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Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*

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INTRODUCTION

The purpose of these WHO Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products is to set globally applicable standards for the conduct of such biomedical research on human subjects. They are based on provisions already promulgated in a number of highly developed countries including Australia, Canada, European Community countries, Japan, Nordic Countries (Denmark, Finland, Iceland, Norway and Sweden) and the United States. These guidelines inevitably vary somewhat in content and emphasis, but all are consonant with regards to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the interested countries. Every care has been taken, in developing the WHO Guidelines as a practicable administrative tool for use by WHO's Member States, to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultation, to seek formal acceptance of the Guidelines by Member States as a contribution to harmonization of national standards and to facilitating movement of pharmaceutical products internationally. No question arises, however, of challenging or replacing existing national regulations or requirements. The objective is to provide a complementary standard that can be applied worldwide. In countries where national regulations or requirements do not exist or require supplementation, relevant government officials may designate or adopt, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted.

The Guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, but protect the rights and safety of subjects, including patients, and ensure that the investigations are directed to the advancement of public health objectives.

The Guidelines are intended specifically to be applied during all stages of drug development both prior to and subsequent to product registration and marketing, but they are also applicable, in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and, in particular, to every newly-trained doctor.

Glossary

The definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

adverse event
Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

adverse reaction
A response to a pharmaceutical product that is noxious and unintended and which occurs at doses normally used or tested in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse or dependence and interactions with any other product should be considered adverse reactions.

audit of a trial
A systematic examination, carried out independently of those directly involved in the trial, 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, e.g. whether data reported or recorded in the case-report forms (CRFs) are consonant with those found in hospital files and other original records.

case -report form (CRF)
A document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

clinical trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

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 do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:

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

Phase II
These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess 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 extensive therapeutic trials.

Phase III
Trials in larger (and possibly varied) patient groups with the purpose of determining the short- 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, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV
Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on 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 premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

comparator product
A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

confidentiality
Maintenance of the privacy of trial subjects including their personal identity and all personal medical information.

contract
A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation/distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.

contract research organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

escape treatment
Any supplementary treatment provided to relieve the trial subject of symptoms caused by the investigated disease in the clinical trial. Escape treatment is often used in order to alleviate pain in placebo-controlled trials.

ethics committee
An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report
A comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal.

Good Clinical Practice (GCP)
A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP Guidelines published by WHO *(1)*.

informed consent

A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (see Appendix 1).

inspection
An officially-conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in this document.

investigator
A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

investigational labelling
Labelling developed specifically for products involved in a clinical trial.

investigational product (synonym: study product)
Any pharmaceutical product (see definition) or placebo being tested or used as a reference in a clinical trial.

investigator's brochure
A collection of data for the investigator consisting of all the relevant information on the investigational product(s), including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated.

monitor
A person appointed by, and responsible to, the sponsor or Contract Research Organization (CRO) for the monitoring and reporting of progress of the trial and for verification of data.

patient/subject file
A collection of data consisting of all relevant information on the patient or subject (such as hospital file, consultation records or special subject file) that permits the authenticity of the information presented in case-record forms to be verified and, where necessary, completed or corrected. The conditions regulating the use and consultation of such documents must be respected.
pharmaceutical product
Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

protocol

A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

quality assurance relating to clinical trials
Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting, and professional or personnel qualifications.

raw data
All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies in the form of photocopies, microfiches etc. Raw data can also include photographic negatives, microfilm or magnetic media (e.g. computer diskettes).

serious adverse event
An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures (SOP)
Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

study product (synonym: investigational product)
Any pharmaceutical product or placebo being tested or used as reference in a clinical trial.

trial subject
An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control The individual may be:
– a healthy person who volunteers to participate in a trial;
– a person with a condition unrelated to the use of the investigational product;
– a person (usually a patient) whose condition is relevant to the use of the investigational product.

validation
Action of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

verification (validation) of data
The procedures carried out to ensure that the data contained in the final report match original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer print-outs and statistical analyses and tables.

witness
A person who will not be influenced in any way by those who are involved in the clinical trial, who is present and may provide assistance if required when the subject's informed consent is obtained, and documents that this consent is given freely by signing and dating the informed-consent form.

1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

1.1 *Justification for the trial*
It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified.

1.2 *Ethical principles*
All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki (see Appendix 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) and non-maleficence (doing no harm) as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS)*(2)* or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles. (See chapters 3 and 4).

1.3 *Supporting data for the investigational product*
Pre-clinical studies that provide sufficient documentation of potential safety and eventual clinical application of a pharmaceutical product are a prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that the it is of suitable quality for the intended investigational use. The pharmaceutical, pre-clinical and clinical data should be adapted to the appropriate phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for the planning and conducting of subsequent trials.

1.4 *Investigator and site(s) of investigation*
Each investigator should have appropriate expertise, qualifications and competence to undertake a proposed study.Prior to the trial, the investigator(s) and the sponsor should establish an agreement on the protocol, standard operating procedures (SOP), the monitoring, and auditing of the trial, and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently (see chapter 4).

