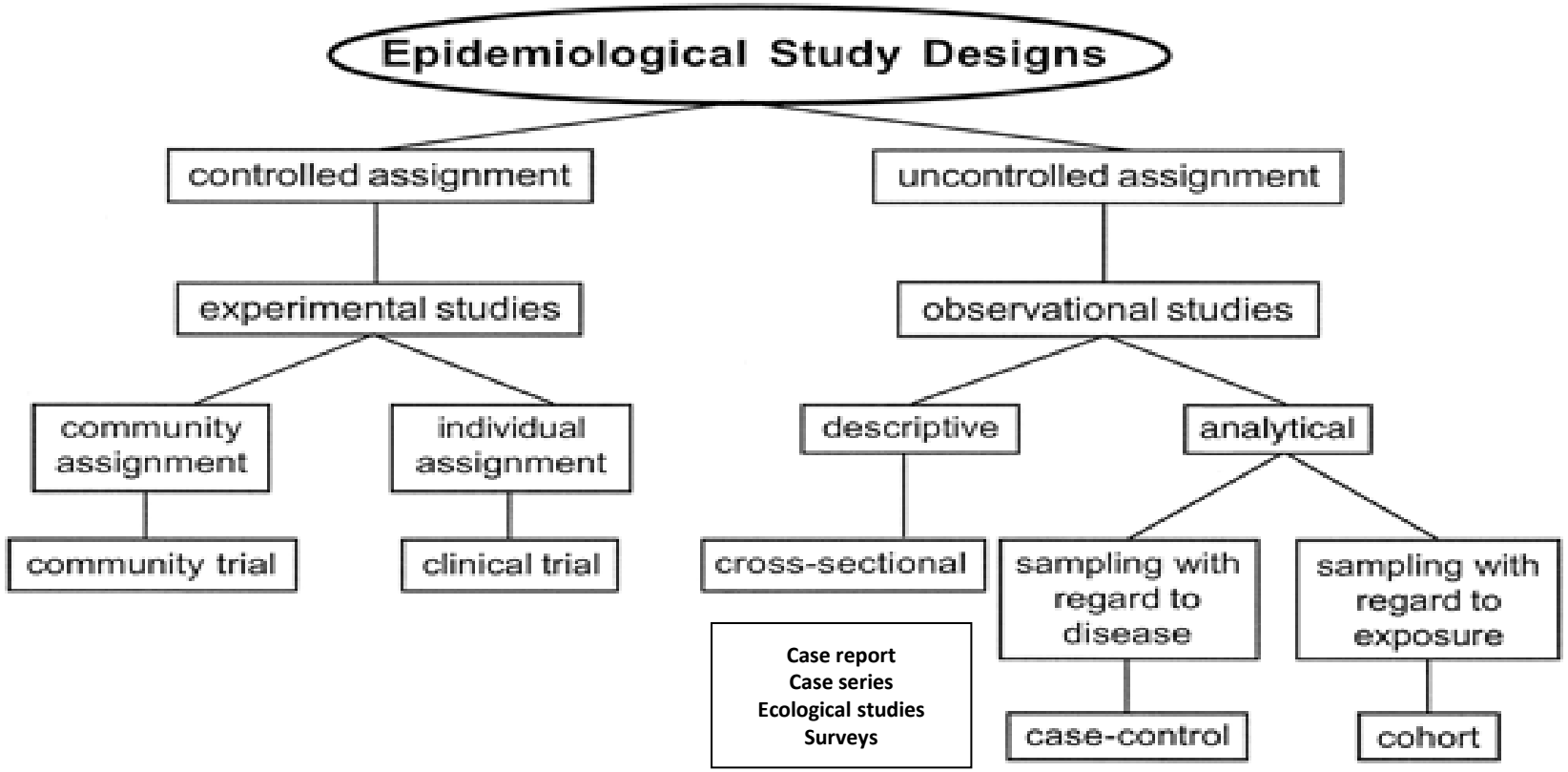
Overview of study designs

Dr Munir Abu-Helalah

MD,MPH,PHD

Associate Professor of Epidemiology and Preventive Medicine

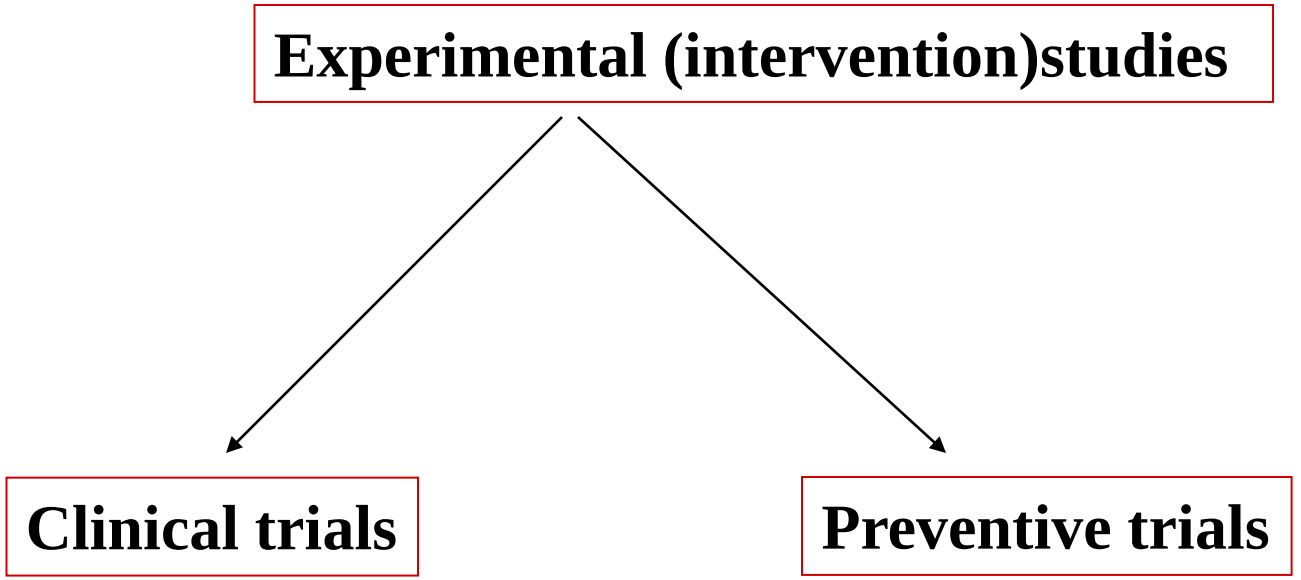


Source: Waning B, Montagne M: *Pharmacoepidemiology: Principles and Practice*: http://www.accesspharmacy.com

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.

