Research Methodology Workshop

Study Type

What type of question?

- **Frequency**: how common is it?
- **Aetiology**: What caused this?
- **Intervention**: Does this intervention work?
- **Diagnosis or test evaluation**: How accurate is this test?

Epidemiologic Study Designs

Descriptive studies (frequency/pattern)

- Cross-sectional
- May be cohort studies

Analytical studies (causes of diseases/ new treatments/ new tests)

- Cohort, case-control, ecologic, analytic cross-sectional, before and after study, RCTs

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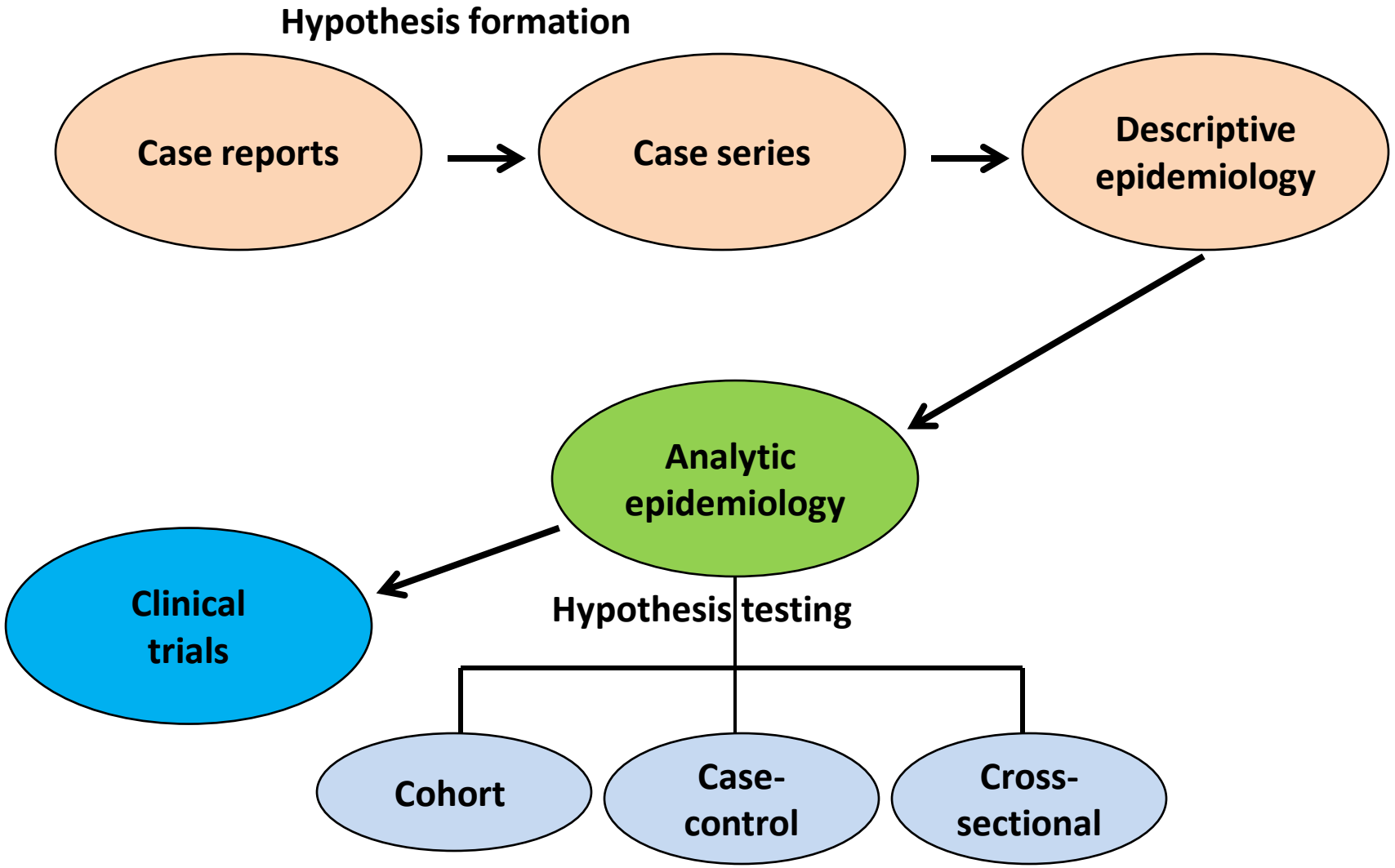
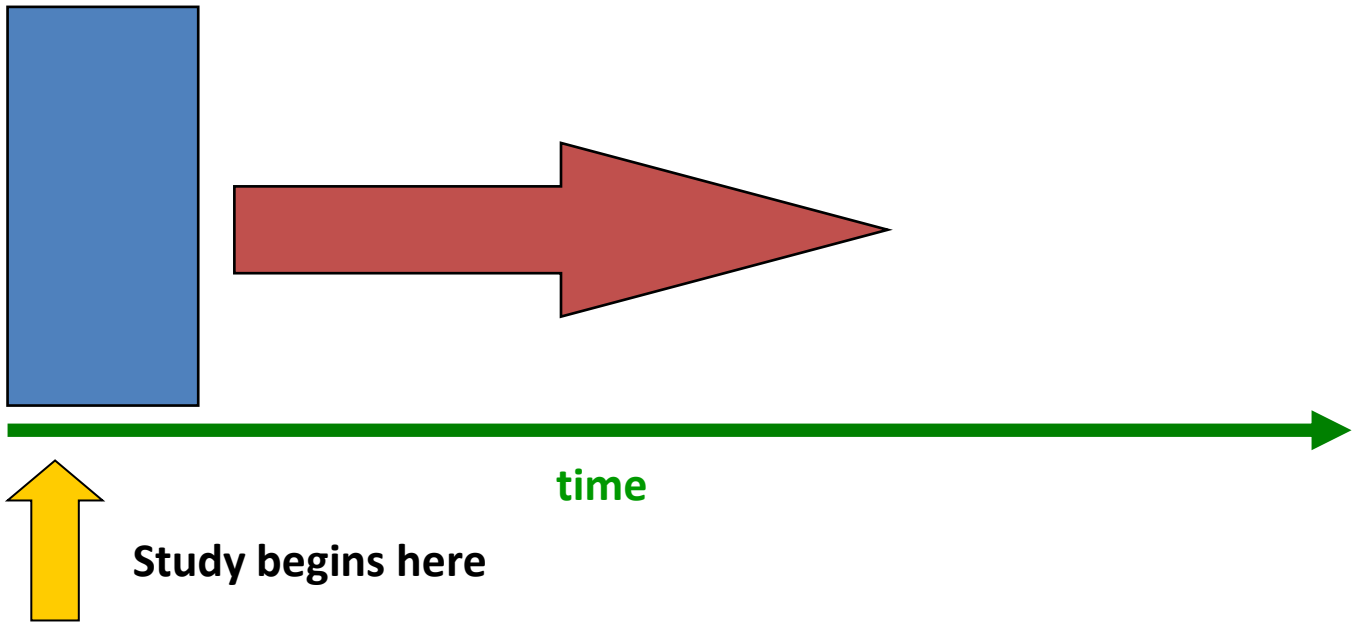
Study Design Sequence



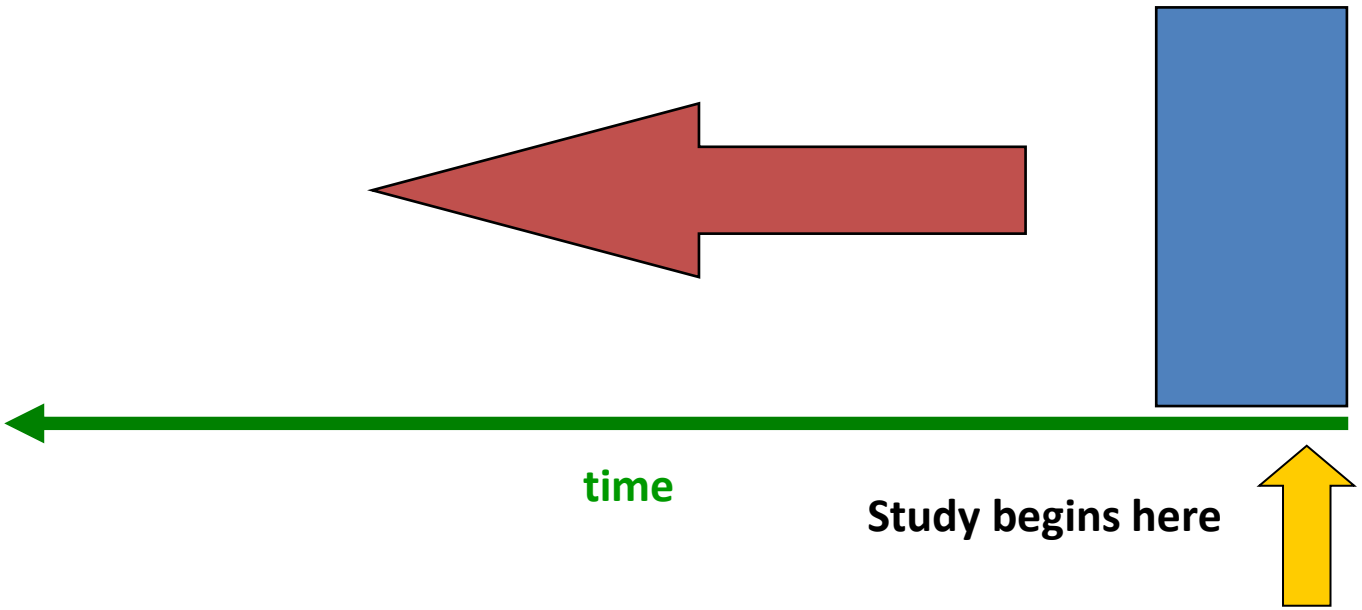
Timeframe of Studies

- Prospective Study - looks forward, looks to the future, examines future events, follows a condition, concern or disease into the future



