DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket NO. 95D–0219]

International Conference on Harmonisation; Draft Guideline on Good Clinical Practice; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Good Clinical Practice.'' This guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to define ''Good Clinical Practice'' and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

DATES: Written comments by October 2, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:
Regarding the guideline: Bette L. Barton, Center for Drug Evaluation and Research (HFD–344), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1032.
Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization, and FDA is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

On May 9, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Good Clinical Practice'' should be made available for public comment. The draft guideline is the product of the Efficacy Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's final guideline.

The draft guideline is intended to define ''Good Clinical Practice'' and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, well-being, and confidentiality of trial subjects are protected and that trial data are credible. The objective of this ICH GCP Guideline is to provide a unified standard for the European Union, Japan, and the United States that is consonant with the standards of Australia, Canada, the Nordic countries, and the World Health Organization.

This guideline should be followed when generating clinical data that are intended to be submitted to regulatory authorities. The principles established in this guideline should also be applied to other investigations that involve therapeutic intervention in, or observation of, human subjects.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

Interested persons may, on or before October 2, 1995, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Guideline for Good Clinical Practice

Introduction

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. This standard has its origin in the Declaration of Helsinki. Compliance with this standard provides public assurance that the rights, well-being, and confidentiality of trial subjects are protected and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guideline should be followed when generating clinical data that are intended to be submitted to regulatory authorities.

The principles established in this guideline should also be applied to other investigations that involve therapeutic intervention in, or observation of, human subjects.

1. Glossary

1.1 *Adverse Drug Reaction (ADR)*

All noxious and unintended responses to a medicinal product (i.e., where the relationship between an adverse event and product cannot be ruled out) related to any dose.

1.2 *Adverse Event (AE)*

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

1.3 *Amendment (to the protocol)*

See *Protocol Amendment.*

1.4 *Applicable Regulatory Requirement(s)*

Any law(s) and regulation(s) addressing the conduct of clinical trials.

1.5 *Audit*

A systematic and independent examination to determine whether trial-related activities were conducted and analyzed according to the protocol, sponsor's standard operating procedures (SOP's), good clinical practice (GCP), the applicable regulatory requirement(s), and whether the trial reports accurately reflect the procedures carried out, and the data collected.

1.6 *Audit Certificate*

A written statement by the sponsor's auditor documenting/confirming that an audit of clinical trial-related activities has been conducted.

1.7 *Audit Report*

A written evaluation by the sponsor's auditor of the accuracy of the audited trial data, and the adherence of the trial to the protocol, the sponsor's SOP's, to GCP, and to applicable regulatory requirement(s).

1.8 *Audit Trail*

Traceable documents or proof for audit of GCP and/or applicable regulatory requirement(s), which include the essential documents, and allow reconstruction of the course of events.

1.9 *Case Report Form (CRF)*

A printed, optical, or electronic document designed to record all of the protocol required information that is to be reported to the sponsor on each trial subject.

1.10 *Clinical Trial*

Any systematic study in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of investigational products, and/or to identify any adverse reactions to investigational products, and/or to study absorption, distribution, metabolism, and excretion of these products with the object of ascertaining their safety and/or efficacy.

1.11 *Clinical Trial/Study Report*

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analysis are fully integrated into a single report.

1.12 *Comparator (Product)*

An investigational or marketed product, or placebo, used as a reference in a clinical trial.

1.13 *Compliance (in relation to trials)*

Adherence to all trial-related requirements, GCP requirements, and applicable regulatory requirements.

1.14 *Confidentiality*

Maintenance of secrecy of the sponsor's proprietary information and the subject's source data.

1.15 *Contract*

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may act as the basis of a contract.

1.16 *Coordinating Investigator*

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

1.17 *Contract Research Organization (CRO)*

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related responsibilities.

1.18 *Direct Access*

Direct access refers to permission for domestic and foreign regulatory authorities, and the sponsor's auditors and monitors, to see, review, analyze, verify, and reproduce any records and reports that are important to evaluation of the clinical trial. When accessing trial-related documents, the regulatory authorities, and the sponsor's monitors and auditors, will take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities.

