Study design

Research: is an organized and systematic way of finding better answers to questions , assessment or evaluation of problem that affect individuals, communities or health systems and provides knowledge that allows for change to occur- change that improve the quality of health and health care.

purpose of medical research :

a- earn how systems in human body work,

why we get ill, and how to get back to health and stay fit,

and how to prevent illnesses and diagnosis.

b- It can provide evidence for policies and decisions on health development

Areas of Research:

- Problem(s) discovery, finding
- Impact of the problem
- Epidemiology of the problem: Size, etiology / risk factors
- Pathogenesis
- Management
- Prevention

Study Methodology: a systematic study that follows a pattern and

produces testable results.(step-by-step pathway)

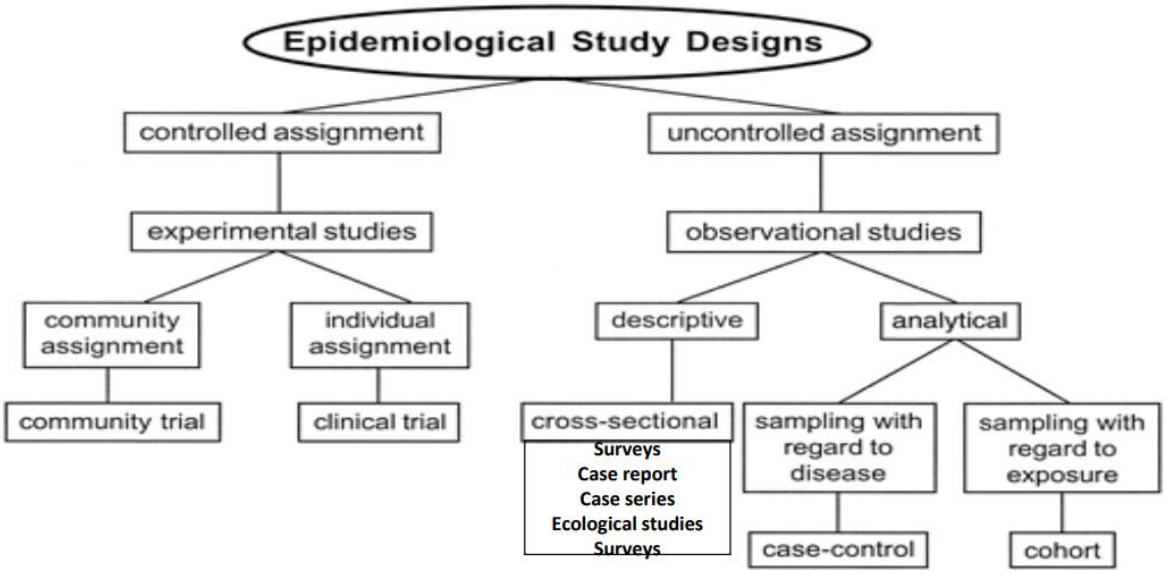
Advantage : avoids the problem of multiplicity.

Research Methods: Research Methods are the tools and techniques for

doing research.

Study design: A study design is a specific plan or protocol for conducting the study, which allows the investigator to translate the conceptual hypothesis into an operational one.

IMPOTANT CHART



Experimental studies: involve intervention in ongoing processes to study any resulting change or difference.

observational studies: identify variables to be measured, but human intervention is not a part of the process.

Observational epidemiology:

a. Descriptive analysis (Person place time)

Case reports and case series

Ecological (correlational)

Cross-sectional

- Provides information about disease patterns or drug use problems by

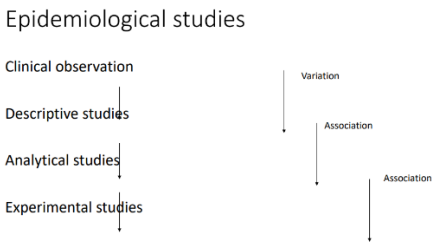
various characteristics of person, place, and time.

b. Analytical (rely on the generation of new data)

Case Control

Cohort

- used to generate hypotheses regarding the causes of disease or drug use problems.



Prospective studies: Watches for outcomes, such as the development of a disease, during the study period and relates this to other factors such as suspected risk or protection factor(s)

Note: The outcome of interest should be common; otherwise, the number of outcomes observed will be too small to be statistically meaningful (indistinguishable from those that may have arisen by chance.

