NEGIDA's

Handbook of Medical Research

Ahmed Negida

Your easiest guide to learn the basic concepts of biomedical research

NEGIDA'S

Handbook of Medical Research

Part I: Clinical Research Methodology

Table of Contents

About the author,

Ahmed Negida, MBBCh

Medical Education

Ahmed Negida has studied Medicine & Surgery Bachelor (MBBCH) at the School of Medicine, Zagazig University, Egypt within the period from 2012 to 2018.

Clinical Research Experience

Dr. Negida has worked as a Neurosurgery research fellow at Bahçeşehir University, Istanbul, Turkey. He participated in the coordination of three global collaborative surgical research networks since 2014 including the GlobalSurg (NIHR, UK), Global PaedSurg (King's College of London, UK), and Global Neurosurg (OHSU, the USA).

He has also provided several consultations and temporary contract-based services to several organizations including Accsight (Healthcare Integrated Solutions), DataClin CRO, Clinart MENA CRO, Mendel.ai, Maghrabi foundation for community eye health, and the Epidemiology Department of the Egyptian Liver Research Institute and Hospital, Egypt.

Peer-review & Editorial Experience

He is an editor and reviewer in several international peer-reviewed journals including top Q1 medical journals as PLOS one (as an Editor) and Frontiers of Neurology (as an editor, the most cited open-access Neurology journal in the world).

Research Awards & Grants

He was selected to receive travel grants and young investigator awards from eight organizations around the world including: World Society for Stereotactic and Functional Neurosurgery (2019), World Parkinson's Coalition (2019), IBRO-ARC (2018), International MDS congress (2017), European Academy of Neurology (Young Investigators Award 2017), 32nd APAO congress (Prof. Yasuo Tano Travel Grant 2017), WPC (2016), and the ILC (2016).

Research Publications

Despite his young age (24 years), Ahmed Negida has published +60 international research publications with H-index=14 and total citations of +740 (in June 2019). He has also published two international book chapters about research ethics and clinical trial methodology.

Teaching Experience

Since 2014, Dr. Negida has given +50 lectures and workshops teaching research skills to more than 1500 students, faculty members, and researchers in several independent and educational institutions including MEDC, Kasr Alainy Medical School, American University of Cairo, Benha University, Menoufia University, Suez Canal University, Assiut University, and Career Gates and TYT training centres.

Contact information

Email: ahmed.said.negida@gmail.com

Website: www.negida.com

Google scholar: https://scholar.google.com/citations?user=HURlCI8AAAAJ&hl=en

ResearchGate: https://www.researchgate.net/profile/Ahmed_Negida

On Twitter: https://twitter.com/negidamd

Tel: +201125549087

A message from the author to the readers

Dear Colleagues,

This is the first part of my book entitled "*Negida's Handbook of Medical Research*". The printed versions of this part will be available very soon.

Please, note that you are receiving this free copy for educational purpose only. This book is protected; therefore, it is illegal to publish, print, or re-use any part of it without written permission.

The following highlights will help you through the book.

Text in red colour	If you do not understand this sentence, it is OK to escape it and it will not affect your understanding of the basic concept.
Text in yellow background	The next editions of this part and/or the next parts of the book will provide more explanation and examples about this highlighted text.
Text in green background	The statement includes the original basic principles, copied from the original source.

I hope you enjoy it.

Kind Regards,

Ahmed Negida, MBBCh

Digitally signed by Ahmed Said Negida
DN: C=EG, O="Faculty of Medicine, Zagazig University, Egypt", CN=Ahmed Said Negida, E=ahmed01251@medicine.zu.edu.eg
Reason: I am approving this document with my legally binding signature
Location: Zagazig, El-Sharkia, Egypt
Date: 2019-07-30 12:26:46
Foxit Reader Version: 9.1.0

Chapter 1 **General Scheme of Clinical Research**

Step	Requirement
[1] Developing a research idea	▪ Critical thinking ▪ Clinical background ▪ Being a keen observer during clinical practice ▪ Reading clinical research
[2] Reviewing the literature	▪ Finding the keywords of the research question ▪ Developing the search strategy ▪ Searching Medical Electronic databases (PubMed, Cochrane, Google Scholar, EBSCO, EMBASE, SCOPUS, Web of Knowledge, etc.)
[3] Formulating the hypothesis	▪ Being aware of the types of hypotheses
[4] Planning for the study	▪ Discussing the study details with your time ▪ Writing the study protocol according to the template of the institution
[5] Piloting the study	
[6] Gaining Ethical approval	▪ Complying with the requirements and guidelines of your institution Ethics Committee (EC) or Institutional Review Board (IRB).
[7] Study implementation	▪ Clinical skills if the interventional study
[8] Data collection	▪ Data collection tools e.g. Redcap, Surveygizmo, … etc.
[9] Data entry	▪ Using MS Excel, Google sheets, Epiinfo®, etc.
[10] Data analysis	▪ Interpretation of the statistical analysis results ▪ Running the basics statistical tests on some statistical analysis software, e.g., SPSS, R, STATA, SAS, etc.
[11] Writing manuscript	▪ Following the standard reporting checklists ▪ Following the scientific writing rules ▪ English language proficiency
[12] Publication	▪ Presentation skills ▪ Experience in Journal selection ▪ Experience in addressing reviewers' comments

1. Developing the research idea

The first step of a research project is to get a research idea. There are many sources of the research idea. First, research ideas usually emerge while reading the medical

literature; therefore, it is important for researchers to follow the recent advances and publications in their specialties.

Another important source of the research idea is clinical practice. Keen observer physicians are able to notice possible relationships between some variables (i.e., patient age and response to a specific treatment or patient gender and the occurrence of a particular side effect). Therefore, physicians can come up with possible ideas for research through clinical practice. Case reports and case series are other types of publications that are feasible for clinical practitioners.

2. Reviewing the literature

Reviewing the literature is an important step for your research project because it helps you strengthen your background about the topic. Because scientific research is a cumulative process in which each researcher starts from the point where other researchers stopped. Reviewing the literature plays an important role in structuring your research project, improving your ideas by answering the following questions:

- Had anyone investigated this research question before?
- Which research design did they use?
- Which outcomes did they measure?
- What were the key results?
- What were the recommendations for future researchers?

You should follow the recommendations of previous researchers; such recommendations are usually provided in the last paragraphs of the discussion. Further information about literature searching will be discussed in the following chapter (Chapter no 2).

3. Formulating the hypothesis

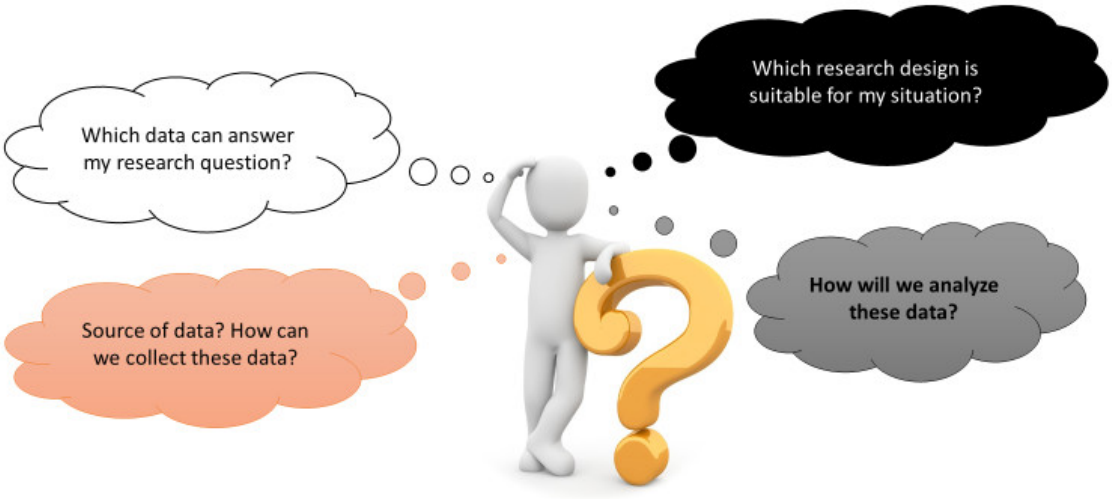
Following a rigorous review of the literature, you should formulate an educated explanation for the research question. The predicted hypothesis adopted by the researcher is referred to as (Alternative Hypothesis; H1), but the opposite hypothesis is referred to as (Null hypothesis; H_0).

Further information about the hypotheses will be discussed in the chapter of "stating the research hypothesis" (Chapter no 3).

4. Planning for your study design, data collection, and data analysis

Planning is the most crucial step in the research process. Proper planning is critical for a successful research project. Poorly designed research studies are not likely to be published in top journals, are likely to be criticized by other scholars, and might not be informative for clinical practice. On the contract, poor research design can be misleading for clinical practice.

In this step, researchers discuss and plan for the methodology of the research study. They write the study protocol, which emphasizes on the study rationale, study aims, and objectives, research hypothesis, study design, data collection methods, as well as the ethical considerations of the research study. Moreover, the study statistician plan for the statistical analysis methods that will be useful to analyze the study data and determine whether the data support rejecting or not rejecting the null hypothesis.



A well-structured detailed research protocol is essential to gain ethical approval from the institutional review board or the ethics committee of your institution. In addition to ethical review, top tier journals usually require prospective protocol registration of clinical trials and systematic reviews to eliminate some sources of bias that might occur by changing the methods during the study implementation process to obtain favorable outcomes. When you perform changes to the details of your registered study, these changes are deposited and registered as old versions of the registration and can be accessed by journal reviewers to evaluate your study. Further information about the protocol writing will be discussed in the chapter of "writing the study protocol" (Chapter no 4).

5. Piloting your study

After you finalize your protocol, you should start piloting the process of data collection, data entry, and data analysis. This may shed light on potential problems that were not considered in the study protocol.

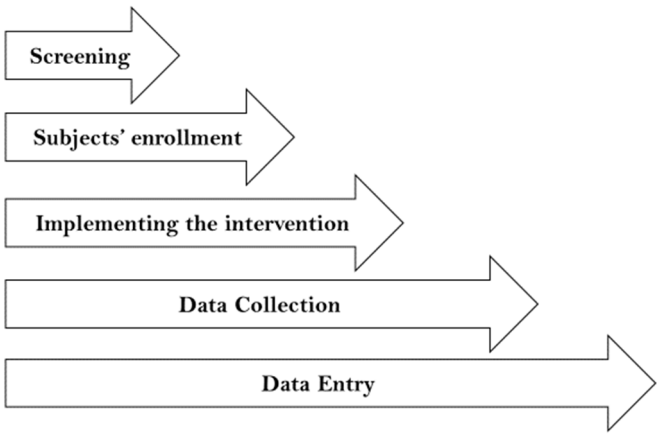
E.g., you are conducting a cross-sectional study to measure the prevalence of depression among medical students in your university using beak depression inventory (BDI). When you start the pilot, you found that many students refuse to respond to the questionnaire. Some students were not accessible. Piloting your study will shed light on some problems that you can handle within your study protocol.

6. Ethical review (Gaining ethical approval)

The institution, where you will implement your study, should review the ethical considerations of your study. The final form of your protocol is sent to the institutional review board (IRB) or the ethics committee of your institution. The approval of your study is important for publication; If you are seeking prestigious international publication for your paper, ethical approval will be required. In addition, when the ethics committee reviews your study, you get a unique identifier code for your study with the registration date. This registration protects your copyrights. It is illegal that someone else registers the same protocol elsewhere without your permission. You should comply with the guidelines of your institution. If the ethics committee supplies you with a form of informed consent, all study participants should give written informed consent before enrolling into the study. During the process of publication, you may be asked about informed consent. In addition, informed consent protects the study investigators. Giving informed consent is important for both the study investigators and the patients to stand on their rights. Further information about the ethical considerations in clinical research will be discussed in chapter no 5.

7. Study implementation, data collection, and data entry

In this step, you enroll eligible subjects into the study process. Interventions are performed. Patients' values are assessed. Patients' records are screened. If data was collected as hard copies, data should be deposited on an electronic database to enable the next step (data analysis).



8. Data analysis

In this step, statistician describes the study population and perform the statistical analyses to provide an answer to your research question. Choosing the appropriate statistical test is based on the hypothesis being tested and the type of data. Further information about the methods of statistical data analysis will be discussed in the following chapters of this handbook.

9. Writing manuscript

Scientific writing is an important skill in clinical research. Proper writing will communicate your research methods and findings easily to the scientific community through successful publication. In addition, the ability to properly write a scientific paper is a skill that is more important than the experience in research methodology and biostatistics. The ability to write, express your opinion, and discuss hot topics in healthcare is essential for publication in biomedical journals. Students, trainees, juniors, and seniors can express their own views and deliver their voice to the scientific community if they have excellent scientific writing skills. Further information about scientific writing will be discussed in the following chapters of this handbook.

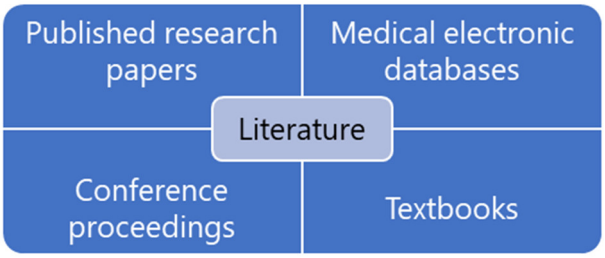
10. Publishing

"Publish or perish" is a common rule that highlights the importance of making your research available to others. The process of publication allows your work to be evaluated and criticized by healthcare physicians and decision-makers and deposited in the scientific literature for future researchers. You can publish your work in a conference and/or an academic journal whether their coverage is national, regional, or international. Further information about how to publish your research paper will be discussed in the following chapters of this handbook.

Chapter 2 Searching the Literature

What is meant by "medical literature"?

The term "Medical literature" refers to all scientific information in the field of medicine. This information includes (1) published articles in scholarly journals, (2) information in textbooks, and (3) abstracts of international conferences.



The Internet has played an essential role in advancing the field of academic publishing. Nowadays, most medical journals and scientific publishers rely on the internet to publish and distribute their publications. These facilitations have led to increasing scientific output and subsequently increased the number of biomedical journals.

To facilitate reaching, accessing, and searching the literature, electronic medical databases have been constructed. These databases include metadata of published articles in scholarly journals. Medical electronic databases vary in their coverage, meaning that a journal might be indexed for one database but not in the other database. Academic journals are selected for indexing based on technical requirements, scientific requirements, or both. Therefore, journals that meet the technical and scientific requirements of the Medline database will have their metadata of published article deposited in PubMed, allowing readers and researchers to identify these articles through PubMed searching.

Importance of literature search

Searching the literature is a crucial step when planning for your research study. Science is a cumulative process where researchers should build on the findings of the previous researchers. Electronic medical databases enable researchers to find and read relevant previous work and make use of it to improve their study concept and design. The advantage of this step is that it allows researchers to rethink better about the methods of their research project. Literature search has other benefits as follows:

- To learn more about a medical topic (educational)
- To find an answer for a case-related question (clinical practice)
- To determine current best practice
- To learn about the most recent advanced in your area
- To improve the methodology of your research project

Literature search vs. Literature review

Literature Search	Literature Review
▪ It is a well-organized search for all the literature published on a specific topic. ▪ Process of search ▪ A step in any research project	▪ A summary of published literature ▪ Collection of information about a specific topic ▪ Obtained through a literature search ▪ Written article

What makes a proper literature search?

- Good keywords
- Good search strategy
- Relevant database

Electronic Databases

Medical databases

I. PubMed

PubMed is a search engine that was developed by the National Center for Biotechnology Information (NCBI) as a part of the US National Library of Medicine® (NLM). PubMed provides access to the Medline database, and it includes selected life science journals. PubMed adds citations daily, and it currently includes about 25 millions citations.

II. CINAHL Plus with Full Text

CINAHL is a database that covers research paper related to nursing and allied health.

III. EMBASE

EMBASE is a European database that is considered a good alternative to PubMed. It includes international research about drug and diseases since 1974.

IV. Cochrane Library

Cochrane is an international research collaborative of researchers around the world. Cochrane library offers the option to search for medical evidence to guide decision making in clinical practice.

Multidisciplinary databases

V. Web of Science

A multidisciplinary database that is developed by Thomson Reuters and is highly selective for journals. It maintains a level of quality requirements and technical requirements for medical journals to be indexed in the Web of Science.

VI. Scopus

Scopus is a large multidisciplinary database that includes abstract and citation of peer-reviewed literature with tools that track authors, analyse research output and visualize research trends over time in a specific topic.

VII. Google Scholar

An interdisciplinary search engine that includes scholarly articles, abstracts, books, and dissertions. Google scholar is a free engine to use. However, it should be used cautiously because, unlike scopus and web of science, Google scholar archieves scholarly material from various sources, including non-peer reviewed articles and low quality scientific publications.

VIII. PsycINFO

This database includes medical articles related to psychology and the psychological aspects of nursing, sociology, business, and education. We use this database if we are investigating a medical topic that is related to psychology, attitudes, and behaviours.

MESH Terms

Medical Subject Headings (MESH) is a comprehensive database of controlled vocabulary that is used the purpose of indexing journal articles and books in the life sciences; it serves as a thesaurus that facilitates searching.

Boolean operators

Using Boolean operators allow a specific search strategy.

"AND"

E.g., If you are searching for papers about "depression" in patients with "Parkinson's disease," you use (AND). By using (AND), search results represent the overlapping area in figure.12. Papers about Parkinson's disease only, and those about depression only are not in the scope.

Parkinson's disease **AND** Depression

"OR"

E.g., If you are searching for papers about "depression" and "Suicide," you use (OR). By using (OR), search results represent both areas A and B in figure XX. Papers about depression only, suicide only, and those about depression and suicide together will all appear among search results.

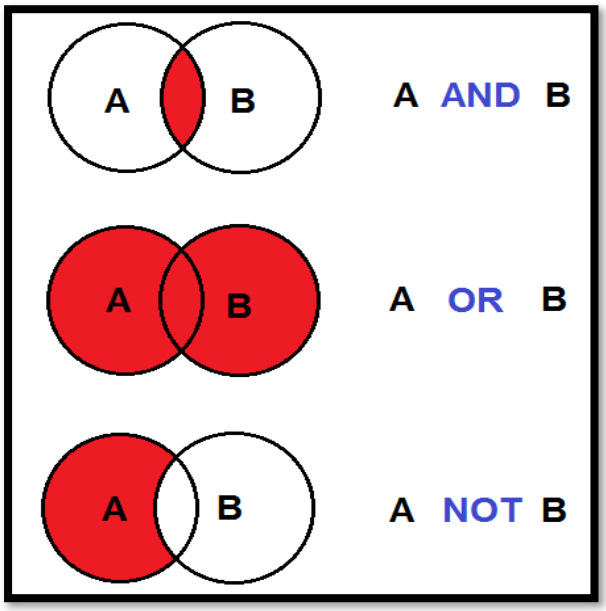
Depression **OR** Suicide

"NOT"

E.g., Deep brain stimulation is a surgical treatment for Parkinson's disease in which electrodes are implanted within the subthalamic nucleus or Globus pallidus internus. If you are searching about clinical trials about Subthalamic deep brain stimulation only, you use (NOT). By using (NOT), search results represent papers in the scope of the former keyword but not including any paper about the latter.

(Subthalamic **NOT** Pallidal) AND (deep brain stimulation) AND Parkinson's disease

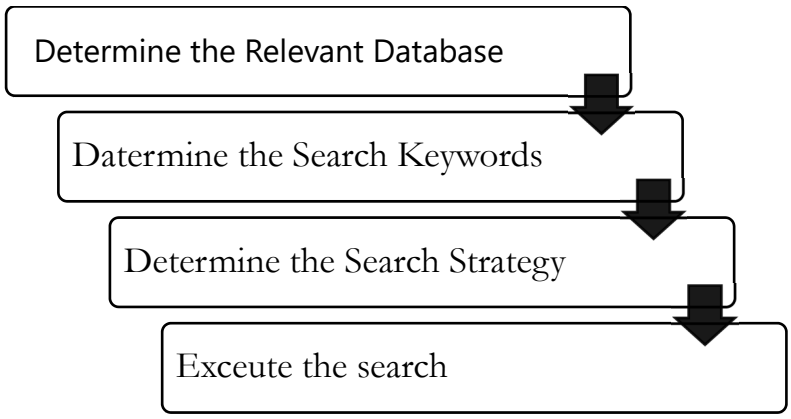
- Parkinson's **AND** Depression = Depression **AND** Parkinson's
- Depression **OR** suicide = Suicide **OR** depression
- Subthalamic **NOT** Pallidal ≠ Pallidal **NOT** Subthalamic



The figure1 shows the functions of Boolean operators

Practical steps of the literature search

The following diagram shows the practical steps of searching the literature.



[1] Determine the relevant database

If the topic is in the biomedical and clinical fields, use PubMed

If the topic is in the medical and psychological fields, use SCOPUS

If the topic is in the medical and engineering fields, use SCOPUS

If the topic is in the national scope, use Google scholar and national databases

[2] Determine the search keywords

Keywords should be derived from the research question whose format depends on the design of the research study. HOW?

In case of an observational study

Indicator + Outcome + Population (if not the general population)		
Example: Is smoking associated with lung cancer?		
Smoking	Lung Cancer	
Indicator	Outcome	Population

In case of an interventional study that includes one intervention

Intervention + Population + Outcome (if specified)		
Example: Is Lorlatinib effective in the treatment of lung cancer?		
Lorlatinib	Lung Cancer	Survival (?)
Intervention	Population	Outcome (?)

In case of an interventional study that includes two interventions

Intervention 1 + Intervention 2 (comparator) + Population + Outcome (if specified)			
Example: Is Lorlatinib better than Crizotinib for patients with Lung Cancer?			
Lorlatinib	Crizotinib	Lung Cancer	Survival (?)
Intervention 1	Intervention 2	Population	Outcome (?)

In case of a diagnostic test accuracy study

Diagnostic Test + Population	
Example: Can Optical Coherence Tomography diagnose Multiple Sclerosis?	
Optical Coherence Tomography	Multiple Sclerosis
Intervention	Population

[3] Determine the search Strategy

In this step, you should include all relevant synonyms, all relevant subtypes, and plan for the search strategy.

Example

Indicator	Outcome	Population
Smoking	Lung Cancer	
Tobacco	Lung neoplasm	
Smok*	Pulmonary Neoplasm	
Cigar*	Lung Carcinoma	
Shisha	Non-small cell lung Carcinoma	
Shesha		
Sheesha		

We conclude that the indicator = (Smoking OR Tobacco OR Smok* OR Cigar* OR Shisha OR Shesha OR Sheesha) while the outcome = (Lung Cancer OR Lung neoplasm OR Pulmonary Neoplasm OR Lung Carcinoma OR Non-small cell lung Carcinoma)

The search strategy should be **Indicator AND Outcome** = (Smoking OR Tobacco OR Smok* OR Cigar* OR Shisha OR Shesha OR Sheesha) AND (Lung Cancer OR Lung neoplasm OR Pulmonary Neoplasm OR Lung Carcinoma OR Non-small cell lung Carcinoma).

[4] Execute the search strategy

- **How to open PubMed®?**

In your browser, type http://www.ncbi.nlm.nih.gov/pubmed (see figure.1)

Figure 2 opening PubMed website in your browser

- **PubMed user interface**

Once you open PubMed, you will find the interface shown in figure.2.

Write in the white box [1] for ordinary search and press advanced option [2] for advanced search.

- **Searching using keywords**

For example, write "Parkinson's disease" in the search box, you will find 79687 items. The page of search results provides some further options; the function of each option is illustrated in figure.3.

- Search filters: To narrow your search scope, you can specify specific article type, a specific population, years from publication, etc.
- Export results: Used to export results as a file or send them via email.
- Display setting: To optimize the number of items per page and whether to show summaries, abstracts, or PMIDs.

- **Using PubMed filters**

To narrow the scope of the search, we chose, e.g., clinical trial (Article type).

The number of search results decreased from 79687 to 4823 items (see figure.4)

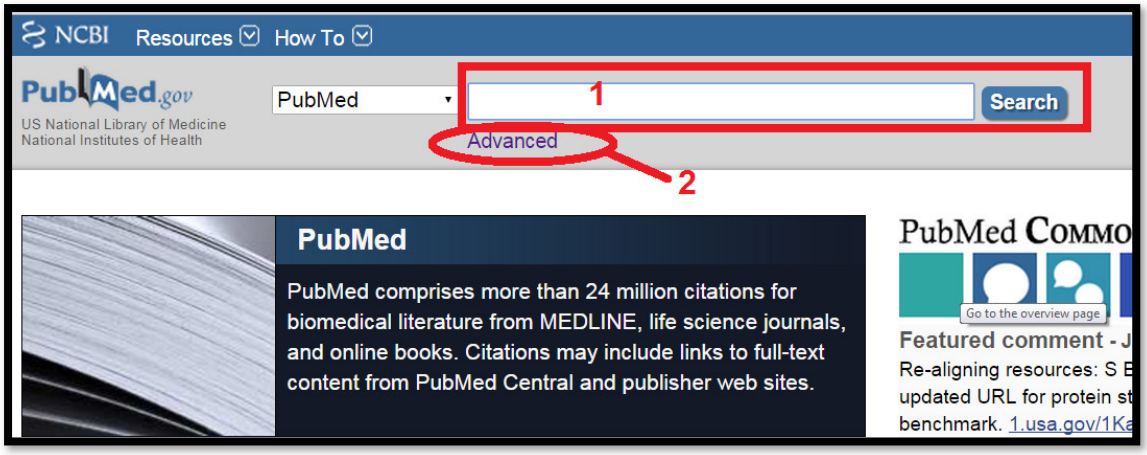


Figure 3 shows the PubMed main page

Figure 3 shows the page of search results for (Parkinson's disease).

