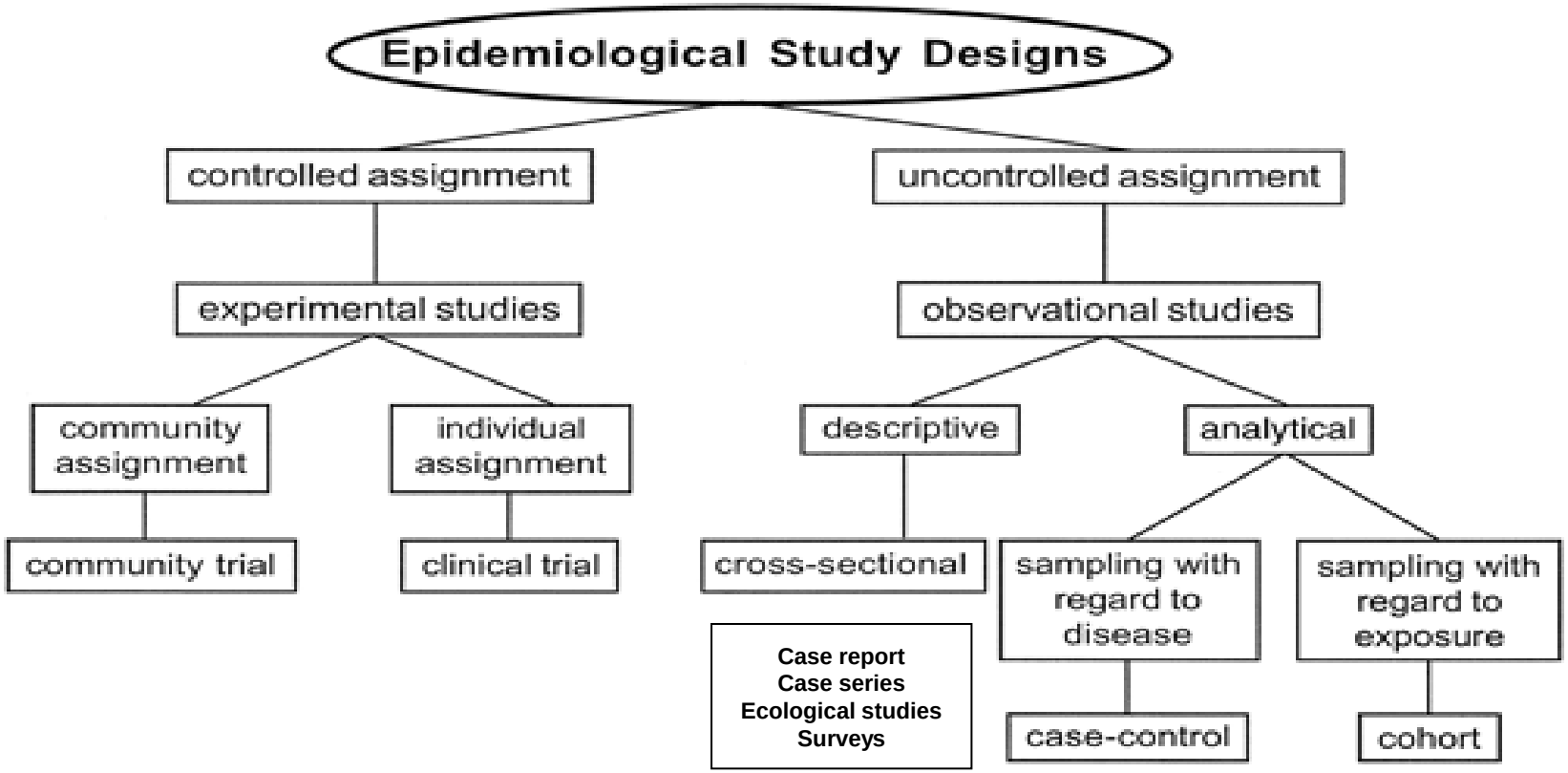
Overview of study designs

Dr Munir Abu-Helalah
MD,MPH,PHD

Associate Professor of Epidemiology and Preventive Medicine
Consultant Clinical Preventive Medicine

Part 1

Descriptive studies



Source: Waning B, Montagne M: *Pharmacoepidemiology: Principles and Practice*: http://www.accesspharmacy.com

Case-control studies

Are studies in which a group of people with a particular disease (the cases) are compared with a group of people without the disease (the controls). The purpose of the comparison is to determine whether, in the past, the cases have been exposed more (or less) often to a specific factor than the controls

- This type of study is done to identify factors that could be responsible for the development of a disease or drug use problem.

CASE-CONTROL STUDIES

- The direction of time

- Cases identified now
- Data on past events collected

CASE-CONTROL STUDY DESIGN

- Designed to assess association between disease occurrence and exposures (e.g., causative agents, risk factors) suspected of causing or preventing the disease.

Case-control studies

- A group of people with a disease are compared to a group without the disease from the same population.
- Compare exposure to risk factors in both groups
- Able to look at many different possible risk factors
- Able to study diseases with a long latency period
- Most common analytic study design seen in the medical literature today

Case-control studies

- In general, the cases included in a case-control study include people with one specific disease only
- But, a case-control study can provide information on a wide range of possible exposures that could be associated with that particular disease
- Useful for the study of rare diseases
- Not suitable for the study of rare exposure
- Relatively small and inexpensive
- Takes a relatively short time to complete
- Can test current hypotheses
- Cannot measure disease incidence

CASE-CONTROL STUDIES

- Cases have the disease of interest

Eg. Cerebral palsy

- Controls do not have the disease

Eg. Healthy babies born at the same time

Two by two table

Exposure	**Outcome** Yes	No	Total
Yes	a	b	a + b
No	c	d	c + d
Total	a + c	b + d	a + b + c + d

