Chapter 1

RESEARCH QUESTION, HYPOTHESIS, DIFFERENT TYPES OF STUDY.

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Any clinical research project arises from a question posed by an investigator. The first step in a project is to have a research idea and formulate it correctly. The passage from the idea to the formulation of the question consists simply in expressing what one intends to do and why.

It must first be verified that the research project is useful, new, ethical, and feasible. In the formulation of the research question must appear the nature of the population to be studied, the factor studied and its judgment criterion, the nature of the comparison if there is one, and the type of study envisaged: cross-sectional study, case-control study, cohort study, randomized trial.

I- ANATOMOPHYSIOLOGY OF RESEARCH: HOW DOES IT WORK?

The structure of the research project is defined in the protocol, which must always be written before starting the study. The protocol is essential for requesting credits, promoting the study, but it is also vital for obliging the researcher to organize his ideas in a logical and efficient way before starting the project.

The research question

It is the uncertainty that the researcher wants to remove, this is the objective of the study. The question is often general at first, but needs to be gradually refined.

For instance :
- Should the French eat more cheese?

The question needs to be more focused. Thereby :
- Does eating more cheese reduce fracture risk?
- Doesn't cheese bring too much cholesterol?
- Don't calcium supplements provide the same anti-fracture benefit as cheese?
- Don't Calcium Supplements Make You Smell Like Cheese?

The rationale (or context)

It is the first part of the protocol, which justifies the question: we focus on the field, thanks to the literature, and we highlight the questions that still arise.

Organization: the different types of studies

A distinction is made between observational studies and intervention studies.
- **Observational studies** can be cross-sectional, when subjects are observed all at once. **Cohort studies** observe subjects over time. Cohort studies are *prospective* if you collect data at the start and then follow the subjects. They are *retrospective* if the data collection is done

after the fact. **Case-control studies** compare subjects who have a disease with another group that does not.

Intervention studies, or clinical trials, test the effect of a drug or non-drug intervention.

The subjects, or patients

The inclusion or exclusion criteria define the target population of the study. The number of subjects to be enrolled is also an important element.

The variables

This is the information to collect. In an analytical study, there will be predictor variables (which have the potential to be causal) and endpoint type variables (it is the result).

Statistics

You should calculate the sample size needed before writing the whole protocol: if the study is not feasible because of an inaccessible size, you should not waste your time. The statistical analysis plan should be planned in advance.

This analysis is based on the notion of hypothesis, which must be clearly stated from the beginning, generally in the form of the research question.

II- THE RESEARCH QUESTION

The question arises from issues that one may encounter in one's own clinical practice, or emerges from previous research work of one's own or other researchers. Often a young researcher will not have enough perspective to design a question and will need the help of a senior.

The origins of the question

Knowing the literature

Before embarking on a new study, it is necessary to know the literature on the subject, and ideally to carry out a systematic review. You have to attend meetings in the field and talk to experts on the subject.

Be open to new ideas, new techniques

You have to listen to lectures and keep a critical mind with regard to commonly accepted ideas. For example, it has long been considered that sciatica by herniated disc should be treated by bed rest, so as to reduce the pressure on the intervertebral disc. In fact, several controlled clinical trials have shown that it does not improve prognosis.

Keep your imagination moving

Clinical observation of patients often brings ideas. Teaching, during its preparation or thanks to the inquisitive questions of certain students, can also be the source of new ideas. Then, you have to be creative to apply the idea, tenacious because the practical difficulties are numerous, and not fear criticism.

Choose a mentor

He will bring experience and knowledge of a subject. It will avoid making certain mistakes and facilitate access to the necessary funding.

Design the right question

A good question must be ***FINE*** : ***F***easible, ***I***nteresting, ***N***ew, ***E***thical.

Feasible

- Number of subjects:

Too many studies cannot answer the question because the sample size is not sufficient. The calculation must be done from the beginning, in a realistic way, and we must not hesitate to rephrase the question in a less ambitious way, or abandon the subject if we cannot answer.

- Technical aspects:

One must have sufficient experience and technical equipment to measure the variables of interest and analyze the data. Working with co-investigators who are more specialized, in particular a biostatistician, often proves essential, so as to have all the desirable technical skills.

- Cost:

The cost of each component of the project must be carefully estimated, knowing that the actual costs often exceed the estimates.

- Stay focused*:*

Don't try to answer too many questions at once.

Interesting

You can't be the only one who finds this question interesting. Talk about it to those who are familiar with the area. It is then necessary to imagine what the results will bring, to what extent they would advance knowledge, influence practices, or guide new research. When this relevance is not obvious, the question must be discussed again.

New

We see too many studies that have already been conducted… A study must make a new contribution. It is the study of the literature and the discussion with the experts that will make it possible not to reinvent the powder gun.

Ethics

If the study involves too much physical risk or invasion of privacy, the study design should be reviewed. In addition, a poorly designed study, which does not allow the question to be answered correctly (insufficient sample size, etc.) is not ethical either.

