## CHAPTER XIII

# DRAFTING THE PROTOCOL

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The protocol is the document that describes the method of the study that we propose to carry out, from the justification to the objectives, from the hypothesis to the methodological constraints. It defines its conditions of realization and its progress.

It is essential to write the protocol at an early stage in the study design process, both for the investigator and those participating in the study, as well as for the ethics committees or the sponsors. Its innovative character, its relevance, the importance of the question asked, as well as the expected impact of the result of the study on the target population will facilitate obtaining adapted funding to the required budget.

In this chapter, a protocol plan is proposed, each step of which is described. Through the drafting of the protocol, we find all the concepts developed in the different chapters of the book.

The plan proposed in this chapter is a general plan that can be used in all situations that can be encountered in clinical research. For a design study that is simpler than an analytical study, all the steps that are described here are not necessarily useful or relevant.

Each of these nineteen steps is not presented in a fixed order. If for the first five and the last nine the proposed order is relatively logical, it is different from the sixth to the tenth stage, where we have much more freedom to consider and order this information according to the sequence which seems the most natural in the context in which we find ourselves.

**These steps are as follows:**

1 - The title
2 - The objective(s)
3 - The justification of the study
4 - The hypothesis(es)
5 - The type of study
6 - The factor(s) studied
7 - Judgment criterion or criteria
8 - Causes of error: biases and confounding factors
9 - Subjects
10 - Data analysis
11 - Data collection and management
12 - Data analysis
13 - A possible pilot study
14 - The ethical implications

15 - Staff
16 - Budget
17 - The calendar
18 - Any annexes
19 - References

## I - THE TITLE

It summarizes the problem we propose to study. It must be clear, precise, sufficiently short and at the same time sufficiently informative.

It may contain information on the type of study proposed. After the title must be mentioned the name of the investigator(s) and that of their institution, as well as the date of development and the number of the version of the protocol.

## II - THE OBJECTIVE(S)

There are four main types of objectives, which must be formulated very clearly and very precisely:

**- The first concerns the prognosis, or the evolution of a pathological state.**
The objective is to know and understand the events that will occur in a patient between the moment when the disease declared itself and the moment when the clinical history ends (by recovery, death or installation of the patient in another physical, mental or social state).

**- The second concerns etiology, or causality.**
Understanding a causal relationship is fundamental for the clinician who will be guided in his work of diagnosis, treatment or prevention. The objective is to highlight a causal relationship between two events or to calculate the strength of the association between two factors.

**- The third concerns the performance of diagnostic tests.**
The objective is to evaluate a diagnostic strategy, or to improve the interpretation of the results of a test.

**- The fourth concerns the impact of an intervention.**
The objective is to evaluate a therapeutic, screening, preventive or educational intervention: does it do more good than harm, what is its cost-utility ratio? While there may be secondary goals, there should only be one primary goal. This must be formulated in clear terms, and the results of the study will refer to it.

## III - THE JUSTIFICATION OF THE STUDY

Research is expensive and time consuming. It can also put patients in situations of discomfort or risk. Emphasis must therefore be placed on the direct impact of its results.

The process of justification begins with a very complete bibliographical research on the subject, in order to identify the weaknesses of the information available on the question that one proposes to study.

It is necessary to define the importance of the problem - incidence, prevalence, morbidity, mortality, etc. - as well as its context, in time, in terms of geographical distribution and population.

**The heart of the justification is constituted by:**

- the description of the mismatch between what is observed and what should be,
- the explanation (or attempted explanation) of this discrepancy,
- a proposed solution to remove this discrepancy.

**It is necessary to insist on:**

- the current nature of the question asked, and the new, unpublished nature of the information that will be provided;
- the level of morbidity or severity of the event in question;
- the size of the population affected by the problem (very specific sub-group versus very large population);
- the possible insertion of the research project in programs currently in progress, or its repercussions on this program;
- the multidisciplinary nature of the project: medical, paramedical, economic, psycho-social or political.

In short, a research protocol is good, and justified, when it is new, relevant, feasible, and ethical.

## IV - THE HYPOTHESIS(ES)

Any research protocol, if it is an analytical study, must explicitly formulate a hypothesis. There are no assumptions in a descriptive study, which essentially aims to describe the distribution of characteristics of a population.