Odds of outcome in exposed = a / b

Odds of outcome in non- exposed = c / d

Outcome odds ratio = (a/b) / (c/d) = ad / bc

CASE-CONTROL STUDIES

Methods of data collection

Case-note review: Completeness

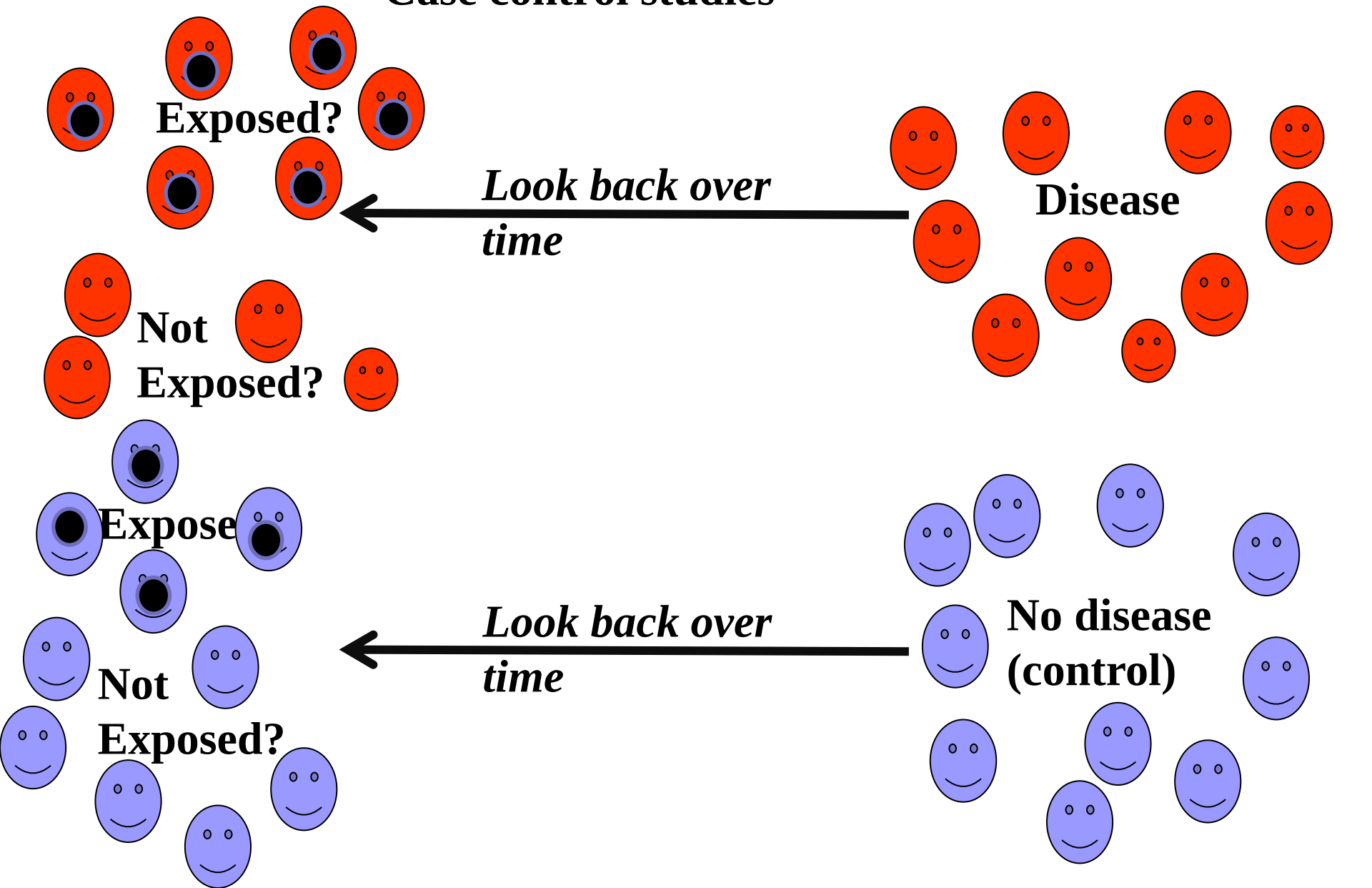
Postal questionnaire: response rate

Interview: Detailed information

CASE-CONTROL STUDY DESIGN

- a smaller sample size is required.
- One key feature of a case-control study, which distinguishes it from a cohort study, is the selection of subjects based on disease status.
- Controls are chosen from the same population yielding the cases

Case control studies



CASE-CONTROL STUDIES

Strengths

- Suited to study disease with long latency periods, but can be used in outbreaks investigations
- Optimal for rare diseases
- Efficient in terms of time and costs: relatively quick and inexpensive
- Allows for evaluation of a wide range of possible causative factors that might relate to the disease being studied
- Odds ratio estimated

CASE-CONTROL STUDIES

Limitations

- Very susceptible to bias (especially selection and recall bias) as both the disease and the exposure have already occurred when participants enter the study. Cases and controls might not be representative of the whole population
- We cannot calculate incidence or prevalence rate of disease
- We cannot be certain that exposure came before disease
- Choice of controls difficult
- Controls do not usually represent non-exposed population
- Past records incomplete
- No absolute risk estimates

Design of case control studies

- **Comparability:Two groups must be as similar to each other as possible so selection of controls is very important. Controls must be as similar as possible to cases – except that they do not have the outcome (disease).**
- **Outcome (disease) must be very clearly defined. (Diagnostic criteria must be clear)**
- **Use objective data about exposure status wherever possible, to reduce the risk of bias**