1.5 *Regulatory requirements*
Countries in which clinical trials are performed should have regulations governing the way in which these studies can be conducted. The pre-trial agreement between the sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application to or notification of the trial to the relevant authority, amendments to the trial protocol, reporting of all adverse events, and notifications to ethics committee). All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In countries where regulations do not exist or require supplementation, relevant government officials may designate, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted. The use of these Guidelines should not prevent their eventual adaptation into national regulations or laws. Neither should they be used to supersede an existing national requirement in countries where the national requirement is more rigorous.

2. THE PROTOCOL

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used; the reasons for proposing that it should be undertaken on humans; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent. Other important items to be included in a clinical trial protocol are listed in Appendix 2.

The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations), review bodies (e.g. institutional review board, peer review committee, ethics committee, drug regulatory authority), constituted appropriately for this purpose and independent of the investigator(s) and sponsor.

3. PROTECTION OF TRIAL SUBJECTS

The personal integrity and welfare of the trial subjects as defined in the Declaration of Helsinki should be the primary concern of all parties involved in the conduct of a clinical trial and the review of the protocol but it is the ultimate responsibility of the investigator, who must also take into consideration the scientific validity of the trial.

3.1 *Declaration of Helsinki*

The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials. Any departures from the Declaration must be justified and stated in the protocol. Independent assurance that subjects are protected can only be provided by an ethics committee and freely obtained informed consent.

3.2 *Ethics committee*

The role of the ethics committee (or other board responsible for reviewing the trial) is to ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, inter alia, by previewing trial protocols, etc. (see Section 2).

The ethics committee should be constituted and operated so that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

The ethics committee should have documented policies and procedures as a basis for its work, which should be available to the public. These should set out the authority under which the committee is established, the number of members elected and their qualifications, a definition of what it will review and its authority to intervene and maintain records of its activities. The documents should also state how frequently the committee will meet and how it interacts with the investigator and/or sponsor.

The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol (including appendices

and amendments) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

The ethics committee has an ongoing responsibility for the ethical conduct of research, and therefore must be informed of all subsequent amendments to the protocol and of any serious adverse events occurring during the trial, or other new information likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be asked for its opinion if a re-evaluation of the ethical aspects of the trial appears to be required, or if there is any doubt regarding the importance of a protocol change or new information.

Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures. The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, itemizing the documents studied and stating the date of review. A list of those present at the committee meeting, including their professional status, should be attached.

When reviewing a clinical trial proposal the ethics committee should consider the following:

a) The acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his or her qualifications, experience, availability for the duration of the study, supporting staff and available facilities.
b) The suitability of the protocol including the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, and the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.
c) The means by which trial subjects will be recruited, necessary or appropriate information will be given, and consent will be obtained. This is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group (see Section 3.3 e–f).
d) The adequacy and completeness of the information, which should be written in a language and at a level of complexity understandable to everyone involved, to be given to the subjects, their relatives, guardians or, if necessary, legal representatives. All such written information must be submitted in its final form to the ethics committee.
e) Provision, if any, for compensation or treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity (a source of legal and financial support) to cover the liability of the investigator(s) and sponsor. (See Section 5.9).
f) The appropriateness of the extent and form of payment through which the sponsor will remunerate or compensate the organization(s) and/or investigator(s) conducting the trial, and the trial subjects, as required by local laws and regulations.
g) The acceptability of proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

3.3 *Informed consent*

The principles of informed consent in the current revisions of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2)* should be implemented in each clinical trial.

a) Information should be given in a language and at a level of complexity understandable to the subject in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, that participation is voluntary and that refusal to participate or withdraw from the trial at any stage will not

prejudice the subject's care, rights and welfare. Subjects must be allowed sufficient time, determined by their health condition and/or the illness, to enquire about details of the trial and to decide whether or not they wish to participate.

b) The subject must be made aware and consent that personal information may be scrutinized during monitoring, auditing or inspection of the trial by properly authorized persons, the sponsor or relevant authorities, and that participation and personal information in the trial will be treated as confidential and will not be publicly available. This principle may be modified by national laws and regulations.

c) The subject must have access to information about insurance, if any, and other procedures for compensation and treatment should he or she be injured or disabled by participating in the trial.

d) If a subject consents to participate after a full and comprehensive explanation of the study, this consent should be appropriately recorded. The explanation should include the aim of the study; the expected benefits for the subjects and/or others; the possibility of allocation to a reference treatment or placebo; the risks and inconveniences – e.g. invasive procedures; and, where appropriate, an explanation of alternative, recognized medical therapy. Consent must be documented either by the subject's dated signature or in agreement with local laws and regulations by the signature of an independent witness who records the subject's consent. In either case, the subject must be informed that signature confirms that the consent is based on information which has been given, and that the subject has freely chosen to participate without prejudice to legal and ethical rights, while reserving the right to withdraw from the study at his or her own initiative at any time, without having to give any reason. If, however, the reason for withdrawal relates to an adverse event(s), the investigator should be informed.

e) Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure – such as medical, pharmacy and nursing students, hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of the hierarchy in case of refusal to participate. Other vulnerable groups whose consent also needs special consideration include patients with incurable diseases, people in nursing homes, prisoners or detainees, the unemployed or people on a very low income, patients in emergency departments, some ethnic and racial minority groups, the homeless, nomads and refugees. If such categories are part of the population to be enrolled in a clinical trial, the ethics committee should consider carefully the appropriateness of the informed-consent process.

f) If the subject is incapable of giving personal consent (e.g. in the case of children or adults who are unconscious or suffering from severe mental illness or disability), the inclusion of such patients in a trial may be acceptable provided: it is permitted by local laws and regulations; the ethics committee is, in principle, in agreement; and the investigator thinks that participation will promote the welfare and be in the interest of the subject. The agreement of a legally acceptable representative that participation will promote the welfare and be in the interest of the subject should also be recorded by a dated signature. If the patient is incapable of giving either signed informed consent or witnessed signed verbal consent, this fact must be documented by the investigator, stating the reasons.

g) In a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her signature.

h) The trial subjects should be informed that they have access to appropriate (identified) persons to obtain further information and medical advice or escape treatment, if necessary.

i) Any information that becomes available during the trial which may be of relevance to the trial subjects must be made known to them by the investigator.

j) The subjects should be informed of the circumstances under which the investigator or the sponsor might terminate their participation in the study.

3.4 *Confidentiality*

The investigator must establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects *(2)*. (See also Section 3.3.)

4. RESPONSIBILITIES OF THE INVESTIGATOR

4.1 *Medical care of trial subjects*

The investigator is responsible for adequate and safe medical care (or dental care, where appropriate) of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 *Qualifications*

The investigator should:

- have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials (decisions relating to, and provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practice medicine or dentistry);
- have good knowledge and experience of the field of medicine/dentistry defined by the protocol;
- be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
- be aware of available relevant data and literature and all information provided by the sponsor;
- have access to human and other resources to assume full responsibility for the proper conduct of the trial;
- be aware of and comply with national regulatory, legal and ethical requirements.

4.3 *Selection of trial subjects*

The investigator is responsible for ensuring the unbiased selection and an adequate number of suitable subjects according to the protocol. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects.

In order to assess the probability of recruiting an adequate number of subjects for the study, it may be useful to determine prospectively or to review retrospectively (e.g. on the basis of the clinic’s records) the availability of potential subjects. The investigator should check whether subjects so identified can or could be included according to protocol.

The patient's own physician should, when relevant and with the patient's consent, be informed of the patient's participation in the clinical trial.

4.4 *Compliance with the protocol*

The investigator must agree and sign the protocol (or another legally acceptable document mentioning the agreement with the protocol) with the sponsor, and confirm in writing that he or she has read, understands and will work according to the protocol and Good Clinical Practice.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and the sponsor. Amendments which are likely to affect the safety of a subject or the conduct of the clinical trial should be submitted in writing to the ethics committee (see Section 3.2) and drug regulatory authority and implemented only after approval has been received.

The investigator may take any steps judged necessary to protect the safety of the trial subject, whether specified in the protocol or not. Any such steps must be documented.

4.5 ***Information for subjects and informed consent***

The investigator is responsible for giving adequate information to subjects about the trial. The current version of the Declaration of Helsinki (Appendix 1), and International Ethical Guidelines for Biomedical Research Involving Human Subjects*(2)* should be followed. The nature of the investigational pharmaceutical product, its stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Information should be given in both oral and written form in a language understandable to the subject. The protocol should state when and by whom such information will be provided, and how the provision of information should be recorded.

Informed consent must be obtained according to the principles described in Section 3.3.

The investigator should also supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact person(s) to contact in an emergency situation.

4.6 ***The investigational product***

The investigator must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product(s), including pre-trial data, as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the clinical trial.

4.7 ***Site of the trial, facilities and staff***

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

The investigator should ensure that he or she has sufficient time to conduct and complete the trial, and that other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand.

The investigator must provide adequate information to all staff involved in the trial.

The investigator must notify or obtain approval for the trial from relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 ***Notification of the trial or submission to the drug regulatory authority***

As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor, should give notification of the trial to, or obtain approval from, the drug regulatory authority. Any submission to the drug regulatory authority should be in writing and dated, and contain sufficient information to identify the protocol.

4.9 *Review by an ethics committee*

Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s) (see Section 3.2). Any submission to and acceptance by the ethics committee should be in writing and dated, and contain sufficient information to identify the protocol or other submitted documents.

