The Republic of Iraq

Ministry of Higher Education and Scientific Research

Al-Furat Al-Awsat Technical University

College of Health and Medical Techniques / Kufa

Community Health Techniques Department

The third stage

Methodology

General objective: the student will be able to prepare the research in a proper manner.

Specific Objective:

1. The student must learn about the different types of studies, how to conduct them, and the objectives and obstacles of each study.
2. Learn about methods of research models and conducting statistical analyses.
3. The student must be able to prepare the research properly.

week	objects
1	Research; definition, characteristics & types, The study population Control group Sampling
2	Design strategies in epidemiological: Descriptive studies
3	epidemiological studies; Descriptive studies Correlation studies Case report & case series studies
4	Cross-sectional surveys Case control studies: Issues in the design conduct of case control
5	Issues in the analysis Issues in the interpretation Limitations
6	Cohort studies: Types of cohort studies Issues in the design & conduct of cohort studies
7	Issues in analysis Issues in the interpretation Limitations
8	Intervention studies Types of intervention studies Unique problem of intervention studies
9	Issues in the design & conduct of clinical trials
10	Analysis of epidemiology studies Evaluation the role of bias Types of bias; control of bias
11	Analysis of epidemiological studies
12-13	Evaluating the role of confounding
14-15	• The nature of confounding • Methods to control confounding in the design

Research Methodology

Research methodology is the specific procedures or techniques used to identify, select, process, and analyze information about a topic.

According to John W. Creswell who states that "Research is a process of steps used to collect and analyze information to increase our understanding of a topic or issue". It consists of three steps:

1.pose a question.

2. collect data to answer the question.

3. present an answer to the question.

What are the differences between research methodology and research methods?

Research methodology is a systematic and theoretical approach to collect and evaluate data throughout the research process.

Research methods consists of all techniques, strategies, and tools employed by a researcher to complete the experiment and find solution to a research problem.

Characteristics of research

 It demands a clear statement of the problem

 It requires a plan (it is not aimlessly " looking" for something in the hope that you will come across a solution)

 It builds on existing data, using both positive and negative findings

 New data should be collected as required and be organized in such a way that they answer the research question(s)

Types of Research Methods

1. Quantitative Research: Quantitative research methods focus on collecting and analyzing quantifiable data to draw conclusions. The key methods for conducting quantitative research are:

Surveys- Conducting structured questionnaires or interviews with a large number of participants to gather numerical data.

Experiments-Manipulating variables in a controlled environment to establish cause-and-effect relationships.

Observational Studies- Systematically observing and recording behaviors or phenomena without intervention.

Secondary Data Analysis- Analyzing existing datasets and records to draw new insights or conclusions.

2. Qualitative Research: Qualitative research employs a range of information-gathering methods that are non-numerical, and are instead intellectual in order to provide in-depth insights into the research topic. The key methods are:

Interviews- Conducting in-depth, semi-structured, or unstructured interviews to gain a deeper understanding of participants' perspectives.

Focus Groups- Group discussions with selected participants to explore their attitudes, beliefs, and experiences on a specific topic.

Ethnography- Immersing in a particular culture or community to observe and understand their behaviors, customs, and beliefs.

Case Studies- In-depth examination of a single individual, group, organization, or event to gain comprehensive insights.

3. Mixed-Methods Research: Combining both quantitative and qualitative research methods in a single study to provide a more comprehensive understanding of the research question.

4. Cross-Sectional Studies: Gathering data from a sample of a population at a specific point in time to understand relationships or differences between variables.

5. Longitudinal Studies: Following a group of participants over an extended period to examine changes and developments over time.

6. Action Research: Collaboratively working with stakeholders to identify and implement solutions to practical problems in real-world settings.

7. Case-Control Studies: Comparing individuals with a particular outcome (cases) to those without the outcome (controls) to identify potential causes or risk factors.

8. Descriptive Research: Describing and summarizing characteristics, behaviors, or patterns without manipulating variables.