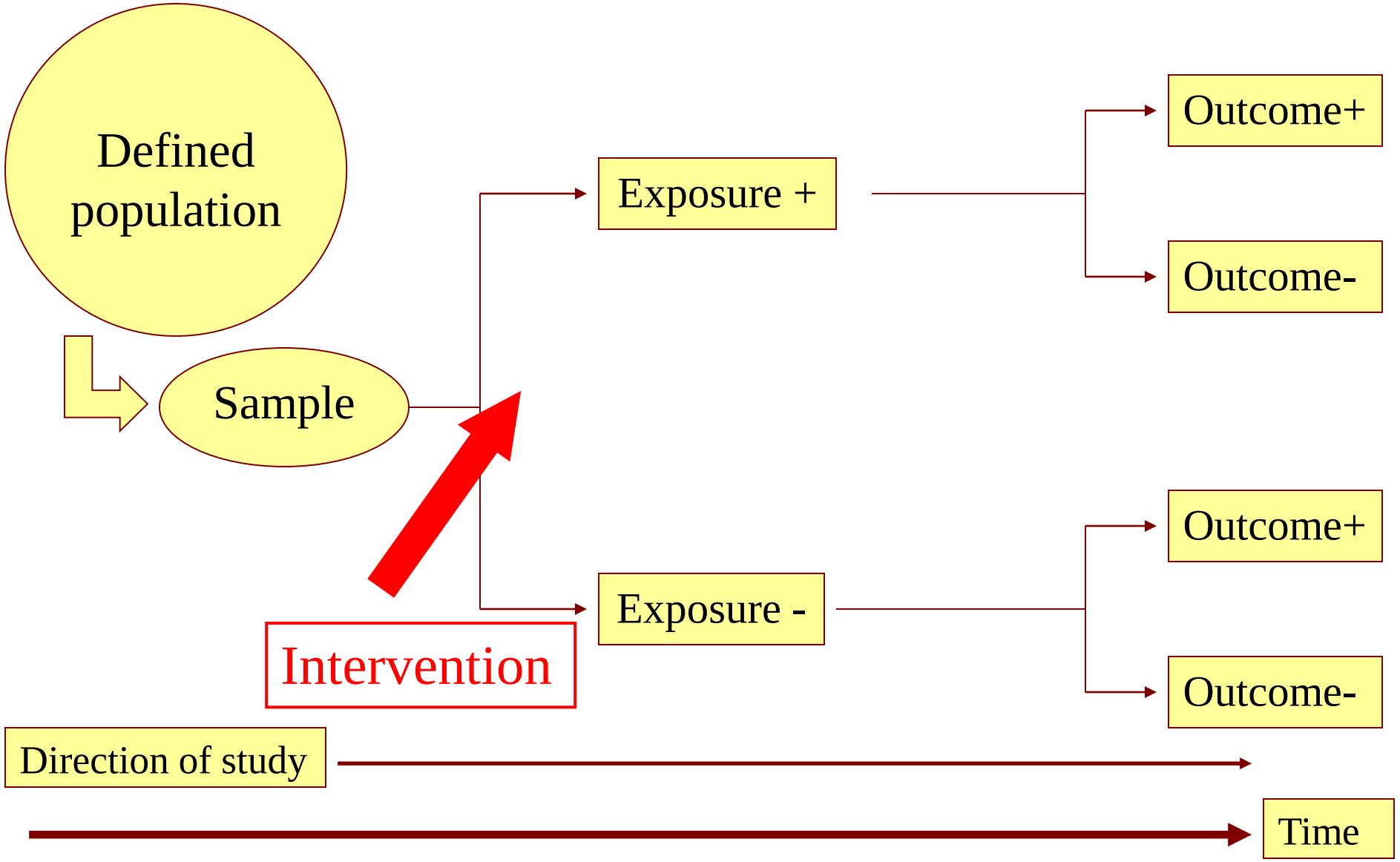
Experimental studies (Intervention)



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.

Clinical trial



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**

Clinical trials

- **Assessment of each subject must involve bias free accurate measure of outcome**

- **Both groups are followed over a defined period of time when the outcome is then measured in both groups.**

What trials assess

- Drugs
- Surgery
- Type of management
- New services

Why Clinical Trials?

1. **Most definitive method to determine whether a <u>treatment is effective</u>.**

-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
6. Drinking water frequently and bladder cancer
7. Not consuming olive oil and breast cancer