A hypothesis is a statement (and not a question) about a possible relationship between the factor(s) studied and the judgment criterion(ies). This assertion must follow logically from the argumentation contained in the justification.

In general, the hypothesis is proposed in the form of the null hypothesis: "there is no association between the factor studied and the judgment criterion" so that the statistical test, constructed from the data collected, allows to calculate the probability that the observed association occurs by chance alone.

The proposition: "there is an association between the studied factor and the judgment criterion" constitutes the alternative hypothesis.

The formulation of the hypothesis must be accompanied by the description of the conditions under which the hypothesis is supposed to be true.

There may be several hypotheses to be tested in a single study, but the fewer the better.

## V - THE TYPE OF STUDY

The researcher must choose a type of study. The choice of the most appropriate type of study depends on the objectives and the question asked, but also on the resources.

**There are two broad categories of study:**

1- descriptive studies, mainly cross-sectional studies or prevalence studies;
2- analytical studies: observational studies, with case-control studies and cohort studies, and experimental studies, with free trials and comparative trials.

Some study types are better suited to some questions *(Table 1)*. The level of proof of the conclusions of the study is all the better as the type of study is better suited to the question asked.

*Table 1 - Most suitable type of study according to the nature of the question asked*

| Nature of the question | Best suited type of study |
|---|---|
| Prevalence | Cross-sectional study |
| Incidence | Cohort study |
| Risk | Cohort study, case-control study |
| Prognosis | Cohort study |
| Etiology, causality | Cohort study, case-control study |
| Intervention | Trial |
| Diagnosis | Cross-sectional study, trial |

## VI - THE FACTOR(S) STUDIED

The factor of interest is defined as an event, condition, exposure, or intervention that is hypothesized to be associated with a health problem, disease, or other outcome of interest.

It is therefore a variable to be measured. There may be several for the same study. The researcher must provide the list in the protocol. It could be:

- descriptive details of an individual;
- data, obtained by questionnaire, on an individual's background, habits or symptoms;
- data obtained by measurement;
- descriptive data on an exposure, a diagnostic, therapeutic, prevention, screening, education or information intervention.

**Clarification should be made on how to measure these variables:**

- questionnaire;
- if it is an instrumental measurement, description of the instrument, and the conditions under which the measurements are carried out (fasting, sitting, after rest, etc.).

These measurement methods, on which the quality of the data and the validity of the results depend, must also take into account the financial and human cost.

## VII - JUDGMENT CRITERION(A)

The judgment criterion, or resulting factor, is defined as the situation or event supposed to be the result of the influence of the factor studied.

These events of interest to both the patient and the clinician or epidemiologist fall into five categories:

- death,
- disease,
- disability,
- discomfort,
- dissatisfaction,
- to which we can add a sixth element, impeachment, which has a more social dimension. It can also be their inverse: survival, recovery, absence of disability, …

The definition of these judgment criteria must be as precise as possible.

A judgment criterion is also a variable. It is the so-called dependent variable, in relation to the factor studied, which is the independent variable.

The same care must be taken in the method of measurement as for the factors studied.

## VIII - CAUSES OF ERROR: BIASES AND CONFOUNDING FACTORS

**A bias is a systematic error** that contributes to producing estimates that are systematically higher or lower than the true value of the parameters to be estimated. It intervenes for example at the level of the selection of the patients who will take part in the study, or on the measurement of the parameters to be studied. All potential biases must of course be identified, anticipated and avoided when designing the study.

**A confounding factor** is a factor that modifies the effects of the studied factor on the judgment criterion, because of its link with both the studied factor and the judgment criterion. At the stage of writing the protocol, the researcher must establish the list of all the known variables likely to behave as confounding factors, and choose a type of study, as well as an analysis strategy, to control for their possible influence. (This is the constraint of observational studies. This does not exist in randomized trials which offer the possibility of controlling for these confounding factors, even if not measured, or unknown, due to randomization.)

## IX - SUBJECTS

The population studied and the subjects involved in the study must be described in the protocol, taking into account several points:

- are we sure that we can generalize the results from the population studied? In other words, are the subjects studied representative of the population to which we want to relate the results?
- will there be enough subjects to study?
- will the response rate of the subjects solicited for the study be correct?
- is the population stable (particularly important characteristic for a longitudinal study)?