9. Correlational Research: Examining the relationship between two or more variables without inferring causation.

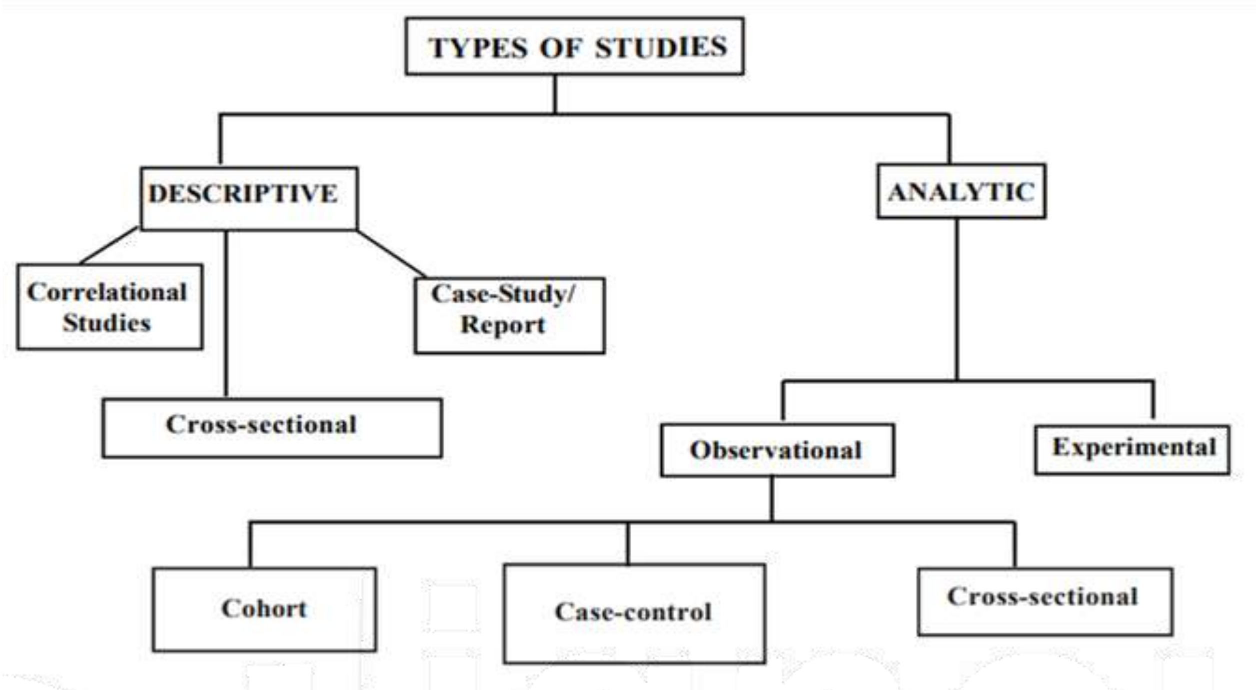
10. Grounded Theory: An approach to developing theory based on systematically gathering and analyzing data, allowing the theory to emerge from the data.

11. Surveys and Questionnaires: Administering structured sets of questions to a sample population to gather specific information.

12. Meta-Analysis: A statistical technique that combines the results of multiple studies on the same topic to draw more robust conclusions.

Researchers often choose a research method or a combination of methods that best aligns with their research objectives, resources, and the nature of the data they aim to collect. Each research method has its strengths and limitations, and the choice of method can significantly impact the findings and conclusions of a study.

DESIGN STRATEGIES IN RESEARCH



DESCRIPTIVE STUDIES

Descriptive studies are concerned with the distribution of disease, including consideration of what population or sub-group do or do not develop the disease, in what geographical location, and how the frequency of occurrence varies over time. Descriptive studies, in fact, seek to delineate the magnitude of the problem in different population groups, say in terms of prevalence and incidence, or to establish normal or abnormal levels of measurements. In simple terms descriptive studies are concerned with describing the distribution of disease or the health condition by person, place or time. Basic indices of person examined in descriptive studies include the demographic and life-style variables such as:

- Age and sex distribution
- Socio-economic status
- Family structure, including marital status and number of single-parent families
- Racial, ethnic and religious composition

• Consumption of various foods, supplements, medicines etc.