Timeframe of Studies

- Retrospective Study - "to look back", looks back in time to study events that have already occurred



Case Report

- Detailed presentation of a single case or handful of cases
- Generally report a new or unique finding
    - e.g. previous undescribed disease
    - e.g. unexpected link between diseases
    - e.g. unexpected new therapeutic effect
    - e.g. adverse events

Case Report

Limitations:

No appropriate comparison group

- Cannot be used to test for presence of a valid statistical association
- Since based on the experience of one person:

  -presence of any risk factor

  - may be purely coincidental

  - not a true epidemiologic design

Case Series

- Experience of a group of patients with a similar diagnosis
- Assesses prevalent disease
- Cases may be identified from a single or multiple sources
- Generally report on new/unique condition
- May be only realistic design for rare disorders

Case Series

- **Advantages**
  - Useful for hypothesis generation
  - Informative for very rare disease with few established risk factors
  - Characterizes averages for disorder
- **Disadvantages**
  - Cannot study cause and effect relationships
  - Cannot assess disease frequency

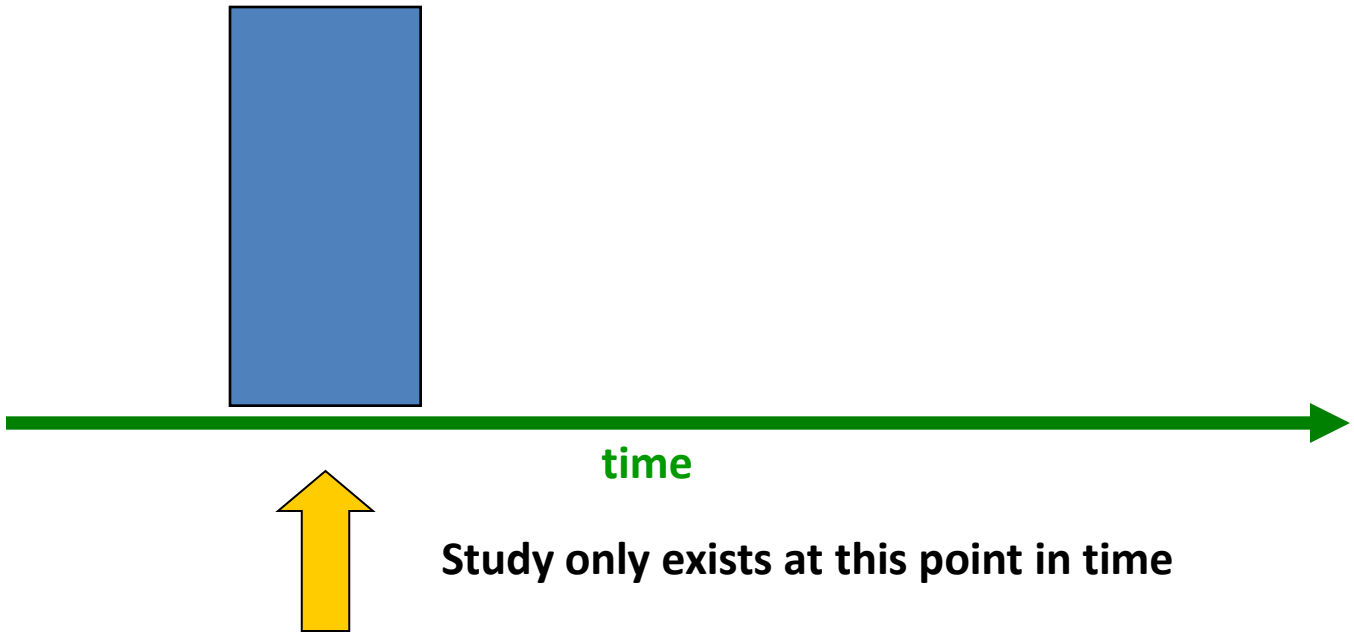
Case Report → One case of unusual findings

Case Series → Multiple cases of findings

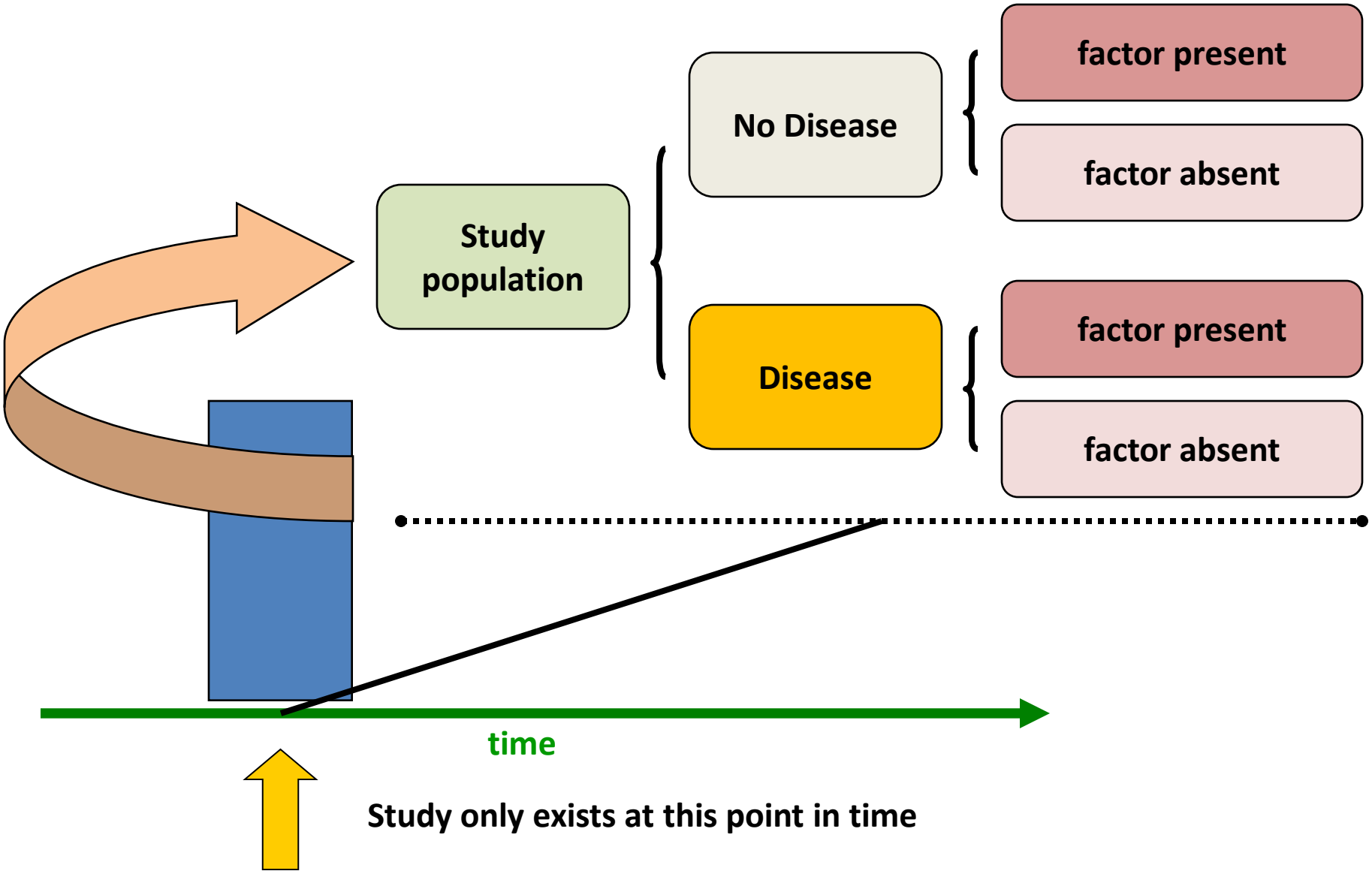
Descriptive Epidemiology Study → Population-based cases with denominator

Cross-sectional studies

- An “observational” design that surveys exposures and disease status at a single point in time (a cross-section of the population)



Cross-sectional Design



Cross sectional studies (Advantages)

- Provide data in terms of magnitude of the disease
- Provide clues to disease aetiology
- Help to generate hypothesis
- Provide data for planning, organizing and evaluating preventive and curative services.
- Contribute to research in terms of disease occurrence by time, place and person.