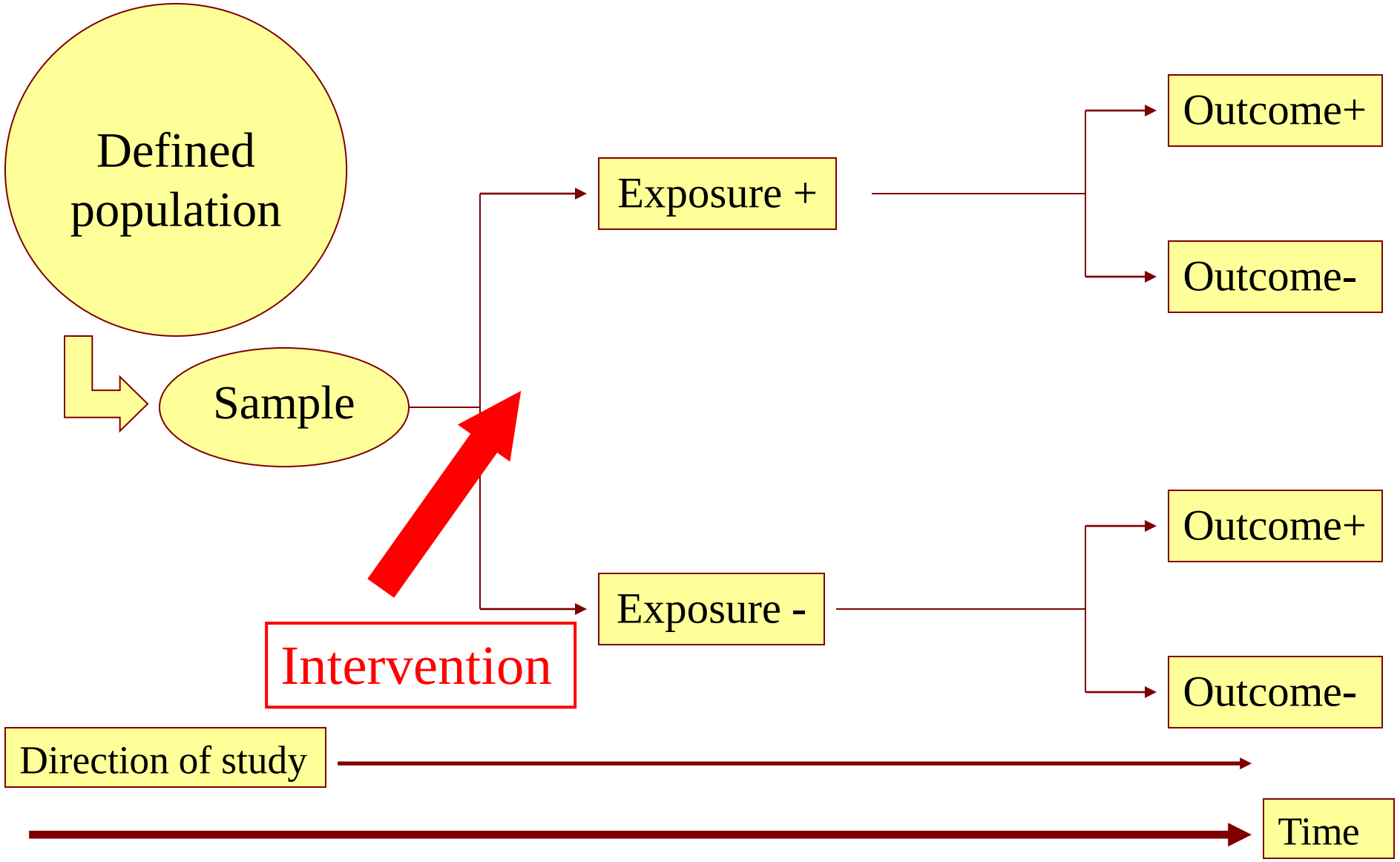
Replication of observational studies may not overcome confounding and bias

Why Performed ?

2. **Determine whether experimental treatments are safe and effective under "controlled environments" (as opposed to "natural settings" in observational designs), especially**

   when the margin of expected benefit is doubtful / narrow (10 - 30%)

Clinical trial



RCT Disadvantages

- **Large trials (may affect statistical power)**
- **Long term follow-up (possible losses)**
- **Compliance**
- **Expensive**
- **Public health perspective ?**
- **Possible ethical questions**
- **As above, may take a long time.**
- **Must be ethically and laboriously conducted.**
- **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

Clinical trial: Study design

It is also related to:

- **Status of existing knowledge**
- **Occurrence of disease**
- **Duration of latent period**
- **Nature and availability of information**
- **Available resources**

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.**

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**
  - **Comparison with currently approved treatments**

Randomized allocation

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

Randomized Controlled Clinical Trial

- Reference: Byar et al. (1976)

  New England Journal of Medicine

- Patients assigned at random to either treatment(s) or control

- Considered to be “Gold Standard”

Ethics of Randomization

- Statistician/clinical trialist must sell benefits of randomization

- Ethics ⇒ MD should do what he thinks is best for his patient
  - **Two MD's might ethically treat same patient quite differently**

- Chalmers & Shaw (1970) *Annals New York Academy of Science*

  1. **If MD "knows" best treatment, should not participate in trial**
  2. **If in doubt, randomization gives each patient equal chance to receive one of therapies (i.e. best)**
  3. **More ethical way of practicing medicine**

- **Bayesian Adaptive designs → More likely assign "better" treatment**

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

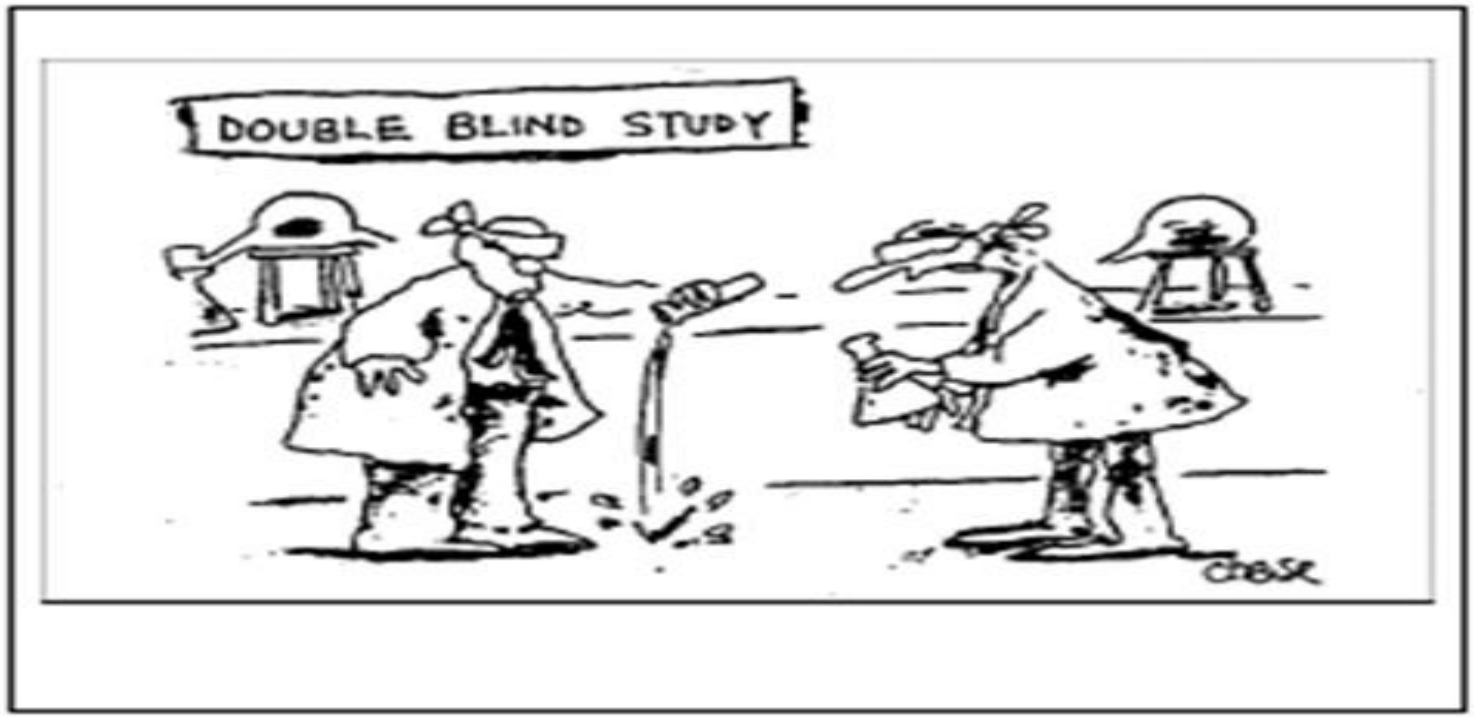
- Clinically relevant
- Easily measured
- Accurately measured