4.10 *Serious adverse events/reactions*

The investigator must take appropriate measures to ensure the safety of clinical trial subjects (see also Section 7). The investigator is also responsible for notifying (with documentation) the relevant health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events or reactions, as governed by national regulations.

4.11 *Financing*

The relationship between the investigator and the sponsor in matters such as financial support, fees, honorarium payments in kind must be stated in writing in the protocol or contract. The protocol or contract should be available to the drug regulatory authority and ethics committee on demand.

4.12 *Monitoring, auditing and inspection*

The investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits (see also Section 6). In addition, the investigator must accept auditing and/or inspection by the relevant health authorities and by persons appointed by the sponsor for quality assurance.

4.13 *Record-keeping and handling of data*

See Section 8.

4.14 *Handling of and accountability for pharmaceutical products for trial*

See Section 10.

4.15 *Termination of trial*

In the case of premature termination of the clinical trial, the investigator must inform the drug regulatory authority, the ethics committee and, where applicable, the sponsor. Reasons for termination must be stated in writing.

4.16 *Final report*

After completion of the trial, a final report must be drawn up and submitted to the drug regulatory authority. The report should be dated and signed by the investigator in accordance with local regulations to verify responsibility for the validity of the data.

4.17 *Trials in which the investigator is the sponsor*

In clinical trials in which the investigator is the sponsor, he or she is responsible for the corresponding functions (see Section 5).

5. RESPONSIBILITIES OF THE SPONSOR

The sponsor is often a pharmaceutical company, but may also be an individual, the investigator, or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a clinical trial. When the sponsor is a foreign company or organization it should have a local representative to fulfil the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for providing the investigational and comparator (if any) products, as well as appropriate information to support the safe use of those products. In addition, the sponsor is responsible for ensuring that the trial is conducted in accordance with sound scientific principles and Good Clinical Practice standards by selecting qualified investigators, providing a protocol and ensuring protocol compliance, establishing the distribution of trial-related responsibilities, and providing facilities, equipment and staff for management of the trial, record-keeping, handling of data, monitoring, and quality assurance. The sponsor is also ultimately responsible for ensuring compliance with applicable legal, ethical, and regulatory requirements (although local regulations may designate certain required activities as responsibilities of the investigator), and for providing compensation and indemnity in the event of trial-related injury or death, according to local laws and regulations.

5.1 ***Selection of the investigator(s)***

The sponsor is responsible for selecting the investigator(s), taking into account the appropriateness and availability of the trial site and facilities, and being assured of the investigator's qualifications and availability to conduct the study.

5.2 ***Delegation of responsibilities***

The sponsor is responsible for agreeing with the investigator(s) on the allocation of protocol-related responsibilities, including data processing, breaking of the trial code, handling of statistics, preparation of trial reports, and preparation and submission of documentation to the ethics committee, the drug regulatory authority, and any other required review bodies. This agreement should be confirmed in writing (protocol, contract, or alternative document) prior to the trial.

The sponsor may transfer any or all clinical trial-related activities to a scientific body (commercial, academic, or other), or to a contract research organization (CRO). Any such transfer should be documented in writing.

5.3 ***Compliance with the protocol and procedures***

The sponsor is responsible for assuring the investigator's agreement to undertake the clinical trial as described in the protocol, and according to Good Clinical Practice, and to accept procedures for data recording (particularly in the case-report form or CRF), monitoring, audits, and inspections. The sponsor and the investigator must sign the protocol or an alternative document confirming this agreement.

Both the sponsor and the investigator should agree to any amendment to the protocol before it is implemented and this should be documented in writing.

Amendments which may affect the safety of the subjects or the conduct of the trial should be submitted in writing to the ethics committee (see Section 3.2) through the investigator or, if applicable, directly by the sponsor. The sponsor should provide justification for the amendments. If required, the amendments should be submitted to the drug regulatory authority. The amendments should not be implemented until all required approvals have been obtained, unless the delay caused by this process is likely to expose the subjects to an immediate hazard or danger.

5.4 ***Product information***

As a prerequisite to planning the clinical trial, the sponsor is responsible for providing the investigator with available chemical/pharmaceutical, toxicological, pharmacological and clinical data (including data from previous and ongoing trials) regarding the investigational product and, where appropriate, the comparator product(s). This information should be accurate and adequate to justify the nature, scale and duration of the trial. In addition, the sponsor must bring any relevant new information arising during the trial to the attention of the investigator.

The sponsor is responsible for preparing and providing to investigators an Investigator's brochure, which must include all relevant information about the product(s) and must be supplemented and/or updated whenever any relevant new information is available.

5.5 ***Safety information***

The sponsor must inform the investigator(s) promptly of any immediately relevant information on safety that becomes available during a clinical trial and ensure that the ethics committee and the drug regulatory authority are notified by the investigator(s) if required (see Section 7).

