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Conduct in Clinical Trials

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Introduction

Clinical trials constitute a prerequisite for the development of new and improved therapeutical tools in medicine. It is therefore of utmost importance that such trials are designed to fulfill high scientific and ethical standards and also are meticulously conducted, recorded, terminated, and reported according to pre-established criteria detailed in the study protocol. Several incidents of scientific misconduct have caused widespread concern within the medical community and among involved authorities and have spurred the development of rules for conduct of clinical trials. Scientific misconduct broadly falls into one of three categories: piracy, plagiarism, and fraud (1). The reason for scientific misconduct can be factors such as pressure to publish in order to get funding, personal ambition, vanity, or direct financial gain. There are three broad approaches to prevent scientific fraud and misconduct: education, training, and the establishment of ethical standards.

In order to set up a general standard for conduct of clinical trials and to ensure the quality of these trials, several authorities have established guidelines for "good clinical trial practice", or GCP (2, 3, 4). Similar guidelines have also been developed in other countries, such as India (5). The *ICH Guideline for Good Clinical Practice* (2), for example, is intended to provide a unified standard for the European Union (EU), Japan, and the United States. This guideline was developed with consideration of GCP in the above-mentioned areas as well as in Australia, Canada, the Nordic countries and the World Health Organization (WHO), and is also relevant to many other countries.

The purpose of this monograph is to review some of the important issues involved in clinical trials intended to follow GCP according to the *ICH Guideline*.

Declaration of Helsinki

The fundamental document regarding ethical guidelines for research in human subjects is the *Declaration of Helsinki* (4, 6), originally adopted by the World Medical Assembly in 1964 with later revisions at regular intervals. The *Declaration* is worded in rather general terms. Consequently, its contents must be interpreted when applied to research that is clinical or non-clinical. Clinical research refers to research related to medical care in which one or more components have potentially diagnostic, therapeutic, or prophylactic value for the patient group concerned. Some important principles of the *Declaration of Helsinki* include the following:

- The researcher should be well qualified and highly familiar with the specific field.
- It must be possible to motivate the research by a favorable risk benefit assessment meaning that it must be scientifically sound. Thus risks and discomfort for the subject must be carefully weighed against the foreseeable benefits of the research and the benefits must exceed the risks.
- Research subjects must be assured of the best possible diagnostics and therapy. For example, research subjects must not receive medical care of a lower standard than they would have received had they not participated in the study. The comparative study is based on not knowing the best alternative in advance.
- The information given to the research subjects must be easy to understand and sufficient to

enable them to determine for themselves whether they wish to participate in the research project or not. The patients' right to withdraw their participation must also be clearly presented in this information.

- It is the duty of the physician to place the health or well-being of the subject above the interests of research.

- Accordingly, the risk benefit analysis is central to the ethical evaluation of research. The research must make it clear that the project has the prerequisites for yielding a positive answer to this essential question; without expected benefit, the risk benefit analysis can never have positive results. This means that the background and significance of a project must be explained and that the results obtained with the methods used can answer the question.

The *Declaration of Helsinki* also emphasizes the responsibility of the researcher for the accuracy of the results and for their interpretation. The *Declaration of Helsinki* has resulted in expansions and interpretations taking into account special ethical problems (7, 8).

Basic Ethical Principles

The conduct of clinical trials must be based on some basic ethical principles (4). These basic principles apply to all relationships between people and involve the following: *respect for individuals*, which means that each one should respect the other's ability and right to self-determination (autonomy) and integrity. In the study situation, the subject's ability to independently decide about information of therapeutical alternatives should be encouraged.

The *beneficial principle* and the *principle of non-maleficience*, which means that each person should strive to do good and guard against or prevent harm, and that others should not be exposed to harm.

The *principle of fairness*, which means that all individuals should be treated equally, if there are no ethically relevant differences among them and that it must be possible to justify differences in treatment with reference to ethically relevant differences among those concerned.

These fundamental principles of ethics may conflict with each other and they may also be interpolated and apply differently in various situations. For example, the requirement to do well may conflict with the requirement of fairness, or with the requirement of respect for the individual, and there are many more examples of this. It is therefore important to do an ethical analysis in practice. It is important to try to identify the concerned parties of interest, the consequences of different alternatives for the concerned parties, and to evaluate these consequences. Some aspects that should be considered when working with an ethical analysis in practice can be summarized schematically illustrating the stakeholders/agents' model (9, 10).

Problem: What is the problem, whose problem is it?