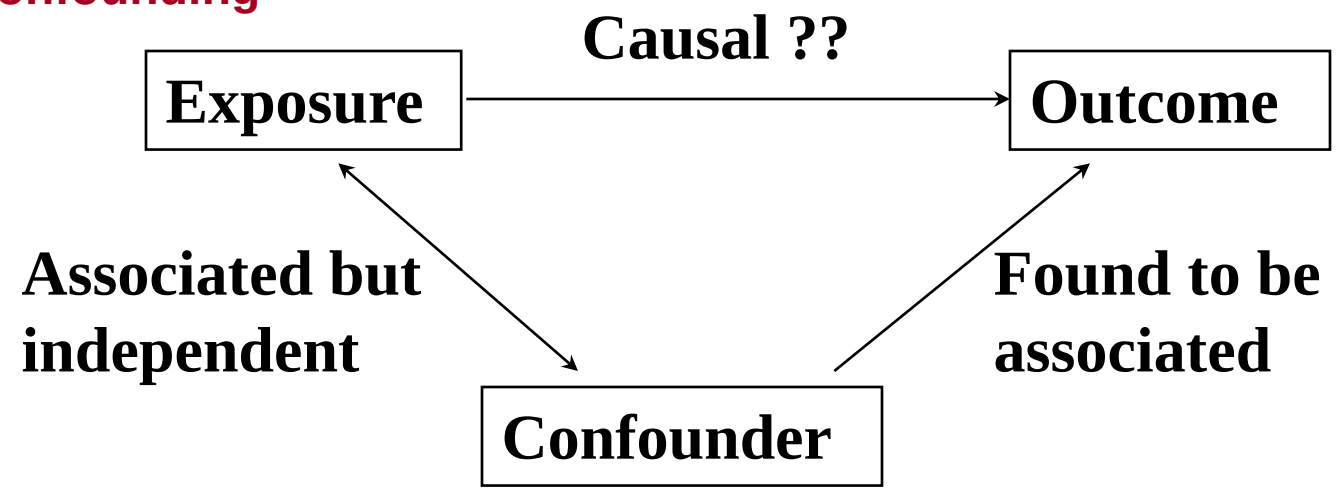
Obtaining cases and controls for case control studies

Study	Source of cases	Source of controls
PROM (premature rupture of membrane)	Hospital patients	Hospital patients
Rheumatoid arthritis	Outpatient clinic	Other outpatient clinic
Cervical screening	GP register	GP register

Confounding

A confounding factor is one that is associated with the exposure and that independently affects the risk of developing the outcome, but that is not an intermediate link in the causal chain between the exposure and the outcome under study

Matching - often used in case-control studies to decrease confounding



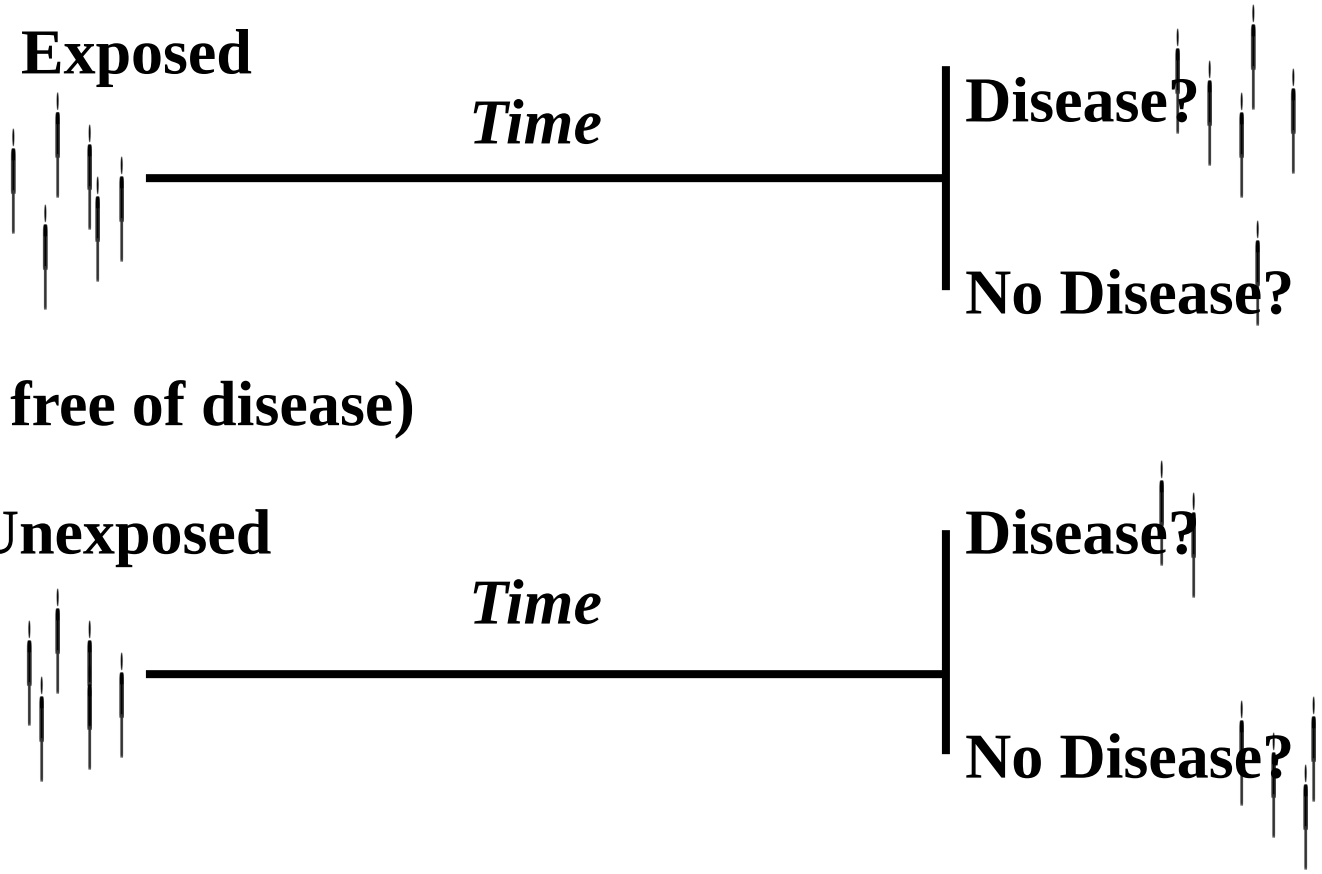
Cohort studies

Cohort (or follow-up) studies

- **Are studies in which people are identified and grouped with respect to whether or not they have been exposed to a specific factor.**