1.19 *Documentation*

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and EKG's) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.20 *Essential Documents*

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

1.21 *Good Clinical Practice (GCP)*

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.22 *Identification Code*

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of subjects' names when the investigator reports on adverse events and other trial data.

1.23 *Impartial Witness*

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who participates in the informed consent process, and who documents (by signing and dating the written informed consent form) that the subject freely gave informed consent to participate in the trial.

1.24 *Independent Ethics Committee (IEC)*

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion, the trial protocols and amendment(s), and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.25 *Informed Consent*

A subject's voluntary confirmation of willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written informed consent form that contains relevant information about the trial and that is signed and dated by the subject or the subject's legally acceptable representative.

1.26 *Inspection*

The act by regulatory authorities of conducting an official review of documents, facilities, records, and any other resources deemed by them to be related to the clinical trial that may be located at the site of the trial, at the sponsor's facilities, at CRO's, or at other establishments deemed appropriate by such authorities.

1.27 *Institution (medical)*

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.28 *Institutional Review Board (IRB)*

See *Independent Ethics Committee (IEC).*

1.29 *Interim Clinical Trial/Study Report*

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.30 *Investigational Product*

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled other than as authorized, i.e., in a way different from the approved form, or when used in a clinical setting other than the one approved, or when used to gain further information about the approved use.

1.31 *Investigator*

A person responsible for the conduct of the clinical trial at a trial site. In the event that a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be

called the principal investigator. See also Subinvestigator.

1.32 *Investigator/Institution*

Expression meaning ''the investigator or institution, if required by the applicable laws and regulations.''

1.33 *Investigator's Brochure*

A compilation of the clinical and nonclinical data on the investigational product that are relevant to its study in human subjects.

1.34 *Legally Acceptable Representative*

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.35 *Monitoring*

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, GCP, and the applicable regulatory requirement(s). A person, designated by the sponsor, who is responsible for the monitoring is a monitor.

1.36 *Monitoring Report*

A written report from the monitor to the sponsor after each site visit and after all trial-related communications (audit trail concept). Reports should include findings and any actions taken.

1.37 *Multicenter Trial*

A clinical trial conducted according to one single protocol but at different centers (institutions), and therefore, carried out by more than one investigator.

1.38 *Nonclinical Study*

Biomedical studies not performed on human subjects.

1.39 *Opinion (in relation to Independent Ethics Committee)*

A professional judgment and/or advice provided by an Independent Ethics Committee (IEC).

1.40 *Original Medical Record*

See *Source Documents.*

1.41 *Protocol*

A document that provides the background, rationale, and objective(s) of the trial and describes its design, methodology, and organization, including statistical considerations.

1.42 *Protocol Amendment*

A written description of the change(s) to a protocol.

1.43 *Quality Assurance (QA)*

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

1.44 *Quality Control (QC)*

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial have been fulfilled. Quality control activities are undertaken by all members of the investigational team, including the staff of the sponsor or contract research organization (CRO), involved with planning, conducting, monitoring, data processing/management, documenting (recording), analyzing, evaluating, and reporting a trial with the objective of performing the trial in compliance with the protocol, GCP, and applicable regulatory requirement(s) and drawing conclusions from reliable data.

1.45 *Randomization*

The process of assigning trial subjects to treatment or control groups using a procedure by which only chance (unbiased) determines the assignments (random allocation).

1.46 *Serious Adverse Event (SAE)*

Any untoward medical occurrence that at any dose:

—Results in death,
—Is life-threatening,
—Requires inpatient hospitalization or prolongation of existing hospitalization,
—Results in persistent or significant disability/incapacity, or
—Results in a congenital anomaly/birth defect.

1.47 *Source Data*

All information in original records, and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source data are contained in source documents (original records or certified copies).

1.48 *Source Documents*

Original documents and records (e.g., laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files) kept at the pharmacy, the laboratories, and at medico-technical departments involved in the clinical trial.

1.49 *Sponsor*

An individual, a company, an institution, or an organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.50 *Sponsor-Investigator*

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.51 *Standard Operating Procedures (SOP's)*

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.52 *Subinvestigator*

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site.

See also *Investigator.*

1.53 *Subject*

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.54 *Trial Site*

The location(s) where trial-related activities are actually conducted.

