Chapter 5
Writing the research protocol

5.1 Introduction

After proper and complete planning of the study, the plan should be written down. The protocol is the detailed plan of the study. Every research study should have a protocol, and the protocol should be written.

The written protocol:

- forces the investigators to clarify their thoughts and to think about all aspects of the study;
- is a necessary guide if a team (not a single investigator) is working on the research;
- is essential if the study involves research on human subjects or is on experimental animals, in order to get the institution's ethical approval;
- is an essential component of a research proposal submitted for funding.

During the process of the development of the protocol, investigators can and should try to benefit from the advice of colleagues and experts in refining their plans. But once a protocol for the study has been developed and approved, and the study has started and progressed, it should be adhered to strictly and should not be changed. This is particularly important in multi-centre studies. Violations of the protocol can discredit the whole study. If the violations are minor, at least that part of the study should be excluded from the analysis.

An additional step, after writing the protocol, particularly in large studies with teams of investigators, is to develop what may be called the operations manual for the study. This will include detailed instruction to the investigators to assure a uniform and standardized approach to carrying out the study with good quality control.

A well-thought out and well-written protocol can be judged according to three main criteria.

- Is it adequate to answer the research question(s), and achieve the study objective?
- Is it feasible in the particular set-up for the study?

- Does it provide enough detail that can allow another investigator to do the study and arrive at comparable conclusions?

The protocol should outline the rationale for the study, its objective, the methodology used and how the data will be managed and analysed. It should highlight how ethical issues have been considered, and, where appropriate, how gender issues are being addressed.

5.2 Format for the protocol

The research protocol is generally written according to the following format.

- Project title
- Project summary
- Project description:
  - Rationale
  - Objectives
  - Methodology
  - Data management and analysis
- Ethical considerations
- Gender issues
- References

Project title

The title should be descriptive and concise. It may need to be revised after completion of the writing of the protocol to reflect more closely the sense of the study.

Project summary

The summary should be concise, and should summarize all the elements of the protocol. It should stand on its own, and not refer the reader to points in the project description.

Project description

Rationale

This is equivalent to the introduction in a research paper. It puts the proposal in context. It should answer the question of why and what: why the research needs to be done and what will be its relevance. A brief description of the most relevant studies published on the subject should be provided to support the rationale for the study.

Objective(s)

Specific objectives are statements of the research question(s). Objectives should be simple (not complex), specific (not vague), and stated in advance (not after the research is done). After statement of the primary objective, secondary objectives may be mentioned. Young investigators are advised to resist the temptation to put too many objectives or over-ambitious objectives that cannot be adequately achieved by the implementation of the protocol.

Methodology

The methodology section has to be thought out carefully and written in full detail. It is the most important part of the protocol. It should include information on the research design, the research subjects, interventions introduced, observations to be made and sample size.

- Research design: The choice of the design should be explained in relation to the study objectives.
- Research subjects or participants: Depending on the type of the study, the following questions should be answered:
  - What are the criteria for inclusion or selection?
  - What are the criteria for exclusion?
  - In intervention studies, how will subjects be allocated to index and comparison groups?
  - What are the criteria for discontinuation?
- Interventions: If an intervention is introduced, a description must be given of the drugs or devices to be used, and whether they are already commercially available, or in phases of experimentation. For drugs and devices that are commercially available, the protocol must state their proprietary names, manufacturer, chemical composition, dose and frequency of administration. For drugs and devices that are still in the experimental stage (or that are commercially available but are being used for a different indication or in a different mode of administration), additional information should be provided on available pre-clinical investigations in animals and/or results of studies already conducted on humans. In such cases, the approval of the drug regulatory agency in the country is generally needed before implementing the study.
- Observations: Information should be provided on the observations to be made, how they will be made, and how frequently will they be made. If the observation is made by a questionnaire, this should be appended to the protocol. Laboratory or other diagnostic and investigative procedures should be described. For established

procedures, reference to appropriate published work is enough. For new or modified procedures, an adequate description is needed, with a justification for their use.

- Sample size: The protocol should provide information and justification about sample size. A larger sample size than needed to test the research hypothesis increases the cost and duration of the study and will be unethical if it exposes human subjects to any potential unnecessary risk without additional benefit. A smaller sample size than needed can also be unethical if it exposes human subjects to risk with no benefit to scientific knowledge. The basis on which sample size is calculated should be explained in the methodology section of the protocol. Calculation of sample size has been made easy by computer software programs. But the principles underlying the estimation should be well understood. These have been explained in Chapter 4.

Data management and analysis

The protocol should provide information on how the data will be managed, including data coding for computer analysis, monitoring and verification. Information should also be provided on the available computer facility. The statistical methods used for the analysis of data should be clearly outlined.