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Cross sectional studies (Disdvantages)

Causal relationship

?

Exposure  **Outcome**

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Analytical studies

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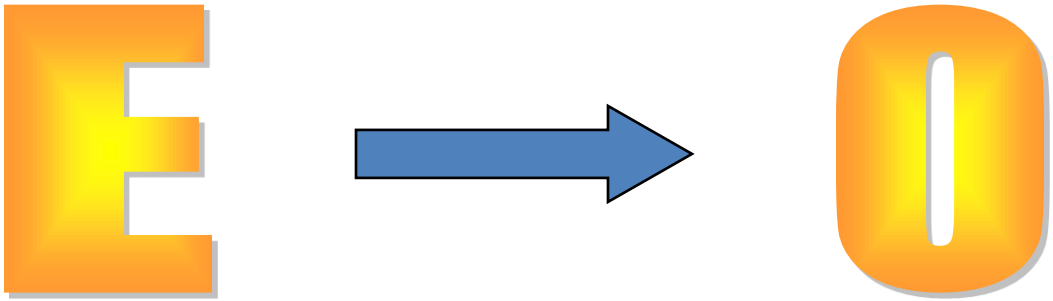
Analytical studies

(comparative studies testing an hypothesis)

- **case-control** (*Begins with outcome (cancer cases and healthy controls)*
- **Cohort** (*Begins with an exposure (smokers and non-smokers)*

Basic Question in Analytic Epidemiology

- Are **exposure** and **outcome** linked?



Exposure **Outcome**

Case-control study design

Case control study

- The case-control study is an analytic epidemiologic research design in which the study population consists of groups who either have (cases) or do not have a particular health problem or outcome (controls).

Case control study: cases (definition)

❖ Who are cases:

- With a Specific Outcome:
  - Presence of Disease / Syndrome
  - Complications / progression of Disease (Severe dehydration crisis)
  - Death (Neonatal mortality)

❖ Selection of cases:

- Conceptual definition
  - Obesity defined as body fat percentage $\geq$ 33%
- Operational definition
  - Body Mass Index $\geq$ 30

Case control study: cases (sources)

❖Where you can find cases:

- Hospitals (Multi-Centric Studies)
- Community
- Industrial Population

Case control study: controls

❖controls:

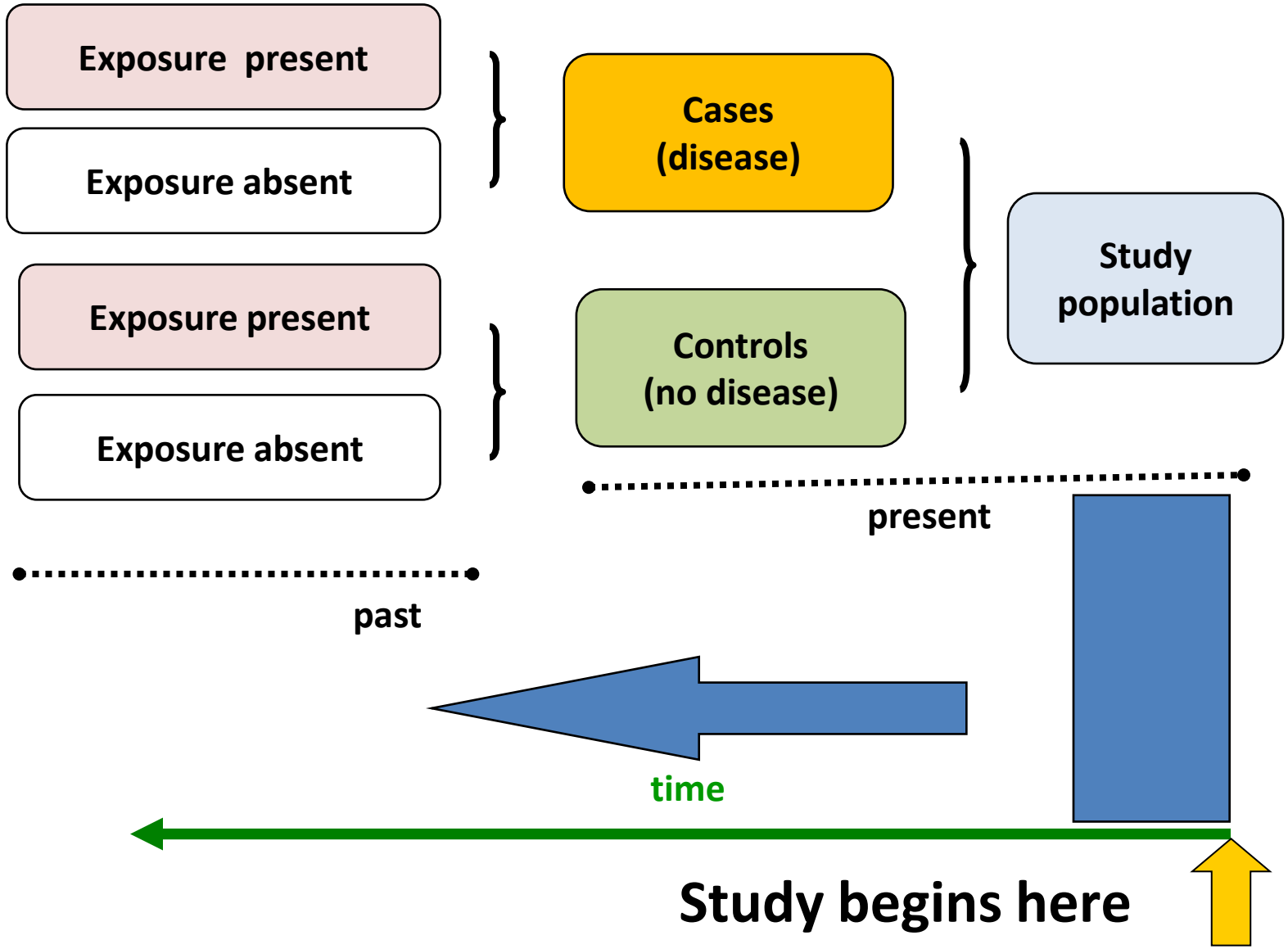
- The controls should come from the population at risk of the disease
  - Men can not be controls for a gynecological condition
  - The controls should be “eligible for the exposure”
- The controls should have same exposure rate as that of the population from where the cases are drawn

Case control study: controls

❖ type of controls:

- Hospital or clinic control
- Dead control
- Controls with similar diseases
- Peer or case-nominated (friend/neighbor) control
- Population controls

Case-Control Design



Case-control study design

	Cases	Controls
exposed	a	b
not exposed	c	d

$$\text{Odds Ratio (OR)} = \frac{ad}{bc}$$

Example

Exposure to fumes	Headache present	Headache absent	Total
Factor present	a=10	b=90	a+b= 100
Factor absent	c=50	d=850	c+d= 900
Total	a+c=60	b+d=940	n=1000

- OR = ad/bc

OR=1, OR<1, OR>1

OR Range	Interpretation
0.0 - 0.3	Strong Benefit
0.4 - 0.5	Moderate Benefit
0.6 - 0.8	Weak Benefit
0.9 - 1.1	No Effect
1.2 - 1.6	Weak Hazard
1.7 - 2.5	Moderate Hazard
> 2.6	Strong Hazard

Case-control study (example)

Q1. In a case-control study 200 people diagnosed with CHD were compared with 400 Healthy people (without CHD) in order to examine the association between smoking and CHD. In case group, 112 persons were smokers while in control group 176 persons were smokers, calculate OR.