1.55 *Unexpected Adverse Drug Reaction*

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert for an approved product).

1.56 *Vulnerable Subjects*

Individuals whose willingness to volunteer in a clinical trial 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 or institution in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency rooms, ethnic minority groups, homeless persons, nomads, refugees, children, and those incapable of giving consent.

1.57 *Well-being (of the trial subjects)*

The physical and mental integrity of the subjects participating in a clinical trial.

2. The Principles of ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol and amendment(s) that have received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

2.7 The medical care given to, and medical decisions made for, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol and amendment(s).

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

3.1 *Responsibilities*

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 To fulfill its responsibilities, the following documents should be submitted to the IRB/IEC: Trial protocols, protocol amendment(s), written informed consent forms, consent form updates, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), safety reports, documents related to payments and compensation available to subjects, and any other documents that the IRB/IEC may require.

The IRB/IEC should review a proposed clinical trial within a reasonable time limit and document their views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

Approval/favorable opinion;

Modifications required prior to approval/favorable opinion;

Disapproval/negative opinion; and

Suspension of any prior approval/favorable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial as documented by a current curriculum vitae.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC should require that more information than is outlined in paragraph 4.8.10 for written informed consent forms, and for written information to be provided to subjects, be given to subjects when, in the judgment of the IRB/IEC, the additional information is necessary to protect the rights and/or well-being of the subjects.

3.1.6 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither present problems of coercion or undue influence on the trial subjects.

3.1.7 The IRB/IEC should ensure that all information regarding payment, including amounts and schedule of payment to trial subjects, is set forth in the written informed consent form. Such payments should not be wholly contingent upon the trial subject's completion of the trial. Prorated payment should be specified in the written informed consent form.

3.1.8 Except where national law does not permit, the IRB/IEC should evaluate whether remuneration is coercive by reviewing the extent to which investigators/institutions may be rewarded/compensated for participation (see 4.4.2, 5.9).

3.2 *Functions and Operations*

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review properly the science and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary concern is in a nonscientific area.

(c) All members independent of the investigator and the sponsor.

(d) At least one member who is independent of the trial site.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings where at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and advice.

3.2.5 The investigator may provide information on any aspect of the trial, but at the time the IRB/IEC makes a decision, the investigator should not participate in the vote/opinion.

3.2.6 An IRB/IEC may invite nonmembers who have expertise in special areas for assistance.

3.3 *Procedures*

The IRB/IEC should establish, document in writing, and follow its procedures that include:

3.3.1 Determining its composition (names and qualifications of the members and the authority under which the committee is established).

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review.

3.3.5 Providing expedited review and approval/favorable opinion of trials involving no more than minimal risk or of change(s) not increasing the risk for a trial for which approval/favorable opinion was provided by the IRB/IEC.

3.3.6 Prohibiting admission of subjects to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7 Prohibiting initiation of changes in the protocol without prior IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the human subjects or when the change involves logistical or administrative aspects of the trial (e.g., change in monitor, phone number).

3.3.8 Providing that the investigator promptly reports to the IRB/IEC:

(a) Changes in a trial implemented to eliminate immediate hazards to the trial subjects.

(b) Changes affecting significantly the conduct of the trial, and/or increasing the risk to subjects.

(c) All serious and unexpected adverse drug reactions (ADR's).

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions.

(b) The reasons for its decisions.

(c) Procedures for appeal of its decisions.

3.4 *Records*

Where required by applicable regulation, the IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

Written procedures and membership lists should be made available upon request from the investigator(s), and/or the sponsor(s), except where national law does not permit.

4. INVESTIGATOR

4.1 *Investigator's Qualifications and Agreements*

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications required by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and other credentials.

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol/amendment(s), in the current Investigator's Brochure, in other information sources provided by the sponsor, and in the available literature.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulations.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspecting by the appropriate regulatory authorities.

4.1.5 The investigator should maintain a written record of appropriately qualified persons, delegated to assume specified investigator trial responsibilities.

4.2 *Adequate Resources*

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 To conduct the trial properly and safely, the investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol/amendment(s), the investigational product(s), and their trial-related responsibilities.