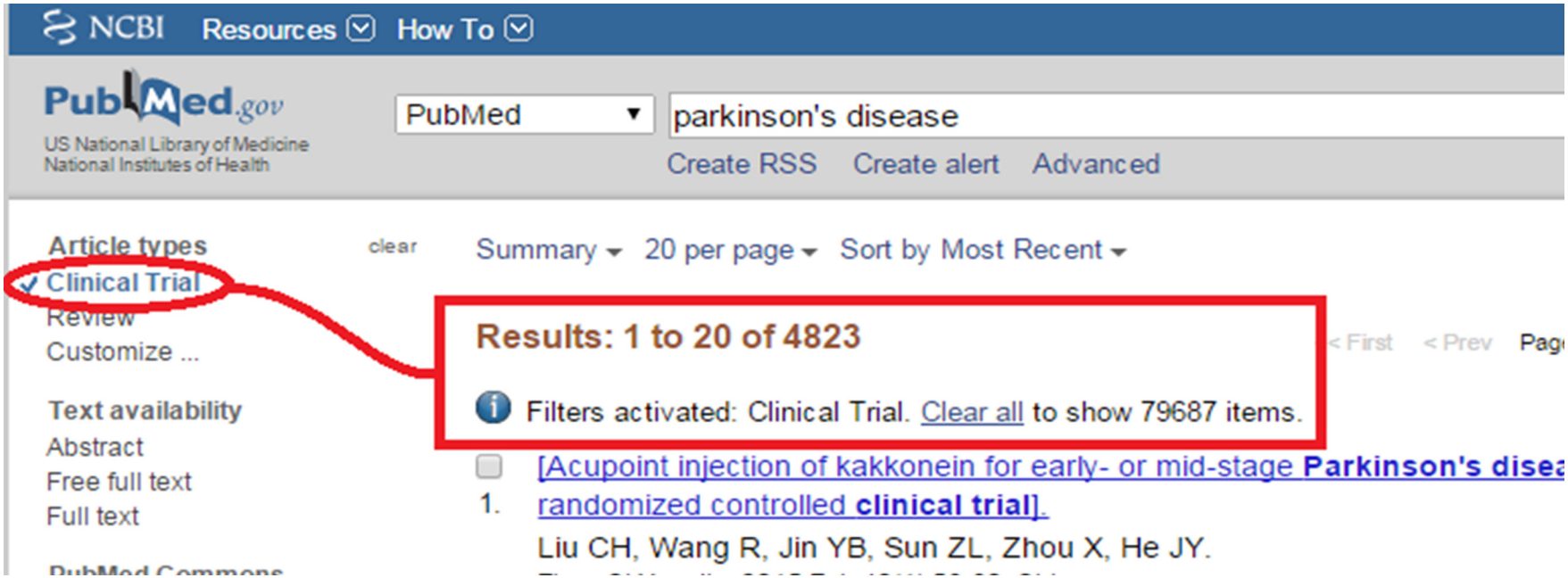


Figure 4 shows how using the filter (Article type: Clinical trial) narrows the number of search results.

- Advanced search page

The advanced search page is shown in figure.5 with illustrations of the functions in this page. Advanced search provides options to search in titles only, title/abstract, journals' names, authors' names …etc. The default option in the builder is to search in "All fields." The history of figure.5 also shows how searching in "title" narrows the search scope than "title/abstract" and "All fields." Figure.6 shows how to combine previous search query from history #1 in a new search query.

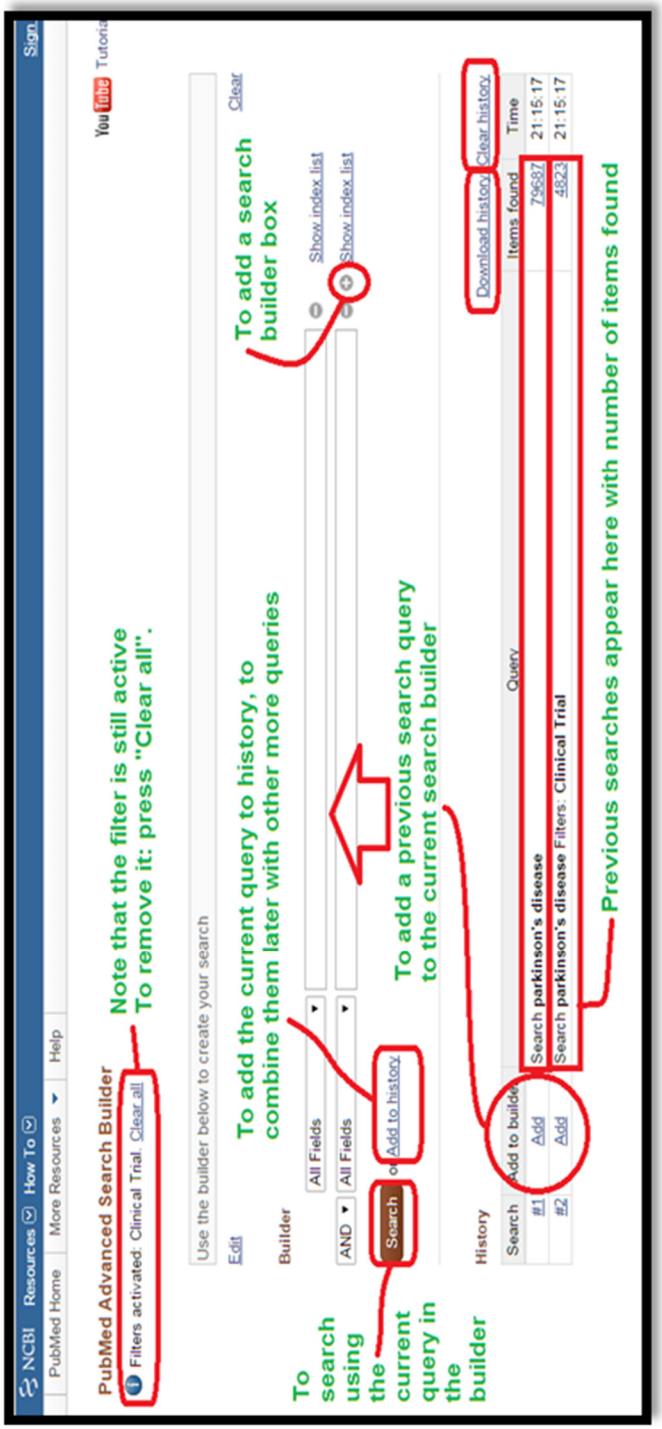


Figure 5 shows an advanced search page with previous search history. The history shows how searching in "title" narrows the search scope than "title/abstract" and "All fields."

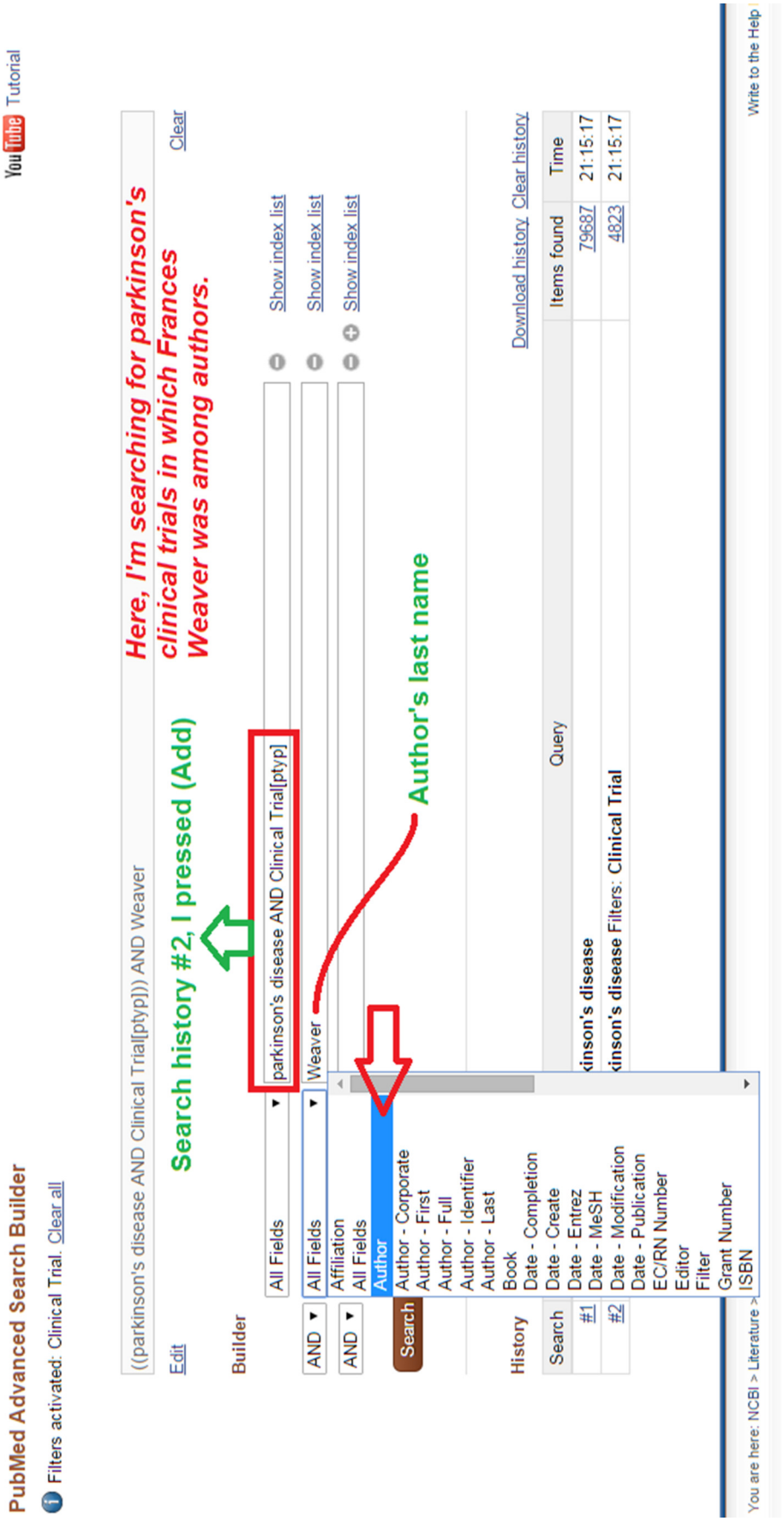


Figure 6 shows searching for clinical trials of Parkinson's disease done by Frances Weaver, Ph.D.

- **Exporting items from PubMed**

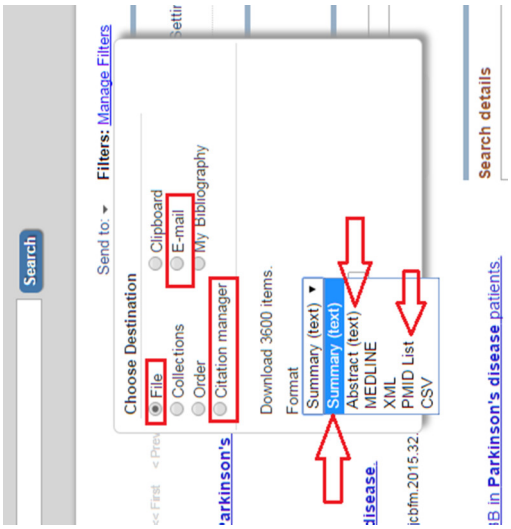


Figure 6 shows different exporting format from PubMed.

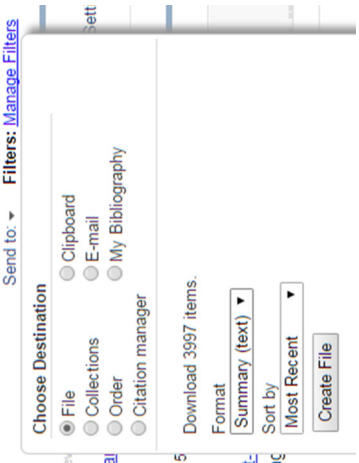


Figure 7 shows exporting results to email.

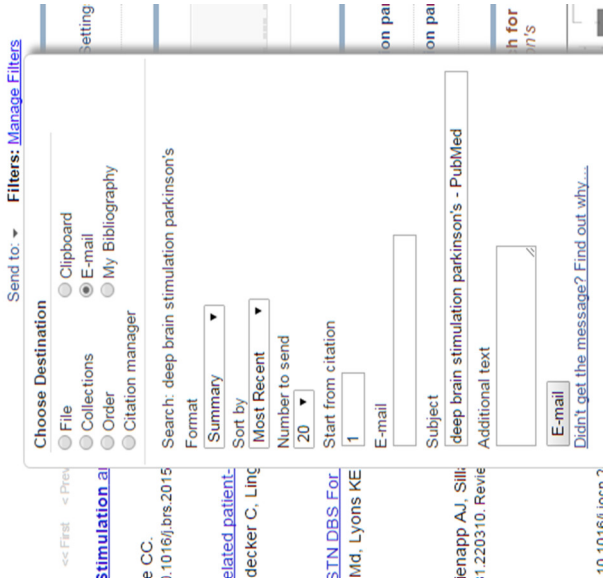


Figure 8 shows exporting results to a file.

- **Opening the abstract page**

When you click on a title from search results, the abstract page opens as in figure XX.

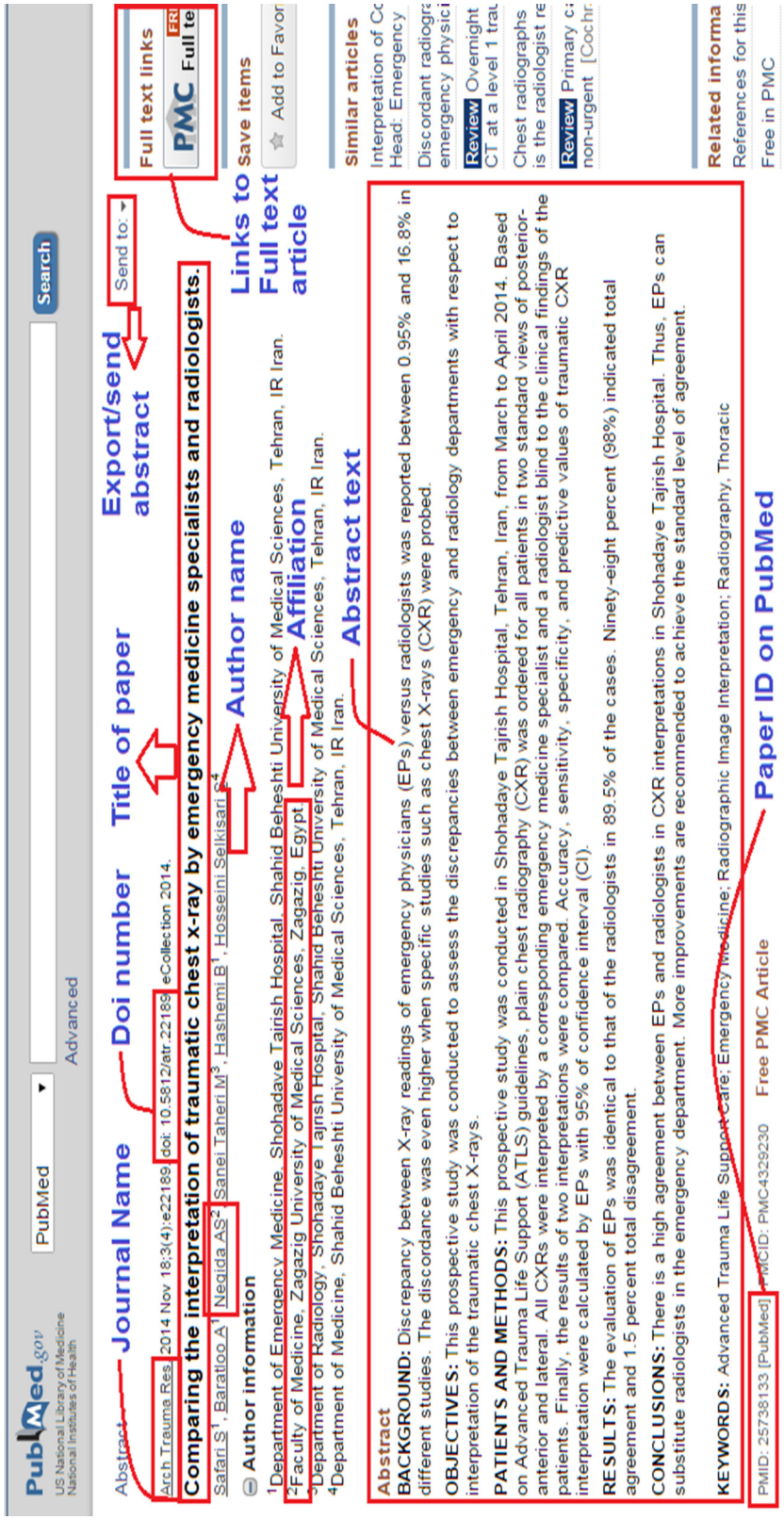


Figure 9 shows the page when you open an abstract

- **Changing display options**

Figure 12 shows the sorting options for search results.

Figure 11 shows changing the number of items shown on each page of search results.

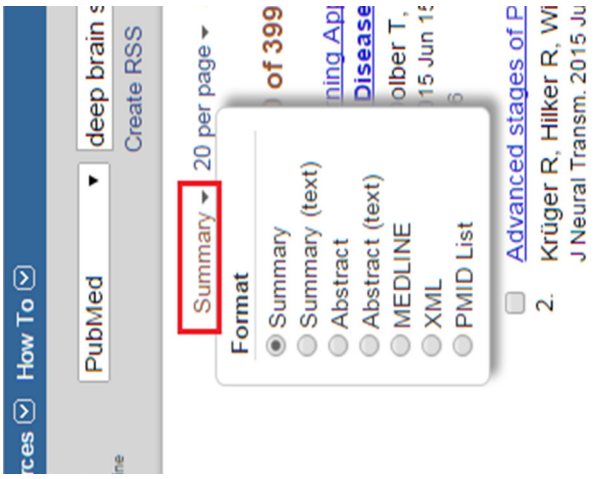


Figure 10 shows changing the format of displaying search results.

Practical training 1

Question 1. Open PubMed

Question 2. Search for clinical trials of aspirin for angina pectoris

Question 3. Search for articles published by Ahmed Negida

Question 4. Search for articles published by researchers from Zagazig University

Question 5. Find the MESH term that includes Titanium Elastic Nails

Question 6. Search for studies about the following research questions "Is the exposure to pesticides increase the risk of Parkinson's disease?"

Question 7. Send the search results to your email

Question 8. Find the articles about "deep brain stimulation."

Question 9. Export the results as "citation manager."

Chapter 3 **Stating the Hypothesis**

A hypothesis is a statement about the predicted study outcomes or an approximation of the direction of the study results. This predictive statement provides an expected answer to the research question from the investigator's point of view.

The alternative hypothesis is generally denoted as H1, and it is a statement that suggests the outcome that the investigator may expect based on their observation or previous knowledge. H1 might be a directional or non-directional hypothesis.

> The directional hypothesis is a type of hypothesis that includes a direction of the effect. For example, when comparing two drugs, we hypothesize that one of them will be superior to the other; this hypothesis is called directional hypothesis.
>
> The non-directional hypothesis is a type of hypothesis that has no definite direction of the expected effect — for example, a cross-sectionals study about the prevalence of depression among patients with renal failure.

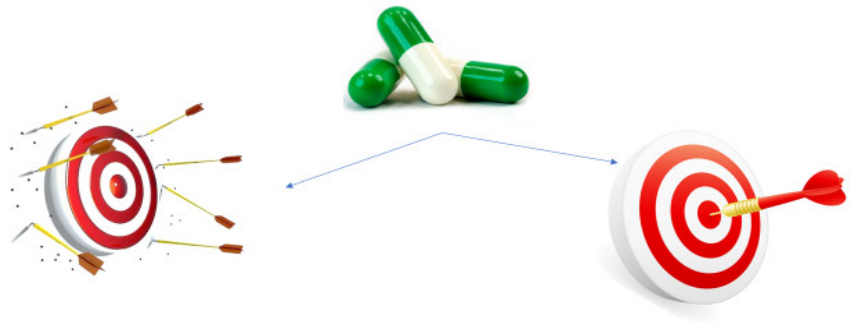
The null hypothesis is generally denoted as H0. It is a statement of the opposite of what an investigator predicts or expects. It is usually a statement that the relationship between the variable or the effect that the researchers are investigating does NOT exist.

Example 1	
Research Question	Do female medical students have higher depression and anxiety than males?
Alternative hypothesis	Female medical students have depression and anxiety more than male students.
Null hypothesis	Female medical students do have depression and anxiety more than male students (same or less than males)
Example 2	
Research Question	Can hand-assisted transperitoneoscopic nephrectomy be advocated over the standard laparoscopic technique for donor living kidney?

Alternative hypothesis	hand-assisted transperitoneoscopic nephrectomy can be advocated over the standard laparoscopic technique for donor living kidney.
Null hypothesis	hand-assisted transperitoneoscopic nephrectomy can NOT be advocated over the standard laparoscopic technique for donor living kidney (NOT superior but same or less).
Example 3	
Research Question	Is Axitinib better than Sorafenib as first-line targeted therapy for patients with metastatic renal cell carcinoma?
Alternative hypothesis	Axitinib is better than Sorafenib as first-line targeted therapy for patients with MRCC.
Null hypothesis	Axitinib is NOT better than Sorafenib as first-line targeted therapy for patients with MRCC.

Example. 4

In a clinical trial to test the efficacy of drug (X) for the treatment of obesity, what are the null and alternative hypotheses?



The drugs X is **not effective**

The drugs X is **effective**

Practical Training 2

Question 10. Select the type of hypothesis regarding the following research question

Is droxidopa more effective than placebo for the treatment of neurogenic orthostatic hypotension? ☐ Directional hypothesis ☐ Non-directional hypothesis

Question 11. Select the type of hypothesis regarding the following research question

What is the prevalence of substantia nigra hyperechogenicity among patients with Parkinson's disease? ☐ Directional hypothesis ☐ Non-directional hypothesis

Question 12. Select the type of hypothesis regarding the following research question

Is Ketorolac better than magnesium sulphate for the management of migraine headache pain? ☐ Directional hypothesis ☐ Non-directional hypothesis

Question 13. Read the following title and determine the alternative and null hypotheses.

Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Andrén O, Steineck G, Adami HO. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. New England Journal of Medicine. 2018 Dec 13;379(24):2319-29.

Alternative Hypothesis	Radical prostatectomy is better than watchful waiting for patients with localized prostate cancer
Null Hypothesis	Radical prostatectomy has equal benefit/harm as watchful waiting for patients with localized prostate cancer Watchful waiting is better than radical prostatectomy is for patients with localized prostate cancer

Question 14. Read the following title and determine the alternative and null hypothesis.

Rutledge T, Atkinson JH, Chircop-Rollick T, D'Andrea J, Garfin S, Patel S, Penzien DB, Wallace M, Weickgenant AL, Slater M. Randomized controlled trial of telephone-delivered cognitive-behavioral therapy versus supportive care for chronic back pain. The Clinical journal of pain. 2018 Apr 1;34(4):322-7.

Alternative Hypothesis	Telephone-delivered cognitive behavioral therapy is better than supportive care for chronic back pain

Null Hypothesis	Telephone-delivered cognitive behavioral therapy has equal benefit/harm as supportive care for chronic back pain Supportive care is better than Telephone-delivered cognitive behavioral therapy for chronic back pain

Question 15. Read the following title and determine the alternative and null hypothesis.

Strand-Holm KM, Fuglsang J, Ovesen PG, Maimburg RD. Diabetes Mellitus and lower genital tract tears after vaginal birth: A cohort study. Midwifery. 2019 Feb.

Alternative Hypothesis	Women with diabetes Mellitus have an increased risk of lower genital tract tears after vaginal birth
Null Hypothesis	Women with diabetes Mellitus **do NOT** have an increased risk of lower genital tract tears after vaginal birth compared to non-diabetics Women with diabetes Mellitus have a similar risk of lower genital tract tears after vaginal birth compared to non-diabetics Women with diabetes Mellitus have less risk of lower genital tract tears after vaginal birth compared to non-diabetics

Question 16. Read the following title and determine the alternative and null hypothesis.

Barzilay R, Calkins ME, Moore TM, Wolf DH, Satterthwaite TD, Scott JC, Jones JD, Benton TD, Gur RC, Gur RE. Association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort. Psychological medicine. 2019 Jan;49(2):325-34.

Alternative Hypothesis	There is an association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort
Null Hypothesis	There is no association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort

Question 17. Read the following title and determine the alternative and null hypothesis if the outcome measure is the overall survival after 10 years

Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Andrén O, Steineck G, Adami HO. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. New England Journal of Medicine. 2018 Dec 13;379(24):2319-29.

Alternative Hypothesis	Patients with localized prostate cancer undergoing radical prostatectomy have higher 10-year survival than those with watchful waiting
Null Hypothesis	Patients with localized prostate cancer undergoing radical prostatectomy have the same 10-year survival rate as those with watchful waiting Patients with localized prostate cancer undergoing radical prostatectomy have less 10-year survival rate than those with watchful waiting

Question 18. Read the following title and determine the alternative and null hypothesis if the outcome is the improvement in pain score measured by the VAS

Rutledge T, Atkinson JH, Chircop-Rollick T, D'Andrea J, Garfin S, Patel S, Penzien DB, Wallace M, Weickgenant AL, Slater M. Randomized controlled trial of telephone-delivered cognitive-behavioral therapy versus supportive care for chronic back pain. The Clinical journal of pain. 2018 Apr 1;34(4):322-7.