Calculating the Odds Ratio

		Disease Status	
		CHD cases (Cases)	No CHD (Controls)
Exposure Status	Smoker	112	176
	Non-smoker	88	224
	Total	200	400

$$\text{Odds Ratio} = \frac{ad}{bc} = \frac{112 \times 224}{176 \times 88} = 1.62$$

Case-control study (advantages)

- - Cheap, easy and quick studies
- - Multiple exposures can be examined
- -Suitable for studying of rare diseases and diseases with long latency
- - Suitable when randomization is unethical
- (alcohol and pregnancy outcome)

Case-control study (disadvantages)

- Subject to bias (selection, recall, misclassification)
- Direct incidence estimation is not possible
- Temporal relationship is not clear
- Multiple outcomes cannot be studied
- If the incidence of exposure is high, it is difficult to show the difference between cases and controls
- Not easy to estimate attributable fraction

Cohort studies

Cohort Definition

- Ancient Roman military unit, A band of warriors.
- Persons banded together.
- Group of persons with a common statistical characteristic. [Latin]
- E.g. age, birth date,

Cohort study: Definition

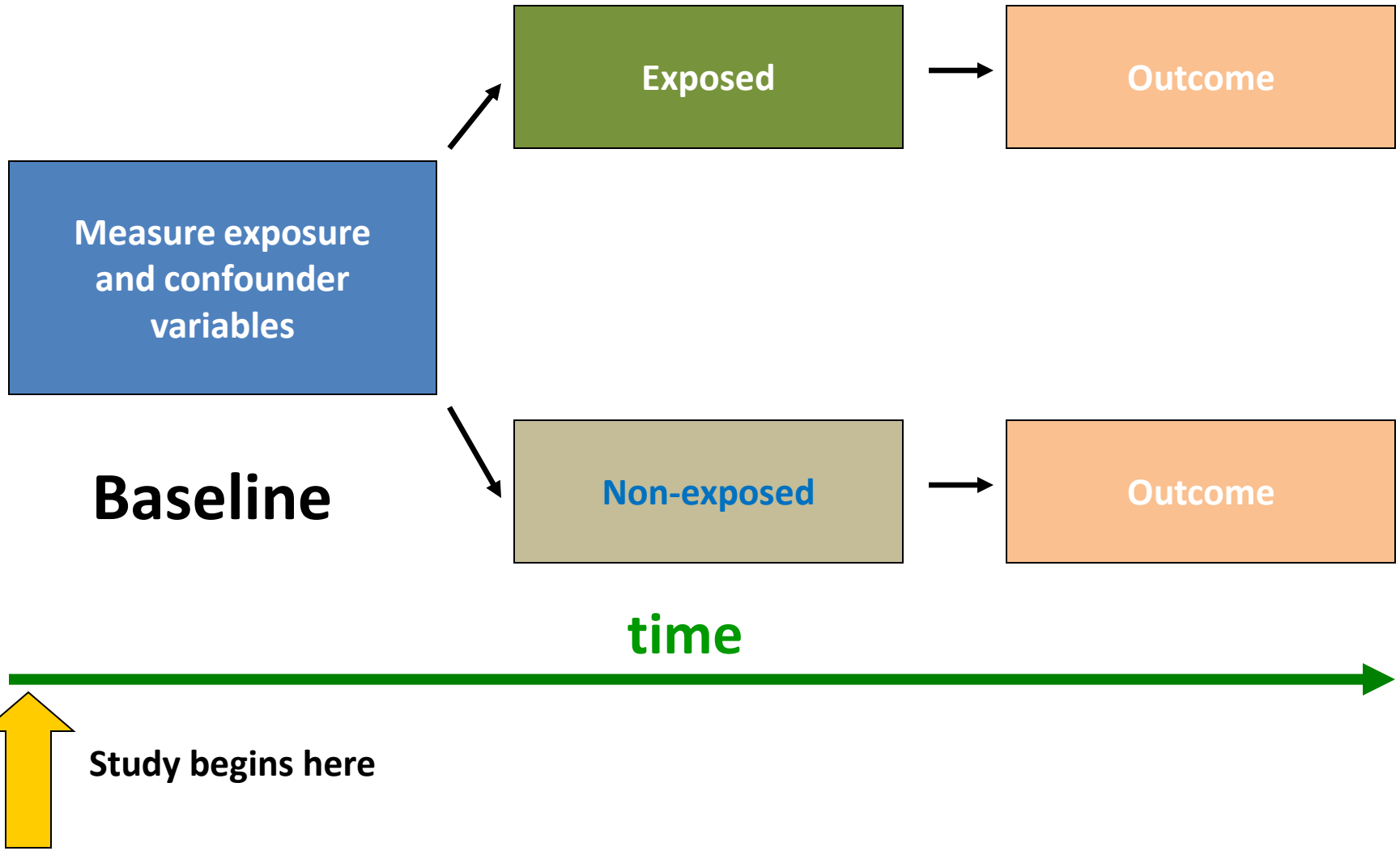
❖ Cohort study is undertaken to support the existence of association between suspected cause and disease

- A major limitation of cross-sectional surveys and case-control studies is difficulty in determining if exposure or risk factor preceded the disease or outcome.

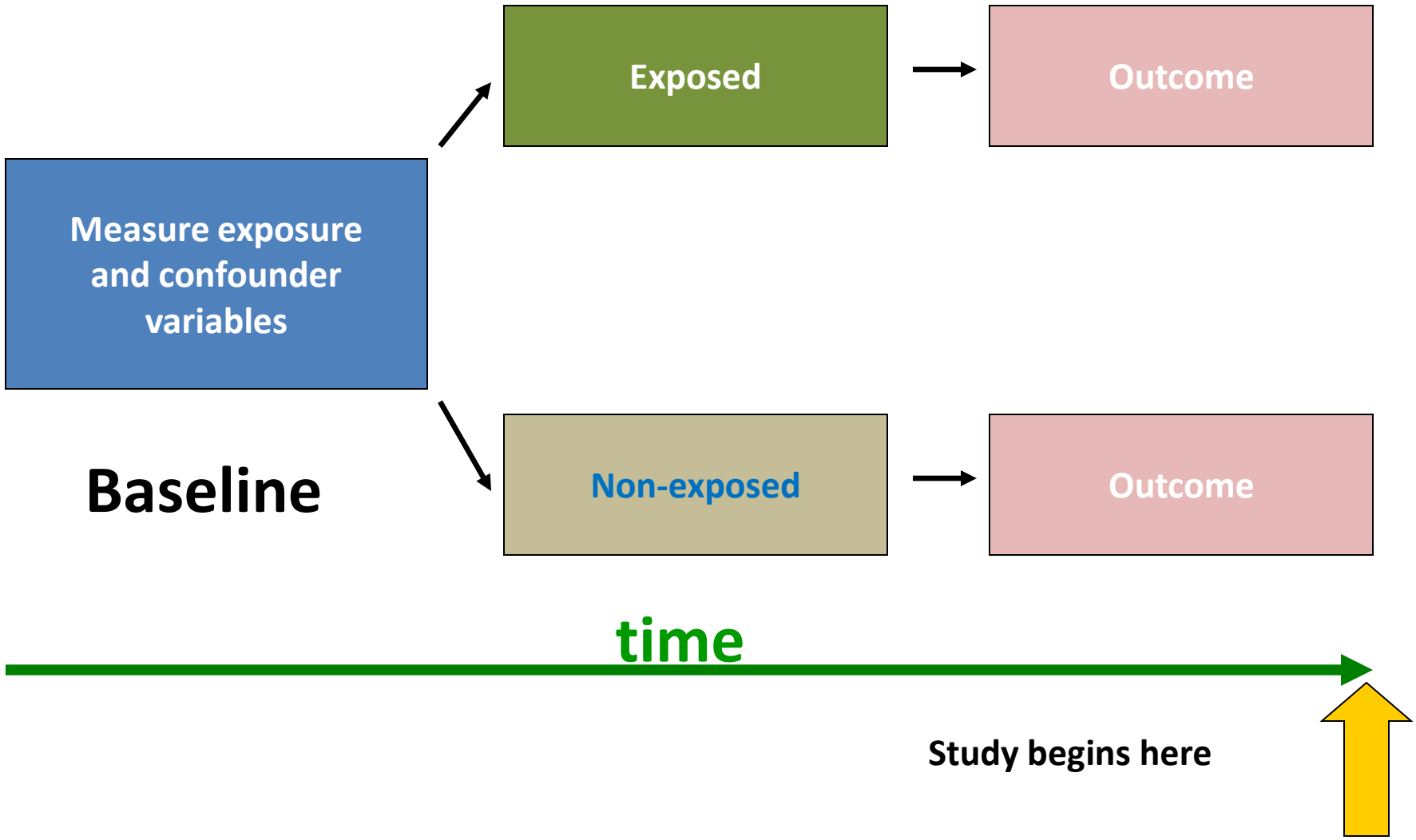
Key Point:

– Presence or absence of risk factor is determined before outcome occurs.