5.6 ***Investigational product***

The sponsor is responsible for supplying the investigational pharmaceutical product(s) and, if applicable, comparator products, prepared in accordance with principles of Good Manufacturing Practice (GMP) (see also Section 10). The product(s) should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration and safeguard blinding procedures (if applicable); appropriate investigational labelling should be affixed.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that, if necessary, an independent laboratory is able to re-check the investigational product(s), e.g. for quality control or bioequivalence.

Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch or serial numbers. The sponsor must ensure that the investigator is able to establish a system within his or her institution for adequate and safe handling, storage, use, return (to the investigator or sponsor) and, if appropriate, destruction of the investigational product(s).

5.7 ***Trial management and handling of data***

The sponsor should appoint appropriate individuals and/or committees for managing and supervising the clinical trial, handling and verifying the data obtained, statistical processing, and preparing the trial report (see Section 8).

5.8 ***Standard operating procedures***

Where warranted by the number or scale of clinical trials conducted, it is recommended that the sponsor establish written standard operating procedures (SOP) to comply with Good Clinical Practice.

5.9 ***Compensation to subjects and investigators***

As required by national law or regulations, the sponsor should provide adequate compensation or treatment for subjects in the event of trial-related injury or death, and provide indemnity for the investigator, except in the case of claims resulting from malpractice and/or negligence. (See Section 3.2 e–f}.

5.10 ***Monitoring***

The sponsor must appoint suitable and appropriately trained monitors and clinical research support personnel, and provide ongoing training to ensure that they are suitably qualified an to keep them up to date with new developments.

5.11 *Quality assurance*
The sponsor should establish a system or systems of quality assurance (including independent auditing) to ensure that the conduct of the clinical trial and the generation, documentation, and reporting of data comply with the protocol, Good Clinical Practice standards and applicable regulatory requirements. The system should operate independently of those involved in conducting or monitoring the trial (see Section 12).

5.12 *Study reports*
The sponsor is responsible for ensuring the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory purposes, whether or not the trial has been completed. The sponsor must also submit any relevant safety information (including safety) that becomes available during the trial and/or annual reports as required by the relevant health authorities.

5.13 *Handling of adverse events*
The sponsor should provide special forms for reporting any adverse event that occur during the clinical trial. The sponsor must investigate promptly, together with the investigator(s), all serious adverse events, take appropriate measures to ensure the safety of trial subjects, and report these events to appropriate authorities in accordance with applicable national requirements (see Section 7).

5.14 *Termination of trial*
If the sponsor elects or is required to terminate the clinical trial prematurely, then the investigator(s), ethics committee and relevant authorities must be notified of this decision, and of the reasons for termination.

6. RESPONSIBILITIES OF THE MONITOR

The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

The main responsibility of the monitor is to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements. The monitor is responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly to the sponsor and the relevant ethics committee(s).

The monitor should follow a predetermined written set of standard operating procedures (SOP). A written record should be kept of all visits, telephone calls and letters to the investigator.

6.1 *Qualifications*
The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical, and/or scientific qualifications, and clinical trial experience. The qualifications most appropriate for a monitor will depend on the type of trial and nature of the product under investigation.

6.2 *Assessment of the trial site*
The monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an adequate number of trial

subjects is likely to be available for the duration of the trial. The monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of standard operating procedures (SOP).

6.3 *Staff education and compliance*
The monitor should ensure that all staff assisting the investigator in the trial have been adequately informed about and will comply with the details of the trial protocol.

6.4 *Data management*
The monitor should assist the investigator in reporting the data and results of the trial to the sponsor, e.g. by providing guidance on correct procedures for completion of case-report forms (CRFs), and by verifying the accuracy of data obtained (see also Section 8).

6.5 *Case-report forms*
The monitor is responsible for ensuring that all case-report forms (CRFs) are correctly filled out in accordance with original observations. Any errors or omissions should be clarified with the investigator, corrected, and explained on the CRF. Procedures should be established for the investigator's certification of the accuracy of CRFs by a signature, initials or similar method. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the clinical trial.

6.6 *Investigational product*
The monitor should confirm that procedures for the storage, dispensing, and return of investigational product(s) are safe, adequate, and properly documented in accordance with local regulations and the trial protocol (see also Section 10.4).

6.7 *Communication*
The monitor should facilitate communication between the investigator and sponsor. The monitor (or some other responsible person designated by the sponsor and known to the investigator) should be available to the investigator at all times for reporting of adverse events or consultation on other trial-related matters.

6.8 Notification of the trial or submission to the drug regulatory authority
The monitor should assist the investigator in notifying the drug regulatory authority of the clinical trial and submitting any necessary documentation.

6.9 *Reports*
The monitor should submit a written monitor report to the sponsor after each site visit and after all relevant telephone calls, letters and other contacts with the investigator. The report should include details of the findings and any actions taken.

7. MONITORING OF SAFETY

7.1 *Handling of and recording adverse events*
In accordance with Sections 4.1 and 4.3 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality.

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the clinical trial.