III- THE HYPOTHESIS

It is an assumption, born of reflection or observation, which leads to predictions, which may be refutable. A study will determine if this assumption is an accurate description of the relationship between the factors being studied.

In general, the null hypothesis is posed: there is no association between the factor studied and the endpoint. The alternative hypothesis is that there is a relationship between the factor studied and the endpoint.

Characteristics of a good hypothesis

A good hypothesis is based on a good question. It should be simple, specific, and stated in advance.

Simple versus Complex

A simple hypothesis includes a predictor variable and an endpoint: early menopause is associated with an increased risk of fragility fracture.

A complex hypothesis contains more than one predictor variable: early menopause, age and thinness are associated with an increased risk of fragility fracture; or more endpoints: smoking is associated with cardiovascular risk and lung cancer.

Complex hypotheses cannot be tested with a simple statistical test.

Specific versus vague

A specific hypothesis leaves no ambiguity about the subjects and variables or how the statistical test will be applied.

Types of assumptions

Null hypothesis and alternative hypothesis

The null hypothesis indicates that there is no association between the predictor variable and the outcome in the population. The null hypothesis is the formal basis of a statistical test. This helps to estimate the likelihood that the association observed in a study is due to chance. The proposition that there is an association is the alternative hypothesis. It cannot be tested directly. It is accepted by default if the statistical significance test rejects the null hypothesis.

Uni- and bilateral alternative hypotheses

A one-sided hypothesis specifies the direction of the association between the predictor variable and the outcome. The hypothesis that menopause increases the risk of fragility fracture is one-sided. A two-sided hypothesis specifies that an association exists; it does not specify the direction. The hypothesis that menopause is associated with fracture risk is two-sided, as it does not specify the direction.

IV- THE DIFFERENT TYPES OF STUDY

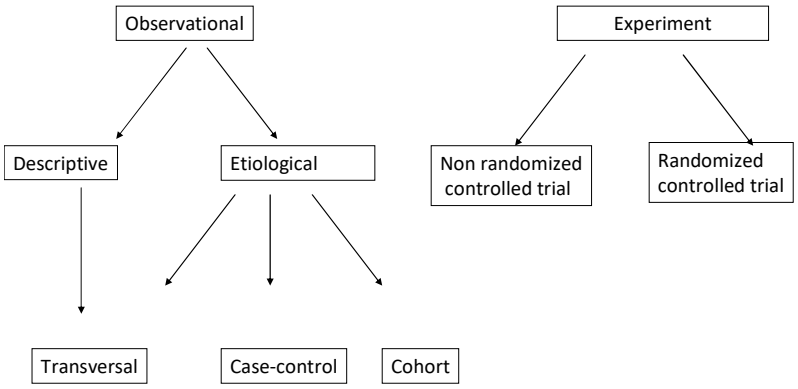

Figure 1. The différent study types

Descriptive studies

They report on a phenomenon, its frequency, its distribution and its evolution. They provide quantitative data on the distribution of a disease or a risk factor. These are cross-sectional studies or prevalence studies, in which a measurement is made at a given time. They

pose the problem of the lack of information on the chronology of events. Easy to carry out, they make it possible to formulate hypotheses to be tested in future analytic studies.

Analytical studies

They determine the role of one or more factors in the etiology or treatment of a disease.

Observational studies

- *Case-control studies:*

The subjects have a disease. The witnesses do not have this disease. Past risk or exposure factors are then explored, and their frequency compared in cases and controls. There are retrospective studies, therefore subject to certain biases (for example of memory), but well suited to the study of fairly rare events.

- Cohort studies:

Subjects are selected based on exposure to certain risk or exposure factors, and are followed for a given period of time to observe the consequences of that exposure.

Experimental studies

Patients are subjected to an intervention and its effects are observed. The reference model of the experimental study is the randomized clinical trial, controlled with respect to the placebo or a reference treatment. However, there are several models:

- Without control group, or in cross-over design:

The subject is his own control.

- With control group:

The randomized trial is the reference, since the only difference between the intervention group and the control group is the intervention, thanks to the random allocation (randomization). The treatment received may be known to the patient but not to the investigator (single-blind), unknown to both (double-blind), or unknown to the patient and to the evaluator (who is different from the one treating, for example with a invasive procedure; this is the pseudo-double blind).

We often define a level of proof according to the type of study carried out, the pinnacle being the randomized controlled clinical trial. However, the type of study depends above all on the question to be answered, and must therefore be adapted to it (Figure 2).

QUESTION RAISED	STUDY TYPE
Diagnostic test	Transversal study, randomized trial
Prevalence	Transversal study
Incidence	Cohort study
Prognosis	Cohort study
Treatment/Intervention	Randomized controlled trial
Etiology and causality	Cohort study, case-control study

Figure 2: different study types in relation to the question raised

CONCLUSION

When the question is formulated, the hypothesis raised and the type of study chosen, the research protocol can be precisely written.