- **The groups are followed up over time to determine whether the incidence of a particular disease is any greater (or less) in the exposed group than in the non-exposed group.**

Cohort studies



Cohort study examples:

- Life expectancy of cerebral palsy children
- Fine needle breast biopsy and breast cancer
- Aspirin intake and colorectal cancer

Cohort study:
Primary purposes

- **Descriptive (measures of frequency)**

– To describe the incidence rates of an outcome over time, or to describe the natural history of disease

- **Analytic (measures of association)**

– To analyze associations between the rates of the outcomes and risk factors or predictive factors

COHORT STUDY DESIGN

- This design is the best observational one for establishing cause–effect relationships. Prevention and intervention measures can be tested and affirmed or rejected.
- Cohort studies take into account seasonal variation, fluctuations, or other changes over a longer period.
- Objective measures of exposure, such as biological markers, are preferred over subjective measures.

COHORT STUDY DESIGN
Strengths

- We can measure incidence of disease in exposed and unexposed groups
- Can get a temporal (time related) sequence between exposure and outcome as all individuals must be free of disease at the beginning of the study.
- Good for looking at effects of rare exposures.
- Allows for examination of multiple effects of a single exposure.
- Not open to bias as much as other types of study
- Direct calculation of the risk ratio or relative risk is possible.
- Provide information on multiple exposures

COHORT STUDY DESIGN

Limitations:

- Not efficient for rare diseases
- Can be expensive and time-cosuming
- Large sample
- Drop-out biases

  If study goes over many years, can get considerable loss to follow up. This can 'dilute' results or lead to bias, and therefore the validity of result can be seriously affected

- Locating subjects, developing tracking systems, and setting up examination and testing processes can be difficult.
- Changes over time in diagnostic methods, exposures, or study population may lead to biased results.

Cohort study: Example

Hypertension as a risk factor for spontaneous intracerebral hemorrhage

Physical Activity and Incident Cognitive Impairment in Elderly Persons

ARCH INTERN MED/VOL 170 (NO. 2), JAN 25, 2010

Background: Data regarding the relationship between physical activity and cognitive impairment are limited and controversial. We examined whether physical activity is associated with incident cognitive impairment during follow-up.

Methods: As part of a community-based prospective cohort study in southern Bavaria, Germany, 3903 participants older than 55 years were enrolled between 2001 and 2003 and followed up for 2 years. Physical activity (classified as no activity, moderate activity [<3 times/wk], and high activity [≥3 times/wk]), cognitive function (assessed by the 6-Item Cognitive Impairment Test), and potential confounders were evaluated. The main outcome measure was incident cognitive impairment after 2 years of follow-up.

Cohort study

Physical activity	**Cognitive impairment** Yes	No	Total
Moderate	160	1363	1523
None (not active as a potential risk factor)	125	459	584
Total	285	1822	2107

Risk of outcome in unexposed (physical active) = 160 / 1523
= 10.5%

Risk of outcome in exposed (inactive)= 125 / 584 = 21.4%

Relative risk =2

COHORT STUDY DESIGN

Retrospective cohorts

- Uses information on prior exposure and disease status.
- All of the events in the study have occurred and conclusions can be drawn more rapidly.
- Costs can be lower
- May be the only feasible one for studying effects from exposures that no longer occur, such as discontinued medical treatments.
- The main disadvantage of a retrospective cohort study is that the investigator must rely on existing records or subject recall.

Ambidirectional Cohort

- Data collected both retrospectively and prospectively on the same cohort to study short and long term effect of exposure

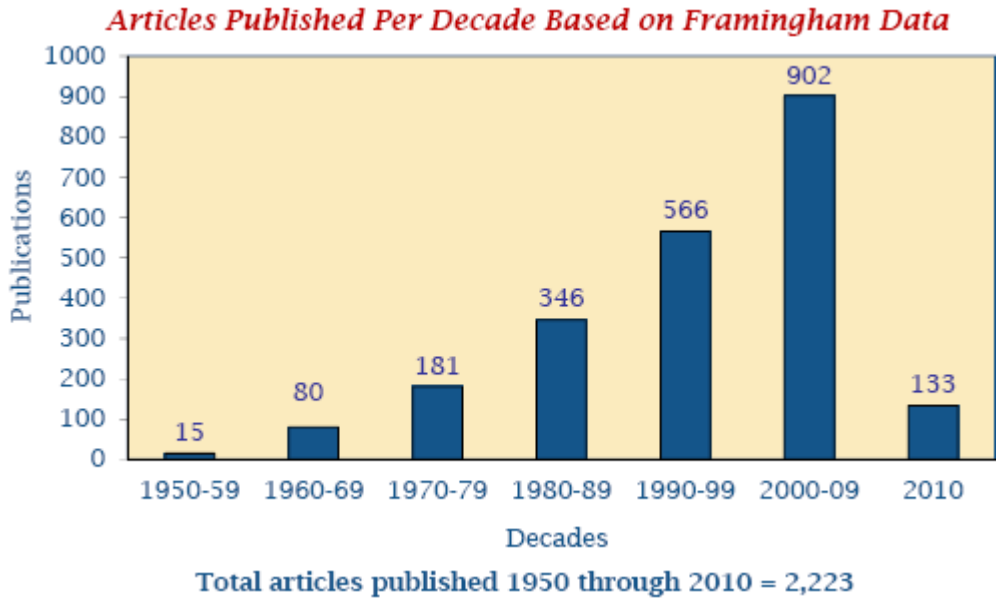
Framingham Heart Study

Approximately 5100 residents of this Massachusetts community are followed for > 30 years.
Selected because of a number of factors has permitted assessment of the effects of a wide variety of factors on the risk of numerous diseases