4.3 *Medical Care of Trial Subjects*

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 For the duration of a subject's participation in a trial, the investigator should ensure that adequate medical care (or dental care, when appropriate) is made available to the subject for trial-related illness(es)/adverse event(s). The investigator should inform the subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. Following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial.

4.3.3 It is recommended that the investigator inform the subject's primary physician, when there is one, with the subject's consent, about the participation in the trial.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 *Communication With IRB/IEC*

4.4.1 Before initiating a trial, the investigator should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects.

4.4.2 Except where national law does not permit, the investigator also should obtain approval/favorable opinion from the IRB/IEC for the trial-related costs and payments (see 3.1.8, 5.9, 5.11).

4.4.3 As part of the investigator's written application to the IRB/IEC, the investigator should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the updated Investigator's Brochure contains important updates on safety information and clinical trial analyses, the investigator should supply a copy to the IRB/IEC.

4.4.4 During the trial the investigator should provide to the IRB/IEC all documents subject to review (see 3.1.2, 3.1.5, 3.1.7, 3.3.8, 4.10, 4.11).

4.5 *Compliance with Protocol/Amendment(s)*

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol/amendment(s) agreed to by the sponsor, and the IRB/IEC and, if required, by the appropriate authority(ies). The investigator/institution and the sponsor should sign the protocol/amendment(s), or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any changes in a trial without agreement by the sponsor and prior review or expedited review by the IRB/IEC, and without documented approval/favorable opinion of an appropriate amendment, except when the change involves logistical or administrative aspects of the trial.

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol/amendment(s).

4.5.4 The investigator may implement a deviation, where necessary, to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation, the reasons, and, if appropriate, the proposed protocol amendment(s) should be submitted: (1) to the IRB/IEC for review and approval/favorable opinion, (2) to the sponsor for agreement, and, if required, (3) to the appropriate authority(ies).

4.6 *Investigational Product(s)*

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator.

4.6.2 Where allowed/required, the investigator may/should assign some/all of the investigator's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist.

4.6.3 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol/amendment(s).

4.6.4 The investigator, or a person designated by the investigator, should clearly explain the correct use of the investigational product(s) to each subject and should check, at each subject visit, that the subject is using the product(s) properly.

4.6.5 The investigator and/or pharmacist should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol/amendment(s) and reconcile all investigational product(s) received from the sponsor.

4.6.6 The investigational product(s) should be properly and safely stored in accordance with applicable regulatory requirement(s).

4.7 *Randomization Procedures*

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should document and explain any unblinding of the investigational product(s) promptly to the sponsor.

4.8 *Informed Consent of Trial Subjects*

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and written information to be provided to subjects.

4.8.2 The written informed consent form and written information to be provided to subjects should be revised whenever new information becomes available that may be relevant to the subject. Any revised written informed consent form, and written trial information should receive the IRB/IEC's approval/favorable opinion in advance of use.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information as approved/received favorable opinion from the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be nontechnical and should be understandable to the subject or the subject's legally acceptable representative.

4.8.7 Before informed consent is given, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time to decide and opportunity to inquire about details of the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to participation in the trial, the written informed consent form should be signed and personally dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If the subject or the subject's legally acceptable representative is unable to read,

an impartial witness should be present during the entire informed consent discussion. After the written informed consent form is read to the subject and orally consented to, and signed and personally dated by the subject, if capable of doing so, or the subject's legally acceptable representative, the witness should also sign and personally date the consent form, attesting that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form should include clear explanations of the following:

(a) The trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s).

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those trial features that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That confidentiality of records that identify the subject will be maintained and will not be made publicly available to the extent permitted by the applicable laws and/or regulations.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The circumstances under which the subject's participation in the trial may be terminated without the subject's consent.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 The subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and signed and dated consent form updates, and a copy of the written trial information to be provided to subjects and its amendment(s).

4.8.12 To the extent that a minor child is capable of understanding and granting informed consent, the minor should give consent and, in addition to the minor's legally acceptable representative, the minor should sign and personally date the written informed consent form if the minor is capable of doing so.

4.8.13 In a nontherapeutic trial (i.e., when there is no anticipated direct clinical benefit to the subject), consent should always be given by the subject and the written consent form should be signed and personally dated by the subject.