Background: What do we know about medical, psychological, social, economic, and other relevant facts in the case?

Concerned Parties: Who are they?

Alternatives: What are they? What are the advantages and disadvantages of the different alternatives?

The Principles of GCP

The principles of GCP involve a number of important issues of which some will be discussed in more detail. The principles are very similar, as outlined in different documents, and are based on the *Declaration of Helsinki*. Some of the important issues are as follows:

- Responsibilities of the investigator
- Responsibilities of the sponsor
- Handling of trial drugs
- Rule of the ethics committee

- Reporting adverse events
- Compensation to subjects and investigators

Other important issues are:

- Specific arrangements for multicenter studies
- Statistics and data management
- Preservation of records

Responsibilities of the Investigator

A clinical trial can be initiated and designed by an investigator with or without sponsorship from a pharmaceutical company. Irrespective of the organization of the study, the ethical rules of the *Declaration of Helsinki* should be followed. The principal investigator should have the qualifications and competence to perform the clinical trial. Thus he/she should be experienced in research or receive scientific support from an experienced colleague. The investigator should have good knowledge of and experience in the field of medicine defined by the protocol and also have the resources for the proper conduct of the trial. The investigator should have good knowledge of the properties, effects, and side effects of the investigational drugs and be familiar with the pre-trial data. The investigator should be aware of and should comply with GCP and the applicable regulatory requirements. The investigator should permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authorities. The investigator should have sufficient time to properly conduct and complete the trial. The investigator should develop the protocol or, if the trial is performed in cooperation with a sponsor, the investigator should have the possibility to participate in designing the protocol. A steering committee can take this responsibility in cases where multiple investigators are participating. The site of the trial and the facilities and staff should have the conditions and skill to carry out the trial according to the responsibilities. The investigator is responsible for ensuring that the number of subjects is sufficient and that the subjects are suitable for the trial. The investigator is responsible for informing the subject about the study, obtaining informed consent, and communicating with the national drug regulatory agency and ethics committee. Monitoring and auditing procedures are an important issue, which should be stated in writing in the protocol or contract. During the course of the trial the investigator is responsible for adherence to the protocol, handling of drugs, handling of data, safety aspects, annual reports, and interim analyses, if applicable. After completion of the trial the investigator is responsible for the care of the subjects so that subjects included in the trial receive appropriate treatment and follow-up. Data records should be completed and a study report written.

Responsibilities of the Sponsor

The sponsor is often a pharmaceutical company but may also be an investigator or another institution that initiates, organizes, and oversees the conduct of a trial. The sponsor has a number of responsibilities and the contacts between investigator and sponsor are usually effected via a monitor. The monitor should ascertain that the investigator, co-investigator, and involved staff are qualified as stated above. During the course of the trial the monitor makes frequent visits to the study sites and evaluates the progress of the trial and the different activities related to the trial. After completion of the trial, the monitor should ensure that all activities within the trial are fulfilled, finished, and retained according to the rules set up in the protocol.

Handling of Trial Drugs

The handling of trial drugs including the supply, control, and quality of the investigational drugs or intended placebo is the responsibility of the sponsor together with the investigator in cooperation with the pharmacy. Detailed instructions have been developed (2).

Role of the Ethics Committee

The *Declaration of Helsinki*, originating from 1964, is the basic document concerning research ethics. The history of the *Declaration* is

interesting. It was preceded by the Nürnberg code in 1947 (4), which evolved against the background of the trials against German physicians and others prosecuted for war crimes in 1945 after the end of World War II. The physicians committed the crime of exposing prisoners in concentration camps to inhumane experiments. In 1931, even before to the Nürnberg code, guidelines were issued for conducting experiments with new therapy on humans by the Ministry of Health in Germany. In these guidelines it was stated that if medicine is to progress, new and as yet insufficiently tried therapeutic methods must be studied scientifically. However, potential benefits of research must be balanced against the physician's duty to safeguard the life and health of subjects participating in a research project. Since the *Declaration of Helsinki*, research ethics committees have been gradually established and are nowadays widely represented at universities and hospitals.