The trial protocol should clearly state the method(s) by which adverse events will be monitored. Provisions should be included to ensure prompt dose reduction or withdrawal of therapy for patients experiencing unacceptable toxic effects. The protocol should describe how information relating to adverse events is to be handled and analysed by the investigator and sponsor, and their responsibilities to report to each other and to the drug regulatory authority. The sponsor should provide special forms for reporting trial-related adverse events.

Consideration should be given to establishing a special committee to monitor adverse events (see also Section 13).

7.2 *Reporting*

Regulations

National regulations vary considerably in their requirements for reporting of adverse events. For serious events, however, accelerated reporting is required.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events or reactions (e.g. serious, previously unknown) to the drug regulatory authority and the ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the trial and on the future use of the product. In reporting, measures should be taken to avoid unnecessary duplication.

The investigator

The investigator has to report serious adverse events to the sponsor immediately and to the drug regulatory authority and the ethics committee as specified in the protocol and in accordance with national regulations. Normally, adverse events associated with the use of the product must be reported to the drug regulatory authority within a specified time limit.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (i.e. the unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code to facilitate data verification by the sponsor or drug regulatory authority and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events should be stated.

After the trial has been completed or terminated, all recorded adverse events should be listed, evaluated and discussed in the final report.

The sponsor

During the trial, the sponsor is responsible for reporting and trial-related adverse events or reactions associated with the use of the investigational product to the local health authority as required by national regulations and to other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as to the drug regulatory authority and relevant authorities in other countries any trial with the same product that has been stopped due to action taken by a regulatory authority, or any other withdrawals of the product from the market for safety reasons. The sponsor should amend the investigator's

brochure as required to keep the description of adverse events updated and to include any other significant new safety information.

8. RECORD KEEPING AND HANDLING OF DATA

The aim of record-keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately, the information gathered on each trial subject into data that can be used in the report.

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of quality of the data and the performance of the clinical trial (the "audit paper trail" concept). Documentation is facilitated by methods such as the use of check-lists and forms giving details of action taken, dates, the individuals responsible, etc.

The allocation of responsibilities for record-keeping and handling of data should be specified in the protocol or other written agreement(s) between the sponsor and investigator(s).
A basic aspect of the integrity of data is the safeguarding of "blinding" with regard to treatment assignment. It starts with the randomization of patients into treatment groups and is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic data handling, confidentiality of the database must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance of the database and for back-up procedures.

8.1 *Responsibilities of the investigator*

a) The investigator has overall responsibility for ensuring the accuracy and completeness of data entry. The investigator must ensure that the observations and findings are recorded correctly and completely in the case-report forms (CRFs) and signed by the responsible person designated in the protocol.
   When conducting a study and using CRFs to report clinical trial data to the sponsor, the investigator must also ensure that the routine requirements for recording of data in the source documents (e.g. hospital and laboratory records, consultation files) are met, particularly those relating to the treatment given to the subject and adverse events.
b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated print-out and back-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

c) All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented.
d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.
e) Data other than those required by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.
f) Units of measurement must always be stated, and conversion of units must always be indicated and documented.

g) The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s) as well as the responsible statistician, in accordance with the applicable regulations.
h) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual subjects in the trial (subject identification code). The investigator may submit the subject identification code list to the drug regulatory authority after the trial, together with the final report, according to national regulations.
i) The investigator should ensure that the subject's participation in the clinical trial is clearly marked in his or her medical records.

8.2 ***Responsibilities of the sponsor and the monitor***

a) When electronic data handling or remote electronic data entry systems are employed, the sponsor must use validated, data processing programs with adequate user documentation. A predetermined set of standard operating procedures (SOP) for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file.

b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns values automatically when data are missing, this should be made clear.

c) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data printout with the original observations and findings.

d) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.

e) The sponsor must maintain a list of persons authorized to make corrections, and prevent unauthorized access to the data by appropriate security systems.

8.3 ***Archiving of data***

As required by national regulations, the investigator must arrange for the retention of the subject identification codes for a sufficient period of time to permit any medical follow-up which may be warranted, including follow-up for delayed toxic reactions. It must be possible to identify each trial subject by name against subject and product container identification codes, treatment assignment, and the CRFs. Subject files and other supporting data must be kept for a period of time required by local regulations. The sponsor or supplier of the product must make appropriate arrangements for the retention of all other essential documentation pertaining to the clinical trial in a form which can be retrieved for future reference. Archived data may be kept on microfiche or electronic or optical record (e.g. compact disc), provided that a hard copy can be made available on request.

The protocol, documentation, approvals and all other essential documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. STATISTICS AND CALCULATIONS

The use of qualified biostatistical expertise is necessary before and throughout the entire clinical trial procedure, commencing with the design of the protocol and case-report forms (CRFs) and ending with the completion of the final report and/or publication of the results.

The sponsor and the investigator should agree where and by whom the statistical work should be carried out. This information and the name of the responsible statistician should be recorded in the protocol.