•stable population,
•had a number of occupations and industries represented
•had a single, major hospital that was utilized by the vast majority of the population
•prepared annually updated population lists that would facilitate follow-up,

Diseases studied included:
•coronary heart disease
•rheumatic heart disease
•congestive heart failure
•angina pectoris
•intermittent claudication
•stroke
•gout
•gallbladder disease
•a number of eye conditions

The Framingham Heart Study



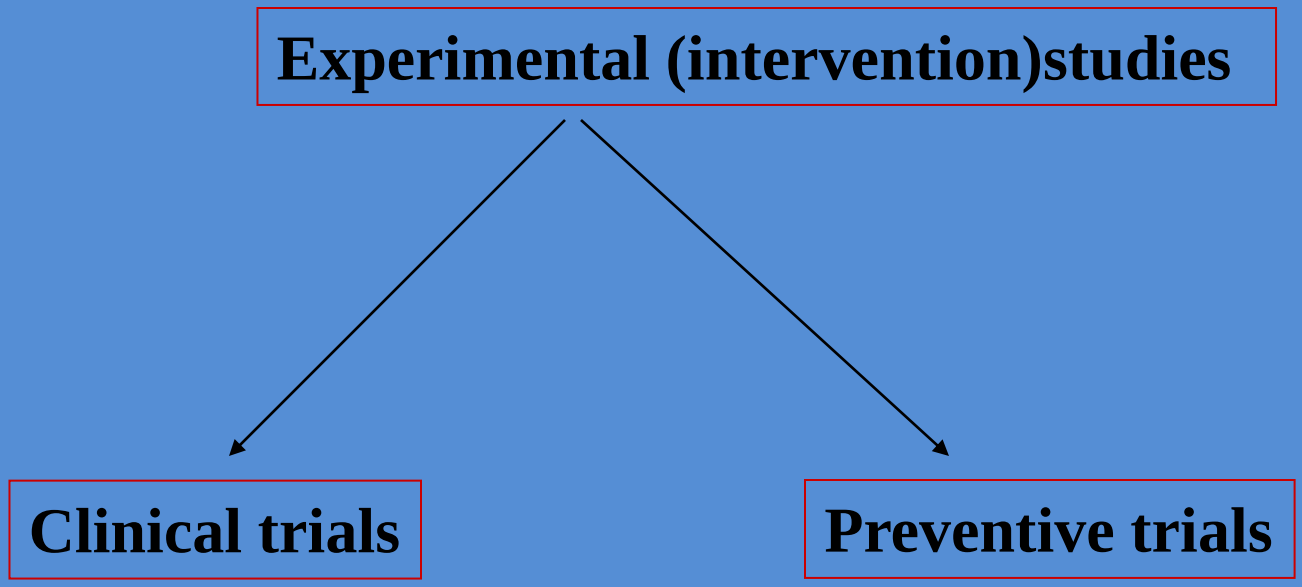
http://www.framinghamheartstudy.org/risk/index.html

- http://www.ajconline.org/article/S0002-9149(00)00726-8/abstract

Experimental Study Design

A study in which a population is selected for a planned trial of a regimen, whose effects are measured by comparing the outcome of the regimen in the experimental group versus the outcome of another regimen in the control group.

Experimental studies (Intervention)



Experimental Study Design

Different from observational designs by the fact that there is manipulation of the study factor (exposure), and randomization (random allocation) of subjects to treatment (exposure) groups.

Why experimental study design?

- Limitations of theory
- Previous disasters

Clofibrate:

Successfully lowers cholesterol

Treated group: reduced CHD incidence, but higher all causes mortality

- Spontaneous improvements
- Importance of small effects

Clinical trials

- **Individuals with particular disease are randomly allocated into experimental or control groups. randomization is used to ensure that both groups are comparable with respect to all other factors except for the one under investigation.**

- **The experimental group is given the agent being tested and the control group is given either an agent in current use or a placebo**

- **Ideally both patients and the observers should be 'blind' to the treatment being given. This in order to reduce bias.**

Clinical trials

- **Are studies of the effect of a specific treatment on patients who already have a particular disease**

- **They are used to evaluate the efficacy of a preventive or therapeutic agent in the treatment or prevention of a disease**

What trials assess

- Drugs
- Surgery
- Type of management
- New services

Why Clinical Trials?

Most definitive method to determine whether a treatment is effective.