Prospective Cohort study



Retrospective Cohort study



Relative Risk

$$RR = \frac{\text{Incidence in the exposed group}}{\text{Incidence in the unexposed group}}$$

- It is also known as Risk Ratio

Cohort study: Example

Smoking	Lung cancer		Total
	YES	NO	
YES	70	6930	7000
NO	3	2997	3000
	73	9927	10000

Find out RR for above data

Cohort study: example

- Incidence of lung cancer among smokers

  70/7000 = 10 per 1000

- Incidence of lung cancer among non-smokers

  3/3000 = 1 per thousand

RR = 10 / 1 = 10

(lung cancer is 10 times more common among smokers than non smokers)

AR = 10 – 1 / 10 X 100

= 90 %

(90% of the cases of lung cancer among smokers are attributed to their habit of smoking

Cohort study: example

- Incidence of lung cancer among smokers

  70/7000 = 10 per 1000

- Incidence of lung cancer among non-smokers

  3/3000 = 1 per thousand

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AR = 10 – 1 / 10 X 100

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(90% of the cases of lung cancer among smokers are attributed to their habit of smoking

Cohort study: example

❖ **Example: stroke incidence rates by smoking category**

	No. stroke	Person years	Incidence rate per 100,000	RR
Never smoked	**70**	**395,594**		
Ex-smoker	**65**	**232,712**		
Current smoker	**139**	**280,141**		
total	**274**	**908,447**		**-**

Cohort study: example

❖ **Example: stroke incidence rates by smoking category**

	No. stroke	Person years	Incidence rate per 100,000	RR
Never smoked	**70**	**395,594**	17.7	Ref (1)
Ex-smoker	**65**	**232,712**	27.9	1.57
Current smoker	**139**	**280,141**	49.6	2.80
total	**274**	**908,447**	30.1	**-**

Cohort study:

Strengths

- We can find out incidence rate and risk
- More than one disease related to single exposure
- can establish cause - effect
- good when exposure is rare
- minimizes selection and information bias

Weaknesses

- losses to follow-up
- often requires large sample
- ineffective for rare diseases
- long time to complete
- expensive
- Ethical issues

Epidemiologic Study Designs

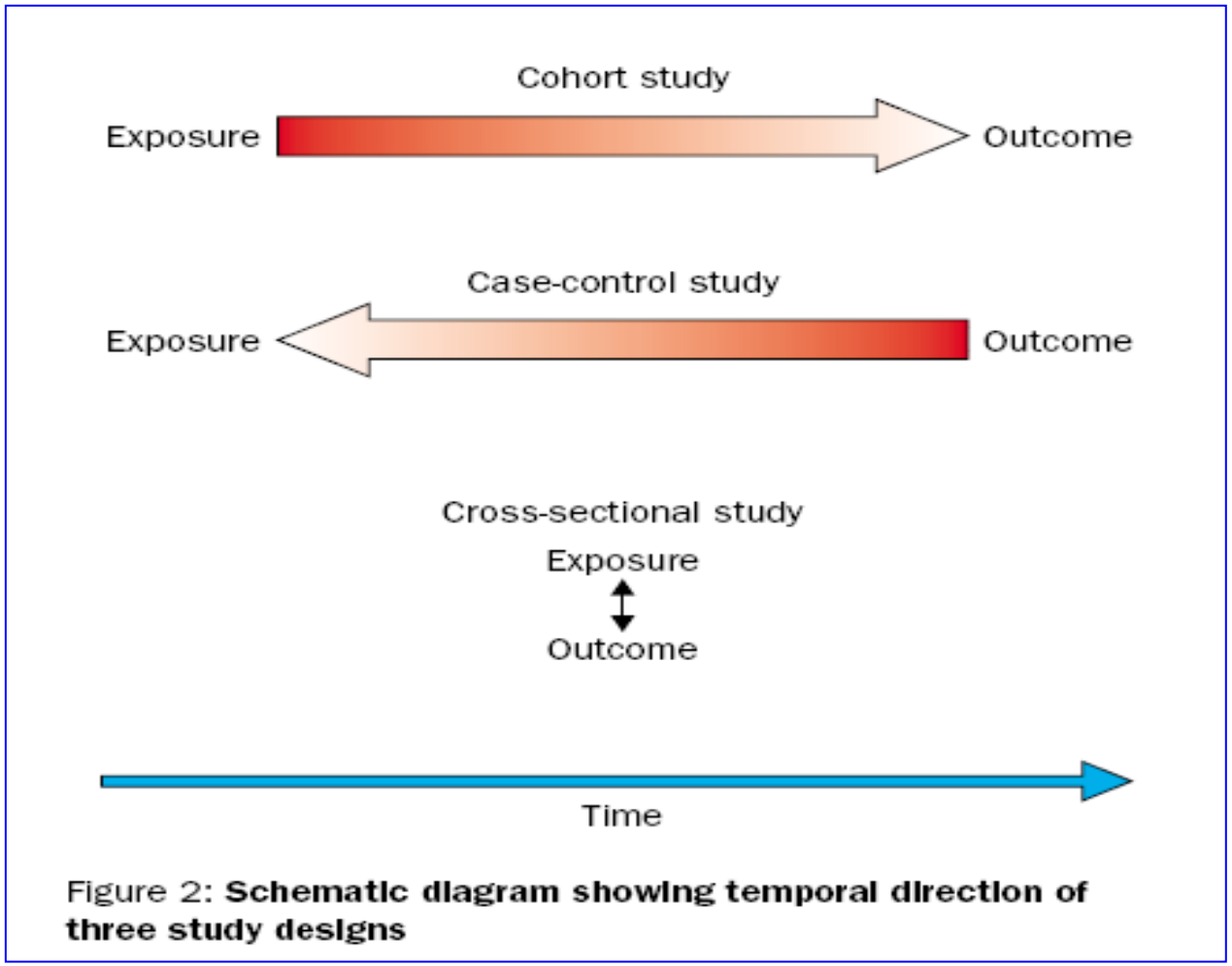

Figure 2: **Schematic diagram showing temporal direction of three study designs**

Grimes & Schulz, 2002 (www)

Experimental studies

Experimental studies

- We are interested in the consequences of some treatment on some outcome.
- The subjects in the study who actually receive the treatment of interest are called the treatment group.
- The subjects in the study who receive no treatment or a different treatment are called the comparison group.

Historical example

James Lind, 1716–1794

Historical example

- On the 20th of May 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all. … Two of these were ordered each a quart of cider a day. Two others took twenty-five gutts of elixir vitriol three times a day, … and so on. They continued but six days under this course. … The consequence was that 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 six days fit for duty."
- —James Lind, 1747

Randomized Controlled Trials (RCTs)

- a design with subjects randomly assigned to "treatment" and "comparison" groups
- provides most convincing evidence of relationship between exposure and effect
- not possible to use RCTs to test effects of exposures that are expected to be harmful, for ethical Issues

intervention that can be evaluated

- New drugs and new treatment of diseases
- New medical and health care technology
- New methods of primary prevention
- New programs for screening
- New ways of organizing and delivering health services
- New community health programs
- New behavioral intervention programs

intervention that can be evaluated

- New drugs and new treatment of diseases
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Comparison groups

- Therapy vs. no therapy
- Therapy vs. placebo or sham
- Therapy A vs. Therapy B

About Randomization

- Sir R.A. Fisher first developed the concept of experimental randomization in 1925
- J.B. Ambersonand B.T. McMahon (1931) randomized patients by using a coin flip to see who received treatment for tuberculosis
- Sir Austin Bradford Hill introduced the use of random numbers in the allocation of patients in the study of streptomycin and tuberculosis

Amberson JB Jr, McMahon BT, Pinner M (1931). A clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuberc 24:401–435

Example

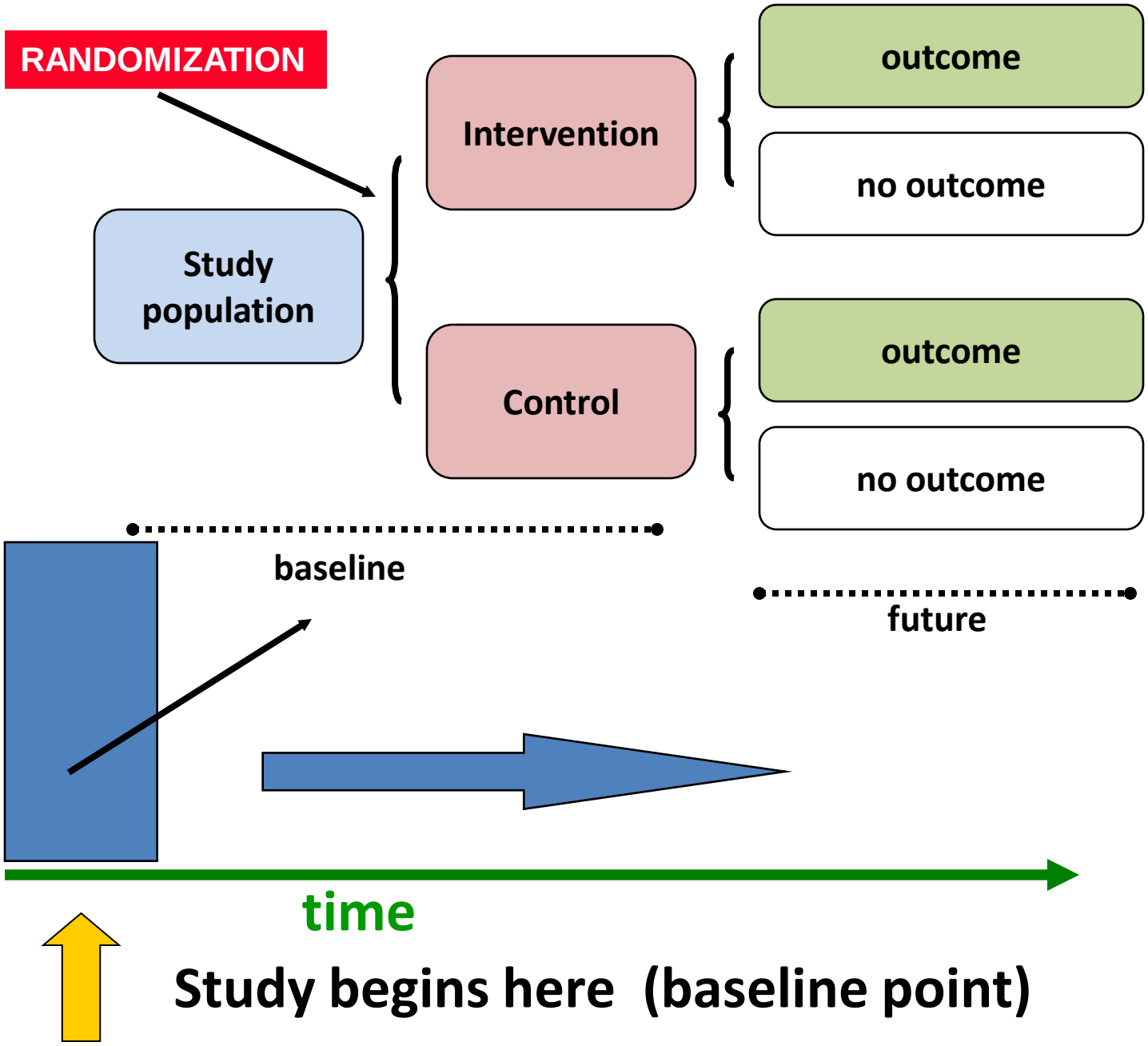
- “The 24 (tuberculosis) patients were then divided into two approximately comparable groups of 12 each. The cases were individually matched, one with another, in making this division. … Then by a flip of the coin, one group became identified as group I (treated group) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinctions in the treatment administered.”