4.8.14 Where prior consent of the trial subject is not possible, the protocol submitted to the IRB/IEC may provide that such consent need not be obtained and that only the consent of the subject's legally acceptable representative, if present, should be solicited. Absence of the subject's legally acceptable representative should require other measures that are described in the protocol to ensure compliance with applicable regulatory requirements. The trial subject or the subject's legally acceptable representative should be informed as soon as possible and consent should be requested.

4.9 *Records and Reports*

4.9.1 The source documents should support the data reported on the CRF, should identify the trial, and should document the dates of the subject's participation.

4.9.2 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF's and in all required reports.

4.9.3 Any correction to a CRF should not obscure the original entry; this applies to both written and electronic corrections (see 5.18.5(n)). Sponsors should provide guidance to investigators or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes made by sponsor's designated representatives in CRF's are necessary, documented by an audit trail, and endorsed by the investigator.

4.9.4 The investigator/institution should maintain the trial documents as specified in the ICH Guideline for ''Essential Documents for the Conduct of a Clinical Trial,'' and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of records, including the subject's original medical records and accountability records for the investigational product(s).

4.9.5 Where there are no applicable regulatory requirements that require the retention of the essential documents for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, the investigator/institution should prevent accidental or premature destruction of records for the period specified in the agreement with the sponsor, which should be at least as long as indicated above.

4.9.6 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 *Progress Reports*

4.10.1 The investigator should routinely submit written summaries of the status of the trial to the IRB/IEC. These reports should be submitted annually or more frequently if required by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor and the IRB/IEC (see 3.3.8) on any problems, changes, or occurrences affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 *Safety Reporting*

4.11.1 All serious adverse events (SAE's) should be reported immediately to the sponsor unless the protocol or other document (e.g., Investigator's Brochure) identifies certain expected SAE's as not needing immediate reporting. This immediate reporting should be followed promptly by detailed, written reports, which should identify subjects by unique code numbers assigned to the trial subjects instead of by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with local regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and/or the IRB/IEC.

4.11.2 In addition, those adverse events and/or laboratory abnormalities, which are identified in the protocol/amendment(s) as critical to safety evaluations, should be reported to the sponsor according to the reporting requirements and within the time periods that are specified by the sponsor in the protocol/amendments.

4.11.3 For all reported deaths, the investigator should supply the sponsor and, where required, the IRB/IEC with relevant information including autopsy reports and terminal medical reports.

4.12 *Trial Termination or Suspension*

4.12.1 If the trial is terminated or suspended by the investigator without prior agreement of the sponsor, the investigator should inform the institution where applicable and the investigator/institution should provide promptly to the sponsor and the IRB/IEC a detailed explanation of the termination/suspension.

4.12.2 If the trial is terminated/suspended by the sponsor, the investigator should provide promptly to the IRB/IEC and the institution, where required, a detailed explanation of the termination/suspension.

4.12.3 If the IRB/IEC terminates or suspends a trial, the investigator should immediately notify the sponsor and provide the sponsor with a detailed written explanation of the termination/suspension.

5. SPONSOR

5.1 *Quality Assurance and Quality Control*

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOP's to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol(s), GCP, and the applicable regulatory requirements.

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure the availability of all trial-related sites and source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspecting by domestic and foreign regulatory authorities.

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

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or a written contract, to assure the quality of the trial-related activities.

5.2 *Contract Research Organization (CRO)*

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related responsibilities to a CRO. However, the ultimate responsibility for the quality and integrity of the trial data should always reside with the sponsor. The sponsor should ensure that the CRO has and implements quality assurance and quality control.

5.2.2 Each trial-related responsibility that is transferred to and assumed by a CRO should be specified in a written contract.

5.2.3 All trial-related responsibilities not specifically transferred to and assumed by a CRO should be considered to be retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial-related responsibilities of a sponsor.

5.3 *Medical Expertise*

The sponsor should designate appropriately qualified medical personnel, who are readily available to advise on trial-related questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 *Trial Design*

5.4.1 The sponsor should utilize qualified experts (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRF's and planning the analysis to analyzing and preparing interim and final clinical trial reports.