-Provide stronger evidence of the effect (outcome) compared to observational designs, with maximum confidence and assurance

- Other designs have more potential biases
- One cannot determine in an uncontrolled setting whether an intervention has made a difference in the outcome.
- Correlation versus causation

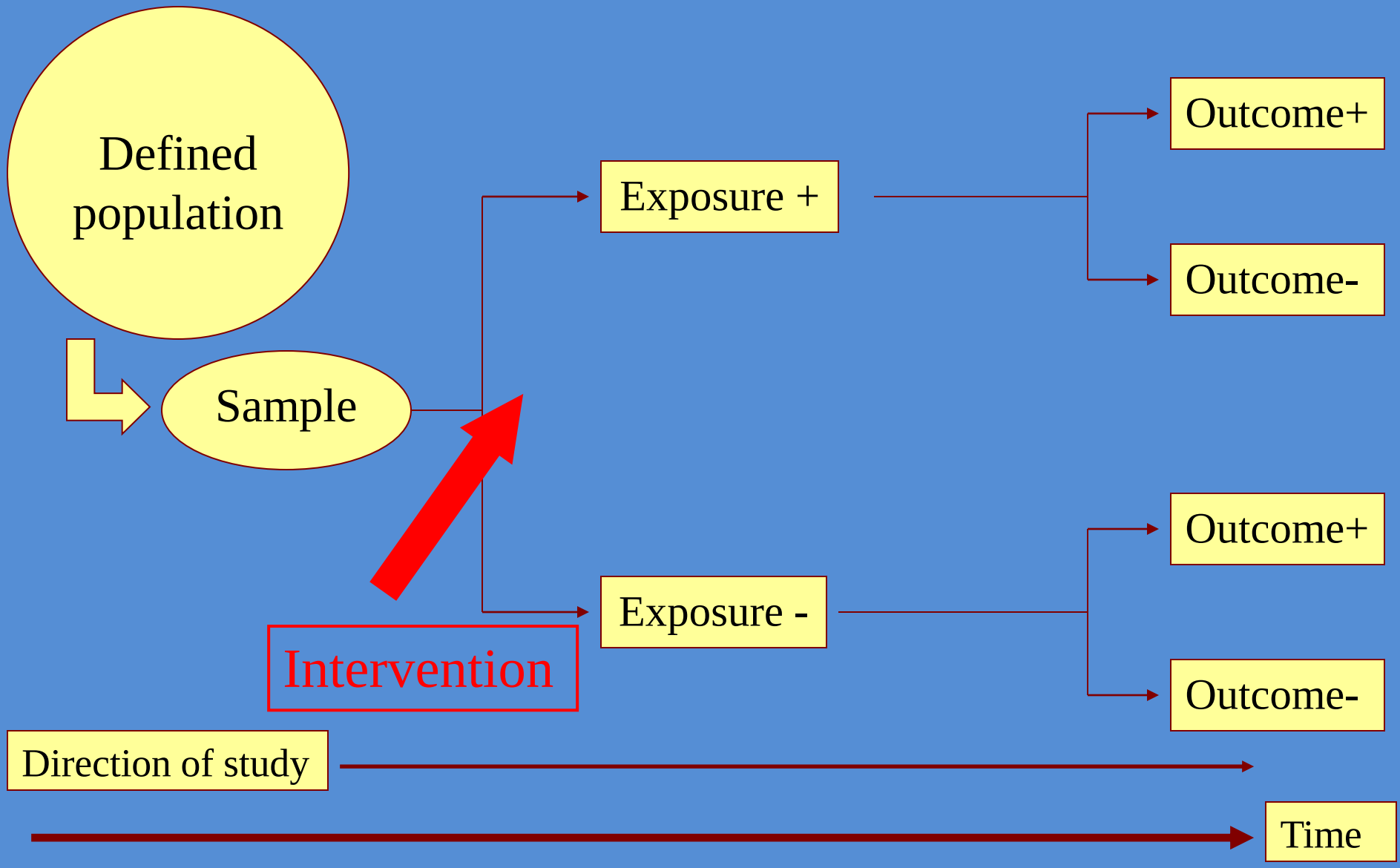
Example: trials of hormone replacement therapy in menopausal women found no protection for heart disease, contradicting findings of prior observational studies

Examples of False Positives

1.High cholesterol diet and rectal cancer
2.Smoking and breast cancer
3.Vasectomy and prostate cancer
4. Red meat and breast cancer

Replication of observational studies may not overcome confounding and bias

Clinical trial



RCT Disadvantages

- Large trials (may affect statistical power)
- Long term follow-up (possible losses)
- Compliance
- Expensive
- Possible ethical questions
- Requires treatment on basis (in part) of scientific rather than medical factors. Patients may make some sacrifice

Clinical trials: choice of Design

Depends on:

- Research Questions
- Research Goals
- Researcher Beliefs and Values
- Researcher Skills
- Time and Funds

Preclinical

- **Biochemical and pharmacological research.**
- **Animal Studies**

Consists of animal studies that determine the toxicity and bioavailability of a drug. Studies involving animal matrices such as rabbit serum, monkey urine, dog or rat plasma, are all examples of preclinical studies.

Phase I Trials

- **Clinical pharmacology- when the drug is given to healthy people estimate toxicity rates using few (~ 10 - 40) healthy subjects.**

The primary objectives of phase I clinical investigation are:

- **Determine the metabolism and pharmacologic activities of the drug in humans**
- **Side effects associated with increasing doses**
- **Early evidence on effectiveness**
- **Obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled and scientifically valid phase II clinical studies.**

Summary of Schemes
(Storer, *Biometrics* 45:925-37, 1989)

A. "Standard"
   - Observe group of 3 patients
   - No toxicity→ increase dose
   - Any toxicity → observe 3 or more
     - One toxicity out of 6 → increase dose
     - Two or more toxicity → stop

B. "1 Up, 1 Down"
   - Observe single patients
   - No toxicity → increase dose
   - Toxicity → decrease dose

Phase II Trials

- **Initial clinical assessment: determines whether a therapy has potential using a few very sick patients.**

The primary objectives of phase II studies are:

- **Identify accurately the patient population that can benefit from the drug.**
- **Evaluate the effectiveness of a drug based on clinical endpoints for a particular indication.**
- **Determine the dosing ranges and doses for phase III studies**
- **Common short-term side effects**
- **Risks associated with the drug.**

Phase III Trials

Rigorous testing: large randomized controlled, possibly blinded, experiments

The primary objectives of phase III studies are:

- **Gather an additional information about effectiveness and safety needed to evaluate the overall benefit-risk relationship of the drug.**
- **provide an adequate basis for physician labeling**