Types of outcomes

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

The need for blinding

- Open
- Single blind
- Double blind
- Triple blind


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

- **<u>Placebo:</u>**
  - 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

Definitions

- **Adverse event:**
  - An incident in which harm resulted to a person receiving health care.
  - **Examples:** Death, irreversible damage to liver, nausea
  - Not always easy to specify in advance because many variables will be measured
  - May be *known* adverse effects from earlier trials

Surrogate Endpoints

- Response variables used to address questions often called endpoints
- Surrogates used as alternative to desired or ideal clinical response to save time and/or resources
- Examples
  - Suppression of arrhythmia (sudden death)
  - T4 cell counts (AIDS or ARC)
  - Cholesterol (heart disease)
- Often used in therapeutic exploratory trials
- Use with caution in confirmatory trials

Summary of trial design

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

Clinical trial

Common problems

- Too few patients
- Failed randomization
- Patients lost to follow-up
- Flawed analysis-interpretation
- Power of study: not big enough

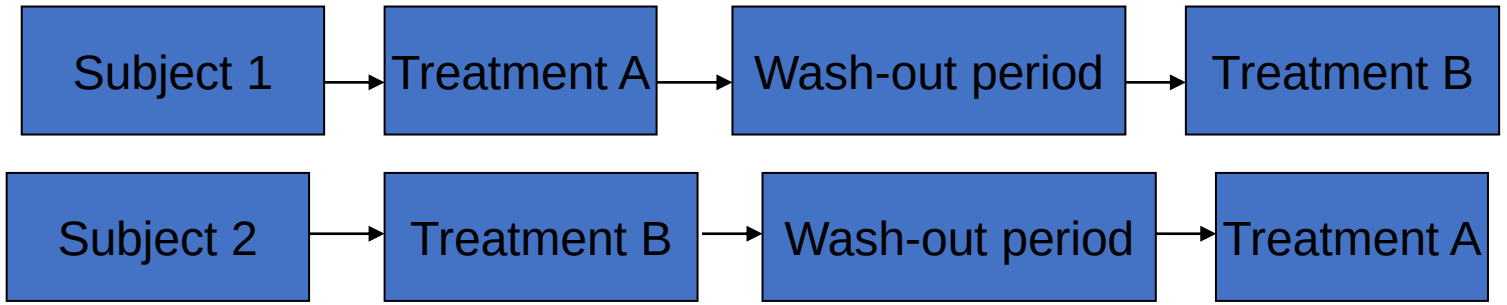
Cross-over clinical trial

Each patient gets both treatments

Half get A then B

Half get B then A

Wash-out period in between



Cross-over clinical trial

- Cross-over design
- Patient as own control

-Reduce variations

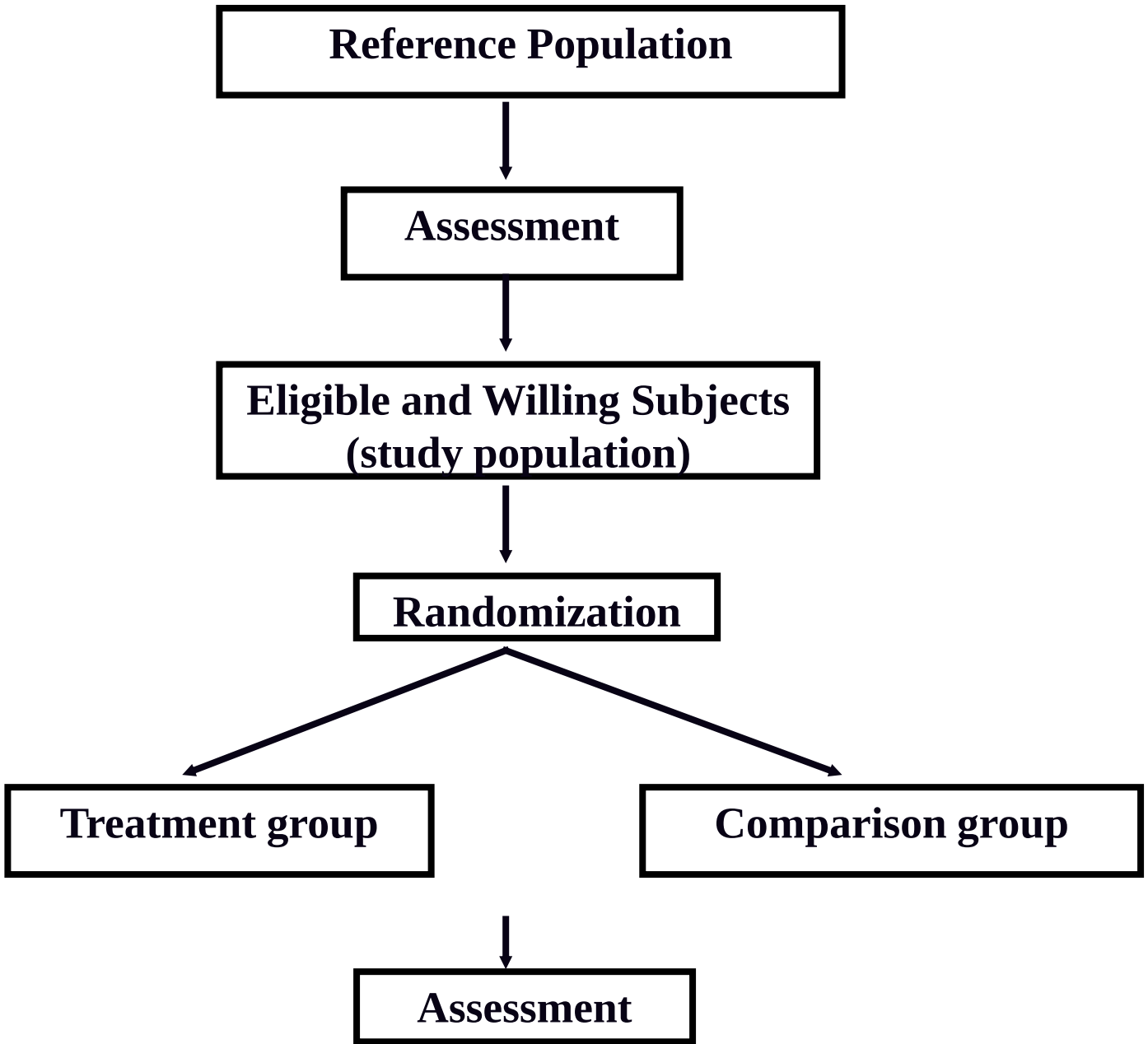
-Much smaller sample size

Requirements: Carry over period(s)

