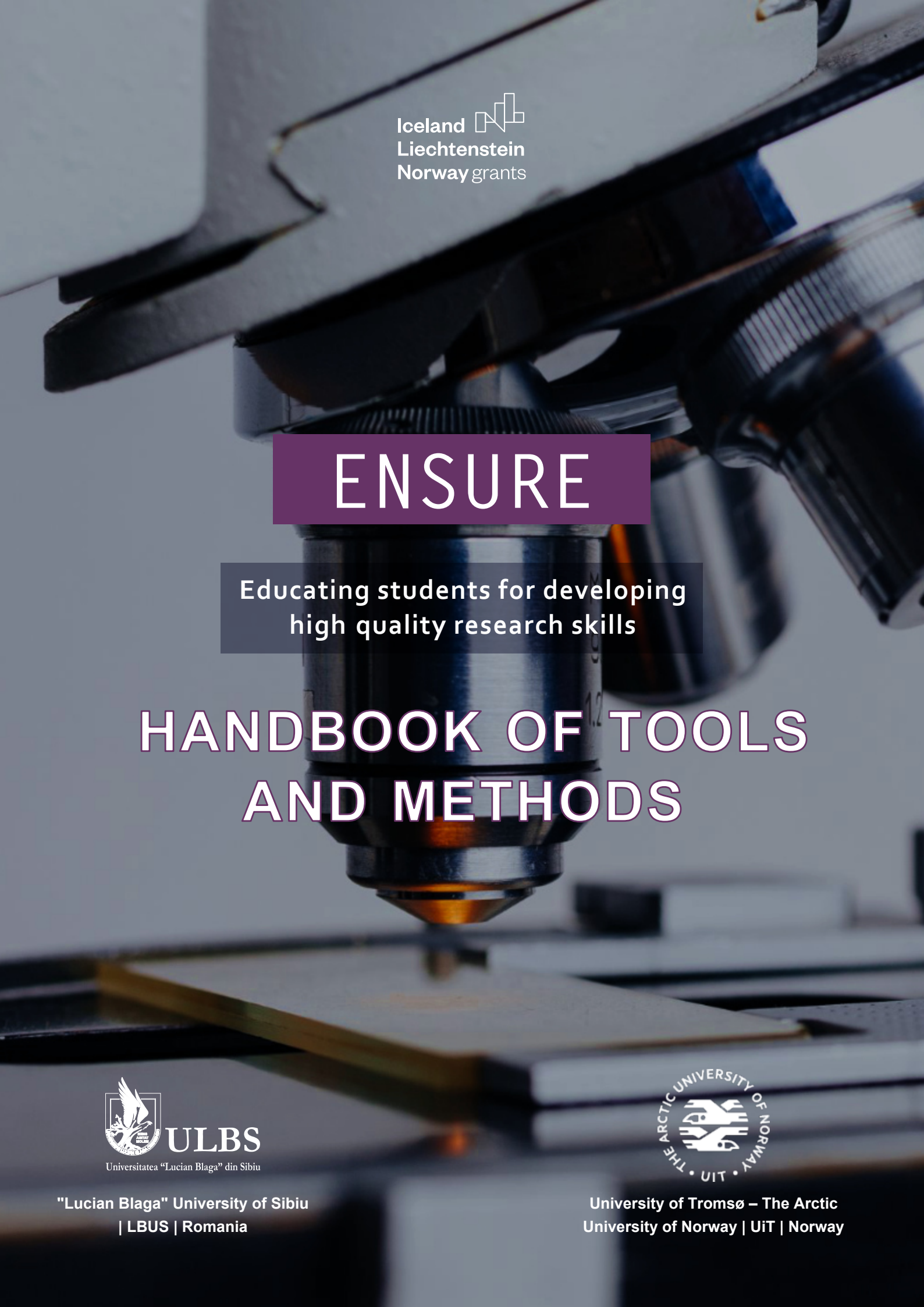

Iceland Liechtenstein Norway grants

ENSURE

Educating students for developing high quality research skills

HANDBOOK OF TOOLS AND METHODS

ULBS
Universitatea "Lucian Blaga" din Sibiu

"Lucian Blaga" University of Sibiu | LBUS | Romania

THE ARCTIC UNIVERSITY OF NORWAY • UIT •

University of Tromsø – The Arctic University of Norway | UiT | Norway

The “Educating students for developing high quality research skills (ENSURE)” project benefits from a 41.810 € grant from Iceland, Liechtenstein and Norway through the EEA and Norway Grants. The aim of the project “Educating students for developing high quality research skills (ENSURE)” is to strengthen the academic and research partnership between LBUS and the UiT through knowledge exchange and cooperation in the field of medicine and medicine-related studies. Also the project strives to foster quality improvement in pedagogical and didactical approaches supported by the use of a learner-centred approach with focus on development of soft-skills as well as on exchange of ideas that facilitate cooperation and joint research.

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Handbook of Tools and Methods
Intellectual Output 1

ENSURE

Table of Contents

Details about ENSURE project

Graduates of medical studies and science-related fields who aim to go into academic and industrial research need to possess beyond excellent specialist skills also abilities to design and conduct experiments, interpret data, manage projects as well as to write scientific reports and papers. Since globalisation has created a global market for research with benchmarks defined and demonstrated through grants as well as through internationally-peer reviewed scientific publications, employment and career advancement has been made dependent on these external criteria. In medicine and study programs related to medicine attaining such key points for one's CV require a long-planning horizon as medical trials and clinical studies tend to run over a long time under strict rules.

Yet existing curricula barely offer any education and training in academic writing, let alone in any of the skills mentioned above. Education in these study programs tends to be lecture-based with no learned-based approaches and work in small groups.

The project at hand aims to remedy this problem by offering short term intensive trainings using a learner-centred approach, where participants are guided to solve real-life problems and attain transversal knowledge and skills for conducting and publishing research. The trainings are composed by sets of modular workshops which can be combined flexibly.

PROJECT OBJECTIVES:

- Provide a set of modules with focus on medicine and medicine-related studies enabling students to build their transversal research-oriented competences and skills
- Create learning materials for students on how to conduct clinical studies, on the ethics and legal provisions of data-usage of in research with humans/patients, how to write research papers and scientific report, on how to develop individual career plans, how to build an international cooperation network, how to identify financing opportunities, how to formulate a project idea and plan
- Provide a learner-oriented methodology for transferring the knowledge using real-life problems where students can apply their knowledge. Support will be offered by teachers through a moderation process both in individual and group settings during workshops.
- Organise a series of workshops wherein students will exercise their transversal research-oriented skills.

TOPICS

TOPICS /TRAINING	TRAINER	UNIVERSITY
Scientific teaching at medical school	Prof. Finn Egil Skjeldestad	UiT
How to conduct/design of clinical studies	Prof. Finn Egil Skjeldestad	UiT
How to deal with uncertainties in clinical practice?	Prof. Frode Forland	UiT
PICOs (Population, Interventions, Comparisons, Outcomes, Study Design)	Prof. Frode Forland	UiT
Legal provision in medical and human-related scientific research	Patricia Mihalache, PhD	LBUS
Ethics in research	Prof. Victor Costache Radu Stroia PhD	LBUS
Search strategies in information systems	Prof. Eirik Reierth	UiT
How to read and assess scientific papers (GRADE)	Prof. Finn Egil Skjeldestad	UiT
Bias in epidemiological research	Prof. Finn Egil Skjeldestad	UiT
Academic writing of project plans, scientific reports	Ioana Mircea PhD	LBUS
Data collection, data cleansing, data visualization and evaluation	Gabriela Candea PhD	LBUS
How to present a project plan/scientific report	Prof. Kak Khee Yeung	LBUS

Literature search for the health sciences

Intended learning outcomes

1. Explain the purpose of literature search for the research process.
2. Select and use scientific databases for advanced literature searches.
3. Build advanced searches, using subject headings, operators (AND, OR, adj/near) and search history.

Why be systematic about it?

"The OHRP found that prior to approving the study, Hopkins researcher Dr. AlkisTogias and the Institutional Review Board failed to uncover published literature about the toxic effects of inhaling hexamethonium. According to the OHRP, this information was "readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung". Togiashad performed a standard PubMed search and consulted standard, current edition, textbooks".

(Savulescu& Spriggs, 2002, p. 3).

CURRENT CONTROVERSY

The hexamethonium asthma study and the death of a normal volunteer in research

Why be systematic about it?

"New research should not be done unless, at the time it is initiated, the questions it proposes to address cannot be answered satisfactorily with existing evidence. Many researchers do not do this—for example, Cooper and colleagues[13] found that only 11 of 24 responding authors of trial reports that had been added to existing systematic reviews were even aware of the relevant reviews when they designed their new studies."

(Chalmers & Glasziou, 2009, p. 87).

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou

Why be systematic about it?

"We used the technique of cumulative meta-analysis (performing a new meta-analysis when the results of a new clinical trial are published) and compared the results with the recommendations of the experts for various treatments for myocardial infarction. Discrepancies were detected between the meta-analytic patterns of effectiveness in the randomized trials and the recommendations of reviewers. Review articles often failed to mention important advances or exhibited delays in recommending effective preventive measures. In some cases, treatments that have no effect on mortality or are potentially harmful continued to be recommended by several clinical experts.".

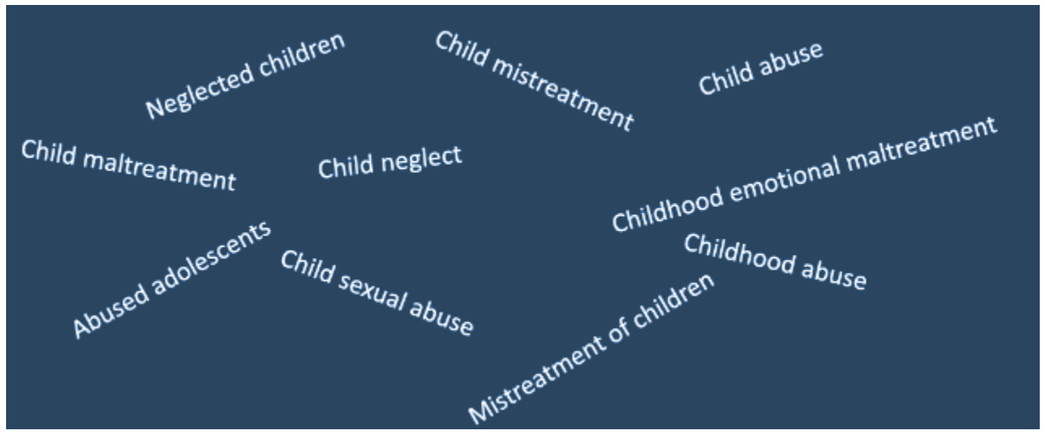
(Antman, Lau & Kupelnick, 1992, p. 240).

A Comparison of Results of Meta-analyses of Randomized Control Trials and Recommendations of Clinical Experts

Why use controlled search vocabularies?

SYNONYMOUS EXPRESSIONS

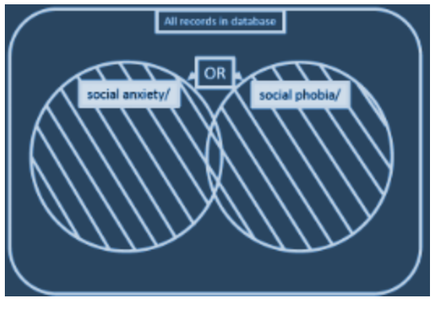
Suppose we want studies on child maltreatment



Why use controlled search vocabularies?

PERIPHERAL MENTIONS

Many sources will mention child abuse, but only peripherally.
Indexers will then not apply the heading (we hope).



OR

Use it to:

- ✓ Combine keywords (controlled and text words) that belong to the same overall concept (i.e., keywords that are synonyms or almost synonyms, or instances of the concept).

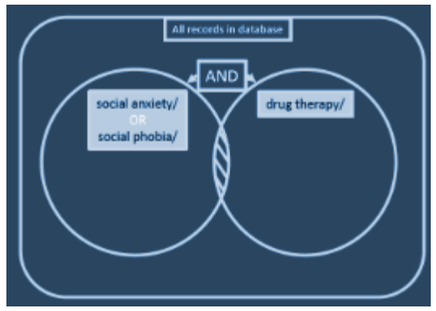
Effects of combining with OR:

- ✓ Expands your search
- ✓ More OR-combinations means more records in your results list

AND

Use it to:

- ✓ Combine keywords (or sets of keywords) from different concepts, in order to capture records that are about both (or all).



Effects of combining with AND:

- ✓ Limits your search
- ✓ More AND-combinations means fewer records in your results list

Interpret/translate scientific hypothesis/objectives into search phrases

1. Periodontal diseases have been shown to carry an increased risk for preterm birth; the rationale for this assumption is based upon the fact that periodontitis may lead to maternal and fetal inflammation, thus triggering the common pathway of preterm parturition syndrome including increased uterine contractility, cervical ripening and decidua/membrane activation
2. In humans, accidental hypothermia (AH) is defined as an unintended lowering of the body temperature to below 35 o C due to exposure to cold environments or a decrease in metabolic rate. The condition has been characterized by different stages of severity based on the prevailing core temperature, as mild AH (32-35 o C), moderate AH (28-32 o C), severe AH (<28 o C), and deep AH (<20 o C).