- if the study requires control subjects, does their mode of selection guarantee that they are similar to the cases?

**Thus the protocol must present:**

- the inclusion criteria, or eligibility criteria, which define the main characteristics of the population involved in the study;
- the exclusion criteria, which define a subgroup of subjects who do not meet the criteria for inclusion, or which could satisfy it, but which present certain characteristics which could interfere with the quality of the data or the interpretation of the results (high probability of being lost sight of, inability to provide correct data, etc.).

**Populations often used are:**

- inpatient populations;
- professional groups;
- special categories of civil servants (soldiers, etc.);
- clienteles of general practitioners;
- or real samples of the general population.

## X - THE SAMPLE SIZE

The sample must be representative of the population to which the conclusions of the study will apply. The sampling technique should be described at the protocol stage. Determining the sample size is an essential part of the protocol.

The validity of the results partly depends on it. It has a fundamental influence on the budget. It depends on:

- the amplitude of the effect that we hope to highlight
- the power of the test used to detect such a difference, if it exists
- the significance threshold chosen to highlight such a difference
- available budgetary resources

## XI - DATA COLLECTION AND MANAGEMENT

Details have already been given on the information to be collected concerning the factor(s) studied and the endpoint(s). Additional information should also be provided on:

- the mode of collection and the calendar;
- the measuring instruments used;
- laboratory techniques;
- field work methods;
- quality control;
- the computer hardware used as well as the technique: type of computer and software, coding and input method.

## XII - DATA ANALYSIS

The protocol must include a description of the statistical analyzes planned in the study and their justification (for taking into account, for example, confounding factors).

The choice of computer equipment is linked to that of the statistical analyses.

**The statistical analyzes are of two types:**

- descriptive statistics, which analyze the distribution of variables;
- analytical statistics, to test the original hypothesis(es) and provide information on the significance of the association revealed between the variables studied.

## XIII - A POSSIBLE PILOT STUDY

It is not always necessary.
It must be carried out on a representative sample. It is useful for:

- train and test the personnel involved in the study;
- assess the acceptability of the procedures;
- assess the response rate;
- estimate the amplitude of the difference to be observed (which is useful for determining the size of the sample).

The pilot study must therefore be planned early enough to allow modifications to the course of the study to be adapted if necessary. You have to estimate your own cost and duration.

## XIV - THE ETHICAL IMPLICATIONS

At the protocol implementation stage, ethical considerations emphasize respect for the person, through issues of confidentiality and the principle of minimizing risk.

The security measures concerning the data must be described: anonymity, limited access, destruction of the data after the end of the study, identification of the subjects impossible during the publication of the results.

The measures taken to guarantee that the patient is not exposed to a risk greater than a risk incurred routinely are also specified.

Obtaining informed consent from a patient involved in the study must also be guaranteed.

Finally, a list of the names and functions of the members of the research team must be provided with the protocol.

## XV - STAFF

Who does what and when? All staff involved in the study should be identified (this step is important for estimating the budget):

- principal investigator
- coordinator
- promoter
- clinical research assistant
- technician (laboratory, electroradiologist, etc.)
- responsible for interrogations
- secretary
- input operator
- computer programmer
- statistician

For some, especially those responsible for the questionnaires, information should be provided on their training and their understanding of the specific objectives of the study.

## XVI - THE BUDGET

This paragraph summarizes all the stages of the study from the point of view of cost. The quality of its presentation, its relevance and its justification are essential for the acceptance of the project by a funding body.

It can be presented in two sections:

- equipment
- management and staff

## XVII - THE CALENDAR

It must specify the duration and time of each step.

## XVIII - ANY ANNEXES

They bring together a number of documents:

- the patient information letter
- the informed consent form
- the approval documents from the various decision-makers or institutions involved in the study (hospitals, ministries, employers, trade unions, etc.)
- the operations manual (questionnaires, input sheets, follow-up letter, etc.)
- the description of measurement methods
- the approval of the ethics committee, when this is acquired

## XIX - REFERENCES

This section gives the references of the various documents cited in the different parts of the protocol.