9.1 *Experimental design*

The scientific integrity of a clinical trial and the credibility of the data produced depend primarily on the design of the trial. In the case of comparative trials, the protocol should therefore describe:

– an *a priori* rationale for the targeted difference between treatments that the trial is designed to detect, and the statistical power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences;
– measures taken to avoid bias, particularly with regard to the randomization, when relevant, and selection of patients.

9.2 *Randomization and blinding*

In case of a randomized clinical trial, the randomization procedure must be documented. Where a sealed code for each individual treatment has been supplied in a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial the protocol must state the conditions under which the code is allowed to be broken and by whom. A system is also required to enable immediate access to the information about treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, this must be justified and documented in the CRF.

9.3 *Statistical analysis*

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be justified and described in the final report of the clinical trial. The statistical analysis should be planned and carried out or verified by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and the monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of statistical analyses should be presented in such a manner as to facilitate interpretation of their clinical importance, e.g. as estimates of the magnitude of the treatment effect, the difference between treatments and confidence intervals, rather than in a form that relies solely on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The sponsor is responsible for ensuring that the investigational pharmaceutical product(s) and, if applicable, comparator products supplied for the clinical trial are of appropriate quality and subject to quality assurance procedures (see Section 5.11).

If significant changes are made in the formulation of the investigational or comparator product during the course of the trial, the results of additional studies (e.g. on the stability, comparative dissolution rate or, as appropriate, comparative bioavailability) should be made available before the new formulation is used in the trial. The studies would demonstrate that the changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product.

10.1 *Supply and storage*

The arrangements made by the sponsor to supply the investigator with pharmaceutical products for the trial should be described in the protocol. The manner in which study products are to be recorded, delivered, dispensed and stored should be detailed.

The principles of Good Manufacturing Practice*(1)* should be applied not only by the supplier of the pharmaceutical product(s), but also by any intermediaries responsible for storing the product(s) temporarily.

Records must be kept of information about the shipment, delivery, receipt, storage, return and destruction of any remaining pharmaceutical products. The investigator should not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the local hospital should assume responsibility for storage, delivery, return and keeping records of the investigational and, when appropriate, comparator product(s). If so, these procedures must be documented to make auditing possible.

10.2 *Investigational labelling and packaging*

The sponsor is responsible for the proper packaging and investigational labelling of the pharmaceutical products used. Study products should be labelled in compliance with the protocol and any applicable national regulations. The investigational label should state that the product is for clinical research purposes only. Investigational label information should be accurate and in a language that is understandable to the subject.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. A coding system should be used to allow for the proper identification of the blinded products given to individual subjects (in case of emergency). In addition, all study products, including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

10.3 *Responsibilities of the investigator*

The investigator is responsible for ensuring:

- Proper and safe handling of the investigational and, when appropriate, comparator products during and after the clinical trial, preferably in cooperation with a pharmacy (see Section 10.1);
- That the investigational product is used only in accordance with the protocol, which implies use only for subjects included in the trial and by designated staff responsible to the investigator, and that this use is documented in such a way as to ensure appropriate dosage;
- That the dosage and instructions for use are correct and that every subject involved understands them properly;
- That unused investigational and, when appropriate, comparator products are returned in accordance with the protocol to the pharmacy or sponsor or destroyed, and that proper records of these activities are kept.

10.4 *Responsibilities of the sponsor and monitor (see also Sections 5 and 6)*

The sponsor is responsible for:

- Supplying the investigational and, when appropriate, comparator product(s), prepared in accordance with principles of Good Manufacturing Practice. The products should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration during transport and storage at intermediate destinations; appropriate investigational labelling should be affixed (see Section 10.2).
- Ensuring that the package of investigational product(s) is of a size suitable for the trial and adequate for the trial subjects.
- Keeping sufficient samples from each batch used in the trial as a reference for control tests and validation of data, as required in national regulations.
- Providing information about the expiry date (month/year) or retest date information in a manner understandable to all staff involved in the trial.

During the visits to the clinical trial site, the monitor should check:

- That all study products for the trial are used exclusively within the limits defined by the protocol.

- That inventory records of study products are in order and that there are sufficient supplies.

- That the expiry dates are not likely to be, or have not been, exceeded.

- That the storage conditions for study products are adequate.

- Procedures for and records of returned and/or unused study products.

11. ROLE OF THE DRUG REGULATORY AUTHORITY

The role of governments is to provide the legal framework for clinical trials. The aim should be twofold: (i) to protect the safety and rights of the subjects participating in a trial, and (ii) to ensure that trials are adequately designed to meet scientifically sound objectives. These aims may be met by several means, including the specification of the investigator's qualifications and requirement for review and approval of the protocol by relevant scientific and/or ethics committees.

Drug regulatory authorities should have a mandate to review protocols and, where necessary, to protect the safety of subjects, to require protocol revisions and/or termination of trials.