Amberson JB Jr, McMahon BT, Pinner M (1931). A clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuberc 24:401–435

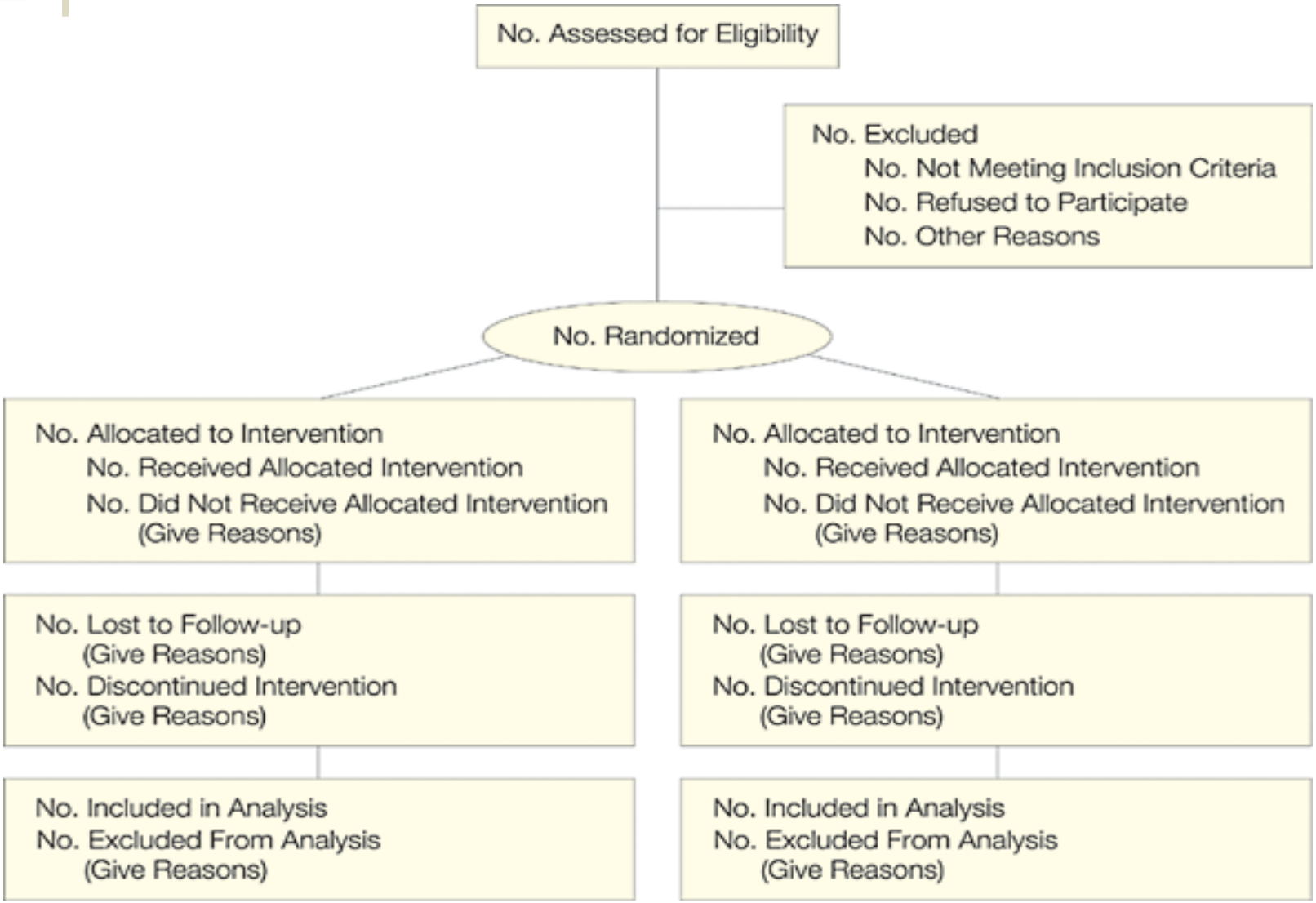
Randomized Controlled Trials

- A trial is an experiment
- A clinical trial is a controlled experiment having a clinical event as an outcome measure, done in a clinical setting, and involving persons having a specific disease or health condition
- A randomized clinical trial is a clinical trial in which participants are randomly assigned to separate groups that compare different treatments

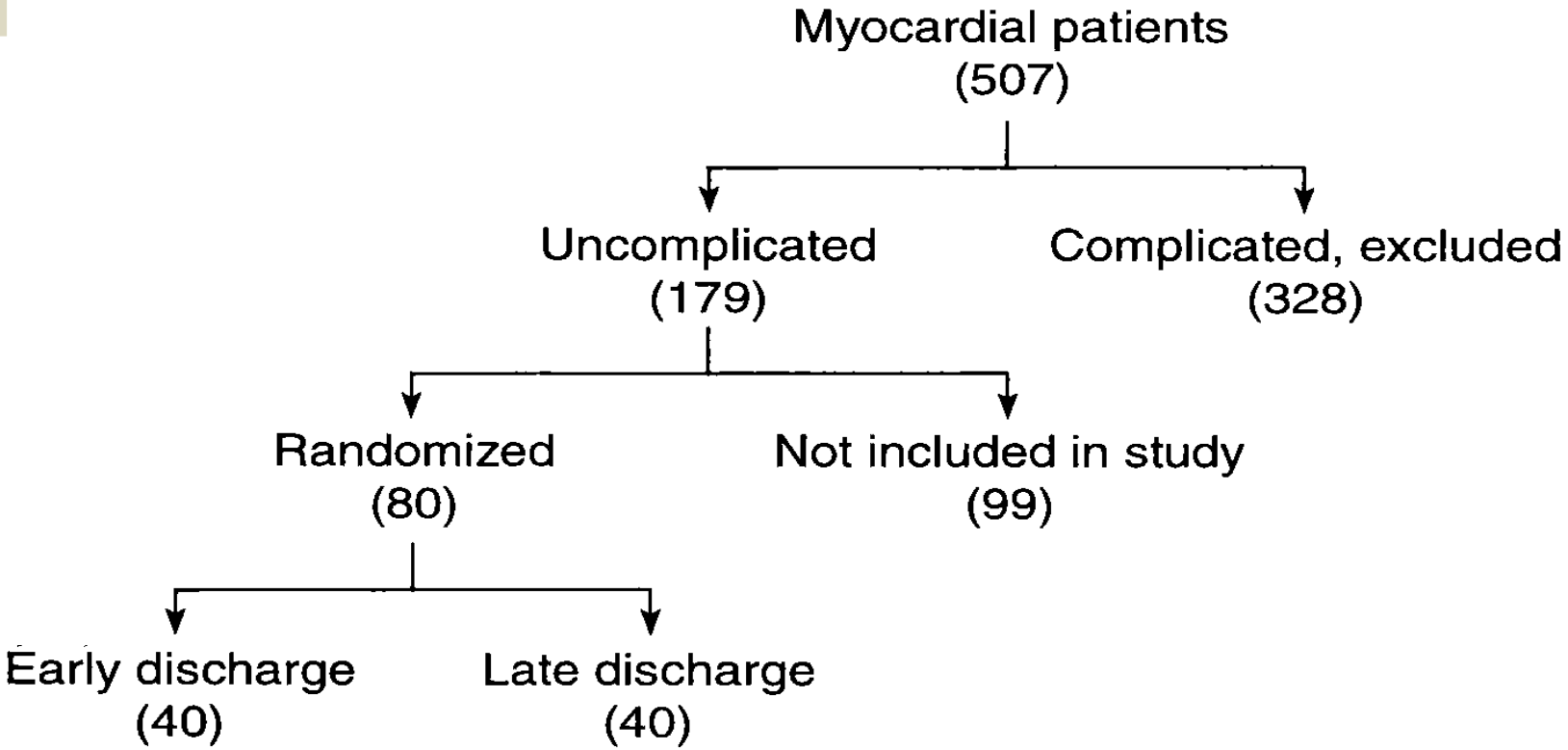
Randomized controlled trial design



Required CONSORT Figure



Randomized Controlled Trials



RCTs: Validity

- ***Internal validity:*** Can the observed differences between groups be attributed to the intervention?
  - Randomization
- ***External validity:*** Are the observed differences in your study representative of patients/subjects in general?
  - Random sampling