Alternative Hypothesis	Patient with chronic back pain who receive telephone-delivered cognitive-behavioral therapy have more improvement in the VAS pain scores than those with supportive care
Null Hypothesis	Patient with chronic back pain who receive telephone-delivered cognitive-behavioral therapy have the same improvement in VAS pain scores as those with supportive care Patient with chronic back pain who receive telephone-delivered cognitive behavioral therapy have less improvement in VAS pain scores as those with supportive care

Question 19. Read the following title and determine the alternative and null hypothesis assuming that the outcome is expressed as the odds of having genital tract injury between diabetic vs. non-diabetic women

Strand-Holm KM, Fuglsang J, Ovesen PG, Maimburg RD. Diabetes Mellitus and lower genital tract tears after vaginal birth: A cohort study. Midwifery. 2019 Feb.

Alternative Hypothesis	Diabetic women have higher odds of genital tract injury compared to those non-diabetic women
Null Hypothesis	Diabetic women have the same odds of genital tract injury as non-diabetic women Diabetic women have lower odds of genital tract injury compared to those non-diabetic women

Question 20. Read the following title and determine the alternative and null hypothesis if the outcome measure is the overall Survival after 10 years the outcome is expressed as the statistical effect size, Hazard Ratio

Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Andrén O, Steineck G, Adami HO. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. New England Journal of Medicine. 2018 Dec 13;379(24):2319-29.

H1	Hazard Ratio=Survival in experimental control/Survival in the control group # If radical prostatectomy is better than watchful waiting Then HR>1
Ho	HR=1 HR<1

Note that if the outcome is undesirable (i.e., mortality rate), then H1 will be HR<1 and H0 will be HR≥1.

Question 21. Read the following title and determine the alternative and null hypothesis if the outcome is the improvement in pain score measured by the VAS and expressed as the statistical effect size, mean difference.

Rutledge T, Atkinson JH, Chircop-Rollick T, D'Andrea J, Garfin S, Patel S, Penzien DB, Wallace M, Weickgenant AL, Slater M. Randomized controlled trial of telephone-delivered cognitive-behavioral therapy versus supportive care for chronic back pain. The Clinical journal of pain. 2018 Apr 1;34(4):322-7.

H1	Mean Difference = improvement in Experimental – improvement in the control group. If telephone-delivered cognitive behavioral therapy achieves more improvement in the VAS pain scores than supportive care Then MD < 0
Ho	MD = 0 MD > 0

Note that in this example, a higher VAS score indicates more pain severity, while lower scores indicate less pain. Therefore, the improvement in pain is represented in negative

values. If the score is in the opposite direction (i.e., more patient satisfaction with higher values), then H1 will be MD>0, and $H0$ will be MD ≤ 0.

Question 22. Suggest a research question (whose hypothesis is directional)

Research question 1	
H1	
H_0	

Question 23. Suggest a research question (whose hypothesis is directional)

Research question 1	
Outcome measure	
Effect size	
H1	
H0	

Question 24. Suggest a research question (whose hypothesis is directional)

Research question 1	
Outcome measure	
Effect size	
H1	
H0	

Chapter 4 **Protocol Writing**

Planning is the most crucial step in the research process. Proper planning is critical for a successful research project. Poorly designed research studies are not likely to be published in top journals, are likely to be criticized by other scholars, and might not be informative for clinical practice. On the contract, poor research design can be misleading for clinical practice.

In this step, researchers discuss and plan for the methodology of the research study. They write the study protocol, which emphasizes on the study rationale, study aims, and objectives, research hypothesis, study design, data collection methods, as well as the ethical considerations of the research study. Moreover, the study statistician plan for the statistical analysis methods that will be useful to analyze the study data and determine whether the data support rejecting or not rejecting the null hypothesis.

Definitions

Research Protocol

- A systematic description of your research study
- Must meet regulatory requirements to justify research and protecting research participants
- Reviewed and approved by the Ethics committee

Research Proposal

- Statement of work (statement of purpose)
- Must meet the requirements of the funding agency
- Reviewed and approved by the funding agency

Importance of the study protocol

A well-structured detailed research protocol is essential to gain ethical approval from the institutional review board or the ethics committee of your institution. In addition to ethical review, top tier journals usually require prospective protocol registration of clinical trials and systematic reviews to eliminate some sources of bias that might occur by changing the methods during the study implementation process to obtain favorable outcomes. When you perform changes to the details of your registered study, these changes are deposited and registered as old versions of the registration and can be accessed by journal reviewers to evaluate your study.

Registration of the study protocol

Clinical trials and systematic reviews should be prospectively registered on the international registration databases before starting the process of data collection or data extraction, respectively. For clinical trials, the United States NIH maintains a database of registered clinical trials called clinicaltrials.gov[1] While for systematic review, the United Kingdom NHS maintains a database of registered systematic reviews called PROSPERO[2]. Nowadays, most medical journals will require your prospective registration ID during the submission and peer-review process.

Publication of the study protocol

Publication of the study protocol is not obligatory. However, many investigators are interested in making their research methods publicly available for the scientific community. Recently, new databases such as protocol.io[3] offer online publication of your study protocol. However, this is not considered a peer-reviewed publication since your protocol is not reviewed by experts in the field prior to publication on the online website. For peer-reviewed protocol publication, some medical journals offer the option of publishing study protocols, especially if your research methods include some novelty in the design or might be useful for the journal readership to read and follow. These journals are BMJ open, journal of internet medical research, and most of the journals published by Biomed Central.

Components of the study protocol

The structure of the study protocol is variable from an institution to another. Investigators should follow the protocol guidelines of their institutions and their corresponding ethics committee or institutional review board (IRB). However, the

[1] Available at: https://clinicaltrials.gov/
[2] Available at: https://www.crd.york.ac.uk/prospero/
[3] Available at: https://www.protocols.io/

following list shows some essential items to be included in the study protocol (for guidance):

- Title Page (General Information)
- Background
- Aim & objectives
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Statistical analysis plan
- Data management
- Ethical considerations
- Publication Policy
- Project Timetable/Flowchart
- References
- Supplements/Appendices

How to write the study protocol

The first step is to retrieve the study protocol template, style, or guidelines from your institutional ethics committee or IRB. Then, start by writing a protocol summary, a two-page description of the summary of your study background, aims, objectives, and methods. The next step is to discuss the protocol summary with your team, supervisors, as well as your team statistician. Once all small details are discussed and you reach an agreement on the final methodology, start drafting the study protocol as per your institutional guidelines. To know more about the style of scientific writing used in research papers and research protocols, you can study the following chapters of this book. When you finish the study protocol, get it revised by all the study team, and get the PI signature on the protocol. Then submit the protocol to your institutional ethics committee or IRB for ethical review and approval.

Audit study

Audit means an evaluation of the current practice. In some institutions, there is a dedicated audit department responsible for continuous monitoring and evaluation of the clinical practice decision, physician performance, and patient outcomes to compare it against the institutional standards (i.e., evaluating success rate and mortality rate following major operations). Some observational research studies might be classified by the audit department as "clinical audit." Once your research study is classified as an audit, ethical approval is no longer required. The classification of your

research study is an audit represents a waiver from ethics committee approval in most institutions. However, many institutions do not make this classification.

Chapter 5 Introduction to Study Designs

Types of Medical Research

	Primary Research	Secondary Research
Basic Medical Sciences	✓	✓
Clinical Research	✓	✓

- Primary Basic Medical Science Research
- Primary Clinical Research
- Secondary Basic Medical Science Research
- Secondary Clinical Research

Primary research vs. secondary research

Primary Research	Primary research presents original data that appear for the first time. Data are not published before.
Secondary Research	Data were published before, and the investigators are retrieving these data to summarize them, add them, re-analyze them, or synthesize new evidence from them. Secondary research includes a summary, collection, and/or synthesis of existing research.

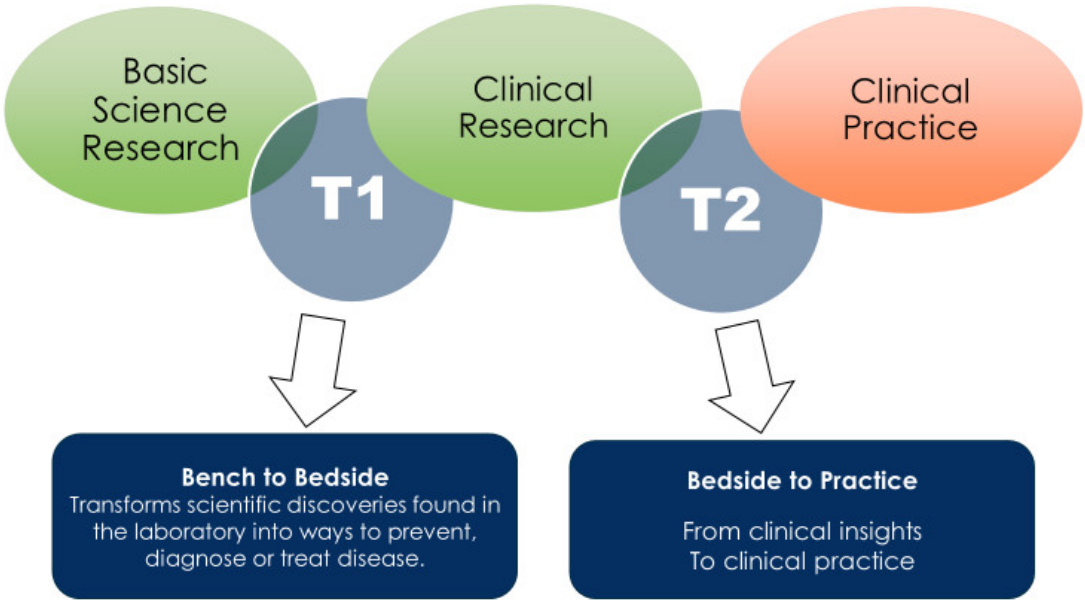
Basic science research vs. clinical research

Basic Science Research	It is called "test-tube research" because it requires well-prepared laboratories. This type of research studies fundamental functions in biology as molecular mechanisms, cell cycle, receptors, and genes. This type of research might involve animal models and tissue cultures. It is usually more powerful and has more scientif rigor since it generates more knowledge. However, it has no direct clinical relevance.
Clinical Research	This type of research deals with patients, and it requires patients not animals. It relies on patient data, and therefore, it has direct clinical relevance (unlike basic science research).

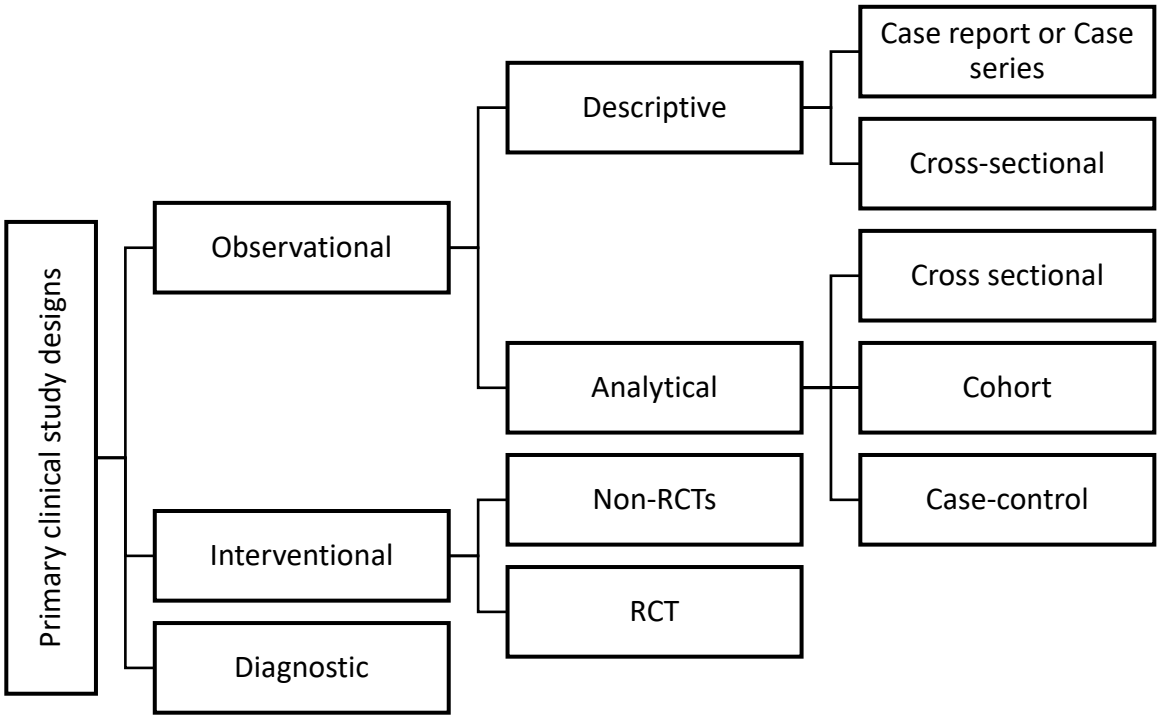
Translational research

It is a type of medical research that translates the findings of basic science research into clinical research (T1) or translates findings of clinical research into clinical practice (T2). For example, basic science research showed that VEGF is implicated in the pathogenesis of renal cell carcinoma. Subsequent basic science research studies

involved developing the drug that can bind to VEGF and testing this drug on the molecular level. The next step is to test this drug in animal models. All these steps are classified as basic science research. When enough preclinical evidence exists about the safety and efficacy of this drug, we will move to clinical evaluation of this drug in humans. This is called "the first in-human trial." Research studies that transfer basic science research findings to clinical evaluation in humans are called translational research (T1).



What are the primary clinical study designs?



Types of Primary Clinical Research

Primary Clinical Research	
Observational	Interventional
This type of studies does not involve any intervention or experiment. The researchers are observing some variables in the patient without exposing the patients to a specific drug or intervention in the context of the research study.	This type of studies include an intervention or an experiementation. This intervention might be a surgical operation, a drug, or any other form of treatment. The investigators manipulate this risk factor to examine its effect on this population.

What is the importance of observational studies?

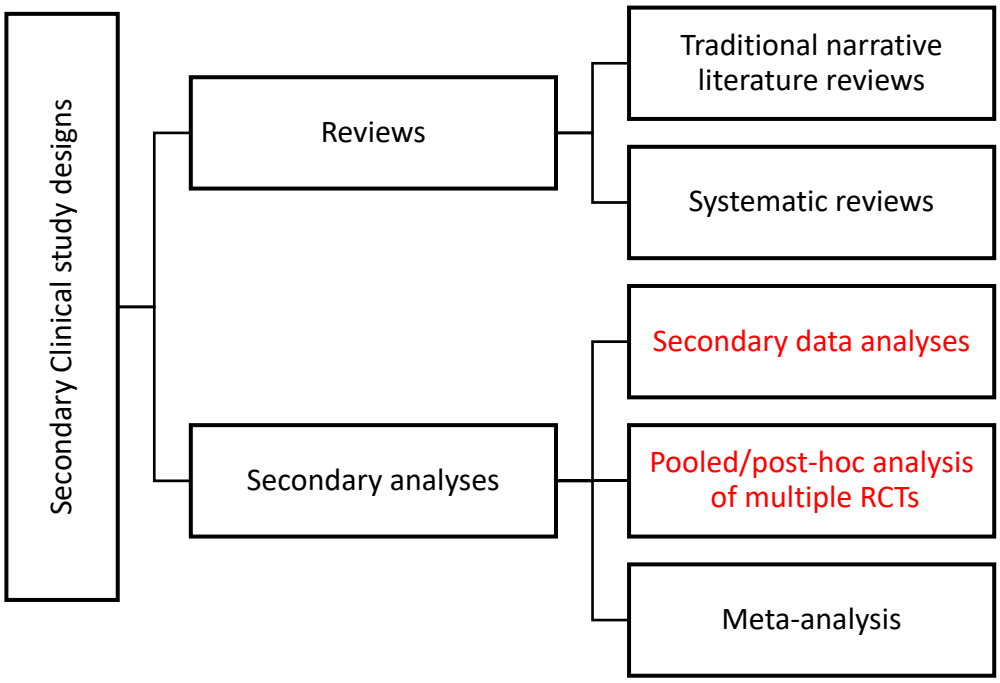
- Unlike interventional studies where the investigators are controlling the experiement, observational studies evaluate the efficacy of drugs in real-life practice without influencing the current practice.
- Observational studies are useful if the experimentation was unethical, e.g., to study the effects of heavy smoking, we could not allocate the study participants to smoke or not to smoke.
- Observational studies are useful if the experimentation was difficult to implement, e.g., to test whether adding chloride to water affect population health, we have to compare the population of two areas that are naturally supplied by water with vs. without chloride. In this example, the researchers can not control which individuals will be supplied by drinking water that includes chloride.
- Clinical trials might include atypical subjects, which makes their results not generalizable on the rarget population. Observational studies rely on real-world data, which makes their results more generalizable to the diseased population. For example, patients who agree to participate in clinical trials are usually different from the diseased population in the clinic (for example, they will be more motivated to the experiment and are more likely to adhere to the treatment, unlike patients who receive the drug in real-life).
- For initial evaluation and generatation of hypotheses, we can use observational studies. If the hypothesis was found to be possibly correct through observational studies, clinical trials might be followed. For example, some investigators suggested that diabetes mellitus share some pathophysiological pathways with Parkinson's disease, which means that antidiabetic medications might be effective in treating Parkinson'd disease. In order to evaluate this hypothesis, observational studies

were data and data suggested that patients who take that antidiabetic medications of piloglitazones are at less risk of developing Parkinson's disease. The next step was to conduct randomized controlled trials testing the efficacy of piloglitazones for patients with Parkinson's disease.

The table shows the definition of the clinical research designs

Study design			
Case report	Describe	Clinical picture	One case
Case series	Describe	Clinical picture	>1 case
Cross sectional	Describe	Prevalence	Study population
Cross-sectional	Analyze	Variables	within population
Cohort study	Compare	Risk	Between two groups
Case-control	Compare	Risk	Between two groups
Clinical Trial	Implement	Experiment	In a group of patients
	Evaluate	Efficacy/safety	
Randomized controlled trial	Evaluate	Efficacy/ Safety	of intervention in two groups of patients

What are the secondary clinical research designs?



Chapter 6 Case Report and Case Series

Definition

The case report is a presentation of a case of a rare condition, unexplained condition, or a new symptom for a known disease. A case report describes one patient while case series report ≥2 cases.

Importance

→ Providing information about rare diseases
→ Describing a new symptoms/association in an existing disease
→ Reporting of epidemiological outbreaks to national and international health authorities

Examples

(1) Xiao B, Deng P, Jin H, Wang H, Cao Y. **Lactic Acidosis and Thrombocytopenia Associated with Linezolid Therapy: A Case Report**. The American journal of case reports. 2018;19:1117.

(2) Browne E, Norton S, David S, Nabi N, Albu C, Rustoum AK, Giri SK. AB002. 221. **Robotic radical nephrectomy during pregnancy: case report and review of the literature.** Mesentery and Peritoneum. 2018 Feb 28;2(2).

(3) Chen C, Natarajan M, Bianchi D, Aue G, Powers JH. **Acute epiglottitis in the immunocompromised host: case report and review of the literature.** InOpen forum infectious diseases 2018 Feb 17 (Vol. 5, No. 3, p. ofy038). US: Oxford University Press.

(4) Goto Y, Uchino Y, Sasaki S, Shirahama N, Nomura Y, Akiba J, Ishikawa H, Akagi Y, Tanaka H, Okuda K. **Complete spontaneous necrosis of hepatocellular carcinoma accompanied by portal vein tumor thrombosis: A case report**. International journal of surgery case reports. 2018 Jan 1;44:220-5.

(5) Richardson C, Muthukrishnan PT, Hamill C, Krishnan V, Johnson F. **Necrotizing epiglottitis treated with early surgical debridement: A case report.** American journal of otolaryngology. 2018 Nov 1;39(6):785-7.

Advice for Writing a Case Report/Case series

- Focus on what makes this case unique/interesting; The publication of the case report depends on how much the case is interesting and useful for the health community.
- You must obtain patient consent to publish their case

- All patient information should be de-identified in the report
- Follow the standard reporting guidelines (CARE statement) as follows:

[1] Introduction

[2] Case presentation

- De-identified demographic information
- Clinical picture, symptoms, and main concerns
- Medical, family, and social history
- Clinical findings
- Diagnostic assessment (difficulty of diagnostic assessment if present)
- Therapeutic intervention (describe management in detail)
- Follow up and outcomes (response, adverse events, re-intervention, unexpected events)

[3] Discussion

- Strengths and limitations in your approach to this case.
- Discussion of the relevant medical literature.
- The rationale for your conclusions.
- The primary "take-away" lessons from this case report.

Note that in case reports, the patient can share their perspective on the report of their case. Patients must give informed consents for their case to be published.

Reference: 2013 CARE Statement Article
Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.

Reference: 2017 CARE Elaboration and Explanation Article
Riley DS, Barber MS, Kienle GS, AronsonJK, von Schoen-Angerer T, Tugwell P, Kiene H, Helfand M, Altman DG, Sox H, Werthmann PG, Moher D, Rison RA, Shamseer L, Koch CA, Sun GH, Hanaway P, Sudak NL, Kaszkin-Bettag M, Carpenter JE, Gagnier JJ. CARE guidelines for case report: explanation and elaboration document. J Clin Epidemiol. 2017 May 18. pii: S0895-4356(17)30037-9. doi: 10.1016/j.jclinepi.2017.04.026. [Epub ahead of print]

Chapter 7 Cross-Sectional Study

Definition

An evaluation of the current status of the population at one point of the time. It is a study that describes the prevalence of a disease or a specific condition in the population at one point in time in the defined population.

Importance

A cross-sectional study is an important design to:

- → Investigate the current prevalence of a condition or a disease in the population at one point of the time. For example, the prevalence of HCV in Egypt or the prevalence of depression among medical students.
- → Test for possible relationships (i.e., associations) between variables in the population at one point of the time. For example, a cross-sectional study about Egyptian population habits and common diseases might reveal that lung cancer is prevalent in the population as well as a smoking habit. Such study can suggest a possible association between smoking and lung cancer, however, owing to the nature of the cross-sectional study, it is not possible to conclude whether smoking was a risk factor for lung cancer or lung cancer was a risk factor for smoking. Although this example is a hypothetical scenario, it is important that the validity of a research design be critically appraised independently from the common knowledge or current practice since they might be incorrect and might bias the interpretation of your research findings.

Types

- → Descriptive cross-sectional study
- → Analytical cross-sectional study
- → Cross-sectional case-control study

Advantages

→ Short time

Cross-sectional studies can be done in short time once the proper sample from the population has been identified and reached; this study design does not include follow up, and therefore, it is relatively inexpensive in time.

→ Low cost

Unlike clinical trials and cohort studies, cross-sectional studies do not cost so much; the study costs might be limited to the costs of the screening tools and the incentives to the study participants. While clinical trials are expensive since they might include the costs of the treatment, patient assessment, the patient follows up, screening tools, incentives, or financial compensations to the study participants.

Disadvantages

→ Lack of information about the timing of exposure and outcome relationships

As we mentioned in the previous example "A cross-sectional study of population habits and common diseases," it was difficult to determine whether smoking was a risk factor for lung cancer or lung cancer was a risk factor for smoking. Such a relationship between the timing of exposure (to a certain risk factor) and developing a disease (developing an outcome) is called a temporal relationship. Cross-sectional studies lack information about the temporal relationships between variables. Therefore, it can only indicate a possible association between variables while the researchers can not emphasize which variable affects the other.

→ Include only prevalent cases

For example, if we design a study to evaluate depression among men with prostate cancer, our study will likely to include only diagnosed prostate cancer cases while neglecting the undiagnosed cases.

Examples

A cross-sectional study that is evaluating the prevalence of HTN in Egyptian medical students.

Sample size calculation for a prevalence study

$$n = \frac{(z^2)P(1-P)}{d^2}$$

Where n=sample size, z= z statistic for the level of confidence, P=expected prevalence, and d=allowable error. This formula assumes that "P" and "d" are decimal values.

Chapter 8 Cohort Study

Cohort study= Incidence Study = Longitudinal Study

Definition

Cohort means a group of the population who share similar characteristics. In clinical research, cohort study refers to the research design that examines the population at least at two points of the time. In the first point, we classify the population according to exposure to a certain risk factor into "exposed" or "not exposed" while in the second point of the time, we classify the population according to the development of the outcome to "positive" and "negative." Therefore, most of the cohort studies include a follow-up period to allow for the outcome to develop after exposure to a certain risk factor.

Examples

Ramchand, R., Ialongo, N. S., & Chilcoat, H. D. (2007). The effect of working for pay on adolescent tobacco use. American Journal of Public Health, 97(11), 2056-2062.

This study uses data collected from high school students from Baltimore, Maryland, and studies the differences in initiation of tobacco use between a cohort of adolescents that started working for pay and a cohort of adolescents that did not work. The results suggest that adolescents who work for pay have a higher risk of initiating tobacco use.

Nichol, K. L., Nordin, J. D., Nelson, D. B., Mullooly, J. P., & Hak, E. (2007). Effectiveness of influenza vaccine in the community-dwelling elderly. New England Journal of Medicine, 357(14), 1373-1381.