Characteristics of place refer to geographical distribution of a disease, as already mentioned earlier, in terms of variation among countries or within the country, such as between urban or slum or rural areas. With regards to time, descriptive studies may examine seasonal patterns, growth patterns or compare frequency data of today with that of 5, 10 or 100 years ago.

Descriptive studies may use information from very diverse sources such as the census data, vital statistic record, data from national surveillance programs, and employment health examination records, clinical records from hospitals and private clinics, as well as, national figure on consumption of food/nutrients, medication or other products.

Since this information is often routinely collected and easily available, descriptive studies are generally far less expensive and time-consuming than analytic studies as you would get to know later in the next unit. In fact, a stimulus to investigation may come from a surveillance activity or descriptive study.

From our description so far, you would have realized that generally, in a descriptive study, the emphasis is on estimation rather than testing. Some of the quantities we might want to estimate are:

1) the prevalence of a disease.

2) the natural history of a disease.

3) the resources required to treat the disease.

4) attitudes and perceptions about the disease condition and so on. Therefore, data so obtained from descriptive epidemiological studies are useful as they provide valuable information to health/nutrition care providers, policy makers and administrators planning for health/nutrition care utilization and for allocating resources efficiently and also planning for effective preventive and therapeutic education programmes.

Further, the descriptive studies present the first important clues about the possible determinants of a disease condition. They are valuable to epidemiologists in describing the disease pattern i.e. reveal patterns associated with a specific disease without an emphasis on pre-specified hypotheses. Hence, these types of studies are sometimes referred to as hypothesis generating studies (to contrast them with hypothesis testing studies). The three important uses of descriptive studies therefore include trend analysis, health/nutrition-care planning, and hypothesis generation (and/or formulating research questions).

There are a number of descriptive study design options, including **correlation studies** of populations, as well as, **case study/report**, **cross-sectional surveys** among individuals.

1. Correlational studies

Correlational research is a type of study design that analyzes the relationship between two or more variables. This type of research helps ascertain whether there is an association between the variables but doesn't determine whether one causes the other. Correlational research studies can have three possible outcomes or relationships between the variables—positive, negative, or no correlation.2

1. **Positive correlation**: An increase (decrease) in one variable leads to an increase (decrease) in the second variable.
2. **Negative correlation**: An increase in one variable leads to a decrease in the other variable and vice versa.
3. **No correlation**: An increase or decrease in one variable does not change the other.

Researchers present results of correlational research using a numerical value called correlation coefficient, which measures the strength of the correlation. A correlation coefficient close to +1 indicates a very strong positive correlation, a coefficient close to −1 indicates a very strong negative correlation, and a coefficient of zero indicates no correlation.

When to Use Correlational Research?

Correlational research can be used in many fields, such as economics, psychology, and medicine to determine if two or more variables are related.

Researchers can choose to use correlational research in the following situations:

1. To find only the association between variables irrespective of the causality of the relationship. That is, correlational research doesn't ascertain whether a change in one variable causes a change in the other variable, but rather only helps understand if they're related. For example, a company observes a decline in the sales of household appliances. Correlational research can help them identify the variables associated with the decline in sales, such as

increasing prices, although it may not be the only variable contributing to the decline.