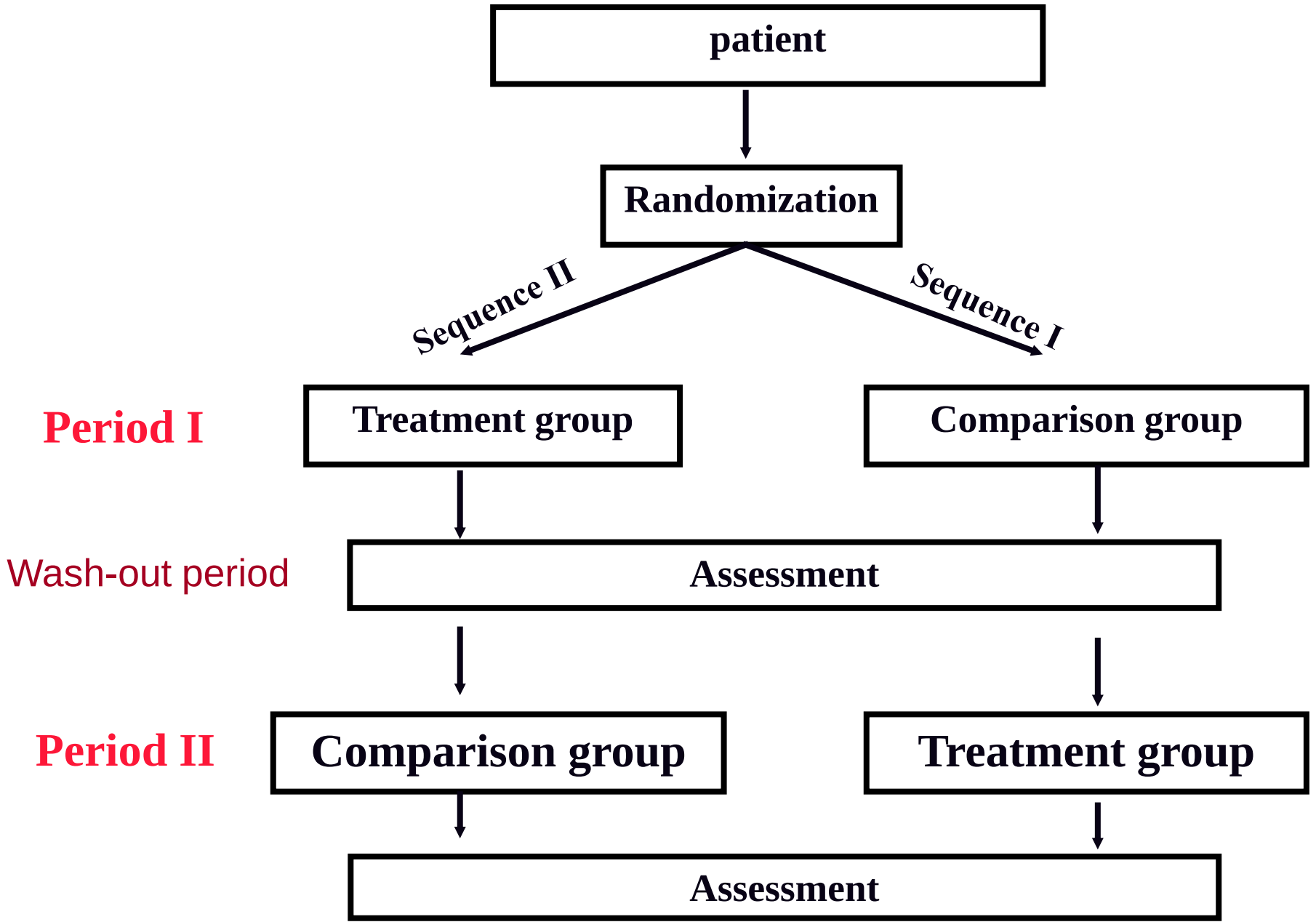
Key elements of RCTs

- Selection of subjects
- Comparison group
- Randomization
- Allocation of treatment
- Blinding (single, Double blind design/placebo)
- Intention to treat analysis in which the treatment and control groups are analyzed with respect to their random allocation, regardless of what happened subsequently
- Ethical considerations

Parallel Design



Crossover 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 community

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**

Examples

- Smoking cessation interventions for secondary schools
- Medical Research participation interventions: one for JU and another intervention for JUST

- Increasing fluoride level within acceptable limits in all drinking water sournces in Aqaba and comparing with Irbid, keeping this as they are.

Primary outcome: dental cases incidence for children younger than the age of 5.