-Prospective studies usually have fewer potential sources of bias and confounding than

retrospective studies.

Retrospective studies: looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study.

Note: Confounding factors and bias are more common in retrospective studies than in prospective studies

Ex: Many valuable case-control studies, such as Lane and Claypon's 1926 investigation of risk factors for breast cancer, were retrospective investigations.

Comparison of Retrospective and Prospective Approaches	
Retrospective	**Prospective**
Inexpensive to conduct	Expensive to conduct
Completed in a shorter time period	Completed over a longer time period
Easier to access a larger number of subjects	More difficult to access subjects and usually requires a larger number of subjects
Allows results to be obtained more quickly	Exposure status and diagnostic methods for disease may change
Useful for studying exposures that no longer occur	Loss of subjects from the study over time may be substantial
Information and data may be less complete and inaccurate	Information and data may be more complete and accurate
Subjects may not remember past information	Direct access to study subjects enhances reliability of data

Case report : is detailed report by one or more clinicians of the profile of a single patient.

Ex: 1961; pulmonary embolism 5 weeks after use on oral contraceptive.

• The most common type of study published in the medical literature.

Clinical investigators can use data to help establish causality

challenge–rechallenge:

• Administration of the drug can be stopped to observe whether the side effect or adverse reaction

diminishes.

• If it does, then administration of the drug can be resumed (the rechallenge) to observe whether

the effect returns, suggesting a possible relationship between the two events.

Case Series: Usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from either the practice of one or more health care professionals or a defined health care setting, e.g. a hospital or family practice.

-describes the characteristics of a number of patients with a given disease. Application: Routine surveillance activities (accumulated case reports). Striking clustering of cases may suggest emergence of new diseases or epidemics.

- A case-series is, effectively, a register of cases then Analyse cases together to learn about the disease. So it help to Helps professionals can build up a picture of the natural history of a disease

• Clinical case-series are of value in epidemiology for:

• Studying symptoms and signs

• Creating case definitions

• Clinical education, audit and research

Population case-series: is a systematic extension of this series but which includes additional cases, e.g. those dying without being seen by the clinicians.

Advantage: Add breadth to the understanding of the spectrum and natural history of disease.

Case series: Limitations

Usually we cannot estimate the prevalence or incidence rate

• Breast cancer registry in Jordan: We cannot provide prevalence rates

without:

1. Population size

2. Time- period of data collection

3. All cases of breast cancer are registered

No control group for comparison

Ecological studies: Are studies in which information on the characteristics and/or exposures of individual members of the population groups are generally not obtained. Existing statistics are used to compare the mortality or morbidity experience of one or more populations with some overall index exposure. care is needed to avoid the 'ecological fallacy' where inappropriate conclusions are made from ecologic data

-These studies are used to describe disease or drug use problems in

relation to some factor of interest

e.g: Comparing cigarette consumption with rates of cancer

Comparing Alcohol consumption with coronary heart disease

NOTES: In ecological studies the unit of analysis is some

aggregate individuals rather than individual persons

▪Geographic areas or time period are often used as a basis for defining aggregates

Ecological studies

▪The analysis centres on determining whether the ecological units with a high frequency of exposure are also unit with a high frequency of disease (+ve correlation) or a low frequency of disease (- ive correlation)

They use data that has already been collected.

• The measure of association between exposure and outcome is the correlation coefficent r.

• This is a measure of how linear the relationship is between the exposure and outcome variables. (Note that correational is a specific form of association and requires two continuous variables

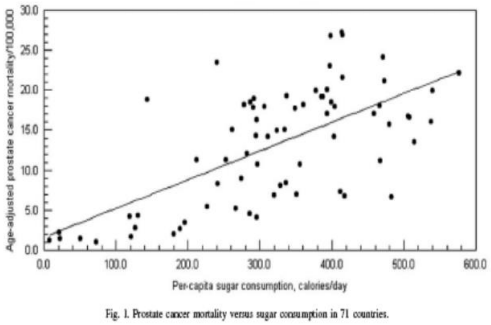


Fig. 1. Prostate cancer mortality versus sugar consumption in 71 countries.

Advantages of an ecological study:

1. An ecological study is quick and cheap to conduct.

2. It can generate new hypotheses.

3. It can identify new risk factors

Disadvantages:

1. It is unable to control for confounding factors. This is often referred to as 'ecological fallacy', where two variables seem to be correlated but their relationship is in fact affected by cofounding factor(s).