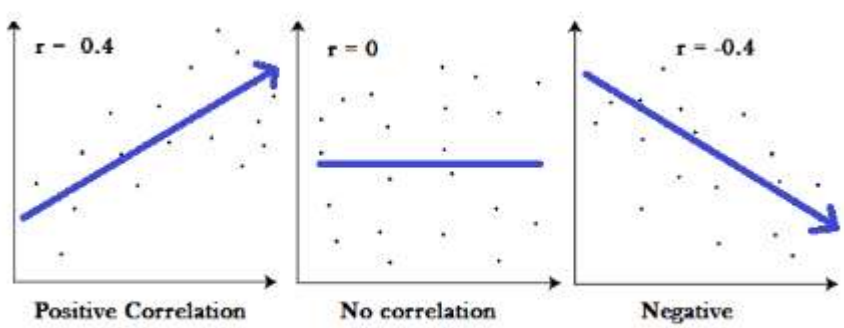
2. When researchers want to understand the effects of variables in a natural setting wherein the variables cannot be controlled. For example, visiting a hospital to ascertain the relationship between department or specialty type and wait time for patients.
3. When researchers think there could be a causal relationship between variables but it would be impossible, impractical, or unethical to manipulate the variables, such as when studying the effects of a traumatic event on individuals.
4. To generate hypotheses or predictions for further research.

How to Collect Data in Correlational Research?

In correlational research, since none of the variables are manipulated, how or where they are measured is not important. For example, participants could visit the researcher at a laboratory to complete tasks and the relationship between the variables could be assessed later, or the researcher could visit a shopping mall to ask people about their attitudes toward the environment and their shopping habits and then assess the relationship. Both these studies would be correlational because the variables aren't manipulated.

Correlation Analysis

Correlation analysis is a method to determine if a relationship exists between variables. This relationship can be depicted through a number called the correlation coefficient. The Pearson correlation method (Pearson's coefficient = *r*) is commonly used to identify the number depicting the strength and linear correlation between two variables. This method uses a scatter plot and the direction of the line drawn in the graph depicts the correlation.



Types of Correlational Research

There are three main types of correlation:

1. Positive and negative correlation
2. Linear and non-linear correlation
3. Simple, multiple, and partial correlation

Correlation Type		Examples
Positive and negative		
Positive	When two variables move in the same direction (when one increases, the other also increases)	Income vs expenditure, time spent on a treadmill vs calories burnt
Negative	When two variables move in opposite directions (when one increases, the other decreases)	Price vs demand, temperature vs sale of woolen garments
Linear and non-linear		
Linear	When there is a constant change in one variable due to a change in another variable	Height vs weight, temperature vs sale of ice creams
Non-linear	When there is no constant change in one variable due to a change in another variable	Production of grains may or may not increase with increase in fertilizer use
Simple, multiple, and partial		
Simple	Only two variables are assessed	Price vs demand, price vs income
Multiple	Three or more variables are assessed simultaneously	Wheat production vs rainfall and manure quality
Partial	Two variables are examined keeping the other variables constant	Production of wheat depends on various factors (rainfall, manure quality, sunlight, etc.) Studying wheat production vs rainfall, keeping other variables constant is a partial correlation

2. Case study

A case study method involves a detailed examination of a single subject, such as an individual, group, organization, event, or community, to explore and understand complex issues in real-life contexts. By focusing on one specific case, researchers can gain a deep understanding of the factors and dynamics at play, understanding their complex relationships, which might be missed in broader, more quantitative studies.

A case study typically includes several key components:

1. **Introductio**n, which provides an overview and sets the context by presenting the problem statement and research objectives;
2. **Literature review**, which connects the study to existing theories and prior research;
3. **Methodology**, which details the case study design, data collection methods, and analysis techniques;
4. **Findings**, which present the data and results, including descriptions, patterns, and themes;
5. **Discussion and conclusion**, which interpret the findings, discuss their implications, and offer conclusions, practical applications, limitations, and suggestions for future research.

The advantages of using case studies in research

Case studies are a powerful research method, offering advantages such as in-depth analysis, contextual insights, flexibility, rich data, and the ability to handle complex issues. They are particularly valuable for exploring new areas, generating hypotheses, and providing detailed, illustrative examples that can inform theory and practice.