1- Randomization

- Random assignment of subjects to study groups:
  - Produces study groups comparable with respect to measured and unmeasured characteristics
  - Removes investigator bias in assigning patients to groups
  - Increases validity of statistical tests
- If allocation of subjects to groups is predictable, it may lead to bias, e.g., decision to participate

Allocation Scheme

- A simple example using a one-digit random number
  - **If two treatment groups are being studied:**
  - **If digit is: assign to:**
  - **0–4 Treatment A**
  - **5–9 Treatment B**

- If three treatment groups are being studied:
  - **If digit is: assign to:**
  - **1-3 Treatment A**
  - **4-6 Treatment B**
  - **7-9 Treatment C**
  - **(0 ignore)**

Allocation Scheme

Example (2 groups)

5	1	1	4	7
6	8	9	0	1

Translated to

B	A	A	A	B
B	B	B	A	A

Example (3 groups)

5	1	1	4	7
6	8	9	0	1

Translated to

B	A	A	B	C
C	C	C	-	A

Stratified randomization

- Stratified randomization is random assignment within groups defined by participant characteristics, such as age or disease severity, intended to ensure good balance of these factors across intervention groups

2- Blinding

- Unblinded, open trial
- Single blind
- Double blind
- Triple blind

❖ Not all clinical trials are susceptible to being blinded

3- Placebo

- A placebo (from the Latin for “I will please”) is a medical treatment (operation, therapy, chemical solution, pill, etc.), which is administered as if it were a therapy, but which has no therapeutic value other than the placebo effect
- A nocebo (from the Latin for “I will harm”) is treatment like a placebo but which has a harmful result

4- Compliance

- **Compliance** is the willingness of the participants to carry out the procedures according to the established protocols (adherence)
- **Drop-outs** are the participants who do not adhere to the experimental regimen during follow-up
- **Drop-ins** are the participants who do not adhere to the control regimen during follow-up

RCTs: Different types

1. Clinical Trial:

   Diagnostic, Therapeutic, Prophylactic, Devices, Procedures, Regimens, Protocols

2. Preventive Trial
3. Risk Factor Trial
4. Cessation experiments
5. Evaluation of health system

RCTs: Different types

1- Clinical Trial

- Concerned with evaluating therapeutic agent, mainly drugs
  - ❖Example: Evaluation of beta-blockers in reducing cardiovascular mortality

RCTs: Different types

2. Preventive Trials:

- Trial of primary preventive measures

❖ Example: Vaccines

- Analysis of preventive trials must result in clear statement about benefits to community, risk involved and cost to health

RCTs: Different types

3. Risk Factor Trials:

- Investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factor for developing the disease

❖ Example: Primary prevention of CHD using clofibrate to lower serum cholesterol

RCTs: Different types

4. Cessation Experiment:

- An attempt is made to evaluate the termination of a habit which is considered to be causally related to disease

❖ Example: Cigarette smoking and lung cancer

RCTs: Different types

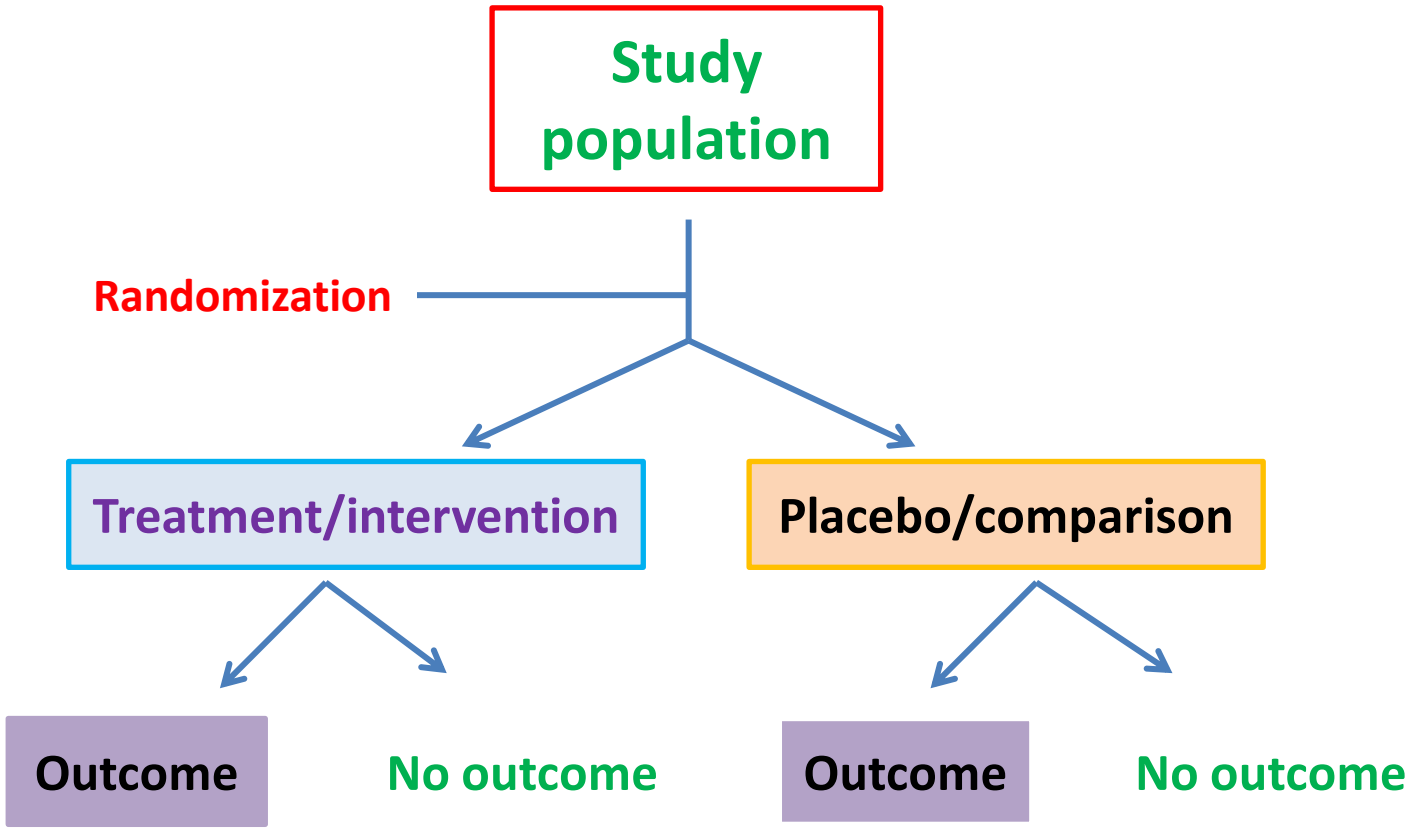
5. Evaluation of Health Services:

- Domiciliary treatment of PTB was as effective as more costlier hospital or sanatorium treatment