To determine the long-term effectiveness of influenza vaccines in elderly people, cohorts of vaccinated elderly and unvaccinated community-dwelling elderly were studied. The results suggest that the elderly who are vaccinated have a reduced risk of hospitalization for pneumonia or influenza.

Importance

Cohort studies are important to determine the association between exposure to a certain risk factor and developing an outcome (or a disease).

Types

→ Aetiological cohort study

Cohort studies that study the etiology of the disease by examining the hypothesis of whether exposure to a particular risk factor has led to the development of the disease of interest.

→ Non-etiological cohort study

Cohort studies that do not study the etiology of the disease but study the clinical outcome of exposure to a specific condition, treatment, or surgery. For example, a prospective cohort study assessing the impact of sofosbuvir antiviral treatment on the 12-week sustained virologic response of HCV patient. In this study, the investigators are following patients with HCV who are treated with sofosbuvir (exposed group) as well as those who are treated with the old traditional interferon based-treatment regimen (non-exposed group) and the two groups are compared after 3 months in terms of the sustained virologic response rate (the outcome of interest). This is an example of a prospective cohort study that does not investigate the etiology of the disease but rather, the response to treatment. In this example, we notice that the risk factor is the sofosbuvir treatment, and the outcome of interest is the virologic response.

Advantages

→ Stronger than case-control studies

Prospective cohort studies include a follow-up period. Therefore, this research design allows the investigators to constantly make sure that no other factors can interfere with the clinical outcome of the patient. Case-control studies lack the option of continuously monitoring the patients to ensure they are not exposed to other confounding variables because case-control studies are restricted by the available data in hospital records.

Disadvantages

→ More expensive

Cohort studies are expensive in time and in cost. The follow-up requires the investigators to keep in contact with the study participants for a long time. It is also important to keep the participants attached to the study as much as possible; therefore, investigators might offer financial incentives to keep the study going.

→ Time-consuming

The follow up of the patients can be time-consuming, especially if the outcome of interest takes several years to develop.

→ Lack of control over risk assignment

Like all observational study designs, cohort studies lack control over the assignment of certain individuals to an exposure. The investigators can not interfere with risk allocation. For example, in a prospective cohort study to determine the association between alcohol consumption and dementia, the investigators can not control which individuals become alcohol drinkers "exposed" and which individuals are not drinking alcohols "non-exposed." The participant allocation to risk factors occurs by nature independently from the study investigators.

→ Susceptible to bias by a differential loss to follow-up

There are several reasons for loss of the patients during the follow up as follows: (1) the patient is no longer willing to participate in the study, (2) the patient changed his residence setting and moved to another place, (3) the patient changes his contact information, (4) the patient condition deteriorated and is no longer capable on participation in the study, or (5) the patient died. Owing to the longitudinal nature of the cohort study, participants might drop out of the study over time, leading to a substantial bias due to incomplete patient data.

→ Confounding bias

See later (chapter of error and bias)

→ Zero-time bias

See later (chapter of error and bias)

→ Does not provide empirical evidence that is as strong as that offered by RCTs

The evidence provided by the cohort study is usually not as powerful as evidence provided by well-designed randomized controlled trials. The main reason for this difference is that cohort studies lack the control over risk assignment (the investigators can not control which participants are exposed to the risk factor). This is not the case in randomized controlled trials where the investigators allocate the study participants to the risk factor (study treatment) by themselves. In randomized controlled trials, the investigators have control over risk assignment, and they randomly allocate the study participants to the study groups (also called the treatment arms). This difference makes the randomized controlled trials being characterized by their high internal validity, and the evidence of well-designed RCTs is usually stronger than cohort studies. Further information about the methodology of clinical trials will be discussed in the chapter of clinical trials.

Example for the analysis of cohort study

A research team aimed to study the association between wound infection and burn. A group of individuals who underwent 2nd or 3rd-degree burn in the last two years was compared with another group who were not exposed to any burn in the last two years. Data of the study are summarized in the following table.

	Burned group	Non-burn group
With skin Infections	45	20
No skin infections	70	100

Incidence of skin infection among the burned group = 45/115=39.1%

Incidence of skin infection among the non-burned group = 20/120=16.6%

RR = 39.1/16.6=2.35

Interpretation of the RR: burned individuals have 2.35 higher risk of skin infection than non-burn individuals.

Chapter 9 Case-Control Study

Definition

A **retrospective**, analytical, observational study often based on secondary data in which the proportion of cases with a potential risk factor are compared to the proportion of controls (individuals without the disease). The common association measure for a case-control study is the **odds ratio**.

Examples

Chambers, C. D., Hernandez-Diaz, S., Van Marter, L. J., Werler, M. M., Louik, C., & Jones, K. L. et al. (2006). Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. New England Journal of Medicine, 354(6), 579-587.

This study used a matched design, matching infants who had persistent pulmonary hypertension with infants who did not have it and compared the rates of exposure to SSRIs.

Importance

Case-control studies are important to investigate the association between exposure to a certain risk factor and developing an outcome (or a disease).

Advantages

→ Useful for initial risk evaluation

For initial risk evaluation, investigators can test their hypothesis from hospital records and existing databases to validate whether there is a possible relationship between the exposure to a particular risk factor and the development of an outcome (or disease). Case-control studies are cheaper in time and costs, and therefore, they are a better method for initial evaluation of the hypothesis. If an association relationship was found significant through case-control studies, the next step is to validate this association in a cohort study.

→ inexpensive evaluation of risk factors

Case-control studies do not cost as much as cohort studies or clinical trials. Since case-control studies usually rely on existing patient data.

→ Useful for rare conditions

For risk assessment in rare diseases, it is incorrect to design a cohort study because the incidence of the disease will be too low that few or no participants will develop the disease. A better solution for studying rare conditions it to design a case-control study that starts with identifying a group of individuals who already have developed the disease "cases" and a control group of those who have not developed the disease "controls" thus overcoming the limitation of the rare condition.

→ Useful for risk factors with long induction periods

In order to assess risk factors with long induction periods through a cohort study, it will be expensive in time. Alternatively, a case-control study is a suitable design in this case in order to save time and provide initial risk assessment.

Disadvantages

→ Weak empirical evidence even when properly done

Case-control studies usually provide evidence that is weaker than those provided by the cohort studies and clinical trials. The reasons are the retrospective nature of the case-control study and the lack of investigator control over confounding variables that occur during the period from exposure to risk factor until the development of the outcome.

→ Lack of control over risk assignment

Same as discussed before in the chapter of cohort studies

→ Limited to the available patient data

A main limitation of the case-control studies is that the investigators can only utilize the data items registered in the existing database (i.e., hospital records). Many other variables that might be important for risk evaluation might be not available.

→ Confounding bias

See later (chapter of error and bias)

Cohort study versus Case-control study

The direction from past to present or from present to future is called prospective direction. While the direction from future to present or from now to past is called retrospective direction.

The major difference is the basis of classifying study groups. If patients were classified according to the exposure to the risk factor (exposed vs. non-exposed groups), this study is a cohort study. If the participants are classified according to the outcome of interest, the study is a case-control study.

All case-control studies are retrospective in terms of time, but not all retrospective studies are case-control. Hence, it is important to consider the subject classification rather than the direction of time.

Example of the analysis of the case-control study

A research team conducted a case-control study to assess the association between eating processed meat and the risk of colorectal cancer. Two groups of individuals were enrolled. The first group includes individuals with colorectal cancer, and the second group includes age- and sex-matched controls without a family history of colorectal cancer. Data of the study are summarized in the following table.

	Cases (CRC)	Controls (Non-CRC)
With diet depending on processed meat	110	75
Diet free from processed meat	90	125

Odds of eating processed meat in the CRC group = 110/90=1.2

Odds of eating processed meat in the non-CRC group = 75/125=0.6

Odds ratio= 1.2/0.6=2

Interpretation of the OR: Colorectal cancer patients were twice as likely to eat processed meat as healthy controls, or the odds of eating processed meat was 2 times higher among CRC patients compared to healthy controls.

Chapter 10 Diagnostic Test Accuracy Studies

Definition

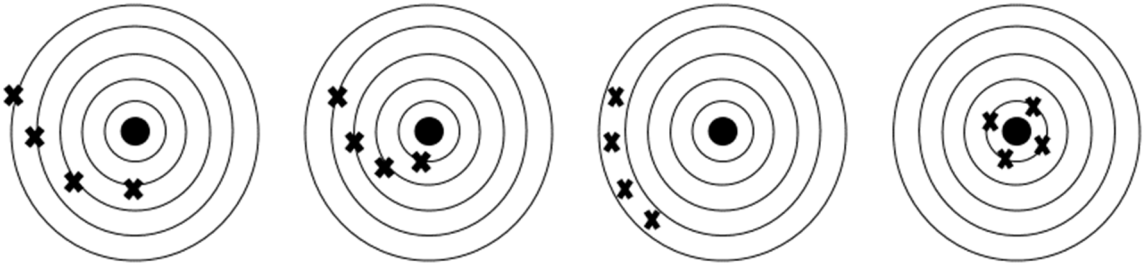
Clinical studies that aim to assess the accuracy of a new diagnostic test compared to a reference standard diagnostic test. The term is abbreviated as DTA studies.

Importance

DTA studies are important to determine the diagnostic accuracy of a new test. They are also important to determine whether this test will be more useful as a screening tool or as a diagnostic tool.

Accuracy vs. Reliability

Accuracy of the diagnostic test refers to correct diagnosis while the reliability of the test means that the test gives the same result on the same patient or population whenever it is tested. We expect an accurate test to give correct diagnosis while we expect a reliable test to give the same result (even if incorrect result) when tested on the same patient. A good test to use in clinical practice should have high accuracy and high reliability. The following diagram shows the different types of tests.



Not reliable	Not reliable	Reliable	Reliable
Not Accurate	Accurate	Not accurate	Accurate

Screening tool vs. diagnostic tool

A good screening test classifies many individuals with the disease and all those who are suspected of having the disease. The aim of the screening test is to catch all suspected individuals who might have the disease. In order to achieve this purpose of enrolling many participants to positive diagnosis, this test is not too confident in the positive diagnosis, which means that some individuals who receive positive diagnosis might not have the disease. However, this is acceptable for screening purpose since suspected individuals who received a positive diagnosis will subject to further screening by other confirmatory tests. The statistical justification of how screening tests work will be explained in the statistics chapters.

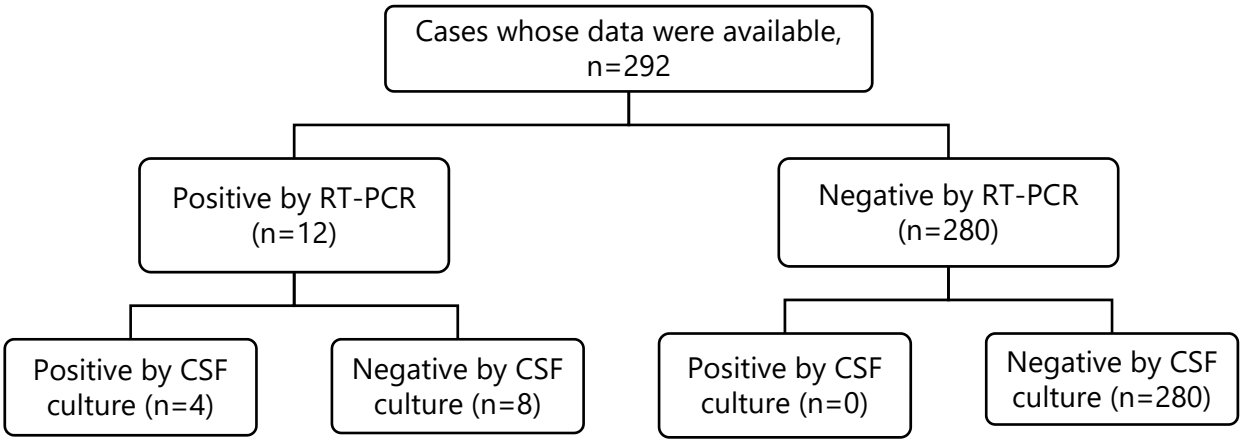
Unlike the screening test, the diagnostic test should maintain high confidence in the positive diagnosis rather than catching many suspected individuals. The aim of the diagnostic test is to confirm that an individual already has the disease.

	Screening tool	**Diagnostic tool**
Catching many suspected individuals from a group of the population (population level)	YES	NO
High confidence in the positive diagnosis of an individual (patient-level)	NO	YES

Examples

Khumalo, J., Nicol, M., Hardie, D., Muloiwa, R., Mteshana, P., and Bamford, C., 2017. Diagnostic accuracy of two multiplex real-time polymerase chain reaction assays for the diagnosis of meningitis in children in a resource-limited setting. PloS one, 12(3), p.e0173948.

In this study, the authors are evaluating the diagnostic accuracy of 2 real-time multiplex PCR assays for the detection of common causes of community-acquired bacterial and viral meningitis in South African children. The authors tested residual CSF samples from children presenting to a local pediatric hospital over a one-year period, whose CSF showed an abnormal cell count. Results were compared with routine diagnostic tests and the final discharge diagnosis. They calculated the accuracy of the bacterial RT-PCR assay compared to CSF culture. The study results are summarized in the following chart.



Chapter 11 **Clinical Trials**

Definition

Experiments that are done in clinical research. These studies are designed so that patients are exposed to the risk factor intentionally.

Importance

To establish a causative relationship between exposure to a certain risk factor and an outcome. Also, to prove the safety and efficacy of interventions.

Types

According to randomization: randomized vs. non-randomized studies

According to the control group: single-arm vs. controlled studies

According to phase: phase I, phase II, phase III, and phase IV

According to design: pragmatic vs. explanatory

Example

Ensrud, K. E., Stock, J. L., Barrett-Connor, E., Grady, D., Mosca, L., Khaw, K., et al. (2008). Effects of raloxifene on fracture risk in postmenopausal women: The raloxifene use for the heart trial. Journal of Bone and Mineral Research, 23(1), 112-120.

This research studied the effect of raloxifene on fracture risk in postmenopausal women and found that the women who took raloxifene over the same five-year period as the women who did not reduce their risk of clinical vertebrate fracture.

Advantage

→ Control over risk assignment

Unlike the observational study designs, clinical trials enable the investigators to determine which participants are allocated to each treatment. This allows investigators to employ random allocation procedures in order to obtain nearly equal study groups.

→ Strong evidence; RCTs are the gold standard studies

Owing to their high internal validity, RCTs are regarded as gold-standard clinical research studies.

Disadvantages

→ Expensive evaluation of risk factors

A disadvantage of the clinical trials is that it is more expensive. In addition to the basic costs of running a research study, investigators of clinical trials have to pay for the costs of the treatment, assessments, and laboratory tests, follow up, and the financial compensation of the patients (if available). That's why several clinical trials nowadays are funded by a third party as governmental agencies, professional associations, or pharmaceutical industries.

→ Experimentation sometimes may be difficult, inappropriate or unethical

Despite its high internal validity, clinical trials are not possible for every research question. Experimentation can be restricted by natural, ethical, social, or religious rules. For example, to assess the risk of lung cancer among smokers, you cannot get two groups of healthy individuals and assign a group to smoke while the other group to no smoking. Although this design will be helpful to establish strong evidence on the relationship between the risk factor and the outcome, it is not ethical, not acceptable, and invalid design.

Randomized trials vs. quasi-experimental trials

Randomized trials	A comparative clinical trial where patients are allocated to the study groups in a random manner (see later, the random allocation and allocation methods).
Quasi-experimental trials	A comparative clinical trial where patients are NOT allocated to the study groups in a random manner but using a quasi-random method. (see later, the quasi-random allocation methods).

Single-arm vs. controlled trials

Single-arm study	A study includes one experimental group only
Controlled study	A study that includes more than one group (experimental vs. control).

Phases of clinical trials

	Control	Sample	Aim
Phase 1	No	10-30	▪ Investigate Safety ▪ Explore efficacy
Phase 2	Yes	100-200	▪ Investigate efficacy compared to placebo (null) ▪ Recording Side effects
Phase 3	Yes	1000-2000	▪ Evaluate efficacy against standard drug ▪ Controlling side effects
Phase 4	----	-----	▪ Post marketing evaluation

Pragmatic vs. explanatory trials

Pragmatic clinical trials	They aim to assess the safety and efficacy of an intervention in order to give a picture of the performance of this drug in clinical practice. Most of the clinical trials are pragmatic clinical trials.
Explanatory clinical trials	These trials are conducted for explanatory purpose with the aim to understand the mechanism of action of the intervention rather than estimating the efficacy of an intervention in the study population.

Random Allocation

In a randomized controlled trial (RCT), patients are randomized to the treatment groups. The random allocation is used to grantee the equal distribution of subjects to the treatment groups. While in the non-randomized controlled trial (also known as a quasi-experimental study), patients are allocated to treatment groups in a non-random manner as patient preference or physician judgment.

Proper methods of patient allocation, "True randomization."

→ Computer-generated random sequence
→ The random sequence generated by a table of randomization
→ The sequence generated by block randomization
→ The sequence generated by the minimization procedure

Quasi-random methods of patient allocation "high risk of bias."

→ Patients are allocated to the study groups according to their preference
→ Patients are allocated to the study groups according to physician opinion
→ Patients are allocated to the study groups according to the day of attendance
→ Patients are allocated to the study groups according to the study hospital

Allocation concealment

A technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment. Allocation concealment prevents researchers from, influencing, which participants are assigned to a given intervention group.

Blinding

A condition when patients are NOT aware of the treatment group they were allocated to. In a blinded study, investigators use a placebo which should be identical to the new drug in terms of the route of administration, shape, color.

- → In single-blinded studies, patients are blinded to the study of drugs.
- → In double-blinded studies, patients and investigators (who give treatment/who assess outcomes) are blinded to the study drugs. But the data safety and monitoring board (DSMB) of the clinical trial are aware of the group medications.
- → In triple-blinded studies, patients, investigators (who give treatment/who assess outcomes) and investigators (who are in the DSMB) are blinded to the study drugs.
- → Assessor blinded trials are used when the outcome assessment is done by masked investigators. It is also recommended when the intervention itself cannot be masked as in most surgical operations.

Placebo

Inert material that is administrated by the control group in blinded studies to overcome and eliminate the psychological effect. In surgeries, blinding is not possible in all studies; most surgery interventions cannot be blinded.

Special forms of placebo

→ Placebo in the double-dummy design

If one of the treatments is parenteral and the other is capsules, the study is called (double-dummy design); we use two placebos. One of the groups will receive (true parenteral drug + Placebo of capsule drug), and the other group will receive (Placebo of parenteral drug + true capsule drug).

→ Sham intervention

Sham surgery is a faked surgical operation that skips the main therapeutic step in the procedure. Please, note that sham intervention is not possible in all surgical situations. The use of sham surgery is ethically controversial in some surgeries where control patients might be exposed to operative risks.

→ Vehicle control

Vehicle control is usually used in dermatology trials. It is used when the intervention is a topical cream, saline, or mineral oil, which is used as a vehicle for a solution of the experimental drug. In this case, the vehicle without the active drug can be applied as a control.

Intention to treat analysis vs. per-protocol analysis

Intention to treat analysis (ITT analysis)	All patients who were randomized to the study groups are included in the final analysis irrespective of any withdrawals or discontinuations. This type of analysis attempt to overcome the attrition bias (see later, the chapter of errors and bias).
Per protocol analysis	In this type of analysis includes patients who have completed the study until the end and have completely adhered to the study protocol. In this type of analysis, patients who discontinue the study drug, withdraw from the trial, or missed in the follow up are omitted from the final analysis.

How to obtain data of the missing individuals for the purpose of ITT

- → If you are running a cancer clinical trial and the primary outcome measure is mortality, search for the patient name in the death certificates of your city.
- → If your institution has a national connected healthcare system, you can attempt to track the patient to their new hospital and attempt to contact them
- → Apply the Last Observation Carried Forward analysis (LOCF); in this analysis, we consider the last observation as the last endpoint assessment of this patient. This should be used cautiously, especially with progressive chronic diseases.
- → Use multiple imputations to expect the final outcome of missing patients. Multiple imputations is a statistical method that involves multiple regression models and adding random numbers to estimate the expected final outcome of missing patients.
- → Assume the worst-case scenario and analyze the study data assuming that the improvement of all missing cases was the same as the worst case in the trial.
- → Assume the best-case scenario and analyze the study data assuming that the improvement of all missing cases was the same as the best case in the trial.

Practical Training 3

Question 25. Investigators designed a study to assess the safety of stem cell implantation in a group of 30 patients with advanced Parkinson's disease. Select the choice that best describes this scenario.

☐ Cohort study ☐ Case-control study ☐ Clinical trial (Phase I)

Question 26. A researcher proposes to introduce a patient education program before surgeries. In order to assess the efficacy of patient education on patient anxiety after operations, which of the following study designs should be used?

☐ Cross-sectional ☐ Cohort ☐ Case-control ☐ Clinical trial

Question 27. In a randomized controlled trial, coenzyme Q10 administration was compared against placebo for patients with early and midstage Parkinson's disease (Coenzyme group: n=300 and Placebo group: n=300). In the coenzyme Q10 group, 20 patients had stomach upset and GI disturbance, while 7 patients in the placebo group had the same complaint. Calculate the RR of this side effect.

Question 28. A researcher suggests a possible association between 5-aminosalicylate administration and neuroprotection against Parkinson's disease. Which of the following study designs would be useful for the initial evaluation of this hypothesis?

☐ Cross-sectional ☐ Cohort ☐ Case-control ☐ Clinical trial

Question 29. What is the importance of cohort and case-control studies?

☐ To estimate the prevalence of a condition in the population

☐ To detect an association between exposure to a risk factor and an outcome

☐ To detect a causative relationship or examine the efficacy of the new drug

☐ To describe a rare disease or a rare symptom for a known disease

Question 30. What is the importance of cross-sectional studies?

☐ To estimate the prevalence of a condition in the population

☐ To detect an association between exposure to a risk factor and an outcome

☐ To detect a causative relationship or examine the efficacy of the new drug

☐ To describe a rare disease or a rare symptom for a known disease

Question 31. What is the importance of clinical trials?

☐ To estimate the prevalence of a condition in the population

☐ To detect an association between exposure to a risk factor and an outcome

☐ To detect a causative relationship or examine the efficacy of the new drug

☐ To describe a rare disease or a rare symptom for a known disease

Question 32. What is the importance of case reports?

☐ To estimate the prevalence of a condition in the population

☐ To detect an association between exposure to a risk factor and an outcome

☐ To detect a causative relationship or examine the efficacy of the new drug

☐ To describe a rare disease or a rare symptom for a known disease

Question 33. In 1995, Ahmed et al. planned a research study to test the hypothesis that smoking contributes to Lung Cancer. Which of the following study designs is not possible?

☐ Cross-sectional ☐ Cohort ☐ Case-control ☐ Clinical trial

Question 34. Researchers assessed whether alcohol is associated with dementia. They enrolled a group of dementia patients and a group of age- and sex-matched healthy controls. The mental status of all individuals was verified by the MMSE, and the two groups are asked about the history of alcohol consumption over the past 20 years. Which of the following study designs best describe this scenario?

☐ Cohort study ☐ Case-control study ☐ Clinical trial (Phase I)

Question 35. In the previous study, which of the following bias might present?

☐ Attrition bias ☐ Recall bias ☐ Confounding bias

Question 36. A team of researchers compared the efficacy of intravenous caffeine citrate vs. magnesium sulfate for reducing pain in patients with acute migraine headache. The study took place in two hospitals; patients were allocated to the treatment according to the hospital to which they present. Which of the following study designs best describe this scenario?

☐ Clinical trial (Phase I) ☐ Quasi-experimental study ☐ RCT

Question 37. Driver et al. conducted a study to evaluate the association between type 2 diabetes and newly reported Parkinson's disease. They included 21,841 participants in the Physicians' Health Study, a cohort of U.S. male physicians. Diabetes and Parkinson's disease were self-reported via questionnaire. Subjects were followed up for 23 years and were compared in terms of the incidence of Parkinson's disease. Which of the following study designs best describe this scenario?

☐ Cross-sectional ☐ Cohort ☐ Case-control ☐ Clinical trial

Question 38. Watson and colleagues studied whether a previous cesarean section at full dilation is a risk factor for preterm birth. They compared two groups of pregnant women, those with a prior cesarean section at full dilation vs. those with a prior term vaginal delivery. Which of the following study designs best describe this scenario?

☐ Cohort ☐ Case-control ☐ Cross-sectional ☐ Clinical trial

Question 39. In the same previous study, data showed that preterm birth occurred in 12 out of 29 in the group with a prior cesarean section at full dilation and 5 out of 37 in the group with a prior term vaginal delivery. Calculate and interpret the risk ratio.

Question 40. A team of researchers designed a study to examine the association between a history of tooth loss and psoriasis risk. They enrolled two groups of participants, first group: patients with psoriasis, and the second group includes healthy controls. Participants were asked to self-report the history of periodontal bone loss. The two groups were compared accordingly. Which of the following study designs best describe this scenario?

☐ Cohort ☐ Case-control ☐ Cross-sectional ☐ Clinical trial

Question 41. In a randomized-controlled trial, the decision about the random allocation method is likely to influence which of the following?

☐ Internal Validity ☐ External Validity

Question 42. In a randomized-controlled trial, the decision about the random sampling method is likely to influence which of the following?

☐ Internal Validity ☐ External Validity

Chapter 12 **Systematic Reviews**

Systematic review is a method for summarizing literature by collecting and criticizing multiple research studies. A systematic review is a method for qualitative evidence synthesis and is regarded as a source for evidence-based practice.

