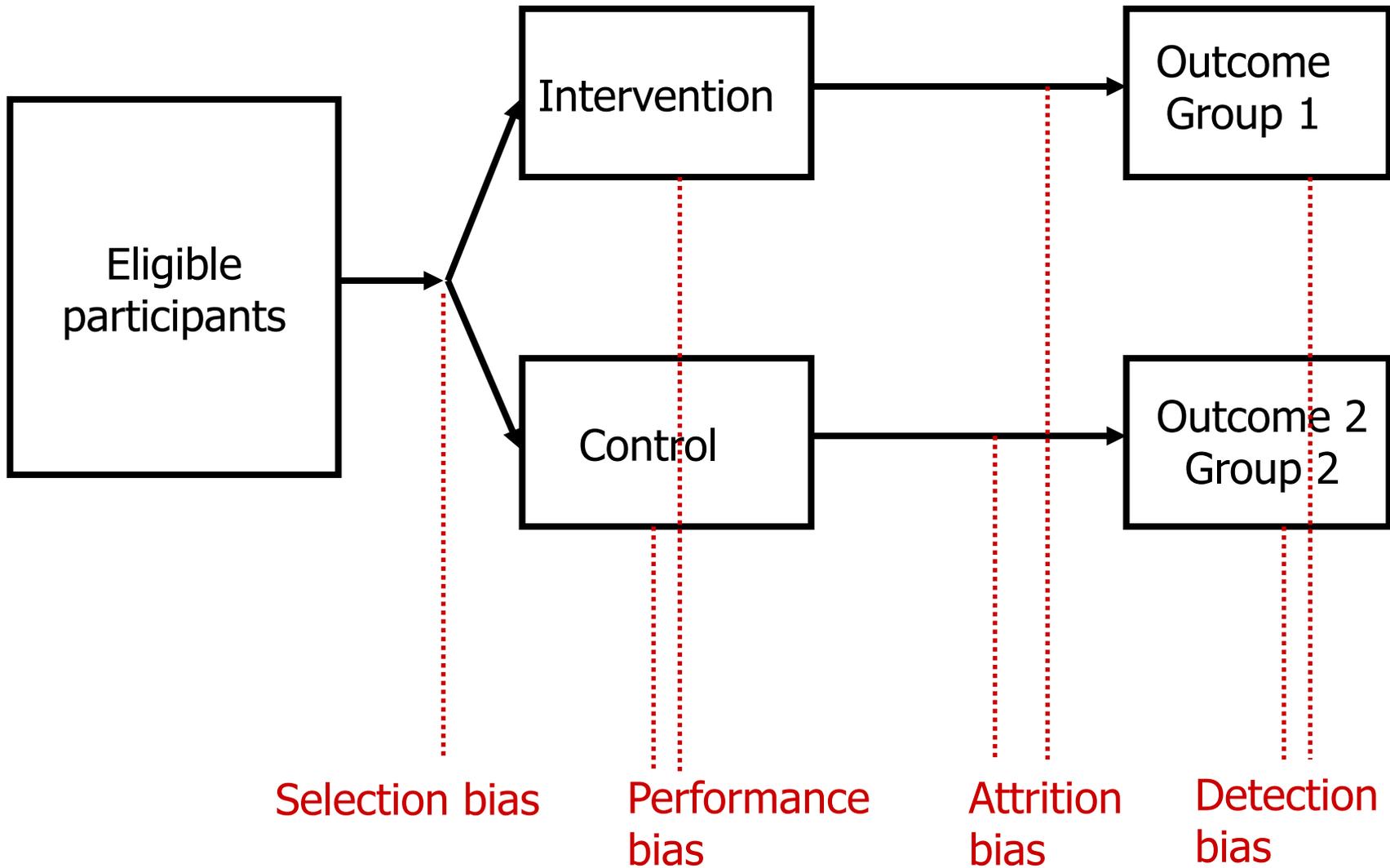
Papp et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet* 2012



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 being evaluated
 - “Detection bias”
 - biased outcome assessment
- **Blinding is not always possible**
- **Blind outcome assessment is especially desirable**





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**



Exercise

- **Consider the short report by Kraaijenhagen et al**
- **What is the study question?**
- **Is the study design appropriate?**