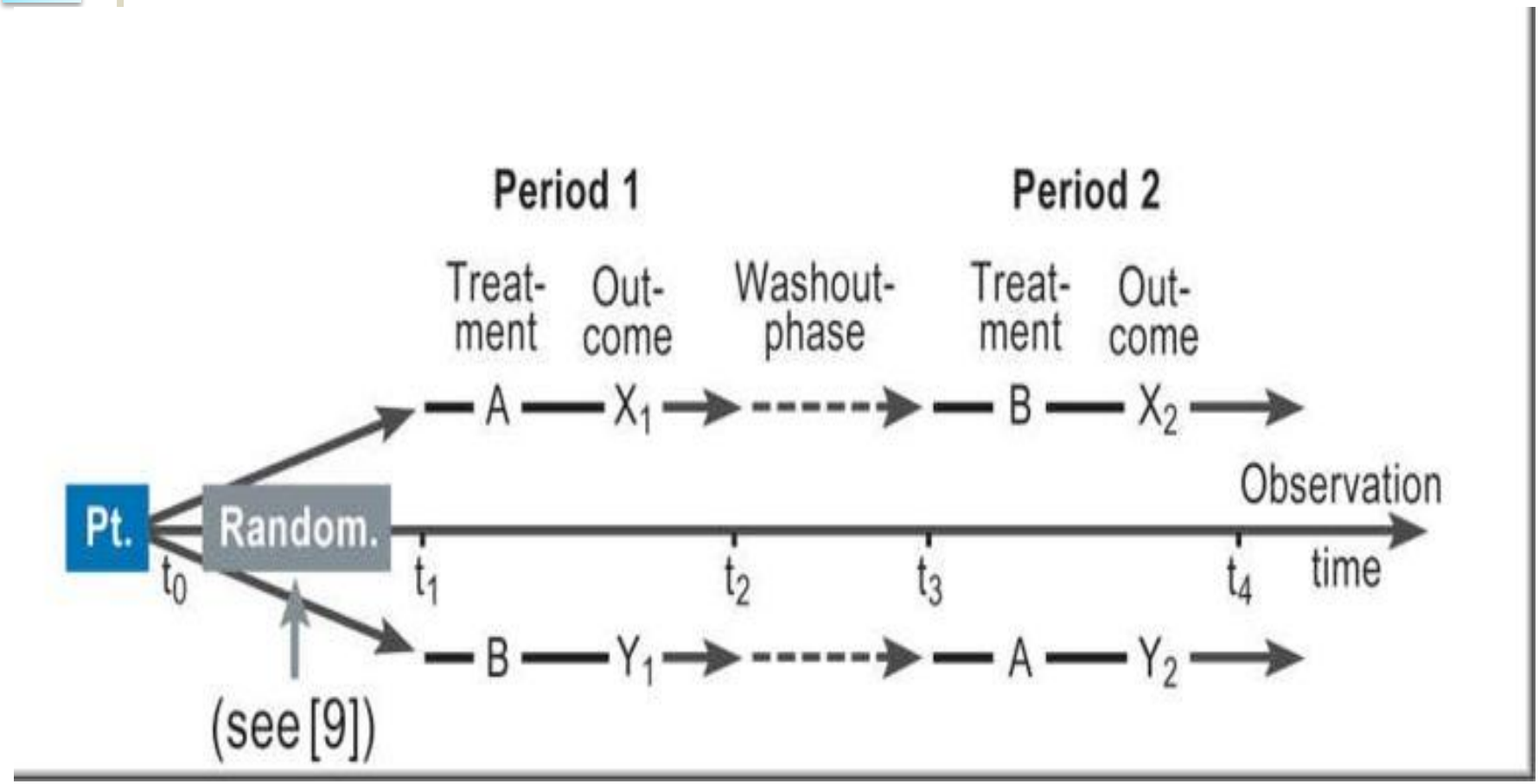
RCTs: Different design

- Parallel treatment or simple
- Crossover
- Factorial

RCTs :Parallel treatment or simple



RCTs: Crossover design



From:
Dtsch Arztebl Int. 2012 April; 109(15): 276–281.

RCTs: factorial design

Physicians' Health Study

- 22,071 physicians, 40–84 years old
- Randomly assigned in 1982 to one of four groups

1. Aspirin only (beta-carotene placebo)
2. Beta carotene only (aspirin placebo)
3. Aspirin and beta carotene
4. Neither (both placebos)

RCTs: Multi-centre trials

- Reasons for Multi-center Trials :

1. To recruit necessary number of subjects within a reasonable time.
2. May assure a more representative sample of the study or target population
3. Enables investigators with similar interest and skills to work together on a common problem

RCTs: Stages of experimentation

- Phase I: dose-finding
- Phase II: preliminary evidence of efficacy
- Phase III: comparisons to standard therapy
- Phase IV: post-marketing surveillance

RCTs: Phases of trials

Phase I studies (clinical pharmacologic studies)

– Test new drug or treatment in a small group of people (20–80) for the first time to evaluate its safety

- Determine levels of toxicity, metabolism, pharmacological effect, and safe dosage range
- Identify side effects

RCTs: Phases of trials

Phase II studies (efficacy studies)

- The drug or treatment is given to a larger group of people (100–300) for efficacy and to further evaluate its safety

RCTs: Phases of trials

Phase III studies (effectiveness studies)

- The drug or treatment is given to a large group of people (1,000–3,000) to confirm its effectiveness, compare it to commonly used treatments, and monitor side effects

Phase IV studies (post-marketing clinical trials)

- The drug or treatment is monitored to gather more information on risks, benefits, and optimal use

RCTs: advantages

- Most efficient for investigating causality
- Ensure 'ONLY ONE' factor is different: confounding factors do not confuse the results
- Ensure that treatments are compared efficiently
- Look for effects of combinations of treatments, interaction between treatments and personal characteristics
- Only study design which can help us evaluate a new treatment (medicine, other procedures etc.)

Randomized Controlled Trials (Advantages)

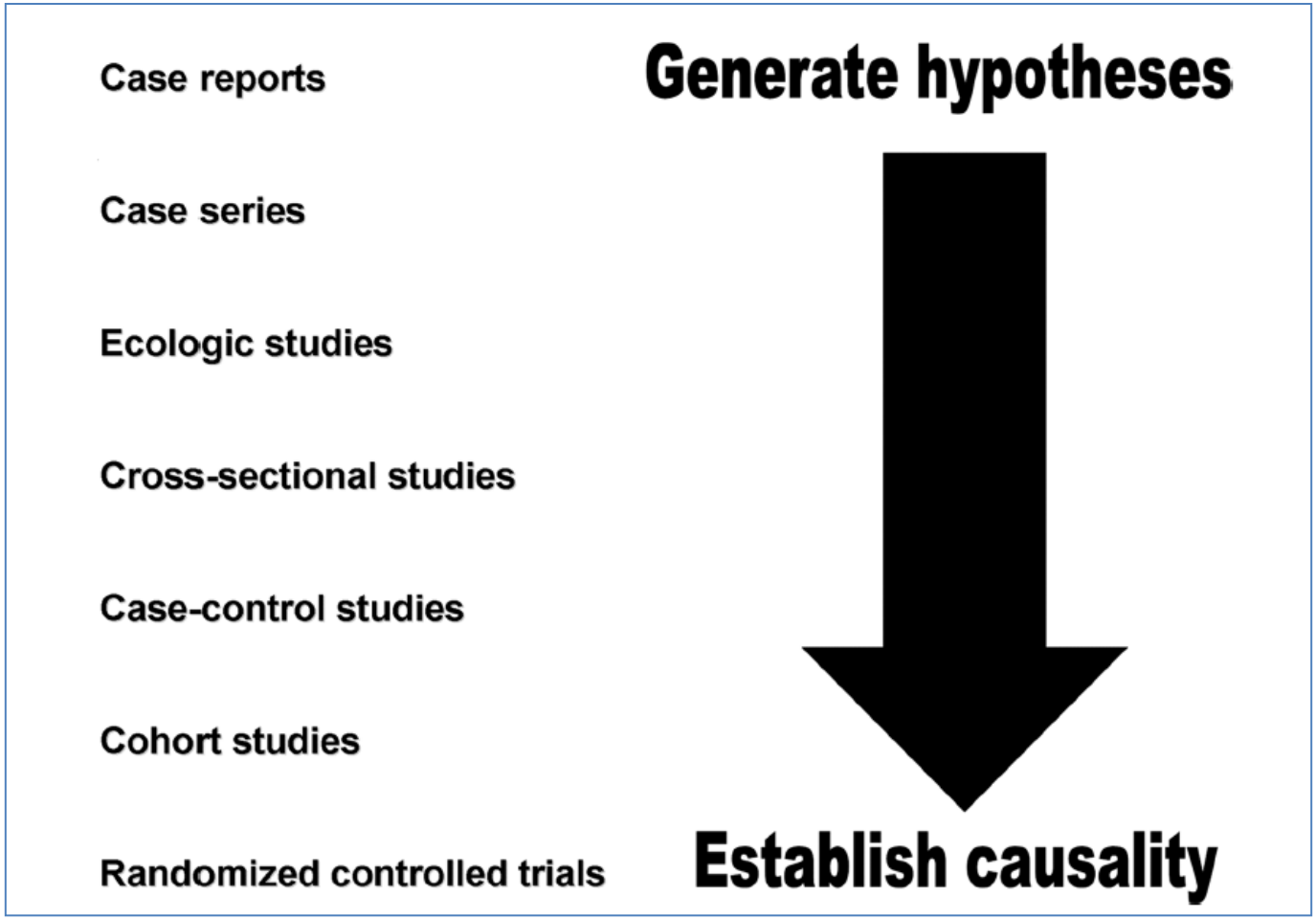
- the “gold standard” of research designs
- provides most convincing evidence of relationship between exposure and effect

❖*trials of hormone replacement therapy in menopausal women found no protection for heart disease, contradicting findings of prior observational studies*

RCTs (Disadvantages)

- **Disadvantages**
  - **Very expensive**
  - **Not appropriate to answer certain types of questions**
    - **it may be unethical, for example, to assign persons to certain treatment or comparison groups**

Hierarchy of Epidemiologic Study Design



Tower & Spector, 2007 (www)