Traditional literature reviews

Literature reviews do not follow a systematic approach in the selection, appraisal, presentation of clinical studies. Therefore, bias is common when selecting and presenting information in traditional reviews. Additionally, literature reviews do not follow a prespecified protocol making them non-reproducible and merely reflecting the opinion of the review authors.

Systematic reviews

Unlike traditional reviews, systematic reviews must follow a prespecified methodology protocol including details of the literature search and criteria of the information source, criteria for study selection, and appraisal, and the methods of handling and presentation of data. Therefore, systematic reviews involve less bias than traditional reviews, making them, when well-conducted, a valuable source for evidence-based practice. Systematic reviews are reproducible, making the procedure of evidence synthesis more transparent and allow updating evidence when new information becomes available.

Reviews of Cochrane Collaboration

Cochrane collaboration[4] is a network of healthcare professionals, researchers, and statisticians who perform high-quality, state-of-the-art systematic reviews for evidence-based practice. Systematic reviews performed by Cochrane collaboration are usually away from financial interests with industry. Cross-sectional evaluations showed that non-Cochrane review sometimes overestimates treatment effect when compared with similar reviews of the Cochrane collaboration.

Registration of Systematic Reviews

The PRISMA statement[5] recommended that prospective registration of systematic reviews should be a requirement for their publication in medical journals.

[4] https://www.cochrane.org/
[5] http://www.prisma-statement.org/

Subsequently, the center for reviews and dissemination has built the PROSPERO database[6] for prospective international register of systematic reviews.

Importance of Systematic Reviews

Clinicians and researchers should not rely on individual studies. Even well-conducted studies can give incorrect estimates. In 2005, Ioannidis et al. found that 32% of large studies (cited more than 1000 times) presented contradictory results that were proved later to be incorrect.

Hundreds of research papers are published every day in worldwide medical journals. The magnitude of published literature in each field is rapidly increasing beyond the capacity of individual researchers and physicians highlighting the need for a well-structured summary of the literature collecting, criticizing, and presenting data from multiple studies.

Additionally, in a clinical setting, the limited time of physicians warrants a trusted summary of the recent clinical evidence. Because they act as a less biased source for evidence-based practice, systematic reviews are rapidly replacing traditional reviews.

Systematic reviews and meta-analysis might have a lifesaving protentional, especially when a small but clinically significant effect estimate is not clear in individual studies — for example, (1) Sudden Infant Death Syndrome and (2) Streptokinase for myocardial infarction.

Types of systematic reviews

Systematic reviews can be classified according to the design of included studies into three categories:

(1) Systematic reviews of observational studies

This type of reviews includes observational studies which can be either (i) cross-sectional studies (to estimate the prevalence of a condition) or (ii) case-control and cohort studies to estimate the effect of exposure to a certain risk factor on the clinical outcome.

(2) Systematic reviews of diagnostic test accuracy studies (DTA reviews)

This type of reviews aims at the evaluation of the accuracy of diagnostic tests. Such reviews are based on data from diagnostic test accuracy studies (DTA studies) where a group of the population is screened by the new test, and the ability of this test to detect positive and negative cases is presented in comparison to the standard

[6] https://www.crd.york.ac.uk/prospero/

diagnosis (index test). As we explained earlier (Chapter 12) that multiple parameters are calculated to represent the accuracy of the test. Some of these parameters are empirically based on the diagnostic accuracy of the test only while other parameters might be influenced by the magnitude of the disease in the underlying population (i.e., predictive values). Given that DTA studies are likely to be heterogenous in terms of the reference test and the source of the study population, DTA reviews should be approached cautiously. Guidelines for performing a DTA review is not explained in this book. However, the Cochrane Handbook of DTA review is a recommended source for further information.

(3) Systematic reviews of interventional studies (clinical trials)

The most important type of systematic reviews is concerned with estimating the safety, efficacy, and cost-effectiveness of treatments. Such reviews are usually based on data from clinical trials where participants are allocated to receive either the experimental or control treatment.

Steps of the systematic review

1- Defining the review question

2- Defining the eligibility criteria

3- Searching the literature

4- Screening of relevant records

5- Quality assessment of included studies

6- Data extraction from included studies

7- Evidence synthesis and data presentation

Defining the review question

The review question of systematic reviews must be specific and supported by clear eligibility criteria. Unlike traditional reviews, systematic reviews usually cover a narrow scope. A systematic review of intervention should satisfy the PICO domains (population, intervention, comparator, and outcome).

For example, Safety and Efficacy of titanium elastic nails compared to spic cast for children with femoral fractures

Defining the eligibility criteria

Review authors should specify clear eligibility criteria based on which relevant studies are included in the evidence synthesis process.

Searching the literature

The term "medical literature" includes medical books, electronic databases, medical journals, and conference proceedings. To run a systematic review, review authors should run a comprehensive literature search to identify all relevant studies. Commonly used databases are PubMed, Scopus, ISI, Embase, EBSCO, Google Scholar, and Embase. The search strategy of systematic reviews should by sensitive rather than specific to ensure including most of the relevant reports and avoid missing potential data. Additionally, searching clinical trial registries (e.g., www.clinicaltrials.gov) is important to reduce publication bias by identifying unpublished studies.

Publication bias

The condition that positive results are more likely to be published than negative results in publication bias. This differential selection of work to be published will introduce bias to medical literature. Common reasons for publication bias are: (1) authors are not more motivated to report and publish positive results, (2) journal editors are more likely to accept papers reporting positive results, and (3) funding agencies are more likely to sponsor the publication of positive results. Additionally, some funding companies might withhold the publication of negative results.
As an effort to reduce publication bias in systematic reviews, the review authors should search several indexing databases and try to identify unpublished studies either by asking experts or searching clinical trial registries.

Screening of relevant records

Following a literature search, review authors will apply the eligibility criteria on the retrieved citations. Because the literature search might yield thousands of citations, it will not be practical to screen the full-text articles of all these citations. Therefore, we recommend that screening is performed at least on two levels. The first step is to screen titles alone or titles and abstracts. Although the title and abstract alone cannot confirm the inclusion of an article in the review, such initial screening is mainly important in excluding irrelevant articles (Rule OUT > Rule IN).

Remove duplicates before the screening

In case that the review authors retrieved citations from multiple sources, it is important that they remove duplicate citations before starting the screening process to save time by avoiding screening the same citations again. The reason is that there is considerable overlap between indexing databases, especially when using the same keywords. In a survey of systematic review authors, Endnote was the most commonly-used software used for removing duplicates among retrieved citations. However, the process of removing duplicates is not 100% accurate since multiple indexing database might vary in the meta-data of the same article. Also,

the indexing meta-data are not deposited on all indexing databases simultaneously. As a result, the issue number, volume, and year might appear on a database and not on the other. Also, the meta-data of one database might include first and last name of the author while another database reports the initials of middle names. However, such situations are very rare, and most of the duplicates are successfully omitted by bibliographic management software as Endnote.

The first level of screening: Title/Abstract Screening

Hereby, we mention four different techniques for title/abstract screening, which is the first level of records screening.

Screening method (1) Hand screening

Hand screening is a traditional method of records screening. In this technique, review authors print the retrieved citations align with the exclusion criteria. Each citation is then marked as (in) or (out) with a specific code referring to the reason for exclusion.

Screening method (2) rating citations on the software

Another method for screening is to use the rating option in the bibliographic management software. In this technique, all citations are imported together to the bibliographic management software, and each citation is rated according to its eligibility for inclusion in the review (for example 5 starts =included, 1 star = excluded, 3 stars = maybe).

Screening method (3) Excel/Google Sheets

Many review authors are exporting citations from bibliographic management software in the form of spreadsheets on Microsoft Excel or Google Drive, which allows for sharing the sheet with multiple reviews. Each reviewer can read the title or title/abstract then rate each record as (in, out, or maybe) in the corresponding row. This method allows multiple reviewers to screen the same citations on the same file. However, this is not an independent multiple reviewers' screening.

Screening method (4) Semi-automated tools

Recently, semi-automated abstract screening tools have revolutionized the screening process of systematic review work, allowing for multiple review authors to screen records independently from each other. Common examples for these tools are Abstrakr, Covidence, and Rayyan. In these tools, the authors export the citations file from the bibliographic management software (i.e., Endnote) then upload the citation file to the semi-automated screening website. Then, the reviewer can invite other reviewers in his team via emails. Other reviewers can join and participate in the

screening process. The user interface of these website will show the title/abstract and three decisions beside each abstract (Yes, No, May be), once the author click on the decision, the abstract disappears, and another one is shown and so on. This process saves time during the screening process. And finally, the review authors will be able to see the citations on which they disagreed, the citations that they are unsure about (maybe), and the citations that they agreed on their inclusion.

The second level of screening: Full-text Screening

Following title/abstract screening, you will have a considerable number of citations that deemed relevant to your review. The next level of screening is full-text screening. In this step, you download the full-text articles of the relevant records (that were included in the title/abstract screening). Then, review authors read the articles carefully to make sure that these articles fully satisfy the inclusion criteria.

Whatever the method you will use for your review work, it is important that each step in the systematic review be performed at least twice by two independent persons starting from the screening phase. This is important to minimize the possibility of errors. Multiple authors might have different views regarding the eligibility of an article for the review. In such a case, the review authors should resolve the disagreement by discussion.

PRISMA flow diagram

The study selection process is usually represented as the PRISMA flow diagram showing the number of citations retrieved from various sources and the flow of selection through duplicates removal, title/abstract screening, then full-text screening.

Reporting reasons for exclusion

According to recommendations of the PRISMA statement, review authors are encouraged to report the reasons for the exclusion of articles that were omitted during the full-text screening. This can be reported in the PRISMA flow chart, as well.

Automatic Screening; is it possible?

Recently, many researchers are trying to develop software that performs automatic screening. However, till the moment, the accuracy of these algorithms has not exceeded 95% and therefore, are not used now. These techniques rely on bioinformatic methods as neural networks and machine learning to teach the software to select relevant citations to the specified eligibility criteria. We believe that within a few years, future development into this area will yield more accurate software and allow for faster and accurate, fully-automated, screening.

Assessing the quality of included studies

Given that systematic review is the process of gathering and collecting results of multiple studies together, the methodological quality of the included studies is an important concern. The quality of the synthesized evidence from the review is mainly dependent on three factors: (1) type of included studies, (2) number of included studies, and (3) quality of included studies (For further information about the quality of evidence, you can read about the GRADE approach).

It is important to assess that quality of all studies included in the systematic review irrespective of their design, sample size, place, and reported outcomes.

Study Design	Quality assessment tool
Randomized Controlled Trials	Cochrane ROB tool
Non-randomized studies	ACROBAT NRSI & ROBINS-II
Observational studies (Cohort, Case-Control, and Cross-sectional studies)	Newcastle Ottawa Scale (NOS scale)
Diagnostic test accuracy studies	QUADAS-II

Cochrane Risk of Bias assessment tool

In this section, we are focusing on explaining the quality assessment of randomized controlled trials using the Cochrane Risk of Bias assessment tool. In this checklist, the review authors examine the ROB in five domains: (1) selection bias, (2) performance bias, (3) detection bias, (4) attrition bias, (5) reporting bias.

1. *Selection bias*

Selection bias is caused by differences in the baseline characteristics of the study group. This difference might be attributed to weak methods of sequence generation or bias introduced during the allocation to the treatment group. The random sequence generation and patient allocation processes are the two steps where selection bias might be introduced. Therefore, to examine the risk of selection bias, we revise the methods used to generate the random sequence and the methods of allocating patients to the treatment groups "allocation concealment."

2. *Performance bias*

Performance bias is caused by the difference between the two groups in the level of care, physician treatment, or exposure to risk factors. Blinding of patients and study personnel is important to reduce the risk of performance bias in randomized controlled trials.

3. *Detection bias*

Detection bias is caused by the difference between the two groups in the outcome measurement. Outcome assessors might unintentionally overestimate or underestimate patient outcomes during the assessment in the experimental or control groups. Blinding of outcome assessors is important to reduce the risk of detection bias.

4. *Attrition bias*

Attrition bias refers to the difference between the two groups in withdrawals. Since patients were randomly allocated to the treatment groups, these groups are balanced for many known and unknown confounders. The presence of patients in their groups maintains this balance in confounders. Therefore, a substantial loss of patients from the study or a difference between the two groups in withdrawals will introduce bias to the data and allowing for confounding variables to influence the study outcomes.

5. *Reporting bias*

Reporting bias refers to a condition where the authors tend to report some outcomes and hide other outcomes. This might be in the form of (1) reporting statistically significant results and not reporting non-significant outcomes, (2) measuring several outcomes and reporting favorable outcomes only, (3) reporting the planned outcomes using an assessment tools/scores other than the planned per protocol.

6. *Other biases*

The review authors might judge that a study suffers from another source of bias (e.g., the study stopped early due to a data-dependent problem or baseline imbalance between the two groups).

For further information and examples for situations where these biases are high, low, or unclear, you can read on Chapter 8 – Part 2 of the Cochrane Handbook of Systematic Review and Meta-analysis of interventional studies (Edition 2011 accessed at http://handbook-5-1.cochrane.org/).

Data extraction

In this step, the review authors extract all important data from the included studies. Usually extracted data include: (1) study design characteristics: date, setting, country, study design, sample size, groups ... etc.; (2) baseline characteristics/demographics of the studied population; (3) quality assessment domains: method of sequence generation, allocation method, blinding, data completion, outcome reporting, ... etc.; and (4) the study outcomes. Many errors might occur during the data extraction

process. Therefore, multiple reviewers extracting data of the same studies are recommended. Data can be extracted to an online form (built on a survey builder website) or an Excel sheet.

For continuous outcomes††

	Group (1)			Group (2)		
Study ID†	Mean*	SD**	N***	Mean	SD	N
Study 1						
Study 2						

† Study ID = the Last name of the first author + Year of Publication
* Mean or Mean Change in case of pre/post assessment
** SD: Standard deviation of the mean change
*** N: The sample size of the group

For dichotomous outcomes††

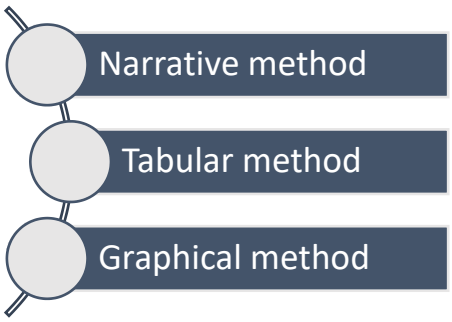
	Group (1)		Group (2)	
Study ID	*No of events*	*N*	*No of events*	*N*
Study 1				
Study 2				

For generic effect size††

Study ID	*ES*	*SE*
Study 1		
Study 2		
Study 3		

†† These tables are for summarization purpose only. The tables indicate the data items required for Review Manager software in order to conduct a meta-analysis. Several other statistical software are also possible with different input forms. For simplification, we present the tables in the format of RevMan.

Presenting the findings



There are many methods to present the results of the systematic review. The narrative method might be used to discuss the evidence and highlight the potential biases in each study. Tabular methods is a better presentation that helps the authors organize the studies according to their design, main findings, and their potential biases. The tabular method is more helpful in the case of evidence derived from several studies. Another method of displaying the systematic review findings is the

graphical method representing the effect estimates reported by the included studies. This graphical presentation is common in Meta-analysis, where the authors employ quantitative analysis methods to pool the effect estimates of multiple studies together. Further information about the methodology of Meta-analysis and their graphical presentation will be discussed in Part II of this handbook.

Chapter 13 **Sampling Methods**

Theoretically, the true effect size in a clinical research study would be obtained only if the investigators enrolled all the target population. For example, the true efficacy of an anti-hypertensive drug will be obtained by testing this drug on all hypertension patients in the world. Thus, we will be 100% sure that this drug is effective.

However, this assumption is not possible in practice. When the research question is concerned with health and disease, researchers will not be able to locate, list, and enroll all the target population since diseases are global in nature. Therefore, in clinical research studies, researchers enroll a sample from the target population rather than the whole target population.

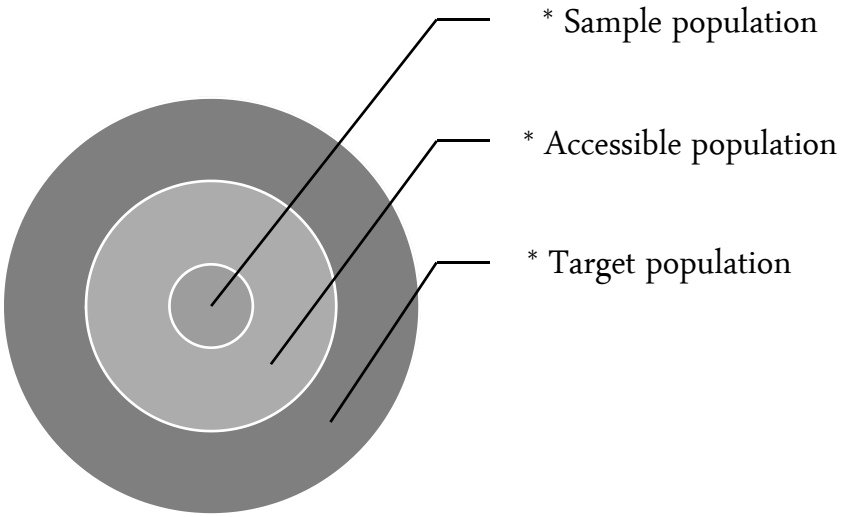


Figure 1 shows a representation of the target, accessible, and sample populations

The target population is defined as all people with the disease or the condition under investigation. The whole population on-which the study results will be applied.

The accessible population is part of the target population that is accessible for the research team, and they can work on it.

The sample population (also known as the study population) is the sample from the target population that is included in your research study. Usually, it is part of the accessible population.

Sampling methods in clinical research can be classified into two major categories: probability and non-probability sampling methods.

Probability sampling methods are sampling methods where the sample will be representative of the target population while in non-probability sampling methods,

the sample will NOT be representative of the target population. Each category includes sampling methods shown in the following diagram (Figure 2).

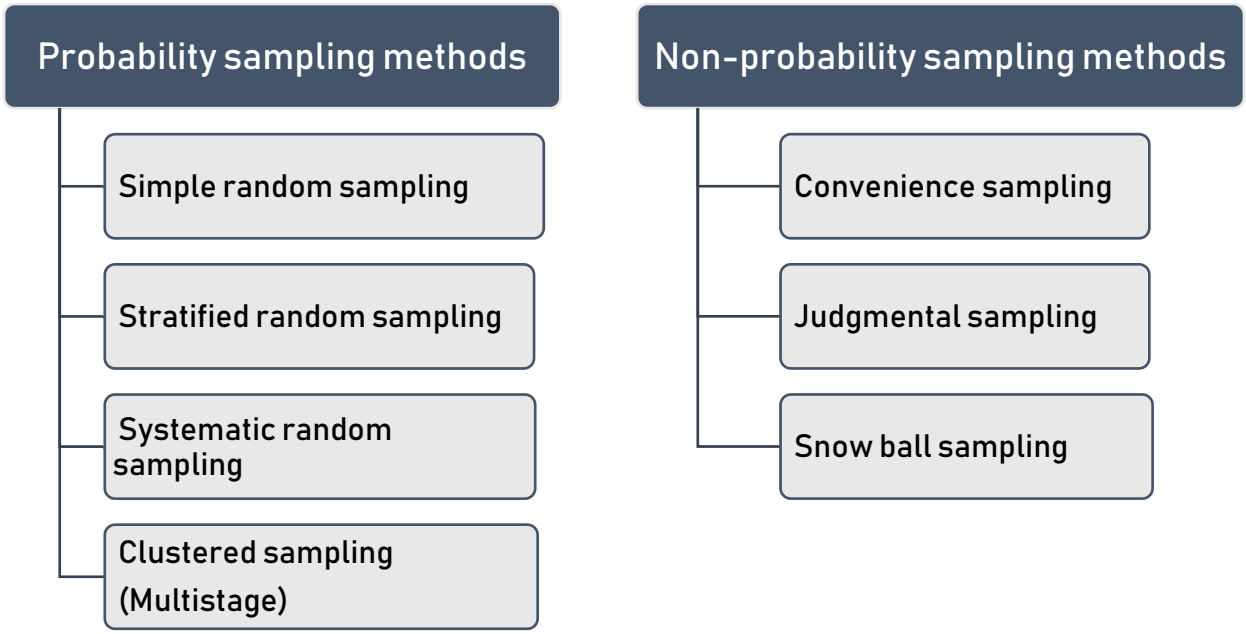


Figure 2 shows the types of probability and non-probability sampling methods

Simple Random Sampling

In simple random sampling, the researchers list the target population from A to Z (from the first to the last one) then select the required sample by simple randomization technique: computer software, random number generator, randomization tables, … etc.

Example

If we have 2000 medical students in our university and our sample size is 400 students, we will list those students alphabetically or randomly from the first to the last one. Then, we will draw 400 students randomly by using a random number generator.

Stratified Random Sampling

Stratified random sampling is the same as the simple random sampling, but the target population is classified according to one of the demographic characteristics into subgroups (strata). Then a random sample is drawn from each stratum (using the same simple randomization technique mentioned previously).

Example

In the previous situation, we want to divide the population according to their gender to males and females. Therefore, we will make a list of male students and another list of female students. A sample of 200 subjects will be drawn from each stratum, separately.

Systematic Random Sampling

In systematic random sampling, the whole population is listed from A to Z (from the first to the last one), and the researchers select subjects on a systematic basis mostly on fixed intervals. To determine these intervals, we divide the required sample size by the total number of the target population.

Example

In the same previous situation, we have 2000 medical students in our university, and our sample size is 400 students. Therefore we will calculate 400/2000 = 1/5, which means that we will select one from every five consecutive students in the list. The first student from is drawn randomly from the first five consecutive students by any simple randomization technique: random number generator, darts, coin tossing, ... etc. Then we add the fixed interval to get the other students in a systematic manner. If the first student (who was selected randomly) is the third one, we will select the third student from every five consecutive students or by another meaning; we will select students on fixed intervals (interval=5) starting from the student number 3 in the list. Therefore, we will include students numbered (3, 8, 13, 18, 23, 28, 33, 38, 43, 48, … till the end).

Clustered Random Sampling

In clustered random sampling, the target population is divided into clusters according to their geographical locations. Each cluster represents a center, hospital, city, or district. The researchers make a list of the clusters and select a random sample from these clusters. Then all population located in the selected clusters is listed from A to Z (from the first to the last one), and a random sample from this population is drawn using the simple randomization techniques mentioned previously. In this type of sampling, there are two randomizations. Therefore, it is sometimes called "multistage sampling method." The first randomization is done to randomly select clusters, then the second randomization is done to select subjects from the population of the selected clusters randomly.

Example

If we are conducting a study on medical students in Egypt, the target population will be all medical students enrolled in the 26 Egyptian universities. Assume our team can cover only seven from the 26 universities, and the required sample size is 3000 students. To employ a multistage random sampling method in this situation, we will first make a list of all 26 Egyptian universities (these universities are the clusters). Then we randomly select seven universities by one of the simple randomization techniques (first random selection). The next step is to retrieve the lists of all medical students enrolled in the 7 selected universities then make another random selection of the 3000 students by any of the simple randomization techniques (second random selection).

Convenience Sampling

It is one of the non-probability sampling methods where the researchers work on the population that is close to hand or easily accessible for them.

Example

In the same previous example, if we employ the convenience sampling method, we will hold a campaign in our university and recruit students who are available to join the study.

Judgmental sampling

In this technique, the researcher judge that a sample can be representative if it satisfies certain demographic criteria. Then, they select the subjects one-by-one to satisfy the criteria they specified. This type of sampling carries a high risk of bias since the whole selection process is based on the judgment of the investigator.

Snow ball sampling

This type of sampling method is not common in clinical research; however, it is common in social science research. This technique is used when the population cannot be located. We first identify one or more subject(s) from the population then gain access through them to other subjects from the population. Therefore, the sample increases over time, which resembles the snow ball that enlarges by moving forward.

Example

To study the mental and cognitive functions of homeless children, we will employ a snowball sampling method since this population is difficult to locate. The first step is to find one subject and ask him to join the study and to help us reach more

homeless children in the region. We will then ask every child to join the study and help us reach their colleagues and so on.

Notes on sampling methods

- To use the probability sampling methods, you should have a sampling frame, which means that you can locate the population and list them from the first to the last one.
- Since diseases are globally prevalent, and it is unlikely to find a database listing all population with a specific disease in a region, most clinical research studies are conducted based on a convenience sampling method.
- The convenience sampling method is the best non-probability sampling method.
- If the population has no sampling frame and cannot be located in a specific location, you can use the snowball sampling method.
- When selecting the sampling methods, the appropriate sampling method differs from one situation to another. The choice of the appropriate sampling method depends on the population location, accessibility, sampling frame, and the investigator preference in the study design.