The Limitations of a Case Study

1. Limited Generalizability

2. Subjectivity

3. Time-Consuming

4. Resource Intensive

5. Replication Difficulties

3. **Cross-Sectional surveys**

A cross-sectional study is an observational study design that examines data on various variables gathered at a single time point within a sample population or predefined subgroup, offering a depiction of the population's characteristics.

Example :

(i) Population-based surveys, e.g., the prevalence of twin births in a village.

(ii) prevalence in clinical studies, e.g., antibiotic resistance in *Clostridium difficile* isolates in a tertiary care hospital.

Types of cross-sectional studies

1.**Descriptive cross-sectional studies:** These characterize the prevalence of one or more outcomes in a particular population, e.g., examining the prevalence of Alzheimer's disease in a target population.

2.Analytical cross-sectional studies: Data are obtained for both exposure and outcome at a specific point in time to compare the outcome differences between exposed and unexposed subjects. Such studies answer how or why a certain outcome might occur, e.g., looking at vascular disease, traumatic brain injury, and family history to explain why some adults are much more likely to get Alzheimer's disease than others.

3.Repeated (or serial) cross-sectional studies: Data are obtained from the same target population at different time points. At each time point, researchers select a different sample (different subjects) from the same target population. Repeated cross-sectional studies can therefore examine changes in a population over time. An example of serial cross-sectional study could be one that investigates the prevalence and risk factors of Alzheimer's disease in adults aged 50-80 years in a specific decade.

Advantages of a cross-sectional study

- Relatively quick and inexpensive to conduct
- No potential ethical issues
- Multiple outcomes and exposures can be studied

- Helpful for generating hypotheses
- Many findings can be used to create an in-depth research study
- Data are obtained from a large pool of subjects, and differences between groups can be compared.

Disadvantages of a cross-sectional study

- Cannot measure incidence
- Deriving causal inferences is challenging as it is a one-time measurement of the apparent cause and effect
- Associations identified might be difficult to interpret
- Cannot determine temporal relations between outcomes and risk factors
- Not suitable for studying rare diseases or sporadic events
- Susceptible to biases
- Cannot be used to analyze trends over a period of time.

Cohort studies

A **cohort study** is a type of observational study that follows a group of participants over a period of time, examining how certain factors (like exposure to a given risk factor) affect their health outcomes. The individuals in the cohort have a characteristic or lived experience in common, such as birth year or geographic area.

While there are several types of cohort study—including open, closed, and dynamic—there are two that are particularly common:

1) prospective cohort studies

In prospective cohort studies, data is collected over time to compare the occurrence of the outcome of interest in those who were exposed to the risk factor and those who were not. This can help ascertain whether the risk factor could be associated with the outcome.

Example: Prospective cohort study are examining the relationship between exposure to pesticides and the incidence of a diagnosis of Parkinson's disease.

researcher recruit a group of healthy participants, all of whom were free of Parkinson's disease at the beginning of your study. then collect data on their exposure to pesticides over time, tracking incidences of Parkinson's disease. After several years, results conclude that those who were exposed to higher levels of pesticides had a higher risk of developing Parkinson's disease compared to those who were not.

2) retrospective cohort studies.

In retrospective cohort studies, your participants must already possess the disease or health outcome being studied prior to joining. The study is then focused on analyzing the health outcomes of those who share the exposure to the risk factor over a period of time.

Cohort studies are particularly useful for identifying risk factors for diseases. They can help researchers identify potential interventions to help prevent or treat the disease, and are often used in fields like medicine or healthcare research.

<u>Example:</u> Retrospective cohort study are interested in how tick-borne diseases spread. researcher interview a cohort of people who have been diagnosed with Lyme disease. ask about the events surrounding their illness, their symptoms, and their medical history prior to being bitten, in order to study the spread of Lyme disease.