Dental caries and preterm birth

Think in «boxes»:

Interpret/translate scientific hypothesis/objective into search phrases

1. Periodontal diseases have been shown to carry an increased risk for preterm birth; the rationale for this assumption is based upon the fact that periodontitis may lead to maternal and fetal inflammation, thus triggering the common pathway of preterm parturition syndrome including increased uterine contractility, cervical ripening and decidua/membrane activation
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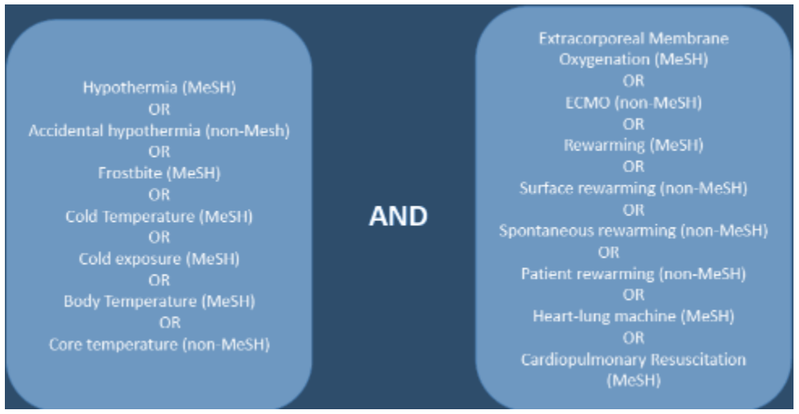
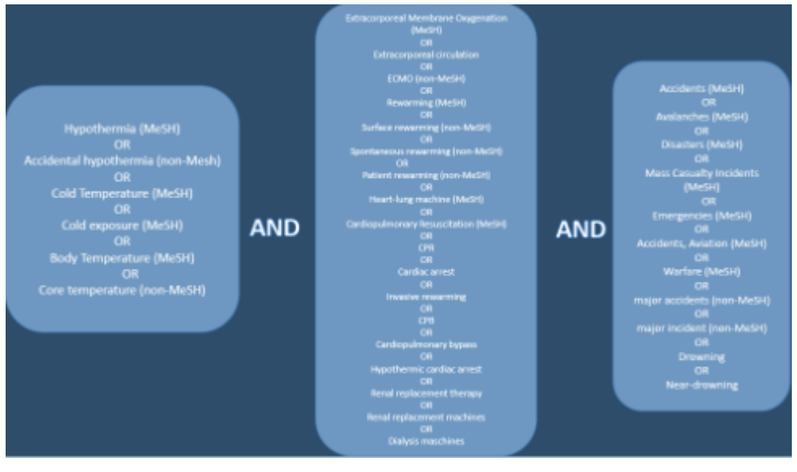
Treatment of accidental hypothermia –a systematic review



Treatment of accidental hypothermia

Think in «boxes»:

Cause AND Intervention AND Hypothermia



Building a decent search is a process

> *"Developing a search strategy is an iterative process in which the terms that are used are modified, based on what has already been retrieved."*
>
> *"There are diminishing returns for search efforts; after a certain stage, each additional unit of time invested in searching returns fewer references that are relevant to the review. "*
>
> (Higgins & Green, 2011, Section 6.4.4, our emphasis).

Database selection - Talk to the library!

Med/health essentials:	**Cross disciplinary:**
Cochrane library (Wiley)	Google Scholar
Medline (Ovid)	Scopus (Elsevier)
Embase (Ovid)	Web of Science (Clarivate)
PsycINFO (Ovid)	
CINAHL (EBSCO)	

How to find the keywords?

1. Use sources you already have, or that you find in intuitive searches.
   a. They must be the kind of sources you want to capture.
   b. Look them up in the database of your choice and make a note of how they are indexed.
2. Use the database interface to find subject headings and entry terms.
3. Mine the brains of experts.

REFERENCES

1. *Savulescu, J., & Spriggs, M. (2002). The hexamethonium asthma study and the death of a normal volunteer in research. Journal of Medical Ethics, 28(1), 3-4. doi:10.1136/jme.28.1.3*
2. *Antman, E. M., Lau, J., Kupelnick, B., Mosteller, F., & Chalmers, T. C. (1992). A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: Treatments for myocardial infarction. JAMA, 268(2), 240-248. doi:10.1001/jama.1992.03490020088036*
3. *Chalmers, I., & Glasziou, P. (2009). Avoidable waste in the production and reporting of research evidence. The Lancet, 374(9683), 86-89. doi:10.1016/S0140-6736(09)60329-9*
4. *Higgins, J. P. T., & Green, S. (Eds.). (2011). Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available at: http://cochrane-handbook.org*

BIAS

National committee for medical and health research ethics, Norway, states:

- Bias in research can cause results to not match reality. Unintended bias can occur in all stages of the research process. Intentional bias is too cheating to count.
- Bias is a challenge in all research. Bias can also easily be defined as a "form of systematic error that can affect scientific studies and interfere with the measurement processes"
- Bias can occur in all phases of a research project, such as during hypothesis generation, planning, execution and funding of studies, collection, processing and interpretation of study data, as well as publication of research data.

What can be done to avoid bias?

1. Bias related to choice of respondents/population?
2. Bias can occur when choosing a method?
3. Bias related to presentation and interpretation of results?
4. Bias linked to the researcher, biased view point, conflict of interest, delusional effect?

BIAS, PICO AND STUDY DESIGN

Bias concepts			PICO	Design	Design
Selection bias	Self selection bias	Referral bias	P	RCT	Cohort/ Case-control/Case series
Recall bias			Exp. Confound.		**Case-control,** retrospective cohorte, retrospective case-series
Diagnostic bias	Misclassification bias		P/Exp./O		All design
Observer bias			O		All prospective studies
Attrition bias	Loss to follow-up bias	Withdrawal bias/ Non-response bias	O		All prospective studies
Publication bias					RCT/Cohort/Case-control/Case series
Publicity bias					

METHODS

We conducted an **unmatched case–control study in three public hospitals in Mexico City**, Mexico (the National Perinatology Institute, Gynecology and Obstetrics Hospital Number 4 of the Mexican Social Security Institute, and the Women's Hospital). All consecutive nulligravid, infertile women 18 years of age or older who were scheduled for diagnostic hysterosalpingography were invited to participate. Infertility was defined by the failure to conceive after one year or more of unprotected intercourse. Criteria for exclusion included previous pregnancy, tubal sterilization, and previous diagnostic laparoscopy. After undergoing hysterosalpingography, the infertile women were classified on the basis of the radiologic evidence as women with tubal occlusion (case subjects) or as infertile controls. From the same hospitals, we recruited a second control group consisting of primigravid women in their first or second trimester. **In face-to-face interviews lasting an average of 20 minutes, all participants were asked about their past use of contraceptives, previous sexual relationships, and history of genital tract infections; the interviews with the infertile women were conducted before they knew whether they had tubal occlusion.** The instruments for recording the results of hysterosalpingography were adapted from the recommendations of the American Fertility Society (now the American Society for Reproductive Medicine).

We recruited 1311 infertile women (358 women with tubal occlusion and 953 controls) and 584 pregnant controls; fewer than 5 percent of the women who met the eligibility criteria declined to participate. We designed the study to have 90 percent power to detect a doublingof the risk of tubal occlusion with IUD use in analyses involving the infertile controls; the study had 87 percent power to detect a doubling of the risk in analyses involving the pregnant controls (two-sided test, 0.05 alpha level).

If we set the power at the standard 80 percent level, we had enough study subjects to detect odds ratios of 1.8 and 1.9 in analyses involving the infertile controls and the pregnant controls, respectively. Before recruitment began, the radiologists met to standardize their approach to classifying tubal pathology. Tubal occlusion was diagnosed if a water-based contrast medium failed to spill from either tube into the peritoneal cavity. Fluoroscopy was used, and the last films were taken 15 minutes after the contrast medium had been injected. The radiologists were unaware of the information collected in the women's interviews. Serologic tests for detecting antibodies to chlamydia are accepted measures of past infection.

All serum samples were processed as recommended by the manufacturer. Our primary exposure variable was the previous use or non use of an IUD containing copper. Other variables that were considered as possibly predictive of tubal infertility included the presence or absence of antibodies to C. trachomatis, the number of lifetime sexual partners, the presence or absence of a history of genital tract infections, the presence or absence of a history of gynecologic symptoms suggestive of infection, the past use or non use of other methods of contraception, family income, education, employment status, and the presence or absence of a history of coitus during the teenage years regarding their most recent sexual partners.

SELECTION BIAS

Participants in research may differ systematically from the population of interest.

For example, participants included in an influenza vaccine trial may be healthy young adults, whereas those who are most likely to receive the intervention in practice may be elderly and have many comorbidities, and are therefore not representative. Similarly, in observational studies, conclusions from the research population may not apply to real-world people, as the observed effect may be exaggerated or it is not possible to assume an effect in those not included in the study.

The effect of HRT on coronary heart disease (CHD) in women. Several studies showed that HRT reduced coronary heart disease (CHD), but subsequent RCTs showed that HRT might increase the risk of CHD disease. The Women in the observational studies on HRT were more health conscious, more physically active, and had higher socioeconomic status than those not on HRT. This **self-selection** of women (**selection bias**) **led to confounding and a "healthy-user bias".**

A study of the prevalence of Parkinson's disease (PD) completed a door to door survey of an entire US county of the approximately 24,000 residents on prevalence day, 1 January 1978, PD was diagnosed in 31 participants. Thirteen of those 31 had never been seen for medical care. In this survey, if another approach to the **ascertainment** of cases had used only the medical care system, all of those who had not received care (over 40%) would not have been identified. Furthermore, there would have been no definitive way of characterizing the bias introduced if only those identified via health records were used.

Selection bias, self-selection bias, healthy-user bias, ascertainment bias, non-response bias

Preventive steps

To assess the probable degree of selection bias, authors should include the following information at different stages of the trial or study:

- ✓ Numbers of participants screened/invited as well as included in study
  - o Responders/non-responders
  - o Screened/not-screened
- ✓ Intervention/exposure groups compared at baseline
- ✓ To what extent potential participants were re-screened

Randomisation (RCT)

OBSERVER BIAS

The process of observing and recording information which includes systematic discrepancies from the truth. "Systematic difference between a true value and the value actually observed due to observer variation".

Many healthcare observations are open to systematic variation. For example, in the assessment of medical images, one observer might record an abnormality but another might not. Different observers might tend to round up or round down a measurement scale. Color change tests can be interpreted differently by different observers. Where subjective judgement is part of the observation, there is great potential for variability between observers, and some of these differences might be systematic and lead to bias. Observation of objective data, such as death, is at much lower risk of observer bias.

Observer bias -preventive steps

- ✓ A key method is to ensure that outcome assessors are blinded to the exposure status of study participants. This can apply to randomized controlled trials, in which an individual has been allocated a particular intervention, and also to observational studies, which track the progress of study participants with different exposures. Achieving blinding might mean separating access for data on exposures from data on outcomes; in a blinded trial the allocation should remain unknown throughout the study (unless it must be revealed for safety reasons).
- ✓ Strategies can also include adequate training for observers in how to record findings, identifying any potential conflicts before recordings commence and clearly defining the methods, tools and time frames for collecting data.
- ✓ Another preventive aspect includes training study observers to become aware of their prejudices and habits, in order to improve accuracy.

Whilst observer bias can be reduced, it is likely that observer bias will always remain, and researchers should be aware of this when analyzing and evaluating data.

Synonymous concepts: Observer bias –detection bias –ascertainment bias

ATTRITION BIAS

Unequal loss of participants from study groups in a trial.

Attrition occurs when participants leave during a study. It almost always happens to some extent. Different rates of loss to follow-up in the exposure groups, or losses of different types of participants, whether at similar or different frequencies, may change the characteristics of the groups, irrespective of the exposure or intervention. Losses may be influenced by such factors as unsatisfactory treatment efficacy or intolerable adverse events. (underreporting of endpoints – “false estimate/effect”.

When participants leave, it may not be known whether they continue or discontinue an intervention; there may be no data on outcomes for these participants after that time.

In some cases, those who leave a study are likely to be different from those who continue. For instance, in an intervention study of diet in people with depression, those with more severe depression might find it harder to adhere to the diet regimen and therefore more likely to leave the study.

Attrition bias -preventive steps

- ✓ Techniques for preventing losses follow-up include ensuring good communication between study staff and participants, accessibility to clinics, effective communication channels, incentives to continue, and ensuring that the study is of relevance to the participants.

  However, for many studies, complete follow up is unlikely.

- ✓ Intention to treat analysis: Because anything that happens after randomization can affect the chance that a study participant has the outcome of interest, it is important that all patients (even those who fail to take their medicine or accidentally or intentionally receive the wrong treatment) are analysed in the groups to which they were allocated.

- ✓ Methods for dealing with missing data include last observation (or baseline value) carried forward, mixed models, imputation and sensitivity analysis using ‘worst case’ scenarios (assuming that those with no information all got worse) and ‘best case’ scenarios (assuming that all got better).

- ✓ A rule of thumb states that <5% attrition leads to little bias, while >20% poses serious threats to validity.

  While this is useful, it is important to note that even small proportions of patients lost to follow-up can cause significant bias. One way to determine whether losses to follow-up can seriously affect results is to assume a worst-case scenario for the outcomes in those with missing data and look to see if the results would change. If this method doesn’t change the study’s conclusions, the loss to follow-up is likely not a threat to the study’s validity.

PUBLICATION BIAS

When the likelihood of a study being published is affected by the findings.

Publication bias as the failure to publish the results of a study “on the basis of the direction or strength of the study findings.”

This non-publication introduces a bias which impacts the ability to accurately synthesize and describe the evidence in a given area. Publication bias is a type of reporting bias and closely related to dissemination bias, although dissemination bias generally applies to all forms of results dissemination, not simply journal publications. A variety of distinct biases are often grouped into the overall definition of publication bias.

Preventive steps -publication bias

- ✓ Certain journals have made the solicitation and publication of null results a part of their core mission. However, many of the documented barriers to publication cannot be addressed by the presence of journals receptive to null results.
- ✓ The preceding decade has seen various initiatives in the US and EU requiring certain trials to report results directly onto clinical trial registries in structured data format within 12 months of completion, providing an additional data source without the barriers to publication in academic journals. Sadly, there is growing evidence that these laws and guidelines are undermined by loopholes and poor compliance.
- ✓ Authors of systematic reviews and meta-analyses can also take steps to reduce the impact of non-publication on their work. The search for evidence should not be limited to only journal articles indexed in repositories such as PubMed or Ovid. Authors can and should search for results through other routes including trial registries, regulatory documents, and contacting trialists of known or suspected unpublished work.
- ✓ They can also use statistical methods to estimate if their sample of studies is likely impacted by publication bias.

Drug-industry-funded research–publication bias

- A Cochrane review concluded that drug-industry-funded studies overestimated efficacy and underestimated potential side effects (Lundh A et al., 2012)
- These are examples of reporting bias and publication bias

Renal denervation

Renal denervation (RDN) is a minimally invasive procedure to treat resistant hypertension.

The procedure uses radiofrequency ablation to burn the nerves in the arteries.

This process causes a reduction in the nerve activity, which decreases blood pressure?

Renal denervation(1)

Indication: Treatment-resistant hypertension

- Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Simplicity HTN-2 Trial): a randomised controlled trial.
- Results: Intervention:
  - o BP reduced by 32/12mmHg
  - o Treatment as usual: 1/0 mmHg
- Conclusion: Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

Lancet. 2010;376(9756):1903

- SymplicityHTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months.
- Results: Office blood pressure reduced
  - o 25/11 mmHg at 6 months
  - o 32/14 mmHg after 24 months
- Good efficacy!!