2. It cannot link exposure with disease in individuals .

3. Its use of average exposure levels masks more complicated

relationships with disease.

4. Its units of study are populations not individuals. Therefore, the disease rates linked with population characteristics and the association observed at group level does not reflect association at individual level

CROSS-SECTIONAL STUDY DESIGN (prevalence studies): They are studies of total populations or population groups in which information is collected about the present and past characteristics, behaviors, or experiences of individuals and their disease or exposure status determined at one point in time

Cross-sectional studies: advantages:

• Relatively quick

• Data on all variables is only collected once. These studies involve a single data collection and, thus, are less expensive and more expedient to conduct.

• Sample size depends on the question

• Standard measures used

• Prevalence estimated (Point prevalence)

• The prevalence of disease or other health related characteristics are important in public health for assessing the burden of disease in a specified population and in planning and allocating health resources. They provide information and data useful for the planning of health services and medical programs., local or national levels.

• Good for descriptive analyses and for generating hypotheses, Cross-sectional studies are often used as an initial exploration of a hypothesis prior to conducting a case-control or follow-up study

(More effective in identifying chronic diseases and problems)

Disadvantages:

• They cannot show cause–effect relationships.

Difficult to determine whether the outcome followed exposure in time or exposure resulted from the outcome. It is often difficult to separate cause and effect as the measurement of exposure and disease at any one point in time

• If the sample is not representative, results are representative only of the individuals who participate in the study

Example : prevalence of sickle cell anaemia in the Easter region of the KSA does not represent the who country.

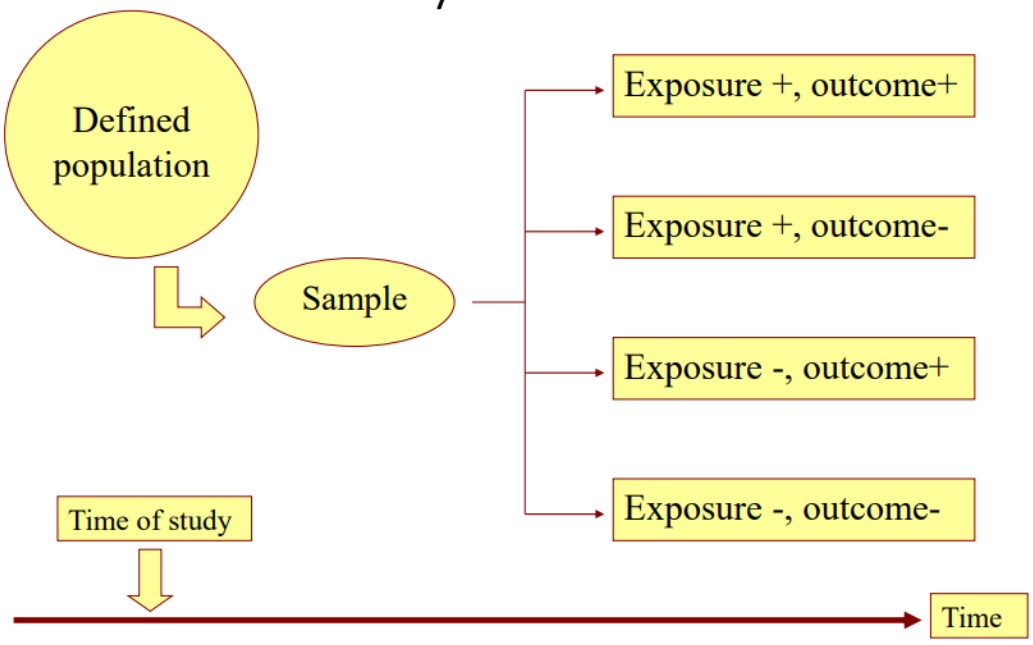
• Not suitable for studying rare diseases or diseases with short duration short incubation periods

• Unable to measure incidence

• Associations identified may be difficult to interpret.