Advantages of cohort studies include:

- Cohort studies are better able to approach an estimation of **causality** than other types of observational studies. Due to their ability to establish temporality, multiple outcomes, and disease incidence over time, researchers are able to determine with more certainty that the exposure indeed preceded the outcome. This strengthens a claim for a cause-and-effect relationship between the variables of interest.
- Due to their long nature, cohort studies are a particularly good choice for studying **rare exposures**, such as exposure to a new drug or an environmental toxin. Other research designs aren't able to incorporate the breadth and depth of the impact as broadly as cohort studies do.
- Because cohort studies usually rely on large groups of participants, they are better able to control for potentially confounding variables, such as age, gender identity, or socioeconomic status. Relatedly, the ability to use a sampling method that ensures a more representative sample of the population leads to findings that are typically much **more generalizable**, with higher internal validity and external validity.

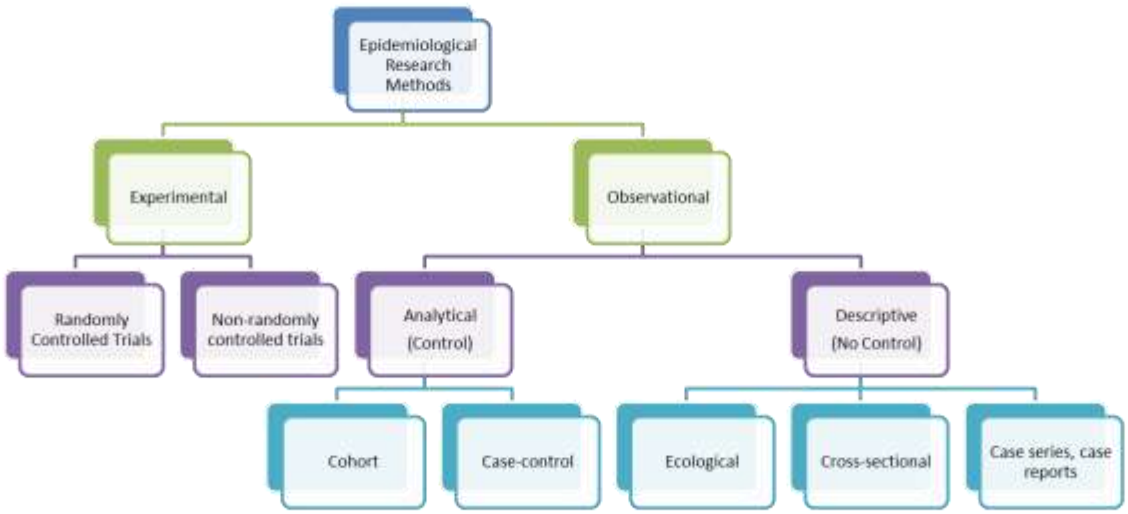
Disadvantages of cohort studies

Disadvantages of cohort studies include:

- Cohort studies can be extremely **time-consuming** and **expensive** to conduct due to their long and intense nature.
- Cohort studies are at **risk for biases** inherent to long-term studies like attrition bias and survivorship bias, as participants are likely to drop out over time. Measurement errors like omitted variable bias and information bias can also confound your analysis, leading you to draw conclusions that may not be true.
- Like many other experimental designs, cohort studies can raise questions regarding **ethical considerations**. This is particularly the case if the exposure of interest is harmful, or if there is no known treatment for it. Prior to

beginning your research, it is critical to ensure that participation in your study is fully voluntary, informed, and as safe as it can be for your research subjects.

Intervention Studies



Introduction:

Intervention (or Experimental) studies differ from observational studies in that the investigator assigns the exposure. They are used to determine the effectiveness of an intervention or the effectiveness of a health service delivery. They can also be used to establish the safety, cost-effectiveness and accceptability of an intervention. In contrast, analytical observational studies (i.e. cohort and case control studies) look at the relationships between risk factors or characteristics of patients and their likelihood of getting a particular disease. There are two types of intervention studies: randomised controlled trials and non-randomised or quasi-experimental trials. The randomised controlled trial is considered to be the gold standard of clinical research because it is the only known way to avoid selection and confounding biases. It approximates the controlled experiment of basic science. The aim of a trial is to apply the conclusions of the experiment to people in the general population.