Implemented as treatment in 80 countries by 2014

Knowledge assessment–how to read literature

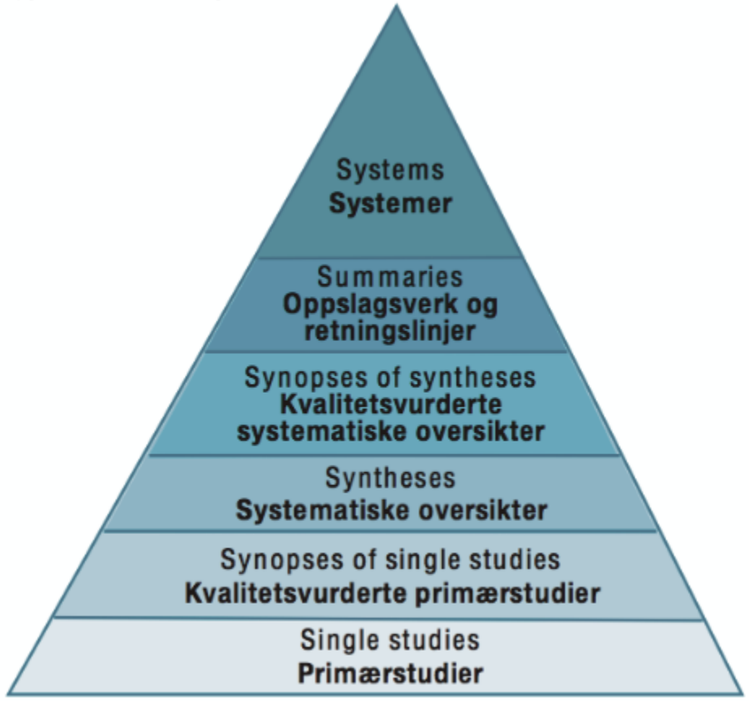
Grading of Recommendations Assessment, Development, and Evaluation

- To formulating questions
- To assess quality of evidence
- To develop recommendations

Clinical questions

- Diagnosis
- Screening
- Prevention
- Therapy/treatment

The knowledge pyramid–a hierarchy



Figur 1 *Kunnskapspyramiden, også kalt 6S-modellen*

Hierarchy of evidence

STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case-Control Studies
- Case-Reports and Case-Series, Non-systematic observations

Rate the quality of evidence for each outcome across studies

RCTs start with a high rating, observational studies with a low rating

Rating is modified downward:
- Study limitations
- Imprecision
- Inconsistency of results
- Indirectness of evidence
- Publication bias likely

Rating is modified upward:
-Large magnitude of effect
- Dose response
- Confounders likely minimize the effect

Final rating of quality for each outcome: high, moderate, low, or very low

What is quality of documentation?

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect is to be substantially different from the estimate of effect
Very low	We have little confidence on the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias

Type of bias	Description	Relevant domains in the Collaboration's 'Risk of bias' tool
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Why checklists?

- Take care of the good studies
- Easier to read studies
- Gives a quick fresh-up
- Time saving–for students/supervisors
- Same language–supervisors and students

SEARCH STRATEGY, SELECTION OF LITERATURE (FLOWCHART SEARCH)

Many students are required to write a critical review of current academic literature in their area of interest - researchers, postgraduates and undergraduates. Developing a great critical review is very important, but not always taught.

In this presentation, you will be guided through this complex process step-by-step, seeing examples, finding information and developing useful questions that will help you plan, draft and refine a critical discussion of what is and is not yet known about your topic.

Step 1: Identify key concepts and terms

Before you begin searching for literature, you need to:

- Define what you are searching for (dissertation or research paper, or a stand-alone assignment - a review of existing publications)
- Decide where to search (PubMed, Medline, OVID etc)
- Develop a search strategy using keywords and citations
- Review your research strategy
- Save your search for future use

Step 2: Select relevant databases and resources

It is easier to search when your research topic is clearly defined. Even if you haven't determined the exact focus of your research yet, spend some time becoming familiar with the research area. Do background research to extend your understanding of the research area and the terminology used in its discussion. Review articles can be useful for gaining an overview of a topic.

Doing some broad preliminary searching may help you understand the quantity of existing literature in your area of interest, and establish a basis for your later more complex searching when you have developed your search strategy.

Search on your topic, journals and articles using some useful databases as:

- Your university's library catalogue
- Google Scholar
- Project Muse (humanities and social sciences)
- Medline (life sciences and biomedicine)
- PubMed (life sciences and biomedicine)

Step 3: Combine search terms with Boolean operators

On PubMed:

- The visualisation is based on the 100 most relevant documents for your search terms
- The size of the circles is proportionate to the number of papers in the top 100
- The knowledge map will highlight some papers in each area

Many will be open access papers with the full text available from the interface, others may need to be accessed via Library for the full text.

How do I search PubMed?

Enter the terms (or key concepts) in the search box.

Suggestions will display as you type your search terms.

How do I search by author?

Enter the author's last name plus initials without punctuation in the search box, and then click Search. Names entered using either the last name + initials format (e.g., smith ja) or the full name format (john a smith) and no search tag are searched as authors as well as collaborators if they exist in PubMed.

How do I search by journal name?

Enter the journal name or abbreviation in the search box.

PubMed search results are displayed in a summary format, see the anatomy of search results page below.

Citations are initially displayed 20 items per page with the most recently entered citations displayed first.

You can mouseover a journal's title abbreviation to display the full journal name.

Step 3:
Combine search terms with Boolean operators

How do I display an abstract?

Click the title of the article to see the abstract. “No abstract available” is indicated on citations without an abstract.

I retrieved too many citations. How can I focus my search?

To limit the number of search results:

- Replace general search terms with more specific ones (e.g., search for low back pain instead of back pain).
- Add additional terms to your search.
- Use the sidebar filters to restrict your results by publication dates, species, article types, etc.
- Click manage filters in the Filter your results portlet to change your My NCBI filter selections.

I retrieved too few citations. How can I expand my search?

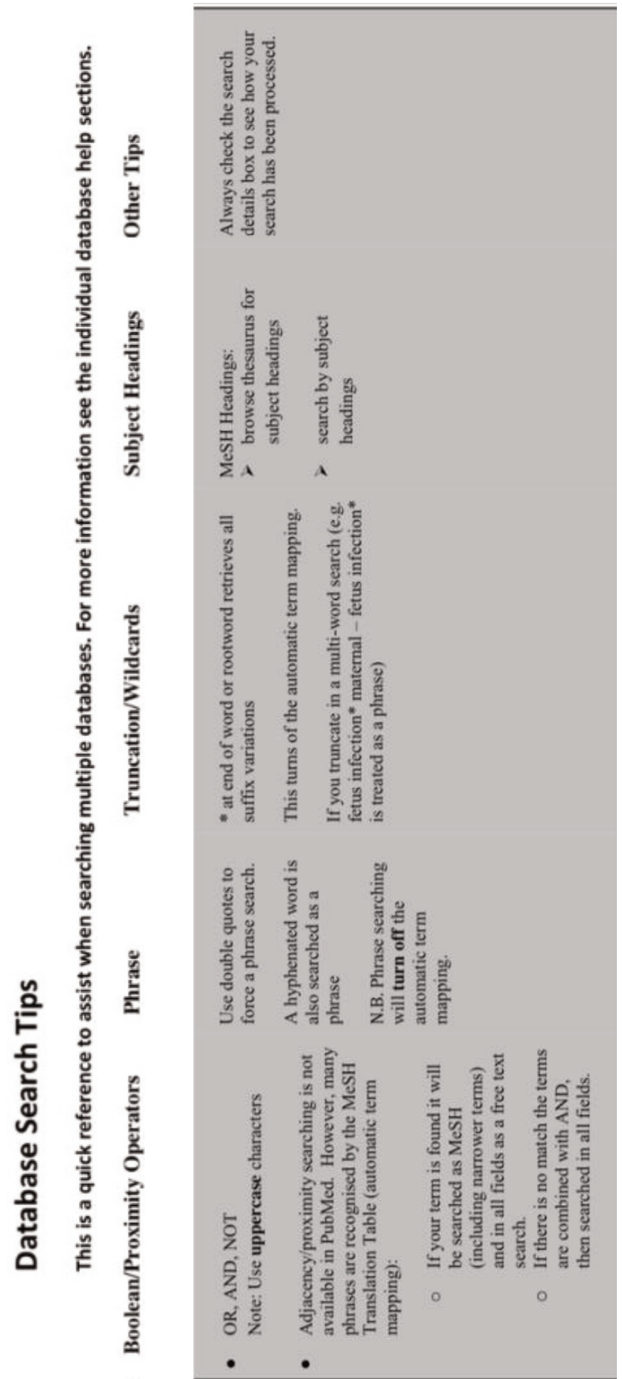
- Click the Similar Articles See all link for a relevant citation to display a pre-calculated set of PubMed citations closely related to the article.
- Remove extraneous or specific terms from the search box.
- Try using alternative terms to describe the concepts you are searching.

Watch video

http://tiny.cc/pub-med

Example

If your search, facial pain sleep disorders, retrieves too few citations consider removing search terms to broader the search and retrieve more citations such as, pain sleep disorders.



Database Search Tips

This is a quick reference to assist when searching multiple databases. For more information see the individual database help sections.

Database	Boolean/Proximity Operators	Phrase	Truncation/Wildcards	Subject Headings	Other Tips
PubMed	• OR, AND, NOT Note: Use **uppercase** characters • Adjacency/proximity searching is not available in PubMed. However, many phrases are recognised by the MeSH Translation Table (automatic term mapping): ○ If your term is found it will be searched as MeSH (including narrower terms) and in all fields as a free text search. ○ If there is no match the terms are combined with AND, then searched in all fields.	Use double quotes to force a phrase search. A hyphenated word is also searched as a phrase N.B. Phrase searching will **turn off** the automatic term mapping.	* at end of word or rootword retrieves all suffix variations This turns of the automatic term mapping. If you truncate in a multi-word search (e.g. fetus infection* maternal – fetus infection* is treated as a phrase)	MeSH Headings: ➢ browse thesaurus for subject headings ➢ search by subject headings	Always check the search details box to see how your search has been processed.

Step 3: Combine search terms with Boolean operators

Different journals may differ in the way they customarily display author names.

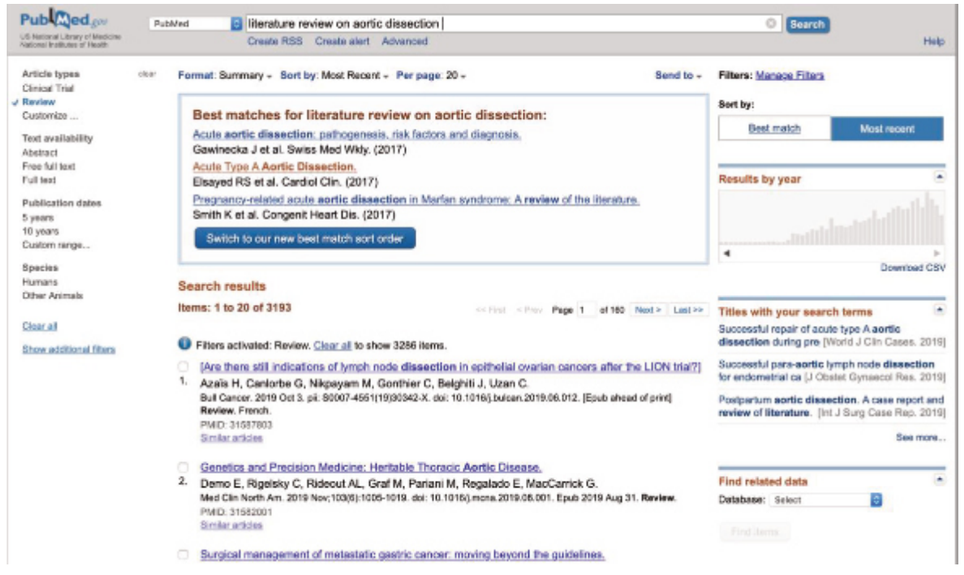
This means you may need to try several ways of entering an author's name to uncover all of their published work. For example:

- Smith,
- J Smith,
- J A Smith,
- John A Smith,
- John Anthony and so on.

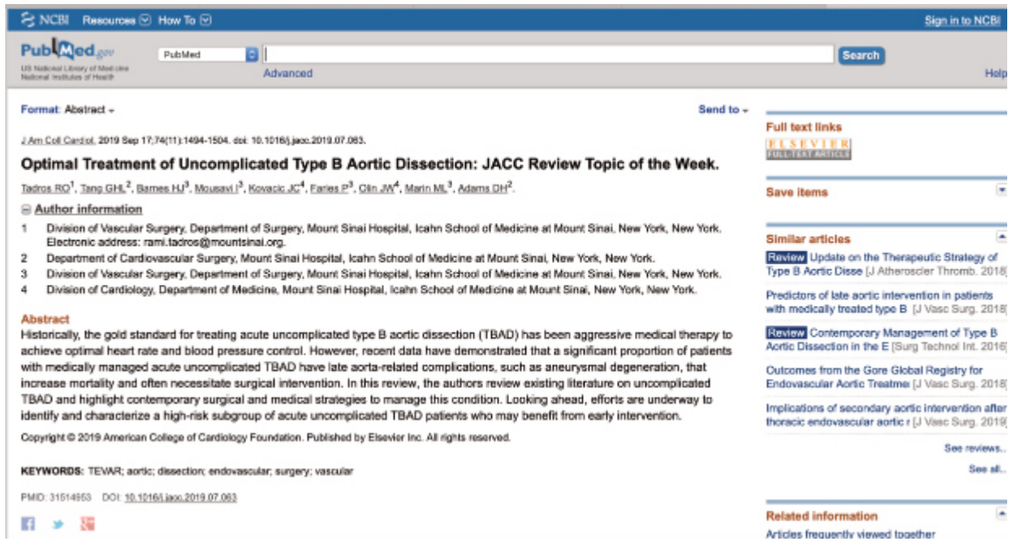
Further to this, databases may vary in the way they read punctuation in searches. If conducting a keyword search for an author name, some databases may need you to enter surname comma first name, while others might need first name surname.