Sampling methods	The assumptions of each method
Simple random sampling or Systematic random sampling	✓ The target population has a sampling frame ✓ Researchers can reach all the target population ✓ The target population can be located somewhere
Stratified random sampling	✓ The target population has a sampling frame ✓ Researchers can reach all the target population ✓ The target population can be located somewhere ✓ Researchers are willing to stratify the population
Clustered random sampling	✓ The target population has a sampling frame ✓ The target population can be located somewhere X Researchers can reach all the target population
Convenience sampling	X The target population has a sampling frame ✓ The target population can be located somewhere X Researchers can reach all the target population
Snowball sampling	X The target population has a sampling frame X The target population can be located somewhere X Researchers can reach all the target population

Chapter 14 **Ethics of Clinical Research**

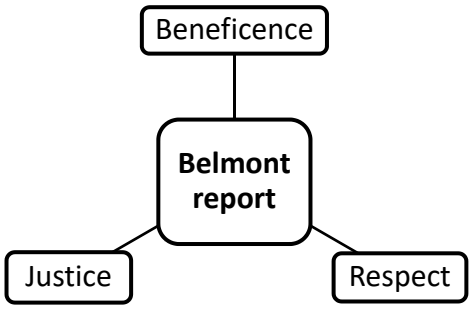
Historical Overview

Nuremberg Code of ethics (1947)

During the 2nd world war, Nazi doctors had done several crimes during human experiments on concentration camp prisoners. As a response of these Nuremberg Trials, the Nuremberg code of ethics was introduced in 1947 as a landmark document in the history of medical research ethics.

Belmont report (1976)[7]

The Belmont report was written by the national commission for the protection of human subjects of biomedical and behavioral research. It outlines three key ethical principles for conducting research with human subjects: respect for persons, beneficence, and justice.



Declaration of Helsinki

The declaration of Helsinki was adopted by the 18th general assembly of the world medical association in Helsinki, Finland, June 1964. It was amended several times in 1975, 83, 89, 96, 2000, 2002, 2004, 2008, and 2013. The declaration of Helsinki is currently the cornerstone of human research ethics in the world.

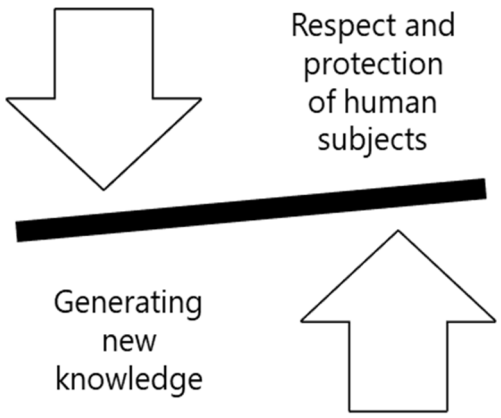
The key principals in the declaration of Helsinki

- DOH states the ethical principles of medical research involving human participants, human material, and human data.
- DOH is mainly directed to physicians and anyone who is involved in medical research on human subjects.
- Physicians main responsibility is the health of their patients, which comes in the first consideration. The International Code of Medical Ethics confirms that "A physician shall act in the patient's best interest when providing medical care."

[7] https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

- The purpose of medical research is to understand the causes, development, and effects of diseases and improve the preventive, diagnostic, and therapeutic interventions.
- All interventions must be evaluated continuously through research studies in order to ensure their safety and efficacy.
- Physicians are responsible for protecting the life, health, dignity, integrity, right of self-determination, privacy, and confidentiality of personal information of the research participants.
- Researchers should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration.
- Researchers who participate in medical research should be qualified ethically, educationally, and scientifically to do research. Research on healthy volunteers must be monitored by an approved and qualified physician.
- Underrepresented groups in the population should receive appropriate chances to participate in research.
- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.
- In medical research, investigators should reduce the risk to a minimum.
- Benefits should outweigh the harm.
- Research must be preceded by careful evaluation of predictable risks to patients, or healthy volunteers enrolled in the study.
- During the study, risks must be monitored and documented by the researcher.

- If risks are found to outweigh potential benefits, investigators should modify or stop the study
- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.



- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
- All vulnerable groups and individuals should receive specifically considered protection.
- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group, and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research.
- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
- The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
- In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.
- The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the

researcher, the sponsor, and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

- The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.
- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.
- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
- After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
- All medical research subjects should be given the option of being informed about the general outcome and results of the study.
- When seeking informed consent for participation in a research study, the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed

consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances, the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with the condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations, the research may be done only after consideration and approval of a research ethics committee.
- The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best-proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- And the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best-proven intervention.
- Extreme care must be taken to avoid abuse of this option.
- In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.
- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
- Researchers, authors, sponsors, editors, and publishers all have ethical obligations about the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
- In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, reestablishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Patient rights

- Autonomy
- Informed consent
- Beneficence
- Non-maleficence
- Justice
- Confidentiality

Informed Consent

Consent involves the procedure by which an individual may choose whether to participate in a research study or NOT.

Direct Consent	Substitute (Third Party) Consent
• Agreement obtained directly from the person involved in the study • Most preferred	• Given by someone other than the person involved in the study • When? A person not having the capacity to make decisions or is dependent on others for his welfare. • Who? Children People with cognitive or emotional disabilities.

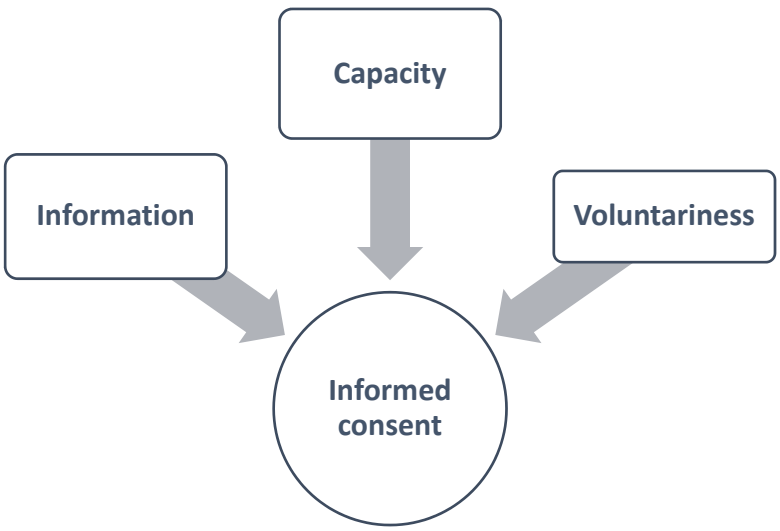
Elements of the informed consent

[1] Capacity

The patient/ person involved should have the capacity to evaluate the information received and make his own choice based on his evaluation

Is the person competent or incompetent?

This is based on his ability to acquire, retain and evaluate information



Incompetent Persons

- Children
- Patients with cognitive or emotional disabilities
- Incarcerated patients

Rights are legally protected by obtaining permission from parents or legal guardians

[2] Information

- What is the information given?
- How was it presented?

The information must be planned and presented by the researcher in a way, making it fully understandable by the participant.

[3] Voluntariness

The free power of choice without intervention of force or threat

Chapter 15 Data Collection Methods

Methods of data collection

Survey forms

Most of the observational epidemiologic studies rely on survey forms. In these studies, patient's information (i.e., depression assessment by HDRS) can be assessed and obtained through the standard questionnaires. Information that can be collected through this method includes sociodemographic characters, lifestyle practices, medical history, medications, knowledge, and attitudes towards something, qualify of life, depression, anxiety, cognition, functional status, and other psychological outcomes that should be assessed by standard questionnaires.

→ Questionnaires can be administered using the following methods

(1) self-administrated

(2) interviewer-administrated in a personal interview

(3) interviewer administrated in a phone call

(4) interviewer-administrated by email or on the internet.

→ Types of questions in surveys

(1) Yes or No questions

(2) Likert type scale (i.e., strongly agree, agree, neutral, disagree, strongly disagree)

(3) interviewer administrated in a phone call

(4) interviewer-administrated by email or on the internet.

The use of validated, standard instruments is strongly recommended in medical research. These tools are better than home-grown scales developed by the research team themselves. It is important to utilize the standard instruments whenever possible; however, if such instruments do not exist, the investigators can develop their own instrument (questionnaire).

→ Requirements to design a home-grown questionnaire

(1) It should be developed by a meeting of experts in the field including a psychometrician

(2) It should be validated against the gold-standard diagnosis

(3) The reliability should be assessed in the population

(4) Before utilizing the tool, it should be piloted in the population

Proxy or informant data

Proxy respondents is a challenging method for data collection in medical research because the accuracy and validity of those respondents should be taken into account. In addition, their knowledge about health-related issues might be different from the study participant and might be variable across the study sample.

However, in some conditions, the investigators must get the required information through proxy respondents. For example, to assess the quality of life of children, researchers have to supply the quality of life domains by his parents. Similarly, patients who have psychological or mental problems can not provide information about their life or health by themselves. Alternatively, their guardian or family act as a source of this information.

Hospital medical records

Hospital records is a widely-available source of data that can be used in research. Hospital records usually include several high-quality data. Therefore, it can be a reliable source to run a clinical study. The decision to rely on patient data should be taken by the investigators during the planning phase (step #4 planning and protocol development) and the decision depends on whether the information in the hospital records are sufficient to run the study, whether it can provide the required sample size, whether the data are recorded in a standardized manner, and whether the data include the full information about the confounding variables.

In any situations, hospital records can be frustrating and confusing since this information was not recorded, abstracted, and deposited in a standardized manner. Various healthcare professional in the same hospital can use different terms or different annotations to describe a specific event or condition. In addition, hospital data might be too old that the current definitions of diseases, their classification, and side effects nowadays might be different from the time when these data were recorded. Moreover, hospital records might be incomplete in some variables, some patient data might be missing, and other variables might be conflicting. It is very important that the research team screen, validate, and assess the quality of the data in the hospital records before deciding whether they can rely on it.

Biological material

Several clinical and translational research studies involve the collection of biological material from the study participants. This might include saliva, urine samples, blood samples, or hair. Biologic materials provide information that will be helpful to obtain information about the genetic factors implicated in the disease and to understand the

pathophysiology of the diseases as well as the physiologic response to some drugs. Investigators who decide to collect biological materials from the study participants must keep an eye on several factors as follows:

(1) Is this specimen invasive?

(2) How often will they have to repeat this specimen?

(3) Does the timing of specimen collection affect the assessed markers?

(4) What is the cost of this specimen?

(5) If they design a multicenter study, the specimen protocol and analysis must be standardized across the study centers to avoid possible errors.

What are the CRF, eCRF, and DDC?

Case Report Forms (CRF)	Paper CRFs are designed for handwritten data. They are cheap to produce and allow the creation of direct copies and faxing. New technology such as optical character recognition allows computers to 'read' the data written by site staff and enter them automatically into a database.
Electronic Case Report Forms (eCRFs)	Electronic CRFs are becoming more and more popular. However, they are much more complicated to produce and need to adhere to strict regulations in Europe and the United States. The computer programs or software must be validated, and every correction that is made to the data entered must be traceable. They must ensure that only authorized persons have access to the program and to the data. Data backups must occur regularly and automatically. Using eCRFs in a study requires all investigator sites to have sufficient and reliable access to computers and the internet. It also requires intensive training of the site staff using the eCRF, which must often also be supported by a help-desk.
Direct Data Capture (DDC)	▪ Laboratory data ▪ Electrocardiogram (ECG) data ▪ Central image reading (Magnetic Resonance Imaging (MRI) results) ▪ Electronic patient questionnaires / diaries

How data are managed in Clinical Research

Starting from data collection until database locking and making it readily available to the statisticians for analysis, study data pass through the following steps:

(1) Data collection

(2) CRF tracking

(3) CRF annotation

(4) Database design

(5) Data entry

(6) Medical coding

(7) Data validation

(8) Discrepancy management

(9) Database lock

Chapter 16 **Bias and Errors**

Random Error

Random error occurs when the recorded value measured by the scale or the device is different from the true value. This error occurs in a random manner. For example, we measure the weight of the patient 3 times using the same scale, and it gives 78.5, 78.6, and 78.4 kg. This type of error might be acceptable in clinical research, and we can overcome it by using the average of all measurements.

Systematic Error

The systematic error occurs when the error takes care in a systematic manner. For example, the scale records 70 kg as a too big value for all the weight measures due to calibration problems. This type of error is NOT acceptable in clinical research.

Bias

Bias is a systematic error in the research methods that leads to skewing the results in a specific direction.

Types of Bias

→ Selection bias

Selection bias is caused by differences in the baseline characteristics of the study group. This difference might be attributed to weak methods of sequence generation or bias introduced during the allocation to the treatment group. The random sequence generation and patient allocation processes are the two steps where selection bias might be introduced. Therefore, to examine the risk of selection bias, we revise the methods used to generate the random sequence and the methods of allocating patients to the treatment groups "allocation concealment."

→ Self-selection bias

It occurs when you let the study participants select themselves to join the study. For example, a survey was sent by email to all physicians registered in your hospital to assess the impact of workload on a physician's anxiety and depression. This survey is likely to be filled and submitted by physicians who have some free time to access their emails and submit the survey. Physicians who are pressured in the workload of the clinic are likely to be excluded from this sample.

→ Performance bias

Performance bias is caused by the difference between the two groups in the level of care, physician treatment, or exposure to risk factors. Blinding of patients and study personnel is important to reduce the risk of performance bias in randomized controlled trials.

→ Detection bias

Detection bias is caused by the difference between the two groups in the outcome measurement. Outcome assessors might unintentionally overestimate or underestimate patient outcomes during the assessment in the experimental or control groups. Blinding of outcome assessors is important to reduce the risk of detection bias.

→ Observer bias

It occurs when outcome assessments are systematically influenced by the assessors' conscious or unconscious predispositions. Assessors might make a biased observation and evaluation because of hope or expectations, often favoring the experimental intervention.

→ Attrition bias

Attrition bias refers to the difference between the two groups in withdrawals. Since patients were randomly allocated to the treatment groups, these groups are balanced for many known and unknown confounders. The presence of patients in their groups maintains this balance in confounders. Therefore, a substantial loss of patients from the study or a difference between the two groups in withdrawals will introduce bias to the data and allowing for confounding variables to influence the study outcomes.

→ Reporting bias

Reporting bias refers to a condition where the authors tend to report some outcomes and hide other outcomes. This might be in the form of (1) reporting statistically significant results and not reporting non-significant outcomes, (2) measuring several outcomes and reporting favorable outcomes only, (3) reporting the planned outcomes using an assessment tools/scores other than the planned per protocol.

→ Zero-time Bias

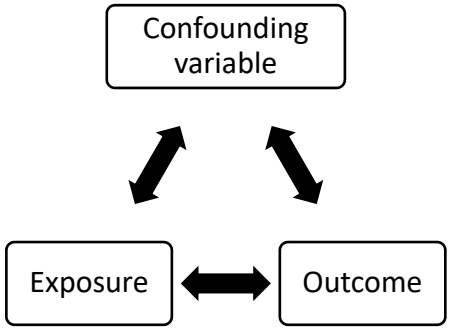
In prospective studies, the study participants might be exposed to the risk factor at different time points. For example, in a cohort study assessing the impact of smoking on the risk of lung cancer. It is likely that the study participants have started smoking at different times. This difference might be a source of bias, especially if the outcome of interest is affected by the duration of exposure to the risk factor.

→ Confounding Bias

A confounding variable is a variable that makes the exposure more likely as it is associated with the exposure but not with the outcome. Due to its association with the true risk factor, this variable can appear as if it is associated with the outcome when there is no true association between it and the outcome; the true association is between the exposure to the true risk factor and the outcome.

Example 1, early studies suggested an association between drinking coffee and cancer of the head of the pancreas. While the actual relationship was between Alcohol consumption and cancer of the head of the pancreases. In this example, coffee is a confounding variable that was an association with alcohol drinking; people who drink alcohol are likely to drink coffee as well. However, the true risk factor for the disease was Alcohol and coffee drinking is regarded as a confounding variable.

Example 2, early studies suggested a beneficial effect of hormone replacement therapy in cardiovascular disease. When these studies were repeated with adjusting (balancing) the socioeconomic status and education of the two study groups, researchers found no benefit for HRT in cardiovascular disease. Results of the early study could be explained that patients with a high socioeconomic level and good education are more likely to care about their health and use HRT while patients with a low socioeconomic level and education were not likely to use HRT. The true relationship was between high socioeconomic level/good education and good cardiovascular health, but the relationship falsely appeared as if it was between HRT and the better cardiovascular profile, which is not correct. In this example, HRT is a confounding variable.



→ Recall bias

It occurs when participants do not remember previous events or experiences accurately or omit details: the accuracy and volume of memories may be influenced by subsequent events and experiences. Recall bias is a problem in studies that have self-reporting, such as case-control study and retrospective cohort studies.

→ Survivorship bias

It occurs when the researcher focuses only on that part of the data set that already went through a pre-selection process and missing those data-points, that fell off during this process (because they are not visible anymore).

→ Cause-effect bias

Our brain is wired to see causation everywhere that correlation shows up.

→ Funding bias

It happens when the results of a scientific study are biased in a way that supports the financial sponsor of the research.

Chapter 17 **Sample Size Calculation**

Calculating the sample size is an important step when planning your research study. The aim of this chapter is to explain the requirements and procedures of sample size calculation for various types of clinical research studies with examples and case scenarios.

Before discussing the requirements and procedures of sample size calculation, it is important first to answer five questions:

(1) What is the meaning of "effect size" or "effect estimate"?
(2) Why do we need a "sample" in clinical research?
(3) What makes a good sample?
(4) What are the sampling methods in clinical research?
(5) What is the meaning of "statistical power"?

Question 1: What is the meaning of "effect size" or "effect estimate"?

Effect estimate or effect size (ES) is the quantitative expression about the magnitude of an effect or phenomenon. The ES is a comprehensive term covering all quantitative measures in-which the effect can be expressed. Therefore, ES includes the mean difference (MD), odds ratio (OR), relative risk (RR), the hazard ratio (HR), prevalence rate, correlation coefficient (r), … etc.

Examples

- In a cross-sectional study to find the prevalence of diabetes mellitus in the Egyptian population, the ES is expressed as the prevalence ratio.
- In a case-control study assessing the association between smoking and lung cancer, the ES is expressed as OR.
- In a clinical trial comparing two anti-hypertensive drugs, the ES is expressed as the MD between the two drugs in lowering the arterial blood pressure.
- In a study comparing two anti-cancer drugs, the ES is expressed as HR of overall survival between the two groups.

Question 2: Why do we need a sample in clinical research?

See the chapter of sampling methods

Question 3: What makes a good sample?

See the chapter of sampling methods

Question 4: What are the sampling methods in clinical research?

See the chapter of sampling methods

Question 5: What is the meaning of statistical power?

Statistical power is the ability of the sample to represent the expected effect estimate. To understand the meaning of statistical power, assume that we are conducting a study to investigate the prevalence of depression among medical students of Zagazig University. Assume that the expected prevalence of depression among this population is 20% based on the estimates of previous studies.

Now, we will assume some sample sizes and look at the probabilities that we can obtain regarding student depression. Firstly, assume we have conducted this study on one student. Therefore, we will have two probabilities: If the student has depression, the prevalence ratio will be 100%. If not, the prevalence ratio will be 0%.

- Therefore, if we have a sample of one student n=1, this sample will be able to represent the estimates of 0% and 100%.
- If we add one more student, the sample will be n=2. This sample can represent the estimates of 0%, 50%, and 100%.
- If we add one more student, the sample will be n=3. This sample can represent the effect estimates of 0%, 33.3%, 66.6%, and 100%.
- If we add one more student, the sample will be n=4. This sample can represent the effect estimates of 0%, 25%, 50%, 75%, and 100%.
- If we add one more student, the sample will be n=5. This sample can represent the effect estimates of 0%, 20%, 40%, 60%, 80% and 100%.

n=1	0% - 100%
n=2	0% - 50% - 100%
n=3	0% - 33% - 66% - 100%
n=4	0% - 25% - 50% - 75% - 100%
n=5	0% - 20% - 40% - 60% - 80% - 100%

Here, we found that a minimum sample of 5 students can represent the expected effect estimate (a prevalence ratio of 20%). However, the probability of finding depression by chance in one out of five students is about 20%! Therefore, this number (n=5) is replicated in the sample size calculation equations till we obtain a large sample with high ability to represent the effect estimate and with a small probability of chance (about 5%).

Requirements of sample size calculation

To calculate the sample size of your clinical research study, you need to know the following:

The main hypothesis of the study

Researchers sometimes plan for primary and secondary objectives and therefore, have primary and secondary endpoints for their studies. Sample size calculation procedure should be based on the primary endpoint (the main objective of the study).

The design of your study

Although sample size estimation is a statistical calculation method, understanding the design of your study will help you identify the relevant calculation method. If you want to calculate the sample size for a case-control study, it is important to know whether this study has an independent or matched design.

Expected ES

Sample size should be calculated based on an approximate estimate for the outcome of interest. This expected estimate can be obtained from (1) previous literature, (2) pilot study, (3) expert opinion, or (4) the minimum clinically important difference (MCID).

The desirable statistical power

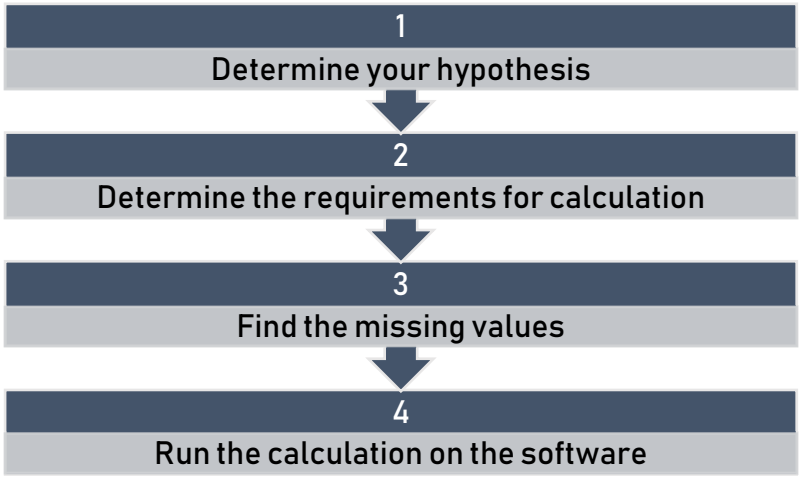
In clinical research, the minimum acceptable statistical power to use in 80%. Therefore, we can calculate the sample size based on a power of 80%, 85%, or 90%.

The acceptable margin of error (alpha)

In clinical research, the acceptable alpha level in sample size calculation is 5% except in non-inferiority and equivalence studies where the alpha level is assumed to be 2.5%.

Steps of sample size calculation

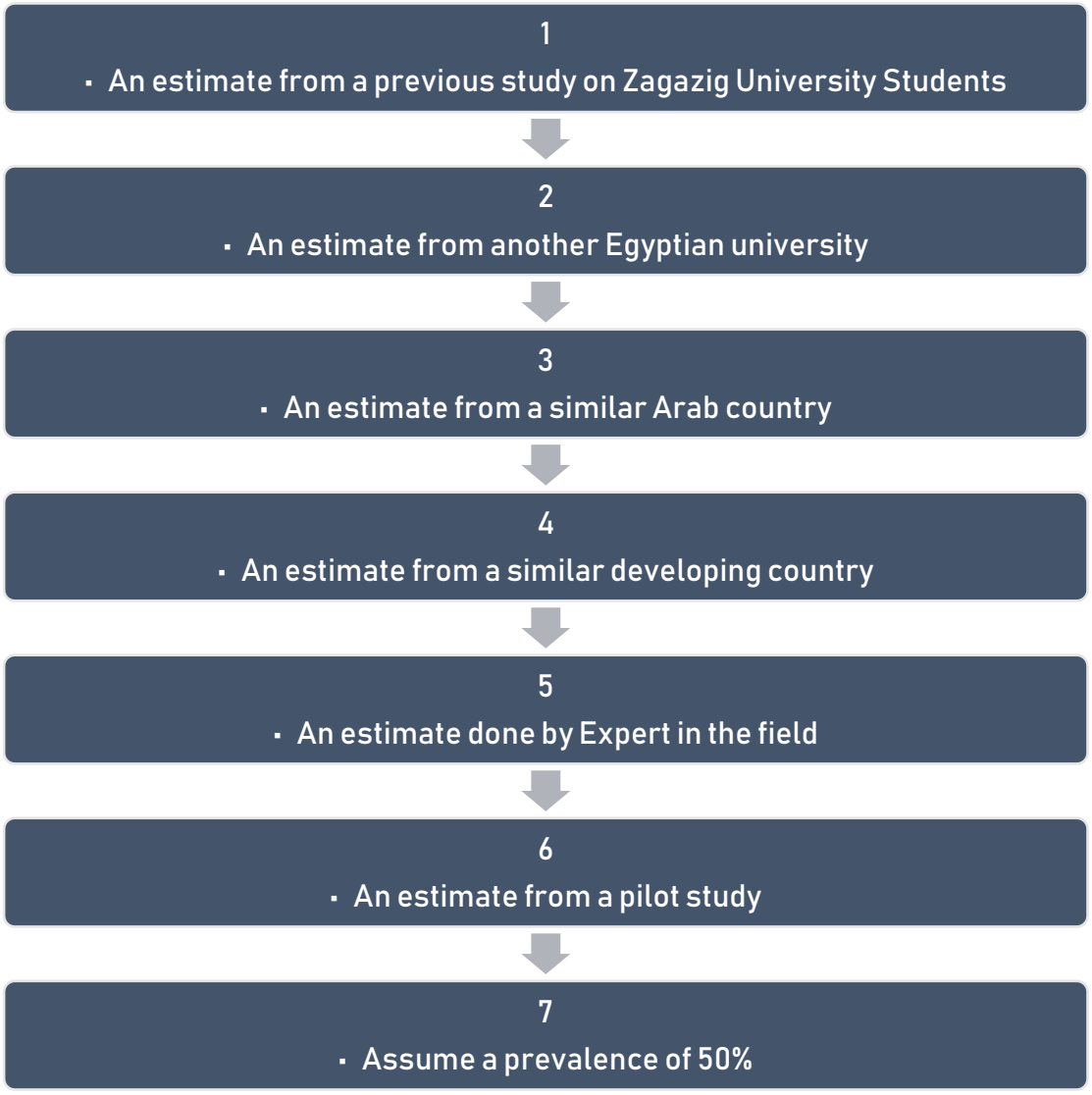
The following diagram shows the general steps of sample size calculation


1
Determine your hypothesis
2
Determine the requirements for calculation
3
Find the missing values
4
Run the calculation on the software

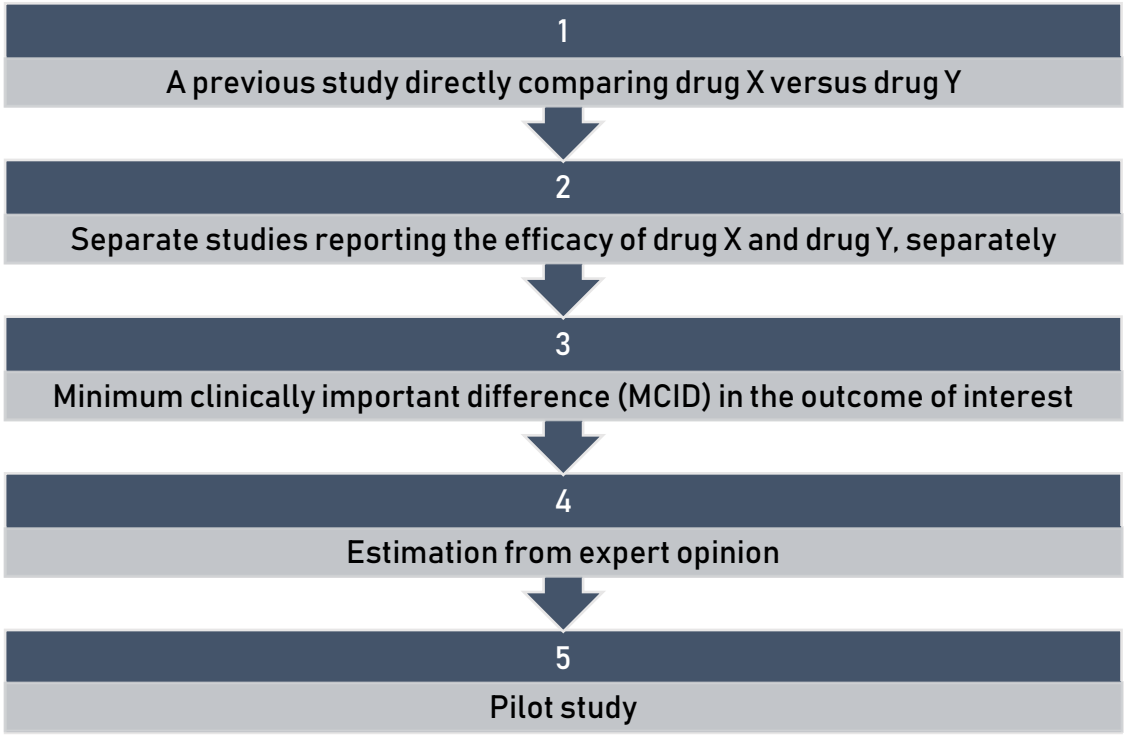
How to Think about ES for sample size calculation

One of the most challenging steps for researchers is to determine the expected ES that will be used for sample size calculation. Hereby, we provide an example of how to think in such scenarios.