Phase IV Trials

- **Post-marketing surveillance: a controlled trial of an approved treatment with long-term follow-up of safety and efficacy.**

The primary objectives of phase IV studies are:

- **Provide additional details required to learn more about a drug's efficacy and/or safety profile.**
- **Study new age groups, races, and other type of patients.**
- **Detect and define of previously unknown or inadequately quantified adverse reactions and related risk factors.**

Types of Clinical Trials

- Randomized
- Non-Randomized
- Single-Center
- Multi-Center
- Phase I, II, III, IV Trials

Purpose of Control Group

- To allow discrimination of patient outcomes caused by test treatment from those caused by other factors
  - **Natural progression of disease**
  - **Observer/patient expectations**
  - **Other treatment**
- Fair comparisons
  - **Necessary to be informative**

Randomized allocation

- Like tossing a coin
- Avoids choosing
- Permits fair comparison

Ethical imperatives

- Must be real doubt
- Obtain inform consent
- Preserve clinical freedom

Defining the patients

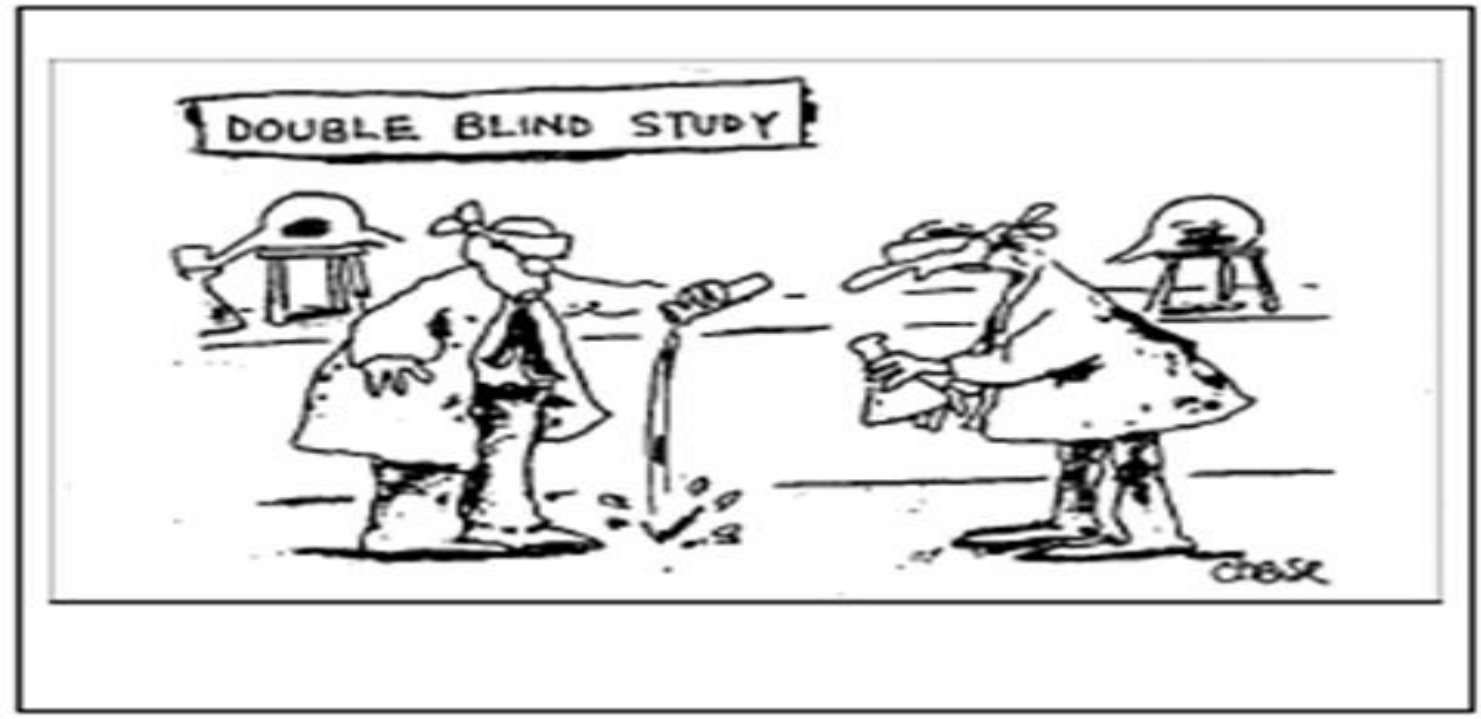
- Diagnostic features
- Eligibility criteria (inclusion and exclusion)

Assessing the outcome

- Clinically relevant
- Easily measured
- Accurately measured

Types of outcomes

- Death
- Clinical measurement
- Symptoms
- Quality of life
- Psychological wellbeing


DOUBLE BLIND STUDY

Definitions

- **Single Blind Study**: A clinical trial where the participant does not know the identity of the treatment received
- **Double Blind Study**: A clinical trial in which neither the patient nor the treating investigators know the identity of the treatment being administered.
- **Triple Blind study: Biostatisticians is also blinded**