For a complete literature searching it is important to be systematic in your approach. This includes developing a plan for your search (including the search terms you will use and the resources you will search), and keeping records of the searches you carry out.

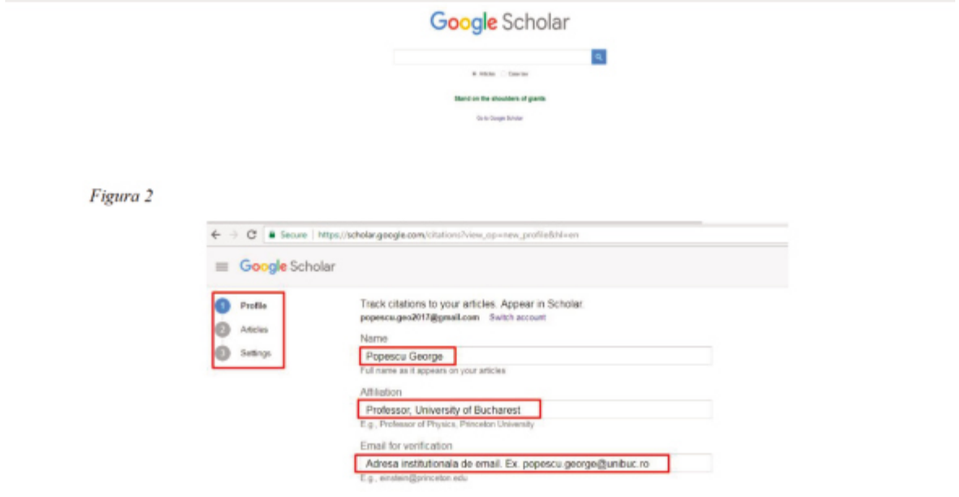
Alternatively, some databases may allow you to do a topic search and refine your results to document type Literature Review or Review.



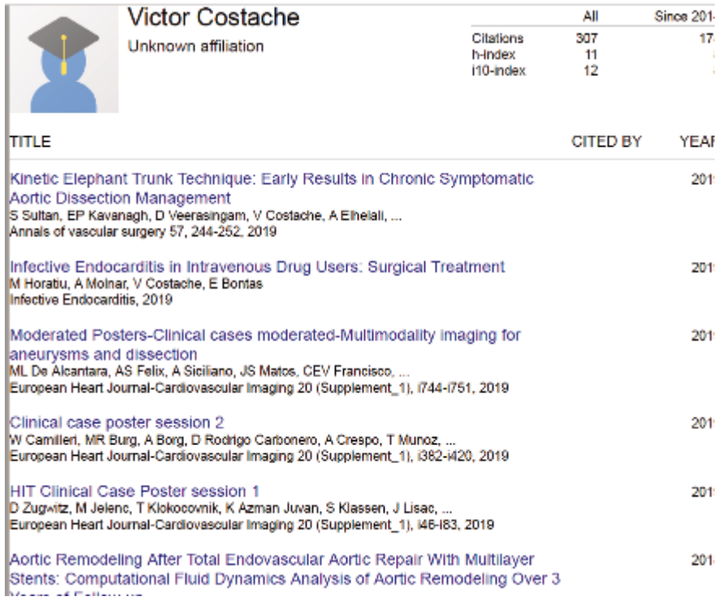
When you find a useful article, check the reference list to identify any important publications that didn't show up in your keyword search, and take note of recurring citations.



If the same authors, books or articles keep appearing in your reading, make sure to seek them out. You can find out how many times an article has been cited on Google Scholar—high citation counts mean the article has been powerful in the field.



Step 3: Combine search terms with Boolean operators



Victor Costache

Unknown affiliation

	All	Since 201
Citations	307	17
h-index	11	
i10-index	12	

TITLE	CITED BY	YEAR
Kinetic Elephant Trunk Technique: Early Results in Chronic Symptomatic Aortic Dissection Management S Sultan, EP Kavanagh, D Veerasingam, V Costache, A Elhelali, ... Annals of vascular surgery 57, 244-252, 2019		201
Infective Endocarditis in Intravenous Drug Users: Surgical Treatment M Horatiu, A Molnar, V Costache, E Bontas Infective Endocarditis, 2019		201
Moderated Posters-Clinical cases moderated-Multimodality imaging for aneurysms and dissection ML De Alcantara, AS Felix, A Siciliano, JS Matos, CEV Francisco, ... European Heart Journal-Cardiovascular Imaging 20 (Supplement_1), i744-i751, 2019		201
Clinical case poster session 2 W Camilleri, MR Burg, A Borg, D Rodrigo Carbonero, A Crespo, T Munoz, ... European Heart Journal-Cardiovascular Imaging 20 (Supplement_1), i382-i420, 2019		201
HIT Clinical Case Poster session 1 D Zugwitz, M Jelenc, T Klokocovnik, K Azman Juvan, S Klassen, J Lisac, ... European Heart Journal-Cardiovascular Imaging 20 (Supplement_1), i46-i83, 2019		201
Aortic Remodeling After Total Endovascular Aortic Repair With Multilayer Stents: Computational Fluid Dynamics Analysis of Aortic Remodeling Over 3		201

Step 4: Evaluate and select sources

You probably won't be able to read absolutely everything on the topic—start by reading the abstract to determine whether the article is useful. You will have to evaluate which sources are most valuable and relevant to your questions.

For each publication, ask yourself:

- What question or problem is the author addressing?
- What are the key concepts and how are they defined?
- What are the key theories, models and methods? Does the research use established frameworks or take an innovative approach?
- What are the results and conclusions of the study?
- How does the publication relate to other literature in the field? Does it confirm, add to, or challenge established knowledge?
- How does the publication contribute to your understanding of the topic? What are its key insights and arguments?
- What are the strengths and weaknesses of the research?

Step 4: Evaluate and select sources

The choice of your review will depend on your topic and discipline: in the science you usually only review recent literature, but in the humanities you might take a long historical perspective (for example, to trace how a concept has changed in meaning over time).

Take notes and cite your sources

As you read, you should also begin the writing process—take notes that you can later incorporate into the text of your literature review. It is important to keep track of your sources with citations to avoid plagiarism.

It can be helpful to make an annotated bibliography, where you compile full citation information and write a paragraph of summary and analysis for each source. This helps you remember what you read and saves time later in the process.

According to the APA (American Psychological Association) citation guidelines, you should write down the last name of the author(s) and the year of publication. When quoting a source it is also required to include the page number(s). This can be done in multiple ways:

- An earlier study in which X and Y were compared revealed that … (Smith, 2017).
- Smith (2017) shows how, in the past, research into X was mainly concerned with …
- In 2017, research was carried out by Smith that indicated that …

As you can imagine, citing a source with 3–5 authors take up a lot of space in the text. That is why you shorten the citation when you use the source a second, third or fourth time. How? Instead of writing down all authors' last names, write only the last name of the first author, followed by "et al.," which means "and others."

- In this research, many participants made use of … (McGuire et al., 2014).
- McGuire et al. (2014) noticed that …

When the source is published by an organization instead of a person, cite the organization's name as the author.

- According to new research … (Microsoft, 2014)

Step 4: Evaluate and select sources

When you copy a quote of a text from another source and place it between quotation marks, you are required to add the page number to the in-text citation.

- This is also true from the business plan: “making an APA Citation Generator is a lot of work, but many students benefit from it” (Swan, 2014, p. 5).

Literature review vs systematic review

You might have heard the term 'Systematic Review'. A systematic review goes further than a literature review in that it aims to locate and evaluate all studies, published and unpublished, relevant to a specific research question. Systematic reviews use explicit, systematic methods to minimise bias and enable verification and replication.

Step 5: Review and refine search results

As you write, you can follow these tips:

- Summarize and synthesize: give an overview of the main points of each source and combine them into a coherent whole
- Analyze and interpret: don’t just paraphrase other researchers—add your own interpretations where possible, discussing the significance of findings in relation to the literature as a whole
- Critically evaluate: mention the strengths and weaknesses of your sources
- Write in well-structured paragraphs: use transitions and topic sentences to draw connections, comparisons and contrasts

Dissertation literature review

If the literature review is part of your thesis or dissertation, show how your research addresses gaps and contributes new knowledge, or discuss how you have drawn on existing theories and methods to build a framework for your research.

Stand-alone literature review

If you are writing a stand-alone paper, you can discuss the overall implications of the literature or make suggestions for future research based on the gaps you have identified.

When done writing your literature review, don’t forget to proofread thoroughly before sharing it with others.

Use references

Justify and support discussion/arguments/points of view

Make comparisons with other research

Demonstrate familiarity with field of research

Consider: What is relevant from the literature review and why is it relevant to your work?

Where is the evidence in the literature review?

Support throughout with references

Refer these ideas/concepts to your study

The conduct of clinical trials/framework

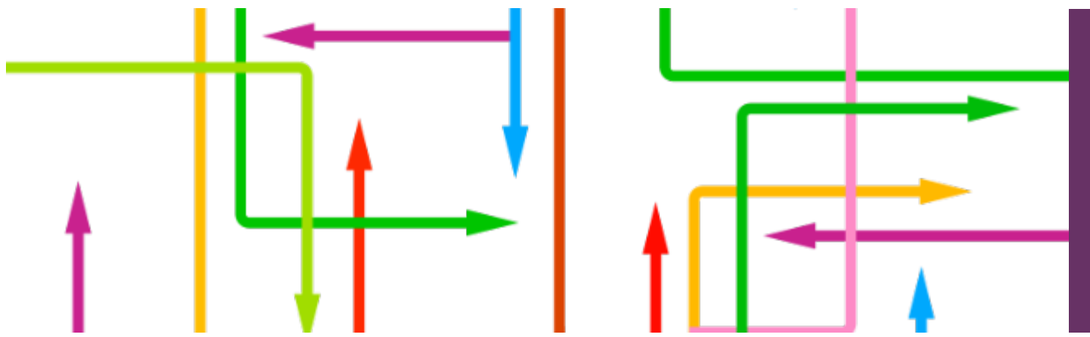
DEFINE THE RESEARCH QUESTION?

Types of questions

Intervention	What should be done about the problem?
Risk factors	What causes the problem?
Diagnosis	Does a person suffer from the problem?
Prognosis	Who will suffer from the problem?
Frequency	How common is the problem?
Contextual phenomena	Which other factors affect the problem and positively/ negatively influence action

RCT randomized clinical trials

1. Know the need for different study designs for different clinical questions
2. Be able to explain how to conduct an RCT
3. Know the limitations of the application of RCT and the applicability of results.

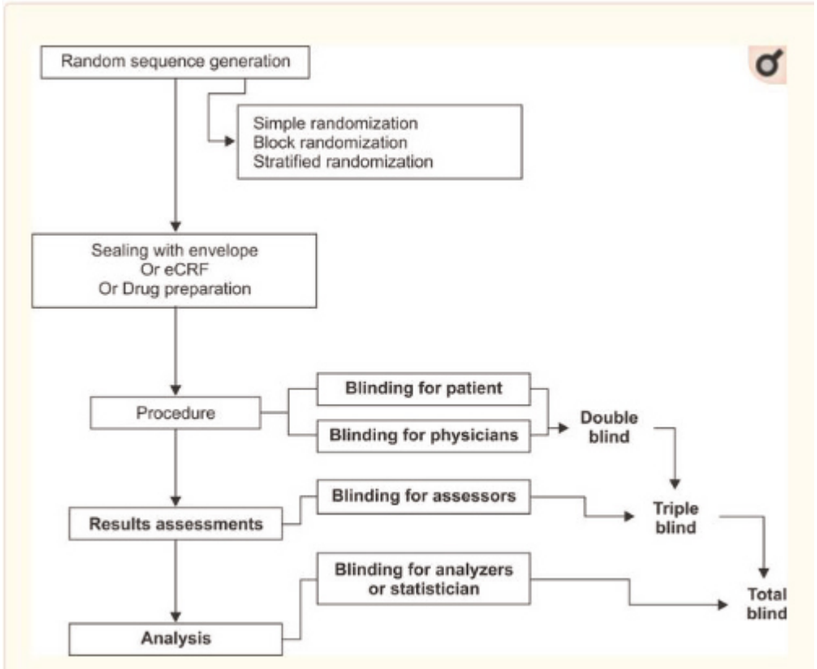


Why randomize?

…to ensure that the two (or more) groups we compare should be equal in every way

History of randomized controlled trials

- 1920s -RA Fisher developed randomization as a basic principle of experimental design
  - o predominantly in agricultural research
- 1940s -Sir Austin Bradford Hill, London School of Hygiene and Tropical Medicine, published use of random numbers to allocate trial participants. ….



RANDOM SEQUENCE GENERATION

Judgement of 'Low risk' of bias	• Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimization* **Minimization may be implemented without a random element, and this is considered to be equivalent to being random.*
'High risk' of bias	• Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number • Allocation by judgement of the clinician • Allocation by preference of the participant • Allocation based on the results of a laboratory test or a series of tests • Allocation by availability of the intervention
`Unclear risk'	• Not enough information

ALLOCATION CONCEALMENT

'Low risk' of bias	• Central allocation (including telephone, web-based and pharmacy-controlled randomization) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes
'High risk' of bias	• Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered) • Alternation or rotation • Date of birth • Case record number
`Unclear risk'	• Not enough information

Simple randomisation–randomization tables

For equal allocation to two groups, predetermine the direction to read the table: up, down, left, right, or diagonal (in protocol). Then select an arbitrary starting point—ie, first line, 7th number:

```
56 99 20 20 52 49 05 78 58 50 62 86 52 11 88
31 60 26 13 69 74 80 71 48 73 72 18 60 58 20
55 59 06 67 02 . . .
```

For equal allocation, equate odd and even numbers to interventions A and B.

Therefore, a series of random numbers 05, 78, 58, 50, 62, 86, 52, 11, 88, 31, represent allocation to intervention A or B.

Alternatively, 00–49 could equate to A and 50–99 to B, or numbers 00–09 to A and 10–19 to B, ignoring all numbers greater than 19 (in protocol).

Any of a myriad of options suffice, provided the assignment probabilities and the investigator adhere to the predetermined scheme (in protocol).

