Chapter 7

Implementing the research project

7.1 Introduction

How should research be done? The answer to this question can be given in one word: well. Whatever the reason for the research, and whatever the kind of research, it should be done well and should conform to established standards of scientific methodology. It has been said that there is only one type of research: good research. Bad research does not deserve the name of research.

It is not enough that the research question has been well conceived, the appropriate research design selected, and a detailed protocol well thought out and written. All these provide a good anatomy for the research. Physiology matters even more. The research should be implemented with scientific rigour.

7.2 Scientific rigour

The English word “rigour” literally means “strictness”. In scientific research, the term rigour is used to imply that:

• the study protocol is being adhered to;
• the research is conducted in accordance with established ethical standards;
• meticulous and detailed records of all observations are maintained;
• methods of measurement are used in an objective way to provide valid and reliable results;
• data are analysed and interpreted using appropriate statistical methods to assess the validity of the results and their generalizability;
• the researchers continue to be well versed with the literature on the subject during the study;
• results are presented in such a way that other investigators can re-analyse the data using the same processes and methods and reach the same conclusions, and other investigators can replicate the study to confirm or refute the findings.
7.3 Pre-testing the protocol

It is always wise to pre-test the protocol after developing it. This is particularly important in large and expensive studies. What appears to be a straightforward and problem-free protocol may prove to have logistic and practical problems in implementation. The pre-test is sometimes called a pilot study. Based on the outcome of the pilot study, the protocol may be modified before the study proper is implemented.

The pilot study can help in determining whether the required number, as well as composition, of study subjects will be recruited within the time frame of the study. The size of the sample may need to be modified, or alternative approaches of recruitment may be explored.

The pilot study can help in testing the methods of measurement. If the study relies on how records have been kept, these records may be checked for accuracy and completion before the study is started. If a questionnaire has been designed, this will need to be pre-tested to check that the questions are clear without any ambiguity and that the answers will be consistent. Modifications may have to be made for the final instrument. If the methodology involves a clinical or laboratory measurement, this has to be tested for inter-rater and intra-rater reliability, i.e. for consistency in results obtained by different workers and by the same worker at different times.

The pilot study can also help in testing the system for data management. Entering and editing the data from the pilot study will show whether the system is working well. This includes designing the forms for recording measurements, choosing a computer, developing programmes for data entry, management and analysis; and planning dummy tabulations to assure that the appropriate variables are collected.

7.4 Monitoring of the study

The study should be monitored. In large clinical trials, a monitor may be appointed with the responsibility of reporting on the progress of the trial and for verification of data. There are two components to monitoring: data management (record keeping and data handling) and data quality (quality assurance and quality control).

Record-keeping and handling of data

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of the quality of the data and the performance of the clinical trial (“the audit paper trail concept”). A basic aspect of the integrity of data is the safeguarding of “blinding” with regard to assignment of subjects to different treatments. Subject files and other supporting data must be kept for a period of time as required by local regulations.
A common problem in research is the tendency of investigators to collect many data, much more than they can analyse or publish. This can result in an excessively large database and increase the chance of inaccuracy. Limiting the data to be collected to the essential data for the study, and eliminating redundancies, will enhance the accuracy of the study. A general advice to investigators is to be parsimonious (not to expand more than is necessary).

**Quality assurance and quality control**

A system for quality assurance must be implemented to ensure that the study is performed and the data are generated, recorded and reported in compliance with the protocol, good clinical practice and national regulations. In clinical trials, all sites and all data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of data and to ensure that the conclusions presented are derived correctly from the raw data. Quality assurance is carried out with the following objectives: to ensure that no data are missing and to ensure that data are precise and accurate.

Missing data will introduce a problem in the analysis of results, whether the data are missing because the measurement was not made or was not recorded. A special type of missing data is loss to follow-up. Loss to follow-up will decrease the number of subjects. Generally, when sample size is estimated, a provision is made for an estimated percentage of loss to follow-up. But this does not completely solve the problem. Loss to follow-up may introduce a bias in the study and discredit its conclusions. The subjects lost to follow-up may be different from the subjects who continued in the study. For example, subjects who develop serious side-effects, complications or even die may be disproportionately represented in the loss to follow-up.

Monitoring during the study can help in reducing the problem of missing data. A computer program can help during data entry to ensure that all data are entered. The computer program will flag missing and out-of-range values.

Inaccurate and imprecise data are a worse problem than missing data, because they may not be discovered after the fact. Only a systematic quality control programme will avoid the problem.

Reliability of measurements is an important component of quality assurance. To test for intra-observer reliability, a common way is to do the measurements twice (test–retest reliability). The results obtained from the first test are then correlated with the second test. To test for inter-observer reliability, a common way is to have the same measurements done by two observers. The results obtained from the first test are then correlated with the second test.
To ensure the quality control of laboratory measurements, blinded duplicates or standard pools can be used. In multicentre studies involving laboratory measurements, a common practice is to have a reference laboratory. This reference laboratory will standardize the test to be used and will periodically send the same sample to the different centres and provide them with feedback on how their results compare with each other and with results as determined in the reference laboratory. This mechanism of quality control is essential before a decision is made to pool the results from the different centres together for analysis.

7.5 Periodic tabulations and reports

Periodic tabulation of the data is useful in the monitoring process. Periodic frequency distribution tables will reveal aberrant values. Periodically looking at the data should never mean breaking the code for blinded studies.