Definitions

- **Placebo:**
  - Used as a control treatment

    1. An inert substance made up to physically resemble a treatment being investigated

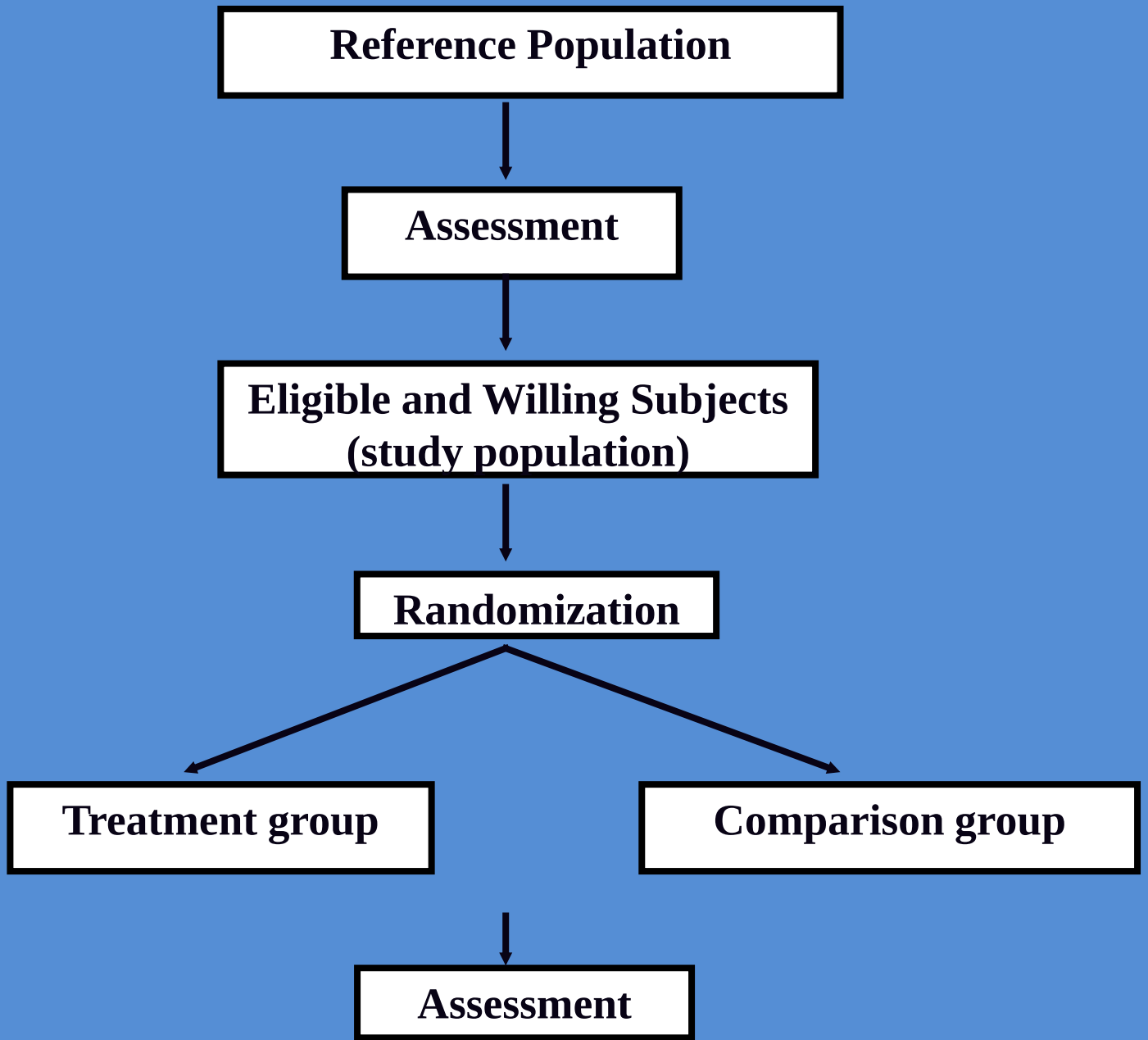
    2. Best standard of care if “placebo” unethical

    3. “Sham control”: Faked surgical intervention with the patient's perception of having had a regular operation

Summary of trial design

- Specify the treatment
- Define study group
- Random allocation
- Blinded outcome assessment
- Fair interpretation

Parallel Design



Preventive trials

Are studies of the effect of a possible preventive measure on people who do not yet have a particular disease. Another type of preventive trial is a study of the effect of a possible preventive measure on whole communalities.

Preventive trials

- **The risk of developing any particular disease among the people who are free from disease is small. Because of this, preventive trials usually require a greater number of subjects than clinical trials, and are therefore more expensive**

- **This expense limits their use to the study of preventatives of extremely common or extremely severe diseases**

  e.g. vaccination to prevent whooping cough

  vaccination to prevent poliomyelitis

- **When a disease occurs rarely, it is more efficient to study those people thought to be at high risk of disease , e.g. vaccine to prevent Hepatitis B**

Preventive trials

- As in clinical trials, the preventatives should be given so that the individuals who do and do not receive the preventative are as comparable as possible. This is often difficult.

- In some types of trials the preventative have to be administered to communities rather than individuals, e.g. water fluoridation to prevent dental caries

Results of a trial to determine whether A vaccine could prevent whopping cough

	No. with Whooping cough	No. without Whooping cough
Number vaccinated 3801	149(4%)	3652(96%)
Number not vaccinated 3757	687(18%)	3070(82%)

Community Trials

- A community participates in a behavioral intervention, nutritional intervention, a screening intervention, etc
- Intervention: Any program or other planned effort designed to produce changes in a target population.
- *Community* refers to a defined unit, e.g., a county, state, or school district.
- Communities are randomized and followed over time.
- Determine the potential benefit of new policies and programs.

Examples:

- A community-level intervention for tobacco control might combine a school curriculum for youth to prevent initiation of smoking
- A media campaign aimed at reducing smoking rate

Thank you!

Community medicine S1

- Register your attendance with your university number
- Make sure that the settings of your phone allow tracking location

Go to settings > privacy> location> services> make sure that location services is ON

Community medicine S2

- Register your attendance with your university number
- Make sure that the settings of your phone allow tracking location

Go to settings > privacy> location> services> make sure that location services is ON

Community medicine S3

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- Make sure that the settings of your phone allow tracking location

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Community medicine S5

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Community medicine S6

- Register your attendance with your university number
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