Block Randomization

- Block randomization is balanced within each block
- The basic idea of block randomization
  - divide potential patients into m blocks of size 2n
  - randomize each block such that n patients are allocated to A and n to B
  - then choose the blocks randomly
- Example: Two treatments of A, B and Block size of 2 x 2= 4
  - Possible treatment allocations within each block are (1) AABB, (2) BBAA, (3) ABAB, (4) BABA, (5) ABBA, (6) BAAB
  - Block size depends on the number of treatments, it should be short enough to prevent imbalance, and long enough to prevent guessing allocation in trials

Block Randomization Design With 3 Blocks of Size 4, Treatments of A & B

Obs	Block	Size
1	1	B
2	1	A
3	1	B
4	1	A
5	2	A
6	2	B
7	2	B
8	2	A
9	3	B
10	3	B
11	3	A
12	3	A

Stratified randomization

- To ensure that the treatment and control groups are balanced on important prognostic factors that can influence the study outcome (e.g., gender, ethnicity, age, socioeconomic status).
- Before doing the trial, the investigator decides which strata are important and how many stratification variables can be considered given the proposed sample size.
- A separate simple or blocked randomization schedule is developed for each stratum.
- Large trials often use randomly permuted blocks within stratification groups.

RCT – STRENGTHS AND LIMITATIONS

Strength

- ✓ Gold standard for assessment of interventions
- ✓ Minimalize bias and confounding

Limitations

- ✓ Time-consuming
- ✓ Costly
- ✓ Limited generalisability
- ✓ Ethical concerns

Case-control design

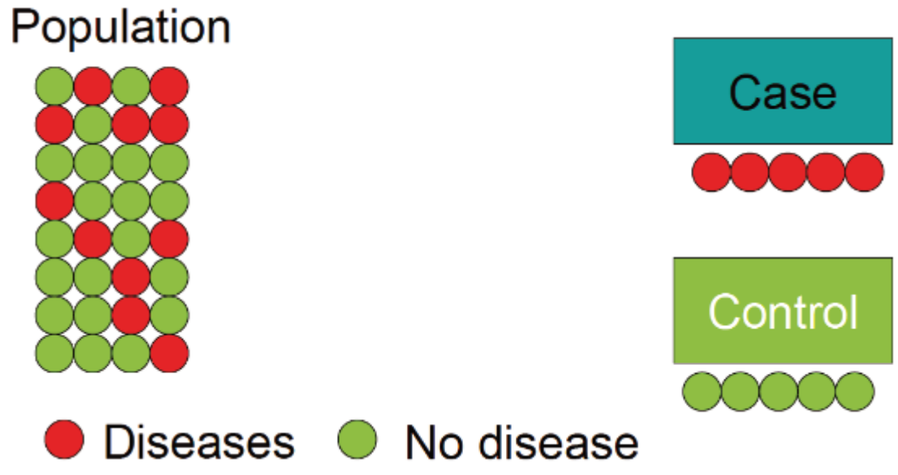
CASE-CONTROL STUDY

Definition

A study that compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls), and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease.

- Case control studies are observational because no intervention is attempted and no attempt is made to alter the course of the disease.
- The goal is to retrospectively determine the exposure to the risk factor of interest from each of the two groups of individuals: cases and controls.
- These studies are designed to estimate odds.

Participants selected on disease status



CASES

Incident cases

1. Comprise cases newly diagnosed during a defined time period
2. The use of incident cases is considered as preferential, as the recall of past exposure(s) may be more accurate among newly diagnosed cases.
3. The temporal sequence of exposure and disease is easier to assess among incident cases.

Prevalent cases

1. Comprise individuals who have had the outcome under investigation for some time.
2. The use of prevalent cases may give rise to recall bias as prevalent cases may be less likely to accurately report past exposures(s).
3. The interpretation of results based on prevalent cases may prove more problematic, as it may be more difficult to ensure that reported events relate to a time before the development of disease rather than to the consequence of the disease process itself.

SELECTION OF CONTROLS

Controls are used to estimate the prevalence of exposure in the population which gave rise to the cases.

- The ideal control group would comprise a random sample from the general population that gave rise to the cases.
- The goal is to select individuals in whom the distribution of exposure status would be the same as that of the cases in the absence of an exposure disease association. That is, if there is no true association between exposure and disease, the cases and controls should have the same distribution of exposure
- Controls should be selected to be a representative sample of the population which produced the cases.

o If cases are selected from a defined population such as a GP register, then controls should comprise a sample from the same GP register.

o If case are hospital based, it is common to recruit controls from the hospital population.

- Recruiting more than one control per case may improve the statistical power of the study, though including more than 4 controls per case is generally considered to be no more efficient.
-

NESTED CASE-CONTROL STUDY

In the nested case-control study, cases of a disease that occur in a defined cohort are identified and, for each, a specified number of matched controls is selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case.

The nested case-control design potentially offers impressive reductions in

- costs
- efforts of data collection, analysis compared with the full cohort approach, with relatively minor loss in statistical efficiency.
- the nested case-control design is particularly advantageous for studies of biologic precursors of disease (biobanks).

Data sources –case-control design

- Standardized questionnaires
- Interviews with the subject
- Interviews with spouse or other family members
- Medical records
- Employment records
- Pharmacy records (national/regional/local)
- Biological samples

Bias in case-control studies

- Selection bias (selection of controls)
- Recall bias (prevalent/incident disease)
- Interviewer/observer bias
  - o recording of exposure information may vary depending on the investigator's knowledge of an individual's disease status

CASE-CONTROL DESIGN

Advantages:

- ✓ Relatively cheap
- ✓ Relatively few people are investigated
- ✓ The result comes quickly
- ✓ Good for studying rare conditions or diseases
- ✓ Less time needed to conduct the study because the condition or disease has already occurred
- ✓ Let you simultaneously look at multiple risk factors
- ✓ Useful as initial studies to establish an association
- ✓ Can answer questions that could not be answered through other study designs

Disadvantages:

- ✓ The information from the case may be affected by the disease
- ✓ Finding good controls can be difficult
- ✓ Cannot calculate incidence
- ✓ Retrospective studies have more problems with data quality because they rely on memory and people with a condition will be more motivated to recall risk factors (recall bias).
- ✓ Not good for evaluating diagnostic tests because its already clear that the cases have the condition and the controls do not

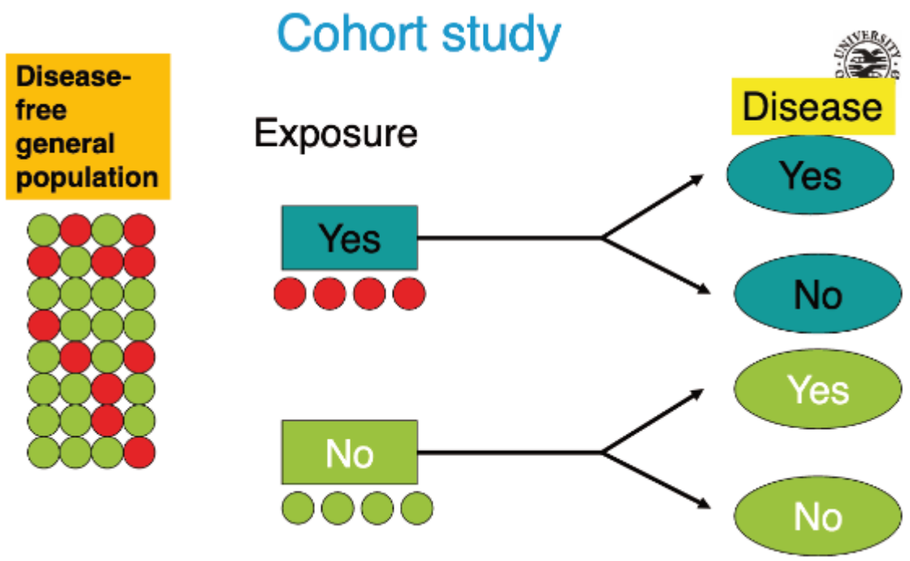
Cohort design

SELECTION OF STUDY POPULATION

- General population
- Repetitive population based studies

  The Tromsø study (7 repetions with biobanks), HUNT (another population based study in Norway)
- Work-related databases
- By residence*
- Other groups
  - Ethnic groups, religious groups
  - Professional databases

    Nurses' Health Study
- Public/private insurance databases
- Military/veteran databases



Potential sources of bias in cohort studies

- o Lost-to-follow-up (< 5% very good, > 20% not acceptable)
- o Attrition rate (> 95% very good, < 80% not acceptable
- o Misclassification of exposure
- □ Differential misclassification (unexposed are exposed; underestimation of the real effect)
- o Misclassification of outcome (over-under-estimation of effect)
- o Missed outcomes (lost-to-follow-up)
- o Healthy worker effect (occupation) –stay healthy –continued participation

Number needed to treat:

- o Prospective studies measure insidence differences
- o Provide information for assessing how many persons who need to be treated to prevent one case from the «outcome»

Strengths of cohort studies

- ✓ Can measure incidence and prevalence
- ✓ Exposure is measured before the onset of disease (in prospective cohort studies, measurement of exposure is unrelated to disease)
- ✓ Demonstrate direction of causality
- ✓ Multiple outcomes can be measured for any one exposure
- ✓ Good for measuring rare exposures, for example among different occupations

Weaknesses of cohort studies

- ✓ Costly and time consuming –sample size –long follow-up time.
- ✓ Prone to bias due to loss to follow-up.
- ✓ Prone to confounding.
- ✓ Participants may move between one exposure category –multiple f-up
- ✓ Knowledge of exposure status may bias classification of the outcome
- ✓ Being in the study may alter participant's behaviour.
- ✓ Classification of individuals (exposure or outcome status) can be affected by changes in diagnostic procedures
- ✓ Poor choice for the study of a rare disease

Data collection, data cleansing, data visualization and evaluation

Data In healthcare

Generated across a variety of sources, data collection in healthcare can also encourage efficient communication between doctors and patients, and increases the overall quality of patient care

Data collection

Data collection is the ongoing systematic process of gathering, analysing and interpreting various types of information from various sources.

Data collection in healthcare allows health systems to create holistic views of patients, personalize treatments, advance treatment methods, improve communication between doctors and patients, and enhance health outcomes

Data is divided into two types:

1. Quantitative — in the form of numbers, e.g. percentages, comparison, etc.
2. Qualitative — in the form of words, e.g. description of quality, appearance, etc.

The data collection instruments include

- questionnaire surveys and patient self-reported data;
- use of proxy/informant information;
- hospital and ambulatory medical records;
- and analysis of biologic materials.

Data collection - questionnaire surveys and patient self-reported data

The information collected in observational epidemiologic studies is collected in the form of patient/participant self-reports on standardized questionnaires which are either self or interviewer administered in person, by phone, or via mail or the internet

Advantages

- ✓ Can collect personal and/or risk factor data not typically contained in hospital/ ambulatory care records
- ✓ Can elicit information in an analytically desirable and standardized manner
- ✓ Can maintain high survey response rates through various financial or other incentives

Disadvantages

- ✓ Validating individual survey responses can be difficult, burdensome, costly, and of questionable utility
- ✓ If response rates are less than desirable, one may question the representativeness of the study sample and its generalizability
- ✓ Responses might differ if questions are asked in-person vs. by phone vs. by mail/internet

Data collection - Proxy/Informant Data

- The collection of information about study participants through the use of proxy respondents can be one of the more challenging tasks for an investigator.
- Informal caregivers are increasingly being recognized as ‘stakeholders’ in many research studies, particularly those that focus on patient reported outcomes such as quality of life.
- In cases of questionable mental status, or non-communicative state of a patient, informants can be very helpful and important in providing information to help establish a ‘baseline’ for a patient.

Data collection - Review of Ambulatory or Hospital Medical Records

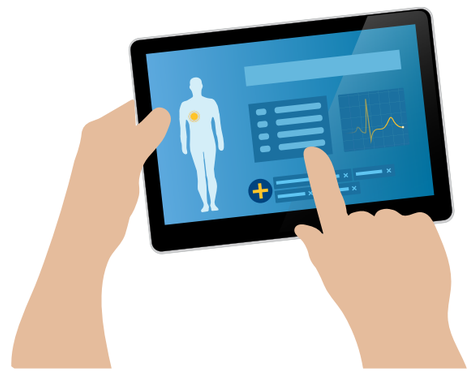
- Information contained in hospital or ambulatory care records may be used either as the sole source of data, or complementary to other instruments used to elicit information.

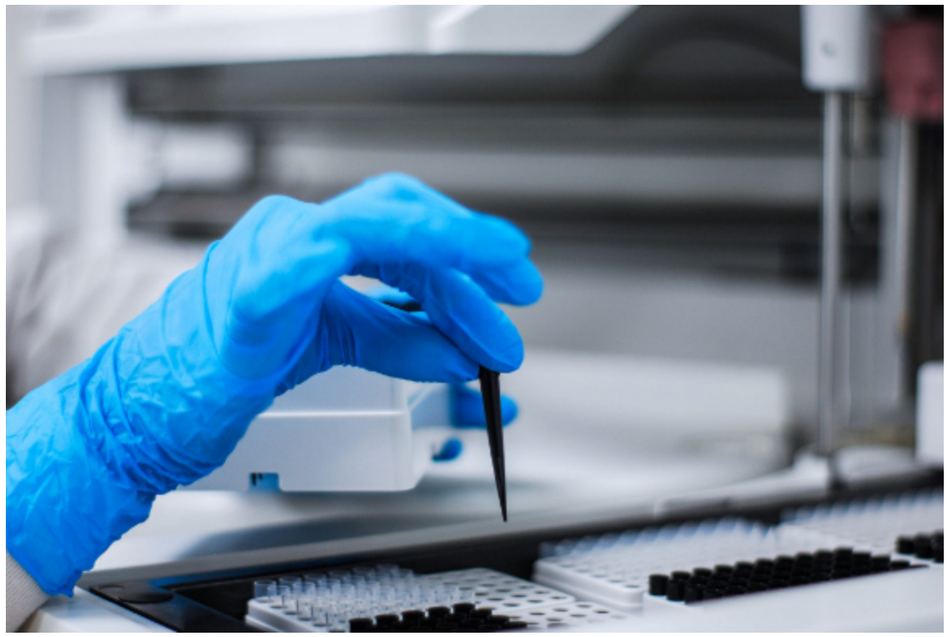
Advantages

- ✓ Readily available and contain much useful demographic and clinical information
- ✓ Can be linked to other follow-up information sources
- ✓ Can be used to characterize the medical history and clinical course of hospitalized and outpatient individuals
- ✓ Can provide data on medication intensity and duration

Disadvantages

- ✓ Often times data contained in medical records are non-standardized and inconsistently collected and recorded
- ✓ Information is often incomplete and/or missing
- ✓ Independent checks on validity and/or reliability are atypically performed
- ✓ Information on etiologic or prognostic factors of importance is often either not obtained or asked about or recorded in a standardized manner





Data collection - Collection of Biologic Material

- Contemporary clinical and translational research investigations involve the collection of biologic samples from study participants (such as hair, saliva, urine, and serum).
- Biologic samples are increasingly being used to profile participants metabolic, proteomic, or genomic status and, thereby, better understand their underlying pathophysiology or their response to a treatment or disease.