An important feature of Randomized Controlled Trials is randomization. Here, participants (volunteers) are assigned to exposures purely by the play of chance (i.e. each participant has a known chance, normally an equal chance of receiving each treatment but the treatment to be received cannot be predicted). This reduces the likelihood of bias in the determination of outcomes and precludes selection bias and confounding bias. If participants and researchers are blinded as to the exposure the participant is receiving (called 'double-blinding'), information bias is also reduced. Allocation of people to treatment and control groups can be done by simple randomization, randomization in blocks, randomization by strata or minimization. Minimization is an acceptable non-random method of group allocation in trials. It considers people who are already allocated and allocates the next patient in such a way as to keep the composition of the two groups as similar as possible with respect to certain specified factors. Determining each allocation is complex, particularly when several factors are involved. It is recommended that specials computer software is used and that allocations are not written down in advance of the study. Despite the complexity, a recruiter can still predict the next allocation. A random element can be introduced to combat this bias.

Trial Types

1. Therapeutic trials (people with disease are given treatment to prevent death or to improve health)
2. Preventive trials for healthy individuals (e.g. a phase in vaccine trials to test efficacy of vaccine)
3. Preventive trials for at-risk groups (used to prevent development of disease)

Both types of preventive trials are concerned with reducing risk of developing a disease

Randomized Controlled Trial Designs

1. Simple or Parallel trials (the most common form)
2. Factorial Trials (where there is more than two 'arms' to the trial, e.g. three different treatment groups and one control group)
3. Crossover Trials (participants swap treatments half-way through; can only really work with chronic long term conditions, self-limiting diseases make it hard to measure effects.)
4. Within-persons Trials (participants may be given two different treatments on two different sites of their body and so act as their own control)

5. Cluster Trials (people are allocated in groups or clusters. Sometimes this is done by geographical area or health center.
6. Historical Controls Trials
7. Equivalence Trials (where a new treatment or intervention is tested to see whether it is better or equivalent to the current treatment; need to be big trials in order to show statistical insignificance)
8. Non-inferiority Trials (where a new treatment or intervention is tested to see whether it is non-inferior to the current gold standard)

Advantages of Randomized Controlled Trials

1. Its study design eliminates confounding bias.
2. If properly designed and conducted, an RCT is likely to be able to determine small to moderate effects. This is something that is difficult to establish reliably from observational studies.

Disadvantages of Randomized Controlled Trials

1. They are not always ethical.
2. Sample size can be too small. This wastes time and patients are included in a trial that is of no benefit to them or others. The larger the sample, the more successful the randomized procedure in removing confounding variables.
3. They can be statistically significant but clinically unimportant.
4. Significant tests can be misleading.
5. They can be expensive.
6. RCTs may not have external validity, that is, the results may not be able to be generalized to the broader community. Unlike the observational study, RCTs use volunteers. Those who volunteer tend to be different from those who do not.

Preparing RCT design

- Systematic Review
    - Defining the study population, sampling, baseline data (sample size can be fixed at the start of trial or sequential, i.e. enrollment and observation continue until a stopping boundary is met).

- Choosing trial design (you may also consider doing a feasibility trial first too)
- Deciding Trial treatment and comparators
- Deciding outcomes
- Internal validity
- Practical issues - recruiting staff, centers, research ethics, insurance (who's liable if someone sues?), licensing authority, development of data collection forms, development of patient information forms, planning data management, recruiting patients, monitoring accrual and compliance, data monitoring and follow .

Research Bias

Research bias is an important concept to understand when it comes to evaluating the quality of research. Bias is a systematic mistake in the planning, execution, or analysis of a study that results in inaccurate conclusions. It can manifest at any point in the research process and exert a notable influence on the dependability and accuracy of the results. In this blog post, we will explore the different types of bias that can occur in research, when and how they may arise, and most importantly, how to identify and avoid them to ensure the highest quality of research.