Regulations should allow for on-site inspections of the quality and reliability of the data obtained, with due concern for confidentiality.

11.1 *General responsibilities*

The national drug regulatory authority should ensure that the protocols for clinical trials are submitted in advance for review and are in accordance with existing national regulations. On the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions or request additional data on a clinical trial or terminate a trial.

The drug regulatory authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor (see Section 6.9). In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

National regulations should specify the procedures for reporting and handling cases of misconduct discovered in connection with clinical trials.

11.2 *On-site inspections*

As permitted by national regulations, the drug regulatory authority may carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the drug regulatory authority by the investigator or the sponsor.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for ease of retrieval.

Inspections may include data audit. The drug regulatory authority should have easy access to all patient files and raw data used for and generated during the trial.

12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The sponsor is responsible for implementing a system of quality assurance in order to ensure that the trial is performed and the data are generated, recorded, and reported in compliance with the protocol, Good Clinical Practice, and national regulations.

All clinical trial sites, 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 assure that the conclusions presented are derived correctly from the raw data. The verification processes must be specified and scientifically justified. Statistically controlled sampling may be used to verify data in a trial.

Quality control procedures must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor, investigational sites, facilities and laboratories, and all relevant data (including raw data) and documentation and reports concerning the data (including subject files) must be available for an audit and for inspection by relevant health authorities. The audit should be conducted by a nominated person(s) or organization(s) independent of those carrying out the clinical trial.

13. CONSIDERATIONS FOR MULTICENTRE TRIALS

Because a multicentre trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multi-centre trials, such as:

- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- the submission of the proposed protocol or protocol amendments to the ethics committee(s), and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved in the trial;
- implementation of the trial;
- the procedures used for the randomization of trial subjects;

ensuring that the quality of the product is maintained during distribution and storage in different locations;
the training of investigators to follow the same protocol;
standardization of methods for evaluating and analysing laboratory and diagnostic data (e.g. establishment of an external quality control system for laboratory assays);
control of adherence to the protocol, including measures to terminate participation of trial sites if necessary;
the role of the monitor(s);
centralized data management and analysis;
drafting of the final report and clearances required;
publication of the trial results.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and knowledge of the investigational pharmaceutical product. One or several committees may be set up for this purpose or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or person(s) should be described in the trial protocol, as should the procedure for nomination.

For example, a committee or an individual could be responsible for overseeing the initiation overall performance of the trial. Similarly, a second committee or person could be appointed to provide advice on policy matters and data collection. A third committee or person could be made responsible to the accuracy and verification of the data obtained. It should be stated in the protocol under what circumstances and how this committee or person can break the trial code. Collaboration between these committee(s) or person(s) is necessary.

A coordinating committee could also be set up or a coordinator appointed with responsibility for the control of the performance and progress of the trial and maintaining contacts with the drug regulatory authorities and ethics committees.

These administrative arrangements will provide adequate assurance that the study will be planned and conducted according to generally accepted scientific principles and Good Clinical Practice.

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References

1. Good manufacturing practices for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-second report, Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), annex 1.

2. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva, CIOMS, 1993, Annex 1.

Declaration of Helsinki**

Recommendations guiding physicians in biomedical research involving human subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a

physician who Is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental designed is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

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***Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989. World Medical Association, Handbook of declarations, Ferney-Voltaire 1992 (unpublished document; available on request from the World Medical Association, 28 avenue des Alpes, 01210 Ferney-Voltaire, France). [Internet address:* http://www.wma.net*/]*

APPENDIX 2

MODEL LIST OF ITEMS TO BE CONTAINED IN A CLINICAL TRIAL PROTOCOL

The trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.

2. Statement of rationale, objectives and purpose of trial.

3. Brief description of the site(s) where the trial is to be conducted

4. Name and address of the sponsor.

5. Name, address and qualifications of each investigator.

6. Description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), and method of and procedure(s) for randomization.

7. Description of trial subjects (criteria for inclusion and exclusion of potential subjects), process of recruitment, types, method(s) and timing of allocation of subjects into investigational groups.

8. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.

9. Description of and justification for the route of administration, dosage, dosage interval and treatment period for the investigational and comparator products, if used. Dose-response relationships should be considered.

10. Any other treatment that may be given or permitted concomitantly.

11. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.

12. Description of how responses are recorded (description and evaluation of methods and frequency of measurement), follow-up procedures and measures to determine the extent of compliance with the treatment among trial subjects.

13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.

14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.

15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case-report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency.

17. Measures to be implemented to ensure the safe handling and storage of investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.

18. Description of methodology to be used to evaluate the results, (including statistical methods) and to report on patients or participants withdrawn from the trial.

19. Time schedule for completion of the trial.

20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.

21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

22. Ethical considerations and measures relating to the trial.

23. Medical care to be provided after the trial, modalities of post-trial treatment.

24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.

25. List of literature referred to in the protocol.