Advantages

- ✓ May provide novel insights into underlying disease pathophysiologic processes
- ✓ Can serve as an important endpoint of relevance
- ✓ Can be linked to other sociodemographic, medical history, and clinical data to obtain insights into disease occurrence and prognosis

Disadvantages

- ✓ Need to be collected under standardized conditions with considerable attention to detail
- ✓ Ongoing quality control procedures needed
- ✓ Need to consider impact of possible biologic circadian variation for purposes of timing and frequency of data collection efforts
- ✓ May need collection of multiple measures at baseline to adequately profile subsequent changes

DATA CLEANSING

Referred to as data scrubbing, data cleansing is the process of detecting dirty data (data that is incorrect, out of date, redundant, incomplete or formatted incorrectly) and then removing and/or correcting the data.

Healthcare data tend to be unstructured for the simple reason that providers tend to format their data in whatever way is most convenient for them with no thought of the need to structure the data so that the cardiology department's data and the mental health department's data are consistent.

Dealing with data in healthcare:

- nowadays there is artificial intelligence which can diagnose cancer from an X-ray image with better accuracy than the best doctors.
- there are Internet of things (IoT) sensors within medical devices which can monitor the heartbeat of a heart attack survivor or the stomach of an individual with an ulcer to ensure their condition does not deteriorate.
- there is the new trend of healthy people using IoT devices to ensure that if they do get cancer or a narrowing of their arteries that they can go to the doctor's surgery before these illnesses develop into something much more severe

Data cleansing – SOURCES

Healthcare data tends to come from lots of different places such as:

- from different specialities such as radiology, or
- from pharmacy, or
- from inpatients or outpatients, or
- from a GP's surgery or
- from a hospital.

Data is typically stored in different ways and using different meta tags, also tend to come in different formats so that the radiology department's data will be full of X-rays, that is, images.

Data cleansing - Deleting cases / records with a missing attribute values

- All cases with missing values would be deleted from the data set.
- This approach is not appropriate for dealing with missing values in medical data.
- There are more than 40% of patients engaged in the research with missing attribute values.
- This approach will dramatically decrease the number of records which will cause the inability to perform data mining to a degree of accuracy as is required.

PROBLEM	EXAMPLE
Detection of duplicate values	name1="J.Kowalski", born1=1978 name2="John Kowalski" , born2=1978
Detection of invalid values	name1= "J.Smith" , hight1=178 name2= "J.Kowalski", high2="tall"
Detection of inconsistent values	born1= "1978", age1=26, id1=781278xxxxx born2= "1960", age2=30, id2=781260xxxxx
Detection of missing values	model1= "Neo 02-Up", serial_no1=5076096 model2= "LCP 201", serial_no2=0 model3= "TRIOS 02-UP",serial_no3=50464083
Detection of values out of scope	Id1=1, height1 =178 Id2=2, height2 =-160
Separation of values embedded inside others	Name1 = "Mr. John Smith" Name2 = " J. Kowalski PhD" Forename1="John", surname1="Smith", title1="Mr." Forename2 ="J.", surname2="Kowalski", title2="PhD."

DATA VISUALIZATION AND EVALUATION

Data visualization is the process of analysing large amounts of data and communicating the results in visual context so that the audience can more easily digest and act upon the information.

Data visualization and evaluation - Free Data Visualization tools

https://informationisbeautiful.net/

https://www.datawrapper.de/

https://www.tableau.com/academic/students

https://www.openoffice.org/download/

How to make a presentation about a scientific report?

Different types of presentations

- CAT: Critically Appraised topic: short summary of the best available evidence, created to answer a specific clinical question. A CAT looks like a short, rigorous version of a systematic review.
- PICO: Problem, Intervention, Control, Outcome
- Presentation about own research work
- Poster presentation
- Presentation about science project: pitch

Research Question

- PROBLEM
- INTERVENTION
- CONTROL
- OUTCOME

General or Local Anaesthesia at EVAR?

- PROBLEM: MYOCARIODAL INFARCTION ANESTHESIA AT EVAR
- INTERVENTION: LOCAL
- CONTROL: GENERAL
- OUTCOME: MYOCARDIAL INFARCTION

Material and methods

- Baseline Characteristics
- All had anti-coagulant therapy
- Start Heparine or LMWH per case
- Profylac LMWH >12u pre-operative
- Anaesthesia type: decide by the anaesthesiologist or surgeon, patient general or loco-regional anaesthesia
- Endpoint: cardiac events
- Secondary endpoints: other complications, length of stay

Statistics

- Dichotome: percentages, chi-2
- Continue variables: mean± SD ANOVA of Mann-Whitney U – test
- Univariable and multivariable logistic regression model for confounding factors and for associations of cardiac events and type of anaesthesia
- The Revised Cardiac Risk score and propensity score were co-variables in model.
- P <.05 = significant

Revised Cardiac Risk Index
1. History of ischemic heart disease
2. History of congestive heart failure
3. History of cerebrovascular disease (stroke or transient ischemic attack)
4. History of diabetes requiring preoperative insulin use
5. Chronic kidney disease (creatinine > 2 mg/dL)
6. Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery
Risk for cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest:
0 predictors = 0.4%, 1 predictor = 1%, 2 predictors = 2.4%, ≥3 predictors = 5.4%

Results

- 57% general
- 43% loco-regional: 26% epidural en 17% local
- INR >1.8 or therapeutic heparin: 7% vs. 2% (p=0.011)
- Length of stay general vs. loco-regional: 3 (2-4) vs. 2 (2-4) days (p<0.01)
- 4 pt (1.3%) died in the general anaesthesia group
- 29 pt (9.6%) cardiac event

Table 1
Baseline characteristics according to anaesthesia type.

	General ($n = 173$)	Locoregional ($n = 129$)	*P*-value
Demographics			
Mean age (SD)	72 (8)	72 (8)	.75
Male gender (%)	155 (90)	120 (93)	.42
Medical history (%)			
Congestive heart failure	16 (9)	21 (16)	.08
Cerebrovascular disease	28 (16)	15 (12)	.32
Hypertension	122 (71)	75 (58)	.03
Hypercholesterolaemia	162 (94)	112 (87)	.05
Diabetes mellitus	44 (25)	22 (17)	.09
Current smoking	77 (45)	52 (40)	.48
Serum creatinin >2 mg/dL	25 (15)	26 (20)	.22
Ischaemic heart disease	74 (43)	64 (50)	.25
Aortic valve stenosis	6 (4)	3 (3)	.74
COPD	81 (47)	51 (41)	.29
BMI > 30	41 (24)	12 (9)	<.01
Risk indices (SD)			
Revised cardiac risk index	1.9 (1.0)	2.0 (1.0)	.25
ASA class	2.5 (.6)	2.5 (.5)	.59
Medication use (%)			
Anticoagulants	29 (17)	17 (13)	.42
Continuated perioperatively	12 (7)	3 (2)	.11
Aspirin	125 (73)	63 (49)	<.01
Clopidogrel	11 (6)	6 (5)	.62

Abbreviatons: SD standard deviation; LVEF left ventricular ejection fraction; COPD chronic obstructive pulmonary disease; BMI body mass index.

General versus loco-regional: higher risk:

- 30 days cardiac events: OR: 3.8 (CI:1.1-12.9; p=0.03)
- Major cardiac events: OR 13.3; CI 1.2-141.8, p=0.03)

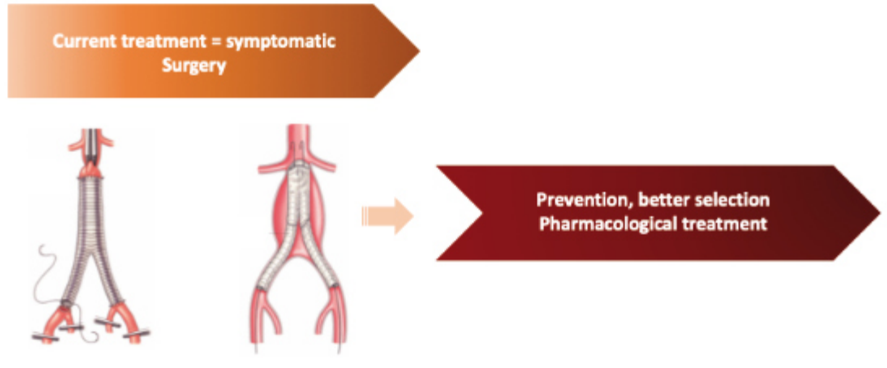
Table 2
30-day cardiac complications.

	General ($n = 173$)	Locoregional ($n = 129$)	*P*-value
	n (%)	*n* (%)	
Cardiac events			
Cardiac death	2 (1.2)	0 (0)	.51
Myocardial infarction	6 (3.4)	1 (.8)	.25
Congestive heart failure	2 (1.2)	0 (0)	.51
Arrhythmia	1 (.6)	0 (0)	1.00
Troponin release	12 (6.9)	5 (3.9)	.32
Composite cardiac endpoints			
All cardiac events	23 (13.3)	6 (4.7)	.02
All but troponin release	11 (6.4)	1 (.8)	.02

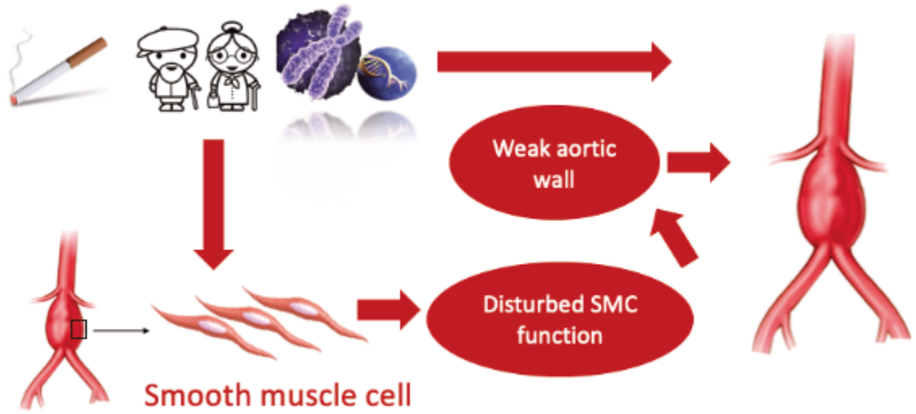
Presentation about own research work

1. What is the key message?
2. How much time to present?
3. Disclosures
4. Introduction to the problem
5. Aim and hypothesis
6. Methods
7. Results
8. Conclusion/ key message

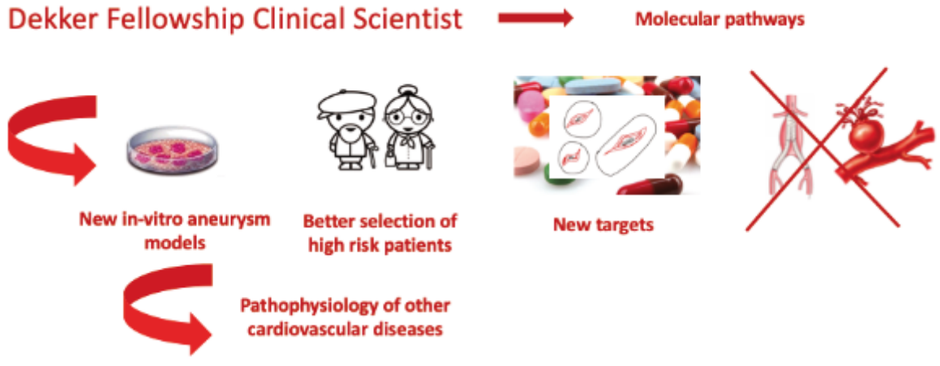
Aortic aneurysms: unsolved problem



Hypothesis



Expected results & impact



CAT or PICO

1. Problem
2. Search on the pubmed
3. References 30-40
4. Introduction/background
5. Hypothesis
6. Aim
7. Method
8. Expected results
9. 3 pgs
10. Figures

Academic writing of project plans and scientific reports

WHAT TO DO BEFORE YOU START WRITING A PAPER?

STEP I: Looking back on your research

- Have you done something new and interesting?
- Have you checked the latest results in the field?
- Have the findings been verified by appropriate analysis and their significance verified?
- Are the methods/measurements valid and reliable?
- Can you describe the scope and limitations of the methods?
- Do your findings tell a nice story or is the story incomplete?
- Is the work directly related to a current hot topic?
- Have you provided solutions to any difficult problems?

If you have answered **"yes"** to all questions, then you can start preparing your manuscript.

STEP II: Thinking over your goals

What type of manuscript?

1. Full-Length Methodology Research (Original articles)
2. Letters/Rapid Communications/Short Communications
3. Case Studies/Case report
4. Review Papers
    - Self-evaluate your work: Is it sufficient for a full article? Or are your results so thrilling that they need to be revealed as soon as possible?
    - Ask your supervisor and colleagues for advice on manuscript type. Sometimes outsiders may see things more clearly than you.

Who is your audience?

- Do you want to reach specialists, multidisciplinary researchers, or a general audience? You will need to adjust information and writing style accordingly.
- Journals, even in similar subjects, reach readers with different backgrounds
- Each journal has its own style; read other articles to get an idea of what is accepted
- Is the readership worldwide or local?

Which journal?