What is bias in research?

Bias in research refers to a systematic error that can occur during the design, conduct, or interpretation of a study, leading to inaccurate conclusions. It can occur at any stage of the research process and can have a significant impact on the reliability and validity of the findings. Some common types of bias include:

- design bias
- sample bias
- selection bias
- performance bias
- reporting bias
- confounding bias
- detection bias
- attrition bias
- language bias

Types of bias

When it comes to research, understanding the different types of bias is crucial. Each type of bias has its own implications and can impact the validity of research findings. By familiarising yourself with these different types of bias, you can improve your critical appraisal skills and ensure that you avoid bias in your own research.

1.Placebo effect

This is a psychological phenomenon where a patient experiences an improvement in symptoms due to the belief that they are receiving treatment. This can inadvertently distort results of clinical trials where a 'placebo group' believes they are receiving the treatment under study.

2.Hawthorne effect

This refers to the alteration of people's behavior when they are aware they are being observed. This awareness can cause individuals to work harder, skewing the results of studies, particularly those involving human performance.

3.Measurement bias

Occurs when data or information is not accurately recorded in a research study. This can stem from errors in data collection, inconsistent measurement tools, or subjective interpretation of data, leading to skewed and unreliable results.

4.Publication bias

This is the tendency for researchers and editors to handle the reporting of experimental results that are positive (i.e., showing a significant finding) differently from results that are negative (i.e., supporting the null hypothesis) or inconclusive, leading to a misleading bias in the overall published literature.

5.Observer/experimenter bias

Is when the person conducting the research allows their expectations or beliefs to influence the results of the experiment. This can lead to distorted data, as the researcher may subconsciously favor results that confirm their own preconceptions or hypotheses.

6.Reporting bias

Is a type of bias where researchers selectively report or omit information based on the outcome of the research or personal beliefs, which can distort the findings and undermine the integrity of the study.

7.Sampling bias

Is when the selection of participants for a research study isn't representative of the whole population. The skewed sample could lead to a misrepresentation of the data and flawed conclusions.

8.Recall bias

This occurs when the participants in a research study may not remember previous events or experiences accurately or they may subconsciously alter their memories. This can lead to skewed data and ultimately impact the credibility of the research results.

9.Selection bias

Occurs when the method of selecting participants or groups for a study produces an outcome that is not representative of the total population. For instance, if the sample group is not randomised or certain groups are excluded, it could produce skewed or incomplete results.

10.Confirmation bias

This is the tendency to favour, seek out, interpret, and remember information in a way that confirms one's pre-existing beliefs or hypotheses, whilst giving disproportionately less consideration to alternative possibilities. This bias can lead to flawed conclusions as it may prevent researchers from accurately assessing all relevant data in a neutral manner.

Confounding variables

Confounding variables (a.k.a. confounders or confounding factors) are a type of extraneous variable that are related to a study’s independent and dependent variables. A variable must meet two conditions to be a confounder:

1.It must be correlated with the independent variable. This may be a causal relationship, but it does not have to be.

2. It must be causally related to the dependent variable.

Example of a confounding variable

You collect data on sunburns and ice cream consumption. You find that higher ice cream consumption is associated with a higher probability of sunburn. Does that mean ice cream consumption causes sunburn?

Here, the confounding variable is temperature: high temperatures cause people to both eat more ice cream and spend more time outdoors under the sun, resulting in more sunburns.

To ensure the internal validity of your research, you must account for confounding variables. If you fail to do so, your results may not reflect the actual relationship between the variables that you are interested in, biasing your results.

For instance, you may find a cause-and-effect relationship that does not actually exist, because the effect you measure is caused by the confounding variable (and not by your independent variable). This can lead to omitted variable bias or placebo effects, among other biases.

How to reduce the impact of confounding variables

1.Restriction

2.Matching

3.Statistical control

4.Randomization