If we are planning for a study about depression among medical students of Zagazig University, we will think about the ES as shown in the following diagram.



If we are intending to compare drug X versus drug Y in a superiority clinical trial, then we will think about ES estimation according to the following flow diagram.



Sample size calculation for prevalence (population surveys)

Requirements

(1) Population size
(2) Expected prevalence
(3) Accepted deviation from the prevalence
(4) Confidence interval

Equation

$$n = \frac{z^2 p(1-p)}{d^2}$$

Steps on Statsdirect®

(1) Open a new report
(2) From "analysis" menu, select "sample size."
(3) Then select "population survey."

Steps on R software®

(1) Write the command "SampleProportionCI(P, 2d, CI)"
(2) Press "Enter"

Steps on Epiinfo software®

(1) Open the software and select "STATCALC."
(2) Select "population survey."
(3) Put the data and check the table

Case Study of Type 2 Diabetes Mellitus in HIV patients

You are conducting a cross-sectional study to estimate the prevalence of diabetes mellitus type II in HIV patients. Data from the literature suggest that a prevalence rate of 15.1%, according to Duncan et al. Calculate the required sample size to detect similar ES.

Case reference

Duncan AD, Goff LM, Peters BS (2018) Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. PLoS ONE 13(3): e0194199.

Case solution

1. Determine the type of hypothesis: sample size based on the proportion

2. Determine the requirements:
- Population size =?
- Expected ES (expected proportion) = 15.1%
- Deviation from the expected proportion =?
- Confidence Level =?

3. Estimate the required values
- Population size: According to the UNAIDS, the estimated number of people living with HIV in Egypt was 7,439 in 2013.
- Deviation from the expected proportion = unknown (assume 3%)
- Confidence interval = 95%

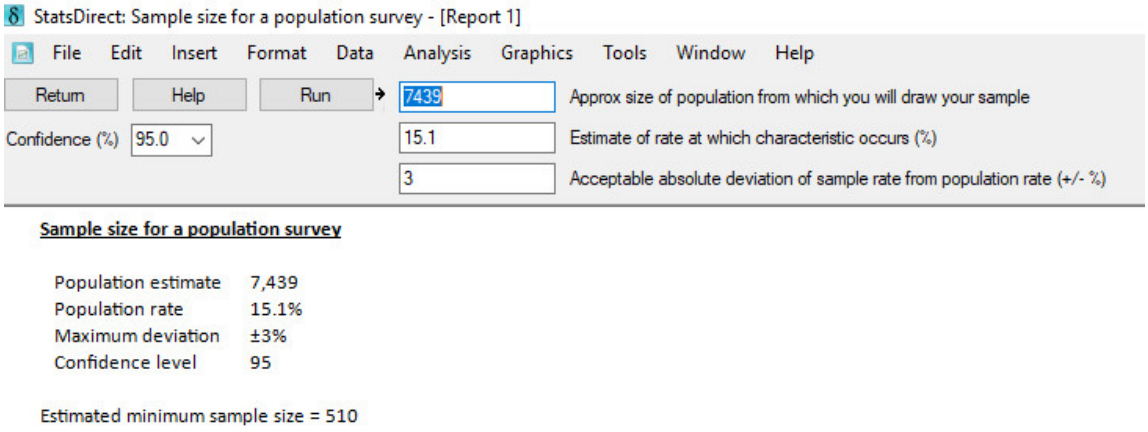
4. Run the calculations

- On R software

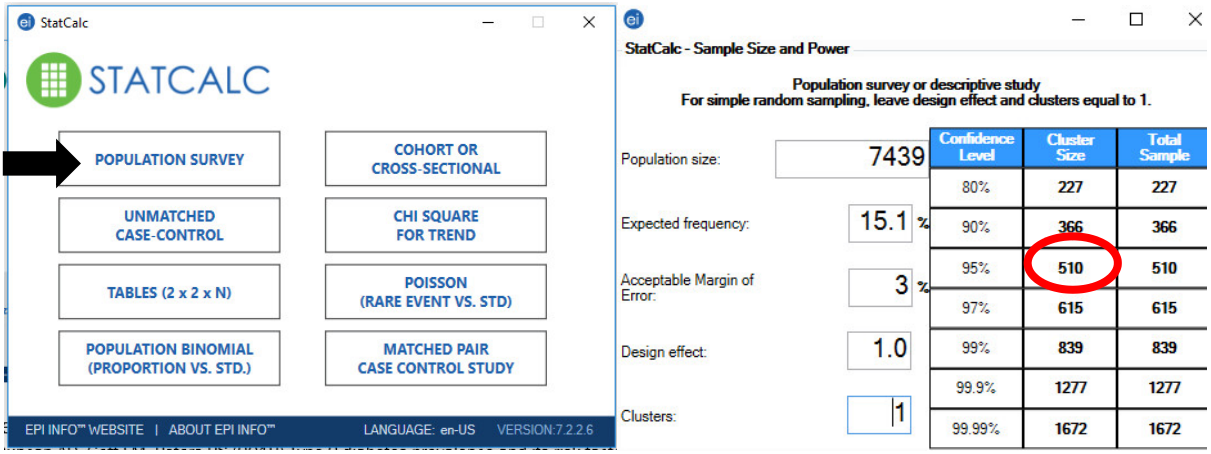
```
> SampleProportionCI(0.151, 0.06, 95)
                      Assumptions
P                           0.151
Confidence interval          0.06
Confidence level             0.95

                         Estimated
Required sample size           548
```

- On Statsdirect



- On Epiinfo


StatCalc
STATCALC
POPULATION SURVEY
COHORT OR CROSS-SECTIONAL
UNMATCHED CASE-CONTROL
CHI SQUARE FOR TREND
TABLES (2 x 2 x N)
POISSON (RARE EVENT VS. STD)
POPULATION BINOMIAL (PROPORTION VS. STD.)
MATCHED PAIR CASE CONTROL STUDY
EPI INFO™ WEBSITE | ABOUT EPI INFO™
LANGUAGE: en-US
VERSION:7.2.2.6
StatCalc - Sample Size and Power
Population survey or descriptive study
For simple random sampling, leave design effect and clusters equal to 1.
Population size: 7439
Expected frequency: 15.1 %
Acceptable Margin of Error: 3 %
Design effect: 1.0
Clusters: 1
Confidence Level
Cluster Size
Total Sample
80% 227 227
90% 366 366
95% 510 510
97% 615 615
99% 839 839
99.9% 1277 1277
99.99% 1672 1672

Sample size calculation for Independent case-control studies

Calculation requirements

(1) The expected odds ratio of exposures between cases vs. controls
(2) Probability of exposure in cases
(3) Probability of exposure in controls
(4) Statistical power
(5) Alpha
(6) Number of controls per subject in the cases group

If you have the odds ratio (OR), you will not need the probability of exposure in cases and vice versa. Only one input of them is required.

Calculation Steps on Statsdirect®

(1) Open a new report
(2) From "analysis" menu, select "sample size."
(3) Then select "independent case-control study."

Case study of the association between vitamin D deficiency and Hashimoto's Thyroiditis

You are conducting a case-control study to investigate the association of vitamin D deficiency and Hashimoto's Thyroiditis. The most recent relevant study in Egypt was done by Bakr et al. where they found that the prevalence of vitamin D deficiency was 76.6% in Hashimoto's Thyroiditis group and 20% in the healthy control group.

Calculate the required sample size to detect similar ES.

Case reference

Bakr, H. G., & Meawed, T. E. (2017). The relevance of 25 (OH) Vitamin D deficiency on Hashimoto's Thyroiditis. The Egyptian Journal of Immunology, 24(2), 53–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29528579

Case solution

1. Determine the type of hypothesis: sample size for case-control study – based on proportions in the case and the control group
2. Determine the requirements
   - The expected odds ratio of exposures between cases vs. controls: NA
   - Probability of exposure in cases = 76.6%
   - Probability of exposure in controls = 20%
   - Statistical power = 80%, 85%, or 90%

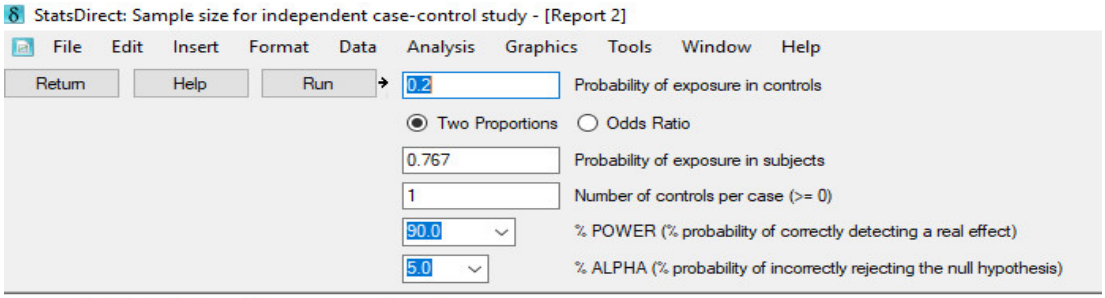
- Alpha = 5%
- Number of controls per subject in the cases group = 1

3. Estimate the required values

No further estimations are required. Here, we have the probability of exposure in cases. Therefore, we do not need to get the OR of the association.

4. Run the calculations

- On Statsdirect software



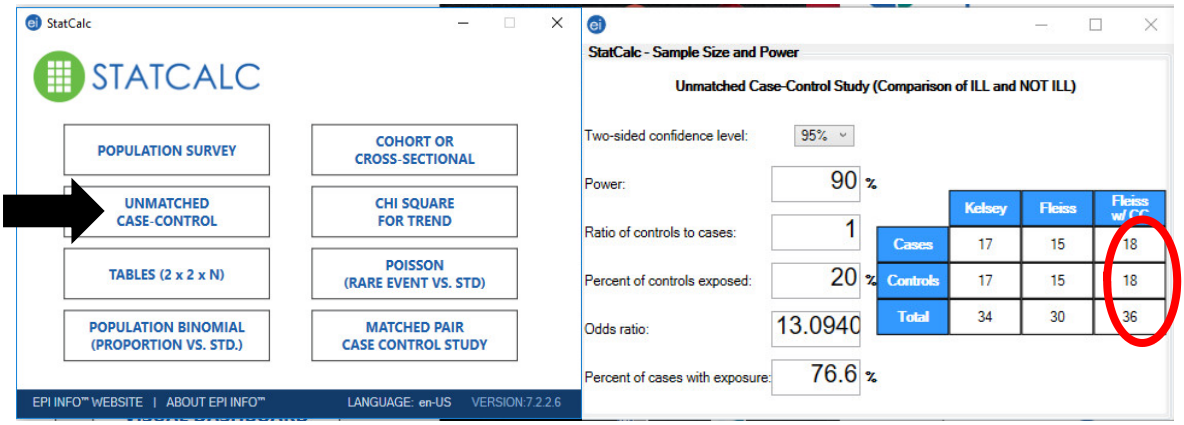
Sample size for independent case-control study

Probability of exposure in controls = 0.2
Probability of exposure in cases = 0.767
Controls per case subject = 1
Alpha = 0.05
Power = 0.9

For uncorrected chi-square test:
N = 15 case subjects and 15 controls

For corrected chi-square and Fisher's exact tests:
N = 19 case subjects and 19 controls

- On Epiinfo software



Sample size calculation for Independent cohort studies

Requirements

(1) Expected relative risk (RR) between exposed vs. non-exposed
(2) Probability of event in the exposed group
(3) Probability of event in the non-exposed group
(4) Statistical power
(5) Alpha
(6) Number of controls per subject in the exposed group

If you have the relative risk (RR), you will not need the probability of an event in the exposed group and vice versa. Only one input of them is required.

Calculation Steps on Statsdirect®

(4) Open a new report
(5) From "analysis" menu, select "sample size."
(6) Then select "independent cohort study."

Case Study of congenital CMV infection and HIV Perinatal Transmission

You are conducting a cohort study to investigate the association between congenital CMV infection and HIV Perinatal Transmission. A recent study by Adachi et al., they reported that among 89 HIV-infected infants, 16 (18%) had CMV versus 42 (4.9%) of 858 HIV-exposed, uninfected infants (p <0.0001).

Calculate the required sample size to detect similar ES.

Case reference

Adachi, K., Xu, J., Ank, B., Watts, D. H., Camarca, M., Mofenson, L. M., … NICHD HPTN 040 Study Team. (2018). Congenital CMV and HIV Perinatal Transmission. The Pediatric Infectious Disease Journal. https://doi.org/10.1097/INF.0000000000001975

Case solution

1. Determine the type of hypothesis: sample size for unmatched cohort study – based on proportions in the case and the control group
2. Determine the requirements
   - Expected relative risk of an event between exposed vs. non-exposed: NA
   - Probability of event in the exposed group = 18%
   - Probability of event in the non-exposed group = 4.9%
   - Statistical power = 80%, 85%, or 90%

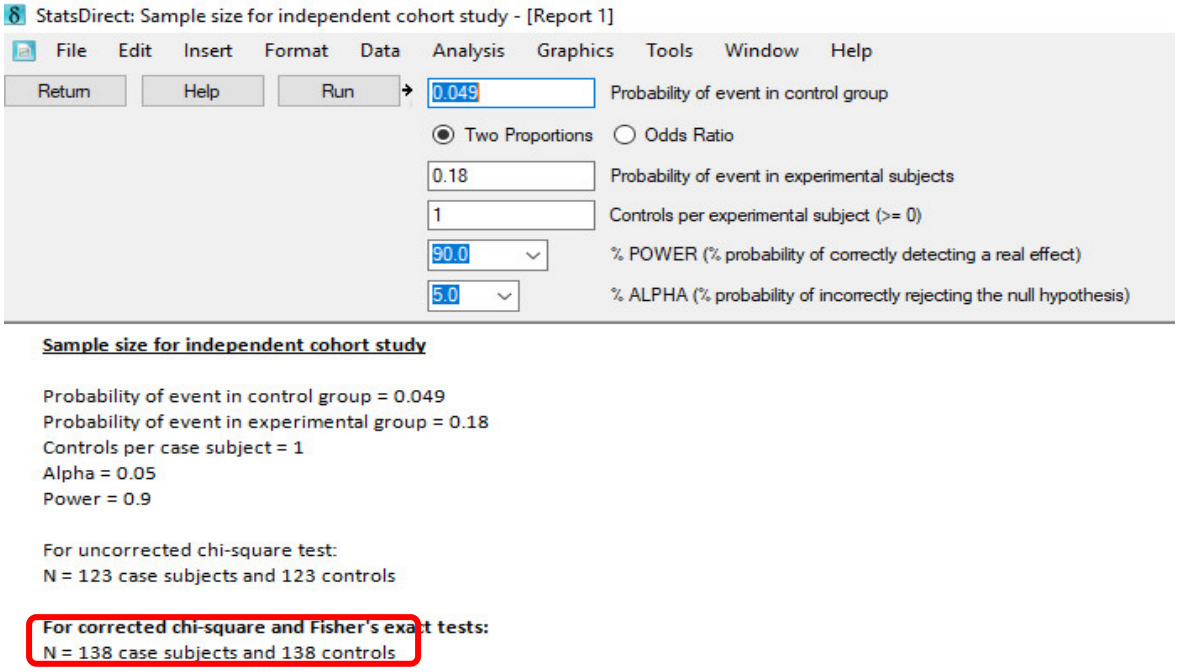
- Alpha = 5%
- Number of controls per subject in the exposed group

3. Estimate the required values

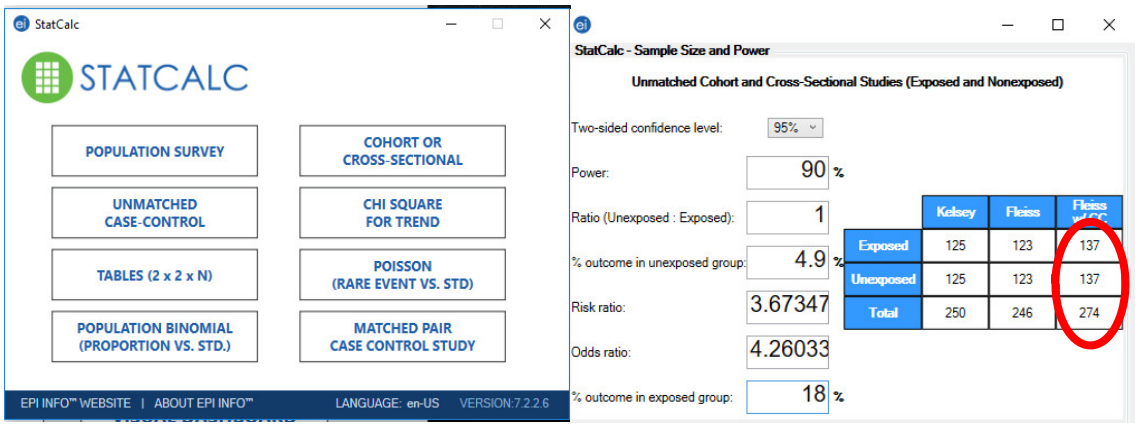
No further estimations are required. Here, we have the probability of event in the exposed group. Therefore, we do not need to obtain the RR of the association.

4. Run the calculations

- On Statsdirect software



- On Epiinfo software



Sample size calculation for matched case-control studies

Requirements (as independent case-control + correlation coefficient)

(1) The expected odds ratio of exposures between cases vs. controls
(2) Probability of exposure in cases
(3) Probability of exposure in controls
(4) Statistical power
(5) Alpha
(6) Number of controls per subject in the cases group
(7) The correlation coefficient (ϕ) for exposure between matched cases and controls

If you have the odds ratio (OR), you will not need the probability of exposure in cases and vice versa. Only one input of them is required.

Calculation Steps on Statsdirect®

(7) Open a new report
(8) From "analysis" menu, select "sample size."
(9) Then select "matched cohort study."

Case study of the association between maternal illiteracy and low birthweight in term pregnancies

You are conducting a matched case-control study to investigate the association between maternal illiteracy and low birthweight in term pregnancies.

A recent matched case-control study by Habib et al. was conducted in rural Pakistan. They reported adjusted OR of illiteracy (aOR: 2.68; 95% CI: 1.59 to 4.38), and the following table was reported regarding maternal education in the cases vs. controls.

Table 2 **Sociodemographic and maternal characteristics of cases and controls (*n* = 950)**

Variables	Cases (*n*)	%	Controls (*n*)	%
Maternal education (years of schooling)				
Illiterate	297	62.5	208	43.8
Primary or less (1–5)	77	16.2	89	18.7
Middle (6–8)	41	8.6	79	16.6
Matric (9–10)	35	7.4	48	10.2
Intermediate and above (>10)	25	5.3	51	10.7

Calculate the required sample size to detect similar ES.

Case reference

Habib, M. A., Greenow, C. R., Ariff, S., Soofi, S., Hussain, A., Junejo, Q., … Black, K. I. (2018). Factors associated with low birthweight in term pregnancies: a matched case-

control study from rural Pakistan. Eastern Mediterranean Health Journal = La Revue de Sante de La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit, 23(11), 754–763.

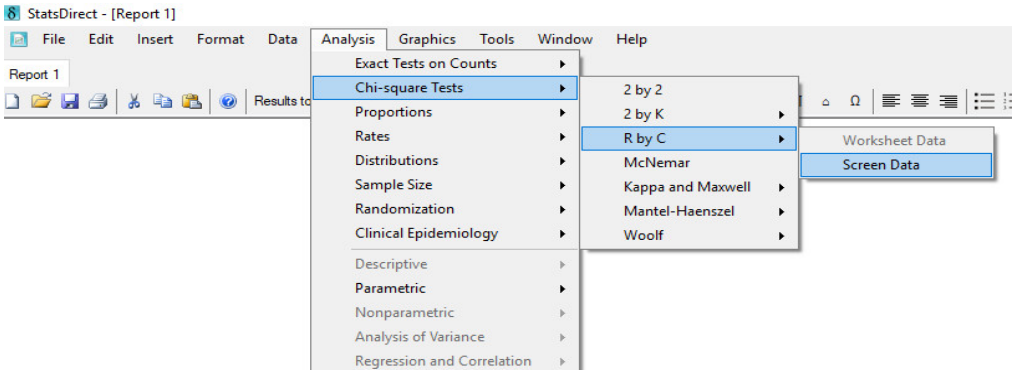
Case solution

1. Determine the type of hypothesis: sample size for matched case-control study – based on proportions in the case and the control group or OR
2. Determine the requirements
   - The expected odds ratio of exposures between cases vs. controls = 2.68
   - Probability of exposure in cases = ?
   - Probability of exposure in controls = ?
   - Statistical power = 80%, 85%, or 90%
   - Alpha = 5%
   - Number of controls per subject in the cases group = 1
   - Correlation coefficient (ϕ) between matched cases and controls = ?
3. Estimate the required values

The following items are missing (require estimation):

- Probability of illiteracy in cases = 297/475 = 62.5% (In Pakistan)
- Probability of illiteracy in controls = 208/475 = 43.8% But this estimate is from rural Pakistan; therefore, this estimate should be changed according to our study place (Egypt). In Egypt, the average rate of women illiteracy is 33.6%, according to the Central Agency for Public Mobilization and Statistics (CAPMAS).
- The correlation coefficient (ϕ) between matched cases and controls = ?

In the previous study, the authors did not report the correlation coefficient of the exposure between the cases and control groups. We can be calculated by the cross-tabulation function in Statsdirect. From "analyze," select "Chi-square test," then "R by C", then "screen data".