Consider:

1. Aims and scope (check journal websites and recent articles)
2. Types of articles
3. Readership
4. Current hot topics (go through recent abstracts)
5. Asking colleagues for advice

Sometimes it is necessary to lower one's sights or return to the lab/clinic to obtain more data

Access to Scientific Database

Lucian Blaga University of Sibiu offers access to different Scientific Databases for its students:

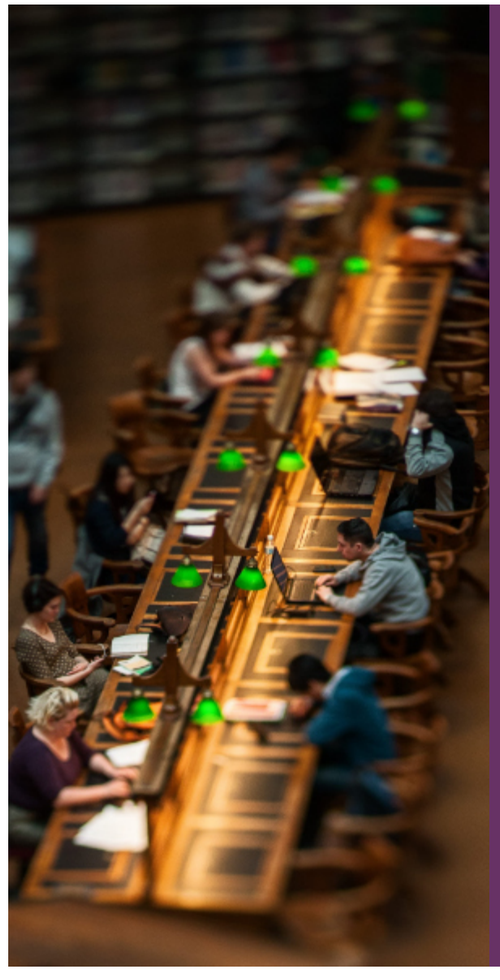
I. Multidisciplinary Database with full-text:

1. ScienceDirect - Journals - Freedom Collection
2. SpringerLink Journals
3. ProQuest Central
4. Oxford Journals
5. EBSCO: Academic Search Complete
6. Sage HSS collection
7. MatSciNet

II. Bibliographical & Bibliometric Database:

1. Thomson- REUTERS Web of Knowledge Web of Science-ISI, Journal Citation Reports, Derwent Innovation Index)
2. Scopus

More information here: http://cercetare.ulbsibiu.ro/doc_DCS/proceduri/acces_baze_date_stiintifice.pdf



Format

Consult and apply the list of guidelines in the “GUIDE FOR AUTHORS”

Ensure that you use the correct:

- Layout
- Section lengths (stick to word limits)
- Nomenclature, abbreviations and spellings (British vs. American)
- Reference format
- Number/type of figures and tables
- Statistics

How to write a quality paper?

1. Title
2. Authors
3. Abstract
4. Keywords
5. Main text (IMRAD)
   - **I**ntroduction
   - **M**ethods
   - **R**esults and
   - **D**iscussions / Conclusions
6. Acknowledgements
7. References

Methods

The METHODS section should be the bulk of the paper and it must provide sufficient information so that a knowledgeable reader can reproduce the experiment.

The METHODS section can be generally divided into several specific parts:

1. Define the population and the methods of sampling
2. Describe the instrumentation
3. Describe the procedures and if relevant, the time frame
4. Describe the analysis plan
5. Describe any approaches to ensure validity and reliability
6. State any assumptions
7. Describe the scope and limitations of the methodology

Results

DO

Use figures and tables to summarize data

Show the results of statistical analysis

Confirm the reliability of the method

Justify the choice of methods

Define the limitations of the method

DON`T

Duplicate data among tables, figures and text

Use graphics that illustrate data that can be easily summarized with text

Graphics

Figures and tables are the most effective way to present results.

BUT:

- Captions should be able to stand alone, such that the figures and tables are understandable without the need to read the entire manuscript
- Captions should not contain extensive experimental details that can be found in the METHODS section

The data represented should be easy to interpret

- Colour should only be used when necessary

Discussion

This is the most important section of the article. Here you get the chance to SELL your data! A huge number of manuscripts are rejected because the DISCUSSION is weak. For some methodology journals, the discussion and conclusions are lumped into one section.

Describe:

- What your results mean?
- Were the methods successful?
- How did the findings relate to those of other studies?
- Were there limitations of the study?

1. Make the Discussion correspond to the Results. BUT DO NOT reiterate the results.
2. DO NOT make “grand statements” that are not supported by the methods or the results Example: “This novel treatment will massively reduce the prevalence of malaria in the third world”
3. DO NOT introduce new terms not mentioned previously in your paper
4. AVOID unspecific expressions such as “higher temperature” or “at a lower rate”; USE quantitative descriptions
5. Speculations on possible interpretations are allowed. BUT these should be rooted in fact, rather than imagination.
6. Compare the published results with your own. BUT DO NOT ignore work in disagreement with yours – confront it and convince the reader that you are correct or better.

Conclusions

Describe

- How your work advances the field?
- Indicate applications of your work.
- Suggest future experiments that build on your work and point out experiments already underway as well.

Better to avoid:

- Downplaying negative results
- Making statements based on personal opinion without scientific support
- Repeating other sections
- Over-emphasizing the impact of your study

Legal provision in medical and human-related scientific research

THE ISSUES OF REGULATIONS IN THE FIELD OF HUMAN SCIENCES

Morality, ethics and deontology in terms of respecting human rights

In order to understand the evolution of regulations in the medical field and humanities over the centuries, it is important to understand the significance of the notions of MORAL, BIOETHICS and DEONTOLOGY, but also the role of enunciating and respecting HUMAN RIGHTS, which have been the basis of all the regulations in bio- medical fields.

Since ancient times, the society has proven the need to define a code of behavior proper to humanistic professions, to frame this type of activity, to prevent possible negative consequences and to trust the members of the society.

The premise from which all these regulations started is the dual concept of GOOD and Evil, which is the foundation of MORAL.

The word MORAL comes from the Latin word "mores" which means good manners, good conduct. Morality represents the set of beliefs, attitudes, habits, feelings reflected in theoretical principles, but also rules and practical rules, whose purpose is to regulate the behavior and relationships of individuals in communities or society. Being determined historically and socially, these principles may differ from one society to another and from one historical moment to another.

All of these principles represent unwritten moral codes, transmitted from generation to generation in the form of moral norms and behaviors, specific to a group, be it family or social.

The word ETHICS derives from the Greek "ethos", having the same meaning as the Latin mores: good manners, good conduct. It is a philosophical discipline that studies the theoretical and practical aspects of morality, providing a set of principles, so written, that must be respected by a certain community or society. Ethical principles are based on the fundamental idea of respecting human rights. Therefore, ethics, as a discipline of study, is the result of the evolution of human civilization and of a higher understanding of the need to respect the human being in all its aspects - biological, spiritual and cultural. Therefore, any field of activity of the company whose object of activity or final beneficiary is the man, will be subject to ethical regulations.

It is thus understood that the evolution of regulations in the medical field and the humanities is closely linked to the level of social and cultural emancipation, to the level of concern of a society towards the individual, but also to the importance it attaches to the differences of sex, age, race , social class, ethnic or religious affiliation.

The term DEONTOLOGY arose from the addition of the Greek words "deon" which means something to be done and "logos", that is, science. Therefore, deontology encompasses a set of moral principles, transposed into behaviors, which must be specifically respected in the exercise of a certain profession. This well defined set of principles specific to each humanistic profession is called the Code of Ethics and has the value of law.

Human rights have been contemporaneous with the history of mankind, as illustrated by the 10 commandments in the Bible, which God dictated to Moses on Mount Sinai. For example, the right to life is protected by the commandment "Do not kill!", The right to property by the commandment "Do not steal!".

Going back to the history of the legal provisions in the field of medical sciences, I will continue to present the most known, but also the oldest written document regulating the medical profession, namely the Hippocratic Oath.

The document belongs to the School of Cos, animated by Hippocrates (460–377 BC), but, although the Oath is attributed to Hippocrates, it is actually much older than the Hippocratic era.

The oath was lodged by the candidates who entered the medical school and not by those who graduated, as is customary nowadays. Doctors have transmitted over the centuries and have followed these principles set out in the Oath.

The invaluable value of the document is given on the one hand by the fact that it concentrates the fundamental principles that must govern the medical practice and, on the other, by its ability to remain current for millennia.

> *“My prescriptions should be made only for the benefit and good condition of the sick, to prevent them from any harm or violence.*
>
> *I will never prescribe a substance with deadly effects, even if I am asked, and I will not give any advice in this regard. I will not give an abortion remedy to a woman.*
>
> *Sacred and clean, I will keep my art and lead my life.*
>
> *I will not operate the stone from the bladder, but I will leave this operation to those who do this job.*
>
> *In any house I will enter, I will do it only for the benefit and welfare of the sick ...*
>
> *Whatever I see or hear during a treatment I will keep it secret, because silence is a duty here.*
>
> *If I respect this oath ... my life and my art will enjoy renown and respect ... if I will betray it ... then the opposite. "*

The oath is not just a collection of principles of medical practice, which brings into question collegiality, fairness, competence, confidentiality and professional responsibility. At the same time, the document also represents a set of moral principles according to which the physician must guide his life:

> *"Sacred and clean I will preserve my art and lead my life ...*
>
> *In any house I will enter, I will do it only for the benefit and welfare of the sick. "*

Here are some of the principles stated in the Oath, whose depth and actuality are impressive:

> *"I swear ... that I will fulfill this oath and his commandments, as much as my strength and reason help me: To respect the one who taught me this art as well as my own parents.*
>
> *To pass on the teachings of this art ... only to those disciples who swore by the custom of the doctors, and to no one else ...”*

The true consecration of human rights was achieved with the Universal Declaration of Human Rights in1948, as a result of the need to protect the individual after the Nazi experiments on prisoners of war and genocide during the Second World War. This represented the turning point that led to the emergence, worldwide, of the legislative provisions, but also the establishment of a branch of science with the role of elaborating and updating the norms of practice in the field of life sciences.

More recently, research on cloning, euthanasia, organ and tissue transplantation, in vitro fertilization are some examples from which we can understand the need to constantly update and adapt the regulatory norms according to the moral-social evolution, but also the scientific advances of the society. These rules are provided for in international treaties to which most countries have acceded.

ETHICS OF MEDICAL SCIENTIFIC RESEARCH

History of medical research regulations

The goals of medical scientific research have always been to advance our knowledge of medical conditions by:

1. Improvement of the methods of diagnosis, treatment and prevention of diseases
2. Understanding the etiology (causes) and pathophysiology (mechanism of production) of certain diseases.

The norms of the ethics of research on human subjects, which are in force today throughout the world, are the result of the international community's reaction to the immoral experiments carried out, so called in the name of science, in different parts of the world, which culminated in the genocide of Nazi experiments.

Many of these experiments, although recorded in the annals of medicine, were not brought to the attention of the public and were left unanswered. Here are some of them: at the beginning of the 20th century, almost 200 children under 8 years old from the British orphanages were injected with tuberculin to study the natural evolution of tuberculosis. In the US, two famous cancer researchers, in the same period, injected cancer cells to residents of a Jewish asylum to track the progress of the disease. Prisoners in a prison in Philadelphia were accepted to be the subjects of medical experiments, with the promise of being released on parole.

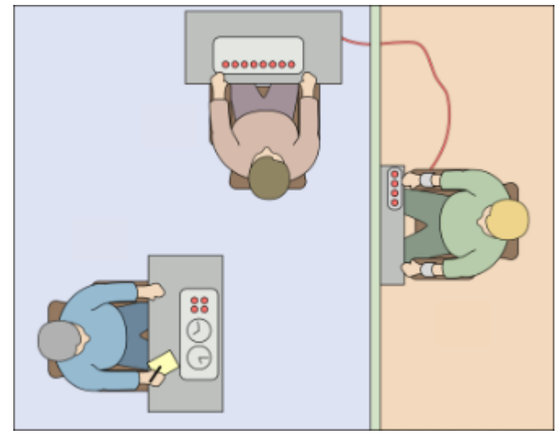
Other experiments have reached the public's awareness and caused reactions from public opinion and international bodies, becoming turning points in the regulation of medical research.

After the end of World War II, inhuman or even deadly scientific experiments, were considered "crimes against humanity" and were tried by the Nuremberg Tribunal in 1947. They they resulted in the adoption of the first code of conduct in scientific research, inspired by the mistakes of this historical episode. The principles introduced by this Code were:

- informed consent (now called informed consent)
- risk-benefit analysis - representing the first recognition of risk theory in medical research
- the recognition of the subject's right to withdraw at any time from the experiment, without being sanctioned (today transposed by the principle of self-determination, of the right to decide with one's own person)

Another historical moment is Wichita, USA, in 1955, when, following the controversies between jurors during a criminal trial, the need arose to regulate how the information regarding the subjects of the research can be obtained and used (who and in what way can use the information) from the perspective of respecting privacy, privacy, human dignity and autonomy. Also, the problem of monitoring the research activities by a specialized jury was raised.

- During the 1960s, psychologist Stanley Milgram studied electric shock experiments, which showed that many people are capable of acting cruelly and immorally when following the orders of an authority, thus raising the issue of "obedience to the authorities".



Another moment that marked the history of regulations in research was the experiment that 300 families of color, disadvantaged from the state of Alabama were subjected, without their knowledge, almost 30 years, in order to track the evolution of untreated syphilis. The experiment continued after the discovery of penicillin, which could have cured them, but which had not been administered, patients infecting other people in time and eventually reaching death in the name of science. The disclosure of the case sparked a great scandal and led to the formation of the Belmont Commission, the most important landmark at the institutional level in the history of the ethics of scientific research. This commission first stated the moral principles of scientific research in the bio-medical field and how they should be put into practice. Another merit of this commission is the imposition of the establishment of research ethics committees that must operate all research institutions, having the role of monitoring the observance of these principles in all research activities.

The researcher and philosopher Tom Beauchamp has the merit of completing and developing these principles in the form of 4 principles that currently represent the basis of all the regulations of the practice in the medical field. These principles are:

I. The principle of non-harm = to do no harm

II. The principle of beneficence = to do good

III. The principle of equality = equal rights and opportunities

IV. The principle of autonomy - the patient's right to self-determination

In the following I will refer to the field of scientific research on human subjects.