• Susceptible to bias due to low response and misclassification

Cross-sectional study



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

Prevalence of outcome in exposed = a / a + b

Prevalence of outcome in non-exposed = c / c + d

Prevalence Rate Ratio (PRR) = $= \frac{a / a + b}{c / c + d}$

Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery

Cross-sectional study

Chemotherapy	Outcome		Total
	With pain	Without pain	
Yes	664	556	1220
No	879	1088	1967
Total	1543	1644	3187

Prevalence of pain among chemotherapy = 664/ 1220 = 54.4%

Prevalence of pain among no chemotherapy = 879 / 1967 = 44.7%

Prevalence Rate Ratio (PRR) = = 54.4 / 44.7 = 1.22

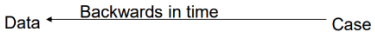
STUDY DESIGN 2

Case control study : 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) from the same population.. 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.

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

▪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

- Cases identified now
- Data on past events collected



Most common analytic study design seen in the medical literature today

Methods of data collection

Case-note review: Completeness

Postal questionnaire: response rate

Interview: Detailed information

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

Useful for the study of rare diseases, Not suitable for the study of rare exposure

Can test current hypotheses

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 estimate

Two by two table

Exposure	Outcome		Total
	Yes	No	
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

Ex: Cases have the disease of interest

Eg. Cerebral palsy

 Controls do not have the disease

Eg. Healthy babies born at the same time

NOTE: -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.

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

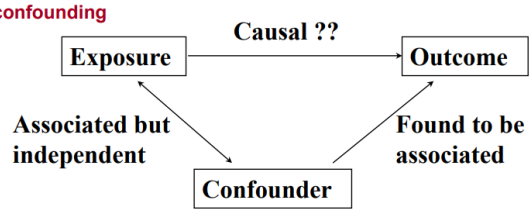
Obtaining cases and controls for case control studies

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 (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 nonexposed group.

examples:

 Life expectancy of cerebral palsy children

 Fine needle breast biopsy and breast cancer

 Aspirin intake and colorectal cancer

▪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 theoutcomes and risk factors or predictive factors

NOTE: 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.

E.x: Hypertension as a risk factor for spontaneous intracerebral hemorrhage

Physical Activity and Incident Cognitive Impairment in Elderly Persons

Cohort study

Physical activity	Cognitive impairment		Total
	Yes	No	
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 cohortstudy 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

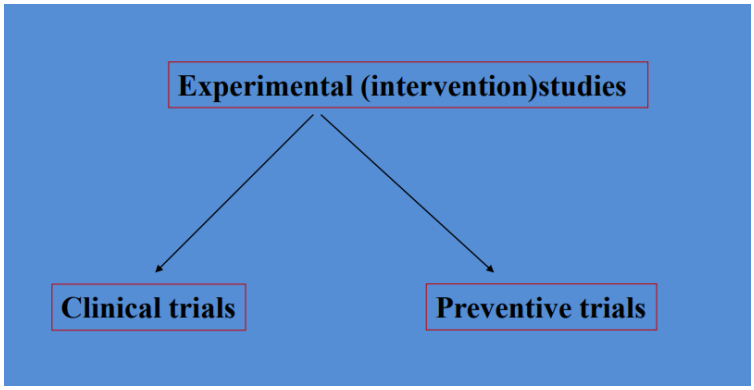
•stable population,

•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

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.
- -Individuals with particular disease are randomlyallocated 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 testedand 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

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

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

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

What trials assess

• Drugs

• Surgery

• Type of management

• New services

Replication of observational studies may not overcome confounding and bias

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

RCT Disadvantages

• Large trials (may affect statistical power)

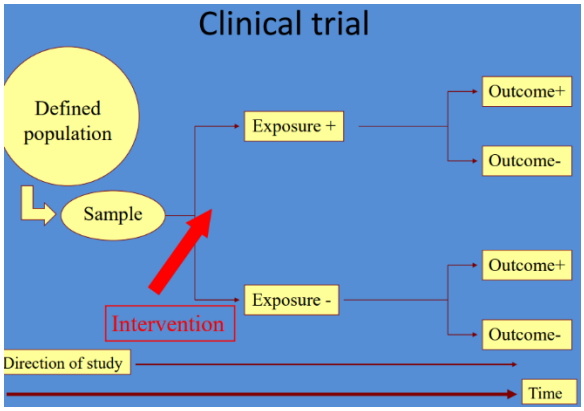
• Long term follow-up (possible losses)

• Compliance

• Expensive

• Possible ethical questions

• Requires treatment on basis (in part) of scientific rather than medical factors. Patients may make some sacrifice



Types of Clinical Trials

• Randomized

• Non-Randomized

• Single-Center

• Multi-Center

• Phase I, II, III, IV Trials

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

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, experimentsThe 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