According to the *ICH Guideline for GCP* (2), the independent ethics committee (IEC) is an independent body constituted of medical/scientific professionals and non-medical/non-scientific members. The legal status, composition, and function of IECs may differ among countries but should require the IEC to act in agreement with GCP. The institutional review board (IRB) is an independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial. This is done by, among other things, approving and providing ongoing review of trial protocols and amendments as well as the methods and material to be used in obtaining and documenting informed consent of the trial subjects. According to the *ICH Guideline for GCP*, the combined IRB/IEC should obtain trial protocols, amendments, written informed consent forms, subject recruitment procedures, safety information that can be evaluated, information about payments and compensation available to subjects, and other issues important for the study to fulfill GCP. The IRB/IEC should also review each ongoing trial at appropriate intervals. From an ethical point of view the IRB/IEC review covers:

- scientific validity of the project;
- ethical problems raised by the project; and
- information given to research subjects.

Written Informed Consent

A fundamental component of a clinical trial is that subjects be informed about the purpose and nature of the study. The subject or the subject's legally acceptable representative should be informed orally and provide written informed consent. The informed consent form should be approved by the IRB/IEC before use, and should be written in language that is easily understood by the research subject or legal representative. The information should be given by the investigator or another suitable person.

The information should include an explanation of the trial. The content that should be addressed is comprehensively described in the *ICH Guideline for GCP*, based on the *Declaration of Helsinki*. Important issues include the purpose of trial procedures, foreseeable risks and benefits, and alternative procedures. Issues regarding payment of expenses to the subject should also be addressed. It should be emphasized that the subject's participation in the trial is voluntary and if the subject wishes to withdraw from the trial at any time, he or she may do so without penalty or loss of benefits to the subject otherwise entitled. The subject should also be informed that the monitor, the auditor, the IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the information.

Compensation to Subjects and Investigators

If applicable, the sponsor should provide insurance or indemnity (legal and financial) to the investigator or the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence. The costs of treatment of trial subjects and compensation to trial subjects should be addressed in accordance with applicable regulatory requirements. Trial subjects should be compensated for expenses and loss of income in connection with the trial, but the reason for the compensation should be specified, otherwise it may be regarded as a "bribe" in order to facilitate recruitment. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/ institution.

Reporting Adverse Events

The trial protocol should clearly state the method and frequency with which adverse events should be detected. The sponsor should expedite reporting to all concerned investigators/institutions, to the IRB/IEC, and to the regulatory authorities of all adverse drug reactions that are serious or unexpected. The severity of the adverse reaction and the possibility of a causal relationship to the drug given should be estimated. Specific time limits for the report should be set up depending on the severity of the reaction.

Other Important Issues

Specific Arrangements for Multicenter Studies
Certain aspects are more complex in multicenter trials and a special administrative system may be required. The responsibility for start up and overall performance of the trial could be the task of a steering committee. A supervisory committee can be appointed to provide advice on policy matters and supervision of data. The supervisory committee should have access to the results obtained in the trial, including adverse experiences. The committee can break the code under certain circumstances and have the option to recommend that the steering committee make changes in the trial plan, such as early termination. The supervisory committee members should be independent from the study.

Statistics and Data Management
Statistical considerations and data management, including the design of case report forms (CRFs), should be an integrated part of the protocol. The CRF should be carefully monitored against source data and any changes or corrections should be documented and signed. Essential elements in the presentation of the results include baseline comparisons of the treatment groups, actual randomized subjects into the trial, and number of subjects allocated randomized treatment. In the interpretation of the results it is essential that results are formally claimed to be significant only if they apply to the hypothesis explicitly stated in the protocol.

Preservation of Records
Both the principal investigator and the sponsor are obliged to retain records and data from the study for safety reasons and to allow audit and inspection. The time frames depend on national regulations and consideration of factors such as insurance programs.

Conclusion

The formal regulations for the conduct of clinical trials have dramatically improved during the last decades and are based on the *Declaration of Helsinki* adopted by the World Medical Assembly in 1964. Several incidences of scientific misconduct have spurred researchers, institutions, authorities, and industry to comply with high ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. These standards are designated good clinical practice (GCP). The *ICH Guideline for GCP*, which is the basis of this monograph, is intended to provide a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. In these guidelines detailed rules have been developed which thoroughly regulate the responsibilities of the investigator, the sponsor, and the conduct of the trial.

Irrespective of formal guidelines, the quality of a clinical trial is no better than its weakest link and therefore the conduct and competence of the investigator, sponsor, and monitor are of utmost importance for the reliability of the results of the study. The design of a study and the performance of the involved parties are crucial from an ethical point of view as research subjects are in the hands of the experts, no matter how comprehensive the information about the trial is. The conduct of a clinical trial is thus a great responsibility for the investigator and sponsor but also a great opportunity to improve and develop clinical medicine for the future benefit of the patient.

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