ETHICS AND DEONTOLOGY OF RESEARCH ON HUMAN SUBJECTS

Principles

The transposition of these principles previously stated in the specific field of scientific research leads to the formulation of the following fundamental principles of scientific research:

- The principle of the legality and ethics of the research. According to this principle, any medical research activity must be carried out with strict observance of the laws in the field of scientific research and of the ethical and professional norms of exercising the medical profession.
- The principle of beneficence, with its two complementary rules: maximizing the benefits for the patient and minimizing the risks
- The principle of justice refers to the right allocation of resources and the free access of the patient to the competent healthcare. Thus, it is considered unfair for a patient to be denied a benefit to which he or she would be entitled or conditioned in any way to obtain it.
- The precautionary principle provides for the analysis of the risk / benefit analysis, which may require the renunciation of the research, in certain situations

Deontological norms in research on human subjects

From the principles set out above, it follows that, in any scientific research, certain rules must be observed:

1. **Risk assessment**, understood to be an undesirable effect. The risk can be: physical, psychological, social, legal or economic, and its likelihood of occurrence is expressed [through levels - minimum, low, high risk. The risk to which a subject may be exposed must be lower than the anticipated benefit to the individual or society.
2. **Responsibility and protection**. The beneficiary of the research must ensure that the research does not harm the well-being or the rights of the subject. For example, the administration for research purposes of drugs should only be done after testing them on animals.
3. **Prior and correct information of the person**. The medical deontology code of the Romanian College of Physicians explicitly provides the information that a person must know (for example the purpose and duration of the study, the benefits and risks, possible alternatives), while maintaining that they must be made known to the person in a language appropriate to its level of understanding.
4. **Consent**. The same document clearly states that any intervention for medical purposes can only be performed after informing and obtaining the free and written consent of the person. Enrollment in medical studies can be done only with the agreement of the subject, with the certainty that he has understood the purpose and methodology of the research and knows that he is free to withdraw at any time.
5. **The choice** of subjects must respect the principle of justice, in order to avoid involving in categories of suitable persons in research due to their vulnerability, for example children or psychiatric patients. There are 2 levels of justice: a social level and an individual level. For example, adults will be enrolled before children, certain categories (such as disadvantaged or institutionalized people) will be enrolled only under certain conditions.
6. **The results** of the research should also reflect the principle of justice. Both positive and negative results will be made public, respecting the methodology for disseminating the results: scientific communications, articles, evaluation reports, specifying the contribution of each researcher.
7. **Completion of the study**. Each participant must be given access to the benefits obtained from the research, and the study protocol should specify how the acquisitions resulting from the research can be accessed.

Research Ethics Committees

The ethics committee is an independent body, made up of members with a profession in the medical/scientific field, but also members with a profession outside this field, whose responsibility is to ensure the protection of the rights, safety and well-being of the subjects included in the clinical study.

Ethics committees have emerged with the development of research in the biomedical fields. They exist all over the world, in order to avoid abuses and unethical or non-conforming studies with scientific study methodologies. The ethics committees approve the studies, monitor their progress and have the means of sanctioning, the regulations being stipulated in the international research protocols to which Romania is a party. In Romania, these committees are under the control of the Ministry of Health, and operate at the level of hospitals and public health centers where clinical studies are conducted.

RULES ON MEDICAL RESEARCH ON HUMAN SUBJECTS IN ROMANIA

At national level, medical practice and scientific research are regulated both by international protocols to which Romania is a party, and by internal norms such as the Health Law of the Ministry of Health or the Framework Contract of the National Health Insurance House.

In Romania, the Medical Deontology Code of the Romanian Medical College, in chapter VI, presents the rules regarding medical research on human subjects. These rules are presented below, and some of them I have extracted for example.

Art. 88. - Medical research on human subjects is done in compliance with the provisions of international conventions and declarations to which Romania is a signatory party.

Art. 89. - The doctor involved in biomedical research has the duty to promote and protect the life, health, intimacy and dignity of the human subjects participating in the research.

Art. 90. - In carrying out medical research on human subjects, special protection must be given to vulnerable populations, such as:

a) economically and medically disadvantaged persons;

b) persons who cannot give their consent for participating in a medical research (minors, incompetent persons, persons who, because of their condition, cannot express their will);

c) persons who are liable to give their consent under pressure (for example, detainees, military personnel);

d) persons who do not benefit from research personnel;

e) persons for whom medical research is combined with medical care.

Art. 91. - In the research on human subjects, the good of the individual prevails over the good of society in general and of science.

Art. 92. - Medical research for the purpose of medical progress should only be done ultimately on human subjects. This should be done in accordance with existing scientific data, other relevant sources of information and data obtained from animal experimentation where possible.

Art. 93. - The main purpose of medical research on human subjects is to improve prophylactic, diagnostic and treatment methods, understanding the etiology and pathogenesis of a disease.

Art. 94. - No research can be undertaken on a person, unless the following conditions are met cumulatively:

a) there is no alternative method to research on human beings, of comparable effectiveness;

b) the risks to which the person may be exposed are not disproportionate compared to the potential benefits of the research;

c) the research project was approved by the competent court after being subjected to an independent examination on its scientific relevance, including an assessment of the importance of the research objective, as well as a multidisciplinary examination of its ethical acceptability;

d) the person being investigated is informed about his rights and the guarantees for his protection;

e) there is the consent of the participants.

Art. 95. - The research protocol must be evaluated by an ethics commission, made up of persons independent of researchers or sponsors. The ethics commission carrying out the project evaluation must be informed about the conduct of the research and has the right to monitor the ongoing research.

Art. 96. - Medical research on human subjects should be performed only by qualified persons in this regard. This person has responsibility for the subjects involved in the research, even if they have expressed their informed consent for participation.

Art. 97. - The clinical experiment (research without therapeutic purpose) is ethically permissible if it does not entail any serious foreseeable risk. Researchers conducting the clinical experiment are obliged to discontinue it if there is a danger of injury to the subject's health or when the subject requires the experiment to be stopped. Medical research on human subjects can only be carried out if the potential benefits outweigh the risks.

Art. 98. - The imposition by force or by misleading the experiment on man is a serious violation of the principles of medical ethics. The participation of human subjects in the research can be done only voluntarily and only after they have been adequately informed about: the purposes, the research methods, the risks and the anticipated benefits. Also, subjects should be informed that they can withdraw from the research at any time, without prejudice to them in any way. The informed consent of the participants must be taken in compliance with the legal provisions.

Art. 99. - The refusal of a patient to participate in a research should not influence the quality of the doctor-patient relationship.

Art. 100. - In the case of minors, the consent will be obtained from the parents or from the legal representative, and the minor's consent to participate in the research is necessary. Maximum caution is required when using minors in medical experiments and only if the risks are minimal.

Art. 101. - In the case of persons incompetent or incapable of expressing their will, the consent will be obtained from the members or from the legal representatives.

Art. 102. - The inclusion in the medical research of the incompetent subjects or who cannot express their will be done only when the research cannot be carried out using competent persons (the physical or mental condition that prevents the obtaining of the informed consent is a necessary characteristic of the only if the risks are minor.

Art. 103. - The doctor must take all necessary measures to protect the privacy of the subjects participating in the research, to maintain the confidentiality of the information about the subjects, and to minimize the impact of the research on the physical, mental integrity and their personality.

Art. 104. - Research done for therapeutic purposes constitutes the application for the first time in man of medical or surgical procedures and will be done exclusively for curative purpose. In such researches there must be a fair proportionality, in favor of the patient, between the risks of the new procedure and the seriousness of the case; the possible dangers of the new procedure do not seriously weigh the probable evolution of the basic disease or of the treatments known and applied until now.

Art. 105 - The use of placebo in medical research combined with patient care is allowed only when there are no proven prophylactic, diagnostic or therapeutic methods for the participating subjects or when patients receiving placebo are not exposed to additional risks.

Art. 106. - The participants in a medical research must have access to the benefits resulting from it, after the conclusion of the research.

Art. 107. - The publication of the results of a medical research on human subjects will be done with respect to the accuracy of the data and only if the national and international ethical norms governing the medical research on human subjects are respected.

Art. 108. - It is forbidden to cause artificial illnesses to healthy people, for experimental reasons.

Art. 109. - In all cases of clinical research, for the human verification of the effectiveness of certain diagnostic or treatment methods, the condition of the voluntary consent of the subject will be strictly respected.

Art. 110. - Human experimentation must respect a number of rules:

a) be preceded by a serious experimentation on the animal;

b) the subject to voluntarily accept, to be a major, in a state of freedom and perfectly informed about the risks;

c) in the case of incurable diseases, in subjects in the terminal stage, the remedy should not cause additional suffering and there are reasonable chances of being useful;

d) remedies that would alter the psychic or the moral consciousness cannot be experienced.

Art. 111. - Any therapeutic or experimental activity on the human being is prohibited for the simple reasons of professional or scientific pride, the result of which the majority of individuals cannot benefit or which harm the cultural or moral principles of the community.

Art. 112. - The experiments regarding the cloning of the human being are forbidden.

CASE STUDY

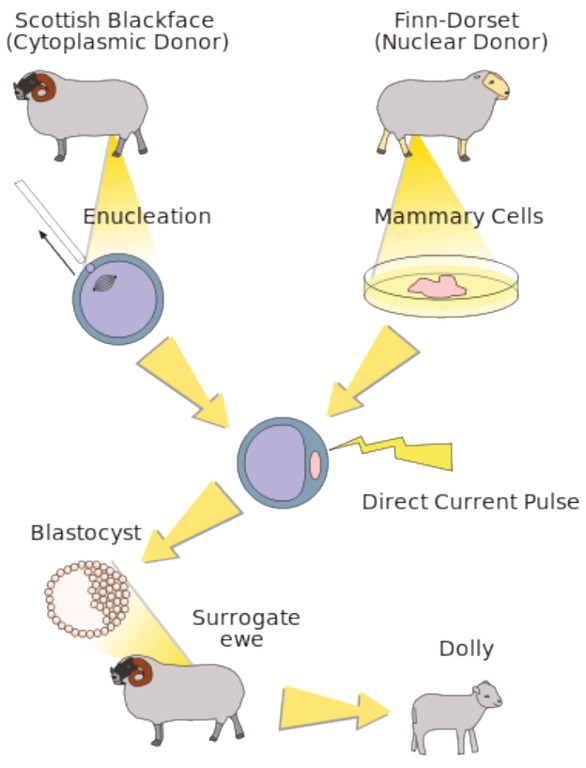
Finally, I chose to present a case study that I consider relevant from the perspective of scientific research and its implications for the future of mankind. It is about the Dolly experiment, the first successful cloning, that made it a jerk in the middle of the years ”90.

But by the time of the cloning of Dolly's sheep, the scientific world had already come a long way in the field of genetics, starting with the first artificial clone, obtained in 1930, by halving the salamander's embryo with the help of a hair, followed by the identification and deciphering of the DNA structure. , in 1953 and the success of combining the DNA of 2 different organisms, in 1973, considered the starting point of genetic engineering. After 1980, embryo division was a practice already known in the scientific world.

From the point of view of the reproduction and formation of new organisms, up to that time it was known and almost unanimously accepted that each cell of the organism contained the genetic material of an individual of a particular species and that, during the evolution of an embryo, each cell was they specialize to form certain organs and to perform certain functions, some cells remaining "asleep".

In 1996, a team of researchers from the University of Edinburgh obtained the first artificially created mammal, starting from the nucleus of an adult somatic cell. They extracted an egg from a sheep to which they extracted the ulnuclear DNA, carrying the genetic information, and implanted genetic material extracted from the udder of a second sheep. The obtained cells were kept 7 days in a culture medium, after which they were implanted in the uterus of a third sheep, which became "surrogate mother". The latter gave birth to Dolly, the perfect copy, until the last woolen thread, of the second sheep, from which the genetic material was harvested, despite the fact that both the cellular organs of the egg harvested from the first sheep , as well as the cells of the surrogate mother's placenta also possessed a genetic heritage.

The diagram below shows the process of cloning Dolly sheep.



Following the announcement of the cloning of Dolly sheep, public opinion reacted violently. Many have accused scientists of "playing God," while others have seen the benefits of using such technology. The image captures a group of protesters carrying a banner with a message addressed to one of the two researchers: "Dear Ian, do not touch people!"

Dolly has aged very quickly, a fact attributed to researchers by genetic inheritance, because the sheep that provided the genetic material suffered from arthritis when their cells were taken. Another cause could have been that Dolly was too protected, living in the lab environment. After 7 years, it was discovered that Dolly also suffered from lung cancer and was euthanized. Her body has been healed and is on display at the Royal Museum of Scotland in Edinburgh.

What makes this experience extraordinary is the researchers' ability to demonstrate that the genetic information contained in a cell can be "awakened" and used, leading to the emergence of a new organism, without fertilization being the basis of this process. The cloned sheep was the first being created from a single cell.

Meanwhile, other sheep, pigs, mice, cats and monkeys have been successfully cloned worldwide. In the case of the cat, the pigmentation of the cloned cat differed from that of the mother, a fact attributed to the influence of the environmental factors during the cell development. Despite these successes, it seems that the failure rate in the case of mammalian cloning is 97%.

Less than a year after Dolly's birth, American physicist Richard Seed announced that he intends to clone human beings, not being the only one who has considered this possibility. In the same year, the company Advanced Cell Technology in Massachusetts, as well as researchers in Italy and other countries, announced they were in a situation where they could clone a human being.

The situation created raised great questions about the ethical nature of such experiments. In response, the US House of Representatives passed a law against cloning people, only accepting cloning of certain organs for implantation purposes.

Human cloning is the process of creating a genetic copy of one that already exists, in the absence of male genetic input. The formation of the embryo no longer implies sexual contact, the existence of a sperm and fertilization, the clone being obtained from any adult human cell, belonging to a man or a woman. The clone or genetic copy will thus present the physical appearance, behavioral, biochemical and physiological characteristics of the cell from which it originated and not of the organism in which the pregnancy was developed. Therefore, a clone will have a single genetic parent. The term is used for artificial cloning, in the laboratory, because there is also a natural cloning, which occurs in the body of the pregnant woman, after fertilization and which leads to the appearance of monozygotic twins.

The purpose of human cloning is not to obtain new individuals, but to obtain stem cells that can replace diseased cells and obtain therapeutic substances. Another purpose is the genetic modification of the organs of some animals so that they can be transplanted into humans. Most religious institutions and governmental and non-governmental organizations strongly oppose human cloning, especially reproductive cloning.

CONCLUSION

In conclusion, research on human subjects must be carried out in compliance with the ethical principles of the research, derived from human rights, in compliance with the deontological principles and the norms that regulate the activity in the field of research. Beyond the provisions regarding the usefulness and the scientific correctness, the moral and ethical aspects of the research can give rise to numerous controversies, and by their results they can also bring spectacular benefits or they can lead to major risks for humanity. But can this Pandora's box be opened once more?

ENSURE

EDUCATING STUDENTS FOR DEVELOPING HIGH QUALITY RESEARCH SKILLS

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