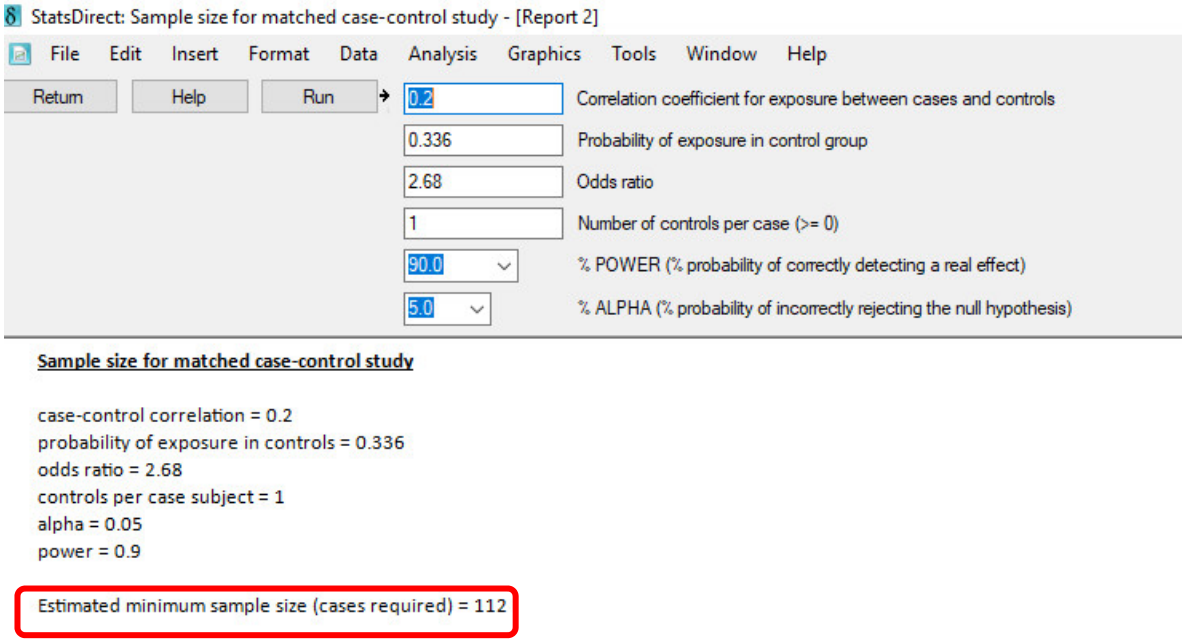


In the table, you should put the data of the distribution of maternal education subgroups in the cases and control groups.

	Cases	Controls
Illiterate	297	208
Primary	77	89
Middle	41	79
Matric	35	48
Intermediate or above	25	51

These data will give a correlation coefficient of 0.2 #

4. Run the calculations



Sample size calculation for Paired cohort studies

Requirements (as independent cohort study + correlation coefficient)

(1) The expected relative risk of the event between exposed vs. non-exposed
(2) Probability of event in the exposed
(3) Probability of event in the non-exposed
(4) Statistical power
(5) Alpha
(6) The correlation coefficient (ϕ) for events between matched subjects

If you have the relative risk (RR), you will not need the probability of an event in the exposed group and vice versa. Only one input of them is required.

Calculation Steps on Statsdirect®

(1) Open a new report
(2) From "analysis" menu, select "sample size."
(3) Then select "paired cohort study."

Case study of the long-term mortality in burn survivors

You are conducting a paired cohort study of long term morality among burn survivors. In a recent matched cohort study by Mason et al., the five-year morality rates were: 995/1965 for the burn survivors group and 4065/8671 for the control group.

Calculate the required sample size to detect similar ES.

Case reference

Mason, S. A., Nathens, A. B., Byrne, J. P., Diong, C., Fowler, R. A., Karanicolas, P. J., … Jeschke, M. G. (2018). Increased Rate of Long-term Mortality Among Burn Survivors: A Population-based Matched Cohort Study. Annals of Surgery.

Case solution

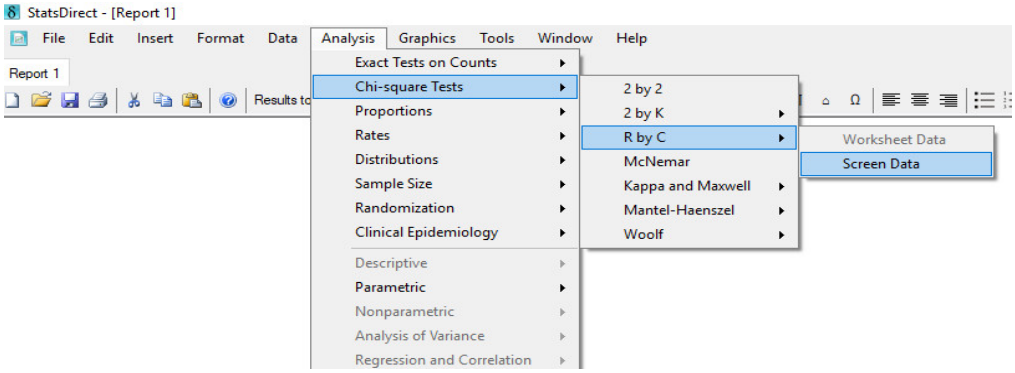
1. Determine the type of hypothesis: sample size for matched cohort study – based on proportions in the case and the control group or OR
2. Determine the requirements
   - The expected relative risk of the event between exposed vs. non-exposed = NA
   - Probability of event in the exposed = 995/1965 = 50.6%
   - Probability of event in the non-exposed = 4065/8671 = 46.8%
   - Statistical power = 80%, 85%, or 90%

- Alpha = 5%
- Number of controls per subject in the exposed group = 1
- The correlation coefficient (ϕ) for events between matched subjects = ?

3. Estimate the required values

The Correlation coefficient (ϕ) between matched subjects is missing.

In the previous study, the authors did not report the correlation coefficient of the event between the exposed and non-exposed groups. This can be calculated by the cross-tabulation function in Statsdirect. From "analyz," select "Chi-square test," then "R by C," then "screen data."

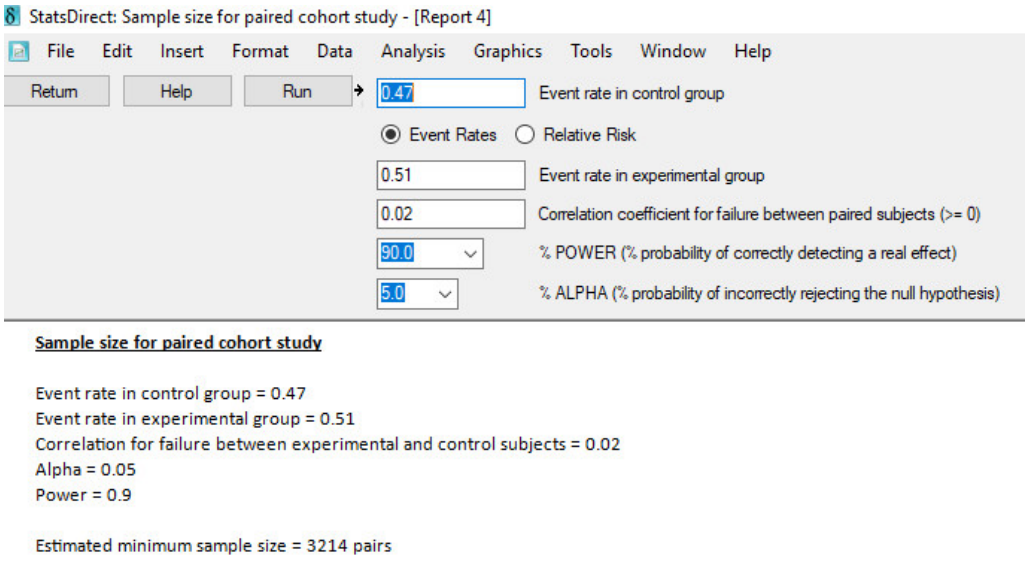


In the table, you should put the data on the distribution of maternal education subgroups in the cases and control groups.

	Burn survivors	Controls
Died	995	4,065
Alive	970	4,606

These data will give a correlation coefficient of 0.02 #

4. Run the calculations



Sample size calculation based on survival analysis

Requirements

(1) Expected Hazard Ratio of median survival times
(2) Median survival time in the experimental group
(3) Median survival time in the control group
(4) Time of recruitment
(5) Follow up duration after recruitment
(6) Statistical power
(7) Alpha
(8) Number of controls per subject in the experimental group

Calculation Steps on Statsdirect®

(1) Open a new report
(2) From "analysis" menu, select "sample size."
(3) Then select "survival."

Case Scenario of olaparib plus paclitaxel vs. placebo plus paclitaxel

You are conducting a study to compare olaparib in combination with paclitaxel versus placebo plus paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy. The recruitment period for this study will be 2 months with a 12 month-follow up.

In a recent comparative study by Bang et al., they reported the following sentence: "Overall survival did not differ between treatment groups in the overall patient population (median overall survival 8.8 months [95% CI 7.4-9.6] in the olaparib group vs. 6.9 months [6.3-7.9] in the placebo group; HR 0.79 [95% CI 0.63-1.00]; p=0.026)"

Calculate the required sample size to detect similar ES.

Case reference

Bang, Y.-J., Xu, R.-H., Chin, K., Lee, K.-W., Park, S. H., Rha, S. Y., … Boku, N. (2017). Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomized, placebo-controlled, phase 3 trial. The Lancet. Oncology, 18(12), 1637–1651.

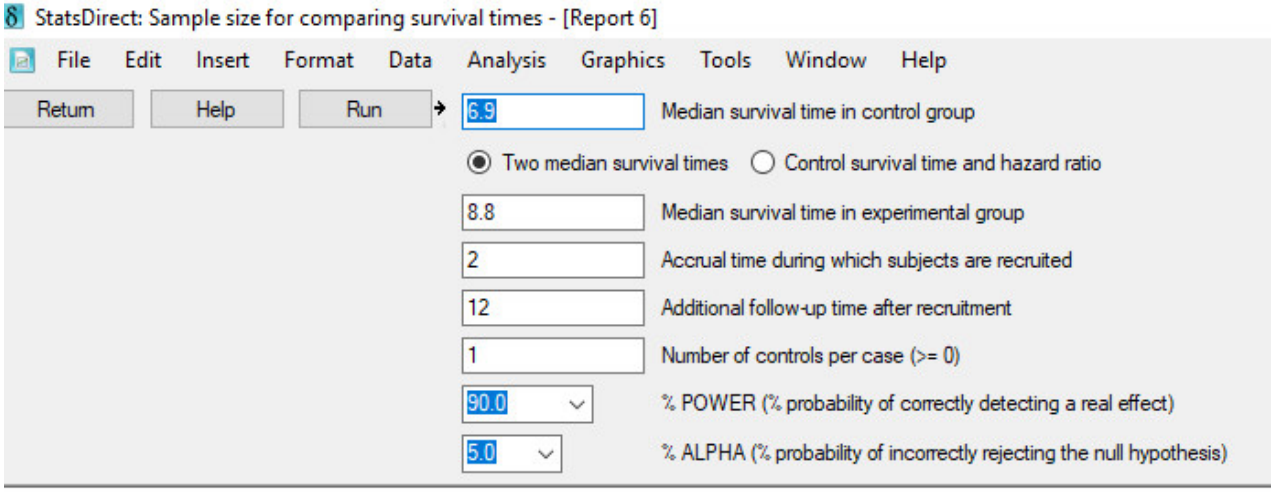
Case Solution

1. Determine the type of hypothesis: sample size based on survival
2. Determine the requirements
   - Expected Hazard Ratio of median survival times = NA

- Median survival time in the experimental group = 8.8 months
- Median survival time in the control group = 6.9 months
- Time of recruitment = 2 months
- Follow up duration after recruitment = 12 months
- Statistical power = 80%, 85%, or 90%
- Alpha = 5%
- Number of controls per subject in the experimental group = 1

3. Estimate the required values: No further estimations are required.

4. Run the calculations



Sample size for survival analysis

median survival time for controls = 6.9
hazard ratio = 1.275362
accrual time for recruitment = 2
additional follow-up time after recruitment = 12
alpha = 0.05
power = 0.9

Estimated minimum sample size = 522 experimental subjects and 522 controls

Sample size calculation based on the correlation

Calculation requirements

(1) Expected correlation coefficient under the alternative hypothesis
(2) Correlation coefficient under the null hypothesis (0)
(3) Statistical power
(4) Alpha

Calculation Steps on Statsdirect®

(1) Open a new report
(2) From "analysis" menu, select "sample size."
(3) Then select "correlation."

Case study of microRNA plasma levels as biomarkers for early detection of prostate cancer

You are conducting a study to investigate the role of microRNAs in plasma as potential biomarkers for early detection of prostate cancer.

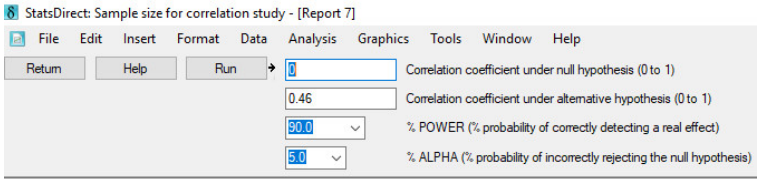
A recent study by McDonald et al. reported the following sentence: "moderate positive correlations with serum PSA were observed for …… miR-34a among cases (r = 0.46; P-value = 0.02)".

Case reference

McDonald, A. C., Vira, M., Shen, J., Sanda, M., Raman, J. D., Liao, J., … Taioli, E. (2018). Circulating microRNAs in plasma as potential biomarkers for the early detection of prostate cancer. The Prostate, 78(6), 411–418.

Case solution

1. Determine the type of hypothesis: sample size based on the correlation
2. Determine the requirements
   - Correlation coefficient under the null hypothesis (0)
   - Correlation coefficient under the alternative hypothesis = 0.46
   - Statistical power = 80%, 85%, or 90%
   - Alpha = 5%
3. Estimate the required values: No further estimations are required.
4. Run the calculations



Sample size for Pearson correlation

Alpha = 0.05
Power = 0.9
Correlation coefficient under null hypothesis = 0
Correlation coefficient under alternative hypothesis = 0.46
Estimated minimum sample size = 47

Sample size calculation for Superiority trials

Calculation requirements

(1) Expected ES*
(2) Type of clinical trial: Cross over or parallel
(3) Allocation ratio between the experimental and control groups
(4) Statistical power
(5) Alpha

* The expected effect size differs according to the type of outcome measure. In case of continuous measures, the required ES will be (1) the expected mean difference between the two arms and (2) the population standard deviation. In the case of binary outcomes (events as death or remission), the required ES will be the rate of each group.

Calculation steps

(1) Open SampSize application on your mobile
(2) Select superiority from the type of trial (superiority, non-inferiority, equivalence)
(3) Select parallel for the design of the study (parallel vs. cross over)
(4) Select normal for the type of outcome data (normal vs. binary)
(5) Put the data into space and click "calculate."

Case study of subthalamic versus pallidal deep brain stimulation for patients with Parkinson's disease

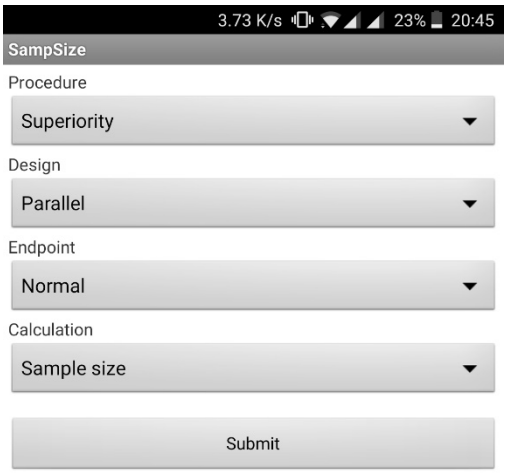
You are conducting a randomized controlled trial to compare the subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) for patients with Parkinson's disease. The primary outcome measure of this study is the improvement in motor function measured by the unified Parkinson's disease rating scale (UPDRS-III). The most recent report comparing the two targets was published by Odekerken et al. where the STN DBS and GPi DBS resulted in 20.3 and 11.4 point-improvements on the UPDRS-III, respectively. The standard deviation of the motor functions (UPDRS-III) of two groups at baseline were 13.5 and 15.5, respectively.

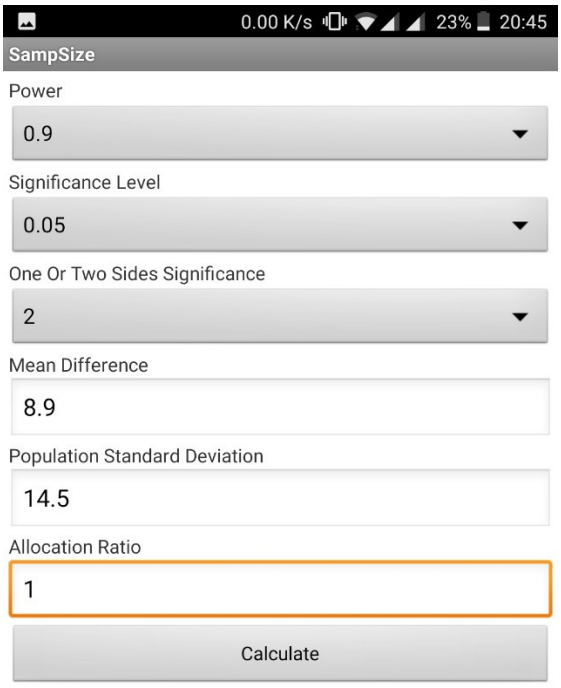
Case references

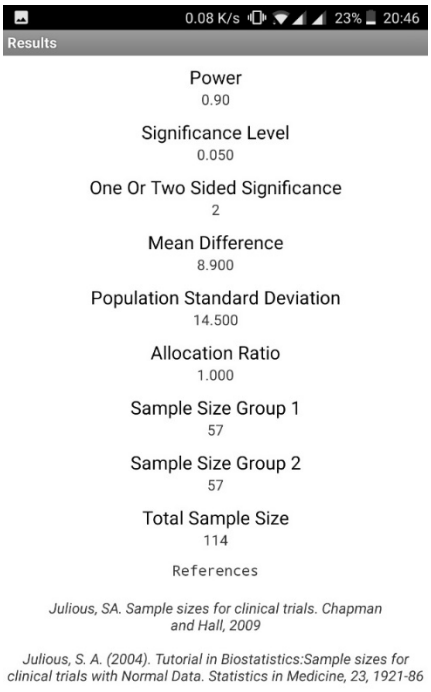
Odekerken, V. J. J., van Laar, T., Staal, M. J., Mosch, A., Hoffmann, C. F. E., Nijssen, P. C. G., … de Bie, R. M. a. (2013). Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomized controlled trial. Lancet Neurology, 12(1), 37–44.

Case solution

1. Determine the type of hypothesis: sample size for superiority trial – continuous data
2. Determine the requirements
   - Expected mean difference between the two arms = 20.3 - 11.4 = 8.9
   - Population standard deviation (within the range 13.5 to 15.5)
   - Type of clinical trial: Cross over or parallel
   - Allocation ratio between the experimental and control groups = 1
   - Statistical power = 80%, 85%, or 90%
   - Alpha = 5%
3. Estimate the required values: No further estimations are required.
4. Run the calculations







Sample size calculation for Non-inferiority trials

Calculation requirements

(1) Expected ES*
(2) Type of clinical trial: Cross over or parallel
(3) Allocation ratio between the experimental and control groups
(4) Statistical power
(5) Alpha
(6) Non-inferiority margin

* The expected effect size differs according to the type of outcome measure. In case of continuous measures, the required ES will be (1) the expected mean difference between the two arms and (2) the population standard deviation. In the case of binary outcomes (events as death or remission), the required ES will be the rate of each group.

Calculation steps

(1) Open SampSize application on your mobile
(2) Select non-inferiority from the type of trial (superiority, non-inferiority, equivalence)
(3) Select parallel for the design of the study (parallel vs. cross over)
(4) Select binary in the type of outcome data (normal vs. binary)
(5) Put the data into space and click "calculate."

Case study of disease activity guided dose reduction of anti-TNF compared with usual care for patients with Rheumatoid arthritis

Biological agents (anti-TNF) are high in cost and are associated with adverse events. Therefore, a disease activity guided dose reduction method has been suggested. We are conducting a non-inferiority randomized controlled trial to compare the disease activity guided dose reduction (DR) versus usual care (UC) for patients with Rheumatoid arthritis. The alternative hypothesis of this study is that disease activity guided dose reduction is not inferior to the usual care.

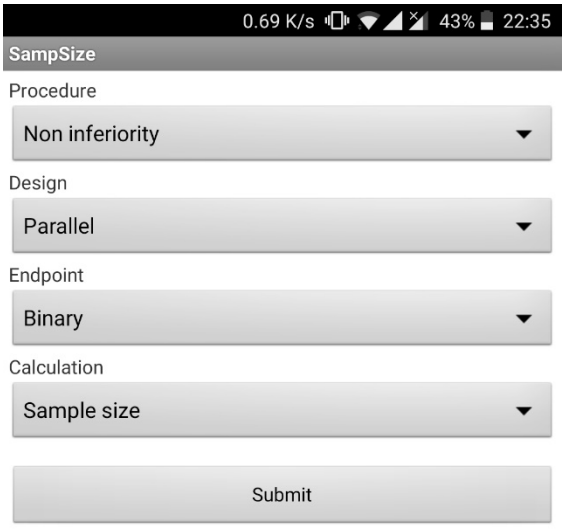
In the recent study, Bouman et al. reported 17% and 14% incidence rate of major flare after 3 years for the DR and UC groups, respectively. Assuming a non-inferiority margin of 20% difference in major flares, calculate the required sample size to detect similar ES.

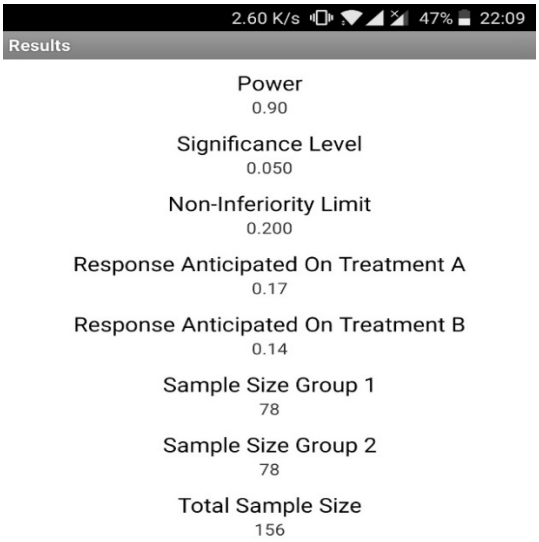
Case references

Bouman, C. A., van Herwaarden, N., van den Hoogen, F. H., Fransen, J., van Vollenhoven, R. F., Bijlsma, J. W., … den Broeder, A. A. (2017). Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomized controlled pragmatic non-inferiority strategy trial. Annals of the Rheumatic Diseases, 76(10), 1716–1722.

Case solution

1. Determine the type of hypothesis: sample size for non-inferiority trial – binary data
2. Determine the requirements
   - Expected ES (rate of flare in each group) = 17% and 14%
   - Type of clinical trial: parallel
   - Allocation ratio between the experimental and control groups = 1
   - Statistical power = 80%, 85%, or 90%
   - Alpha = 2.5%
   - Non-inferiority margin = 20%
3. Estimate the required values: No further estimations are required.
4. Run the calculations





The Minimum Clinically Important Difference (MCID)

Definition

MCID is the minimum difference within a clinical score that accounts for a clinically meaningful change in patient symptoms. MCID is like a cut-off point that determines the threshold of clinical significance within a clinical score.

Examples

Disease/population	Score	MCID
Rheumatoid Arthritis	DAS28	1.20 points
Ankylosing Spondylitis	ASDAS	1.10 points
Ulcerative colitis	Partial Mayo Score	2.00 points
Psoriasis	PASI	3.20 points
Parkinson's disease	UPDRS motor score	5.00 points

How to use the MCID for sample size calculation

Example

We are planning for a randomized controlled trial comparing Adalimumab (experimental drug) and Infliximab (control drug) for patients with psoriasis. The primary outcome measure is PASI, and the population means and SD on this score are 18 and 6 points.

Calculate the required sample size to an MCID of 3.2 points between the two groups with a 90% statistical power under a 5% two-sided alpha.

Sample size calculation for equivalence trials

Calculation requirements

(1) Expected ES*
(2) Type of clinical trial: Cross over or parallel
(3) Allocation ratio between the experimental and control groups
(4) Statistical power
(5) Alpha
(6) Equivalence margin

* The expected effect size differs according to the type of outcome measure. In case of continuous measures, the required ES will be (1) the expected mean difference between the two arms and (2) the population standard deviation. In the case of binary outcomes (events as death or remission), the required ES will be the rate of each group.

Calculation steps

(1) Open SampSize application on your mobile
(2) Select equivalence from the type of trial (superiority, non-inferiority, equivalence)
(3) Select parallel for the design of the study (parallel vs. cross over)
(4) Select binary or normal according to the type of outcome data (normal vs. binary)
(5) Put the data into space and click "calculate."

Want to study more about "Clinical Research Methodology"?

1. The following books are recommended sources to read.

a. Kaura, A., 2013. Crash course evidence-based medicine: reading and writing medical papers-e-Book. Elsevier Health Sciences.

b. Hulley, S.B. ed., 2007. Designing clinical research. Lippincott Williams & Wilkins.

c. Tang, J.L. and Griffiths, S., 2009. Epidemiology, evidence-based medicine, and public health. Asia Pacific Journal of Public Health, 21(3), pp.244-251.

d. Higgins, J.P. and Green, S. eds., 2011. Cochrane handbook for systematic reviews of interventions (Vol. 4). John Wiley & Sons.

2. In his spare time, Dr. Negida provides the following online courses

a. Introduction to Clinical Research

b. Medical Statistics on SPSS

c. Medical Statistics on Stata

d. How to Write and Publish Research

e. How to Calculate the Sample Size

f. Systematic Reviews and Meta-analysis

g. Advanced skills in Meta-analysis

You can find these courses on the online website of Dr. Negida: www.negida.com; You can register for the online courses by filling the following registration form: https://forms.gle/kz6uABZGDSX9hv736

The course coordinators will contact you when the online sessions are arranged. These sessions are usually held as two sessions per week through ZOOM MEETING software.

Best Wishes