Ethical considerations

As outlined in Chapter 4, section 4.12, ethical considerations apply to all types of health research. These include research involving human experimentation, whether the research is of therapeutic or diagnostic nature that is carried out on patients who may expect a potential benefit from their participation, or is of a purely scientific nature for which human subjects volunteer to advance medical science but will not draw any therapeutic or diagnostic benefit. There are also ethical considerations for research involving human subjects but not experimentation. Epidemiological, field and qualitative studies fall under this category. Although no experimentation is involved, such studies can be as intrusive on the individual's privacy and even on communities. The ethics of research involving experimentation on animals has been receiving proper and increasing attention recently.

All research protocols in the biomedical field, particularly if it involves human subjects, must include a section addressing ethical considerations. This includes two components: The first is a written approval of the appropriate ethics review committee, together with a written form for informed consent, where appropriate. The second is a special section, preferably in the format of a checklist, to address all possible ethical concerns. Simply getting the ethical approval is not enough.

Approval by ethics review committees

For studies in humans (or involving human biological materials), the protocol must be approved by the local, institutional or equivalent ethics committee and/or national ethics committee.

For animal studies approval is required from the animal welfare committee of the institute or its equivalent. If no such committee exists, a statement signed by the principal investigator(s) should indicate that the research will be carried out in accordance with the International Guiding Principles for Biomedical Research involving Animals (see 4.12.4).

Informed decision-making

A consent form, where appropriate, must be developed and attached to the protocol. It should be written in the prospective subjects' mother tongue. The consent form has two parts: a) a statement describing the study and the nature of the subject's involvement in it; and b) a certificate of consent attesting to the subject's consent. Both parts should be written in simple language so that the subject can easily understand the contents. As much as possible, the use of medical terminology in writing up the consent form should be avoided. Special care is needed when subjects are illiterate.

The statement should, as appropriate, explain why the study is being done and why the subject has been asked to participate. It should describe, in sequence, what will happen in the course of the study, giving enough detail for the subject to gain a clear idea of what to expect. It should clarify whether or not the study procedures offer any benefits to the subject or to others, and explain the nature, likelihood and treatment of anticipated discomfort or adverse effects, including psychological and social risks, if any. Where relevant, the statement should include a comparison with risks posed by standard treatments or drugs. If the risks are unknown or a comparative risk cannot be given it should be so stated. Finally, the statement should indicate that the subject has the right to withdraw from the study at any time without, in any way, affecting her/his further medical care.

Ethics checklist

The protocol must describe the measures that will be undertaken to ensure that the proposed research is carried out in accordance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (Annex 1).

A checklist must address ethical concerns that could be raised about the methodology, including the research design, selection of subjects, the interventions introduced and the observations to be made.

- Is the research design adequate to provide answers to the research question? It is unethical to expose subjects to research that will have no value.
- Is the method of selection of research subjects justified? The use of vulnerable subjects as research participants needs special justification. Vulnerable subjects include those in prison, minors and persons with mental disablity. Particularly in international research, it is important to ensure that the population in which the study is conducted will benefit from any potential outcome of the research. They should not be doing it to the benefit of another population. Justification is needed for any inducement, financial or otherwise, for participants to be enrolled in the study.
- Are interventions justified, in terms of risks/benefits ratio? Risks are not limited to physical harm. Psychological and social risks must also be considered.
- For observations made, have measures been taken to ensure confidentiality?

Gender issues

It was only recently that attention was drawn to the importance of addressing gender issues in research protocols. The Commission on the Status of Women made the above statement. This was in response to several areas of concern. "Ensure, where indicated, that clinical trials of pharmaceuticals, medical devices and other medical products include women with their full knowledge and consent and ensure that the resulting data is analysed for sex and gender differences."

- Women were often excluded from clinical trials on disease conditions that affect both men and women, on the basis of biological variability, and/or vulnerability. But women were given the same drugs, which had not been tested on them, as men if the drugs proved safe and effective for men.
- Drugs and devices intended for use by women only were sometimes tested on them without their proper informed consent, particularly in poor resource settings.
- When women were included with men as research subjects, gender was not always taken into consideration when results were analysed.

It is well known that genetic and hormonal factors modify the prevalence, behaviour and treatment of diseases of body systems in men and women. But what is less known is that culturally evolved gender-related differences in lifestyle behaviour are also powerful determinants of women's health and account for major differences in the disease burden between males and females, probably more than genetic or hormonal factors. Both biological and gender-related differences can influence the outcome of the research for men and women.

References

The protocol should end with relevant references on the subject.

References and additional sources of information

Commission on the Status of Women Forty-third session. Revised draft agreed conclusions on women and health submitted by the Chairperson of the Commission. New York, United Nations Economic and Social Council, 1999 (E/CN.6/1999/L.2/Rev.1).

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