Randomized allocation

• Like tossing a coin

• Avoids choosing

• Permits fair comparison

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

NOTE: • 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

• 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

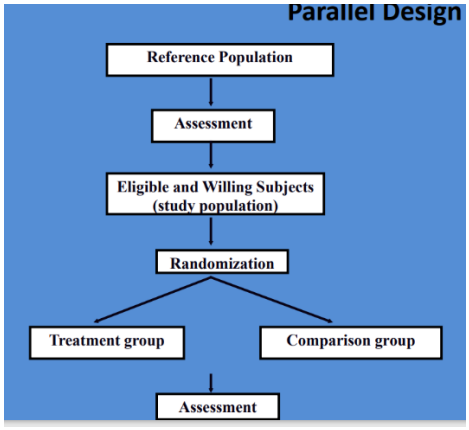
• Specify the treatment

• Define study group

• Random allocation

• Blinded outcome assessment

• Fair interpretation



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

▪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

▪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.

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

Quiz

1- A group of two hundred people were entered into a test, half of them were previously exposed to a certain risk factor. Fifty of those exposed were diseased with a certain disease. And 25 people were diseased but unexposed what is the relative risk? a) 3

b) 5

c) ½

d) 2

e) ¾

D

2- The strongest epidemiological study model of the following is:

a) Cohort studies

b) Descriptive studies

c) Experimental studies

d) Case control studies

e) Analytical studies

C

3- A researcher made the mistake of keeping the null hypothesis of his study question when in fact there was a statistical significance that allows him to reject it. What type of error would he have made? a) Type 1 error

b) Type 2 error

c) Random error

d) Selection bias

e) Systematic bias

B

4- If you knew that the performance of students was ranked to four levels as such: poor< fair< good< excellent , answer the following two questions: . What type of variable is the level of performance: a) Discrete ordinal

b) Nominal

c) Ratio

d) Interval

e) Constant

A

5- A study which compares the link between the history of immunization and autism between 2.000 child with autism and 1,000 child without autism is an example of which type of study:

• Answer: Case-control.

6- The ethical issue is a major problem in:

• Answer: Experimental trials.

7- A group of women was researched in 1990, they collected information to find out whether or not there is a link between their lifestyle and the probability of cancer, what is the type of study:

• Answer: cohort study.

8- The Difference between experimental and analytical experiments

A. in experimental you can manipulate and control exposures but in

analytical you can't.

B. Experimental is concerned with agent, environment and host but.

analytical is concerned with person, place and time.

C. Randomisation is present in one rather than the other.

D. Analvtical is more advanced than experimental.

E. Analytical is stronger than experimental.

Answer: A

9- Odds Ratio (OR) is the best measure of association in which of the following studies

• A. Prospective cohort study.
• B. Ecological study.
• C. Case report stud.
• D. Cohort study because we can calculate incidence.
• E. Case-control study because we can only calculate prevalence.

• Answer: E

10- A study examined the relationship between levels of physical activity and prostate cancer mortality rates in 25 European countries (populations). What study design has been used in this case

• A. Ecological study.
• b. Experimental.
• C. Case study.
• D. Observational study.
• Answer: A

11- One of the following is NOT an advantage of cross-sectional study

• A. Useful for studying rare health events.
• B. Less time consuming than cohort study.
• C. Less expensive than other analytical designs.
• D. Describes the population well.
• E. Generates hypothesis.

• Answer: A

12- Recall bias can be avoided in which of the following study designs

• A. Cross sectional design.
• B. Case control design.
• C. Cohort design.

• D. Case series.

• E. None are correct.

B

13- Which of the following is INCORRECT regarding cross-sectional study

• A. It is an observational study design.

• B. More expensive than other observational designs.

• C. Temporal sequence cannot be determined.

• D. Useful for generating new hypothesis.

• E. Best design to use for disease with long duration of expression.

• Answer: B

14- To determine the effectiveness of influenza vaccines in elderly people, a group of vaccinated elderly, and another group of unvaccinated elderly were studied. They were followed up to for developing influenza. The results suggest that the elderly who are vaccinated had a reduced risk of hospitalization for pneumonia. What study design is this

• A. Case-control study.

• B. cross-sectional study.

• C. Randomized controlled clinical trial (RCT).

• D. Ecological study.

• E. cohort study.

• Answer: E