7.6 Validation of results in qualitative research

The researcher doing qualitative research may use two or more methods (observation, interviews, focus group discussions) to answer the same question, or may use more than one source for data collection. The objective is to enhance the validity and reliability of the results by comparing the data obtained from different methods or different sources. This process in qualitative research is sometimes referred to as “triangulation”. The idea of triangulation originated from a craft used by land surveyors, who increase the validity of a map by incorporating measures from different angles. Multiple and diverse observations can enrich the description of a phenomenon. The researchers may also cross-check interim research findings with the respondents. This is called “respondent validation”.

7.7 Good clinical practice

Results of clinical trials on novel pharmaceutical products have to be submitted to drug regulatory authorities before the products can be approved for general use. The drug regulatory authority will not only look into the results. It will also consider the process by which these results were obtained, and how the research was carried out. The research should have been conducted according to good clinical practice (GCP). The drug regulatory authority will discard any results of research that did not conform to the guidelines for GCP.

GCP is a standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and
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which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product under investigation are properly documented. A World Health Organization technical report provides guidelines for good clinical practice for trials on pharmaceutical products, and is the basis for some of the material in this chapter (WHO, 1995).

Audit is an important component of GCP. An audit is a systematic examination, carried out independently of those directly involved in the clinical trial. Its objective is to determine whether the conduct of a trial complies with the agreed protocol, and whether the data reported are consistent with the records on site. For example, it may check whether data reported or recorded in the case report forms are consonant with those found in hospital files and other original records. The auditor may use statistically controlled sampling to verify data obtained in a trial.

7.8 Research on new pharmaceutical products

Clinical trials of pharmaceutical products should be done in a stepwise fashion. Progress to the next phase should follow the successful completion of the previous phase. The number of subjects in the trial is increased from one phase to the next, as safety and efficacy of the product becomes better established. Animal toxicology studies are usually required, and specific toxicology studies should be completed before moving from one phase to the next.

Clinical trials are generally classified into phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, is given below.

- Phase I clinical trials: These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of the safety, and the pharmacokinetic and, where possible, pharmacodynamic profile of the active ingredient in humans.

- Phase II clinical trials: These trials are performed in a limited number of subjects and are often of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose–response relationships in order to provide an optimal background for the design of expanded therapeutic trials.
• Phase III clinical trials: Phase III trials include larger (and possibly varied) patient groups, with the purpose of determining the short-term and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

• Phase IV clinical trials: Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration, new combinations, etc. are normally considered as trials on new pharmaceutical products.

7.9 Termination of the study

A study on a new pharmaceutical product should be closely monitored. The study should stop if: a) unanticipated, potentially serious side-effects are encountered; or b) the comparative study shows clearly, before the study is completed, that one drug is clearly superior to the other.

7.10 Changes in the protocol

The study should be carried out in accordance with the written protocol. Any subsequent change must be agreed upon and documented. For large studies, standard operating procedures in the form of detailed written instructions should be developed and followed.

The protocol should be adhered to. Unauthorized changes in the protocol are termed violations. Violations of the protocol, if discovered late, discredit the study. If discovered before the analysis, the data should be discarded from the analysis. Minor changes can be made in the protocol if this does not affect the characteristics of the data. Otherwise, the data before and after the change cannot be pooled together. If major changes have to be made in the protocol, data before and after the change should be analysed separately.
7.11 Ethical issues in the implementation of the study

7.11.1 Ethical principles

An ethically acceptable design is only as good as the carrying out of the design. The ethical principle of non-maleficence or “do no harm” implies that during implementation of clinical trials, a “cut-off point” should be defined so that if the proposed treatment proves risky or inferior to the alternative, it should be stopped. The ethical principle of respect implies during implementation that patients should be able to withdraw their consent at any time without losing any benefit.

7.11.2 Experimentation on animals

Ethical approval is needed for animal research from the appropriate local and national authorities. Only investigators and personnel who have the appropriate qualifications and experience should carry out research on animals. Experimental work on animals should only be done in qualified and certified facilities. Research animals should be properly cared for as regards housing, environmental conditions, nutrition and veterinary care. Normally the care of animals should be under the supervision of veterinarians having experience in laboratory animal science. The avoidance or minimization of discomfort, distress or pain to the animal is an ethical imperative. Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anaesthesia in accordance with accepted veterinary practice. At the end of, or, when appropriate, during an experiment, animals that would otherwise suffer severe or chronic pain, distress, discomfort, or disablement, that cannot be relieved, should be painlessly killed.

7.11.3 Scientific honesty

Data should be carefully and accurately collected, without any subjective bias on the part of the investigators. As discussed in Chapter 4, a methodology that is relevant in this regard is the double-blind controlled clinical trial, where the investigators are not aware of the type of medicine the subject is given. In a “triple-blinded” design, patients, clinicians and statisticians (or persons measuring the outcome) are unaware of which group is subject to which intervention. Another research methodology is randomization, whereby it is not up to the investigator to assign particular treatments to different subjects. The decision is made by random allocation.

Deliberate scientific fraud is ethically unforgivable. Fraud involves deliberate deception and may take the form of fabricating data, inventing patients, or manipulating data to provide a desired answer. The pressure to “publish or perish” in academic institutions may be a factor, as well as the practice of drug companies of paying a fee to
the investigator for every patient participating in a clinical trial. Local research ethics committees should have the authority to audit the implementation of the research, and to contact research subjects.

7.11.4 Fiscal honesty

Research programmes and projects are commonly supported by government, private or international funds. The research funds have to be used to meet the expenses as agreed upon in the research proposal. Expenditure has to be documented. Accurate periodic and final financial reports are required and should be submitted.

References and additional sources of information