5.4.2 See Chapter 6 ''Clinical Trial Protocol and Protocol Amendment(s),'' and the ICH Guideline for ''Structure and Content of Clinical Study Reports,'' and other appropriate ICH guidance on trial design and protocols.

5.5 *Trial Management, Data Handling, and Recordkeeping*

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure that only validated data processing systems are used.

(b) Maintain SOP's for using these systems.

(c) Ensure that the systems are designed to allow data changes without any deletion of entered data (i.e., maintain an audit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes.

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any.

5.5.3 The sponsor should ensure the greatest possible accuracy when processing data. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.4 The sponsor should use an unambiguous subject code that enables identification of all the data reported for each subject.

5.5.5 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See ICH Guideline for ''Essential Documents for the Conduct of a Clinical Trial.'')

5.5.6 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.7 If the sponsor discontinues the clinical development of an investigational product for any or all indications, routes of administration, or dosage forms, the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators and all the appropriate regulatory authorities.

5.5.9 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.10 Where there are no applicable regulatory requirement(s) that require the investigator/institution to retain the trial-related essential documents for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product for any or all indications, routes of administration, or dosage forms, it is recommended that the sponsor agree with the investigator/institution to prevent accidental or premature destruction of the essential documents, for a period, which should be at least as long as indicated above.

5.6 *Investigator Selection*

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). The sponsor should select the investigator(s) who is/are qualified by training and experience to conduct the trial(s) and have adequate resources (see 4.1, 4.2). If coordinating committees and/or selection of coordinating investigator(s) are appropriate in multicenter trials, the organization and/or selection is the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement to conduct the trial in compliance with the agreed to and/or approved protocol/amendment(s), and with GCP and the applicable regulatory requirement(s), and to accept procedures for data recording/reporting, monitoring, auditing, and inspecting. The sponsor and the investigator/institution should sign the protocol/amendment(s), or an alternative document, to confirm this agreement.

5.7 *Allocation of Responsibilities*

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related responsibilities to either the sponsor, investigator(s), and/or other parties.

5.8 *Compensation to Subjects and Investigators*

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner should comply with applicable regulatory requirement(s).

5.9 *Financing*

Except where national law does not permit, the financial aspects of the trial should be documented as an agreement between the sponsor and the investigator/institution, and should be reviewed by the IRB/IEC and by the appropriate authority(ies) to evaluate if remuneration is not coercive (see 3.1.8, 4.4.2).

5.10 *Notification/Submission to Regulatory Authority(ies)*

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator), if required by the applicable regulatory requirement(s) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol/amendment(s).

5.11 *Confirmation of Review by IRB/IEC*

5.11.1 The sponsor should obtain from each investigator:

(a) The name and address of the investigator's IRB/IEC.

(b) Statement from the IRB/IEC that it complies with GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, where required, a current copy of protocol/amendment(s), written informed consent forms, and written information to be provided to subjects, subject recruiting procedures, documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may require.

5.11.2 If the IRB/IEC conditions its approval/favorable opinion of the protocol and/or amendment(s), written informed consent form, written information to be provided to subjects and other procedures upon modifications, the sponsor should obtain from the investigator:

(a) A copy of the modification(s) as approved/received favorable opinion by the IRB/IEC.

(b) Documentation that the modification(s) was/were approved/received favorable opinion by the IRB/IEC and the date of the IRB/IEC's approval/favorable opinion.

5.11.3 The sponsor should obtain documentation and dates of any reapprovals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

5.12 *Information on Investigational Product(s)*

5.12.1 When planning trials, the sponsor should ensure the availability of sufficient safety and efficacy data for the product(s), including the available data from investigations and/or marketing worldwide. Sufficient safety and efficacy data from nonclinical studies and/or clinical trials should be available to justify human exposure by the route, at the dosages, and for the duration proposed to be studied during the trial and should be appropriate to the phase, type, and target population of the proposed trial.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available. (See ICH Guideline for ''Investigator's Brochure.'')

5.13 *Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)*

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparators and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), manufactured in accordance with any applicable GMP, and coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product during the course of the clinical development/trial, the results of additional studies (e.g., stability, comparative dissolution rate, comparative bioavailability) demonstrating that these changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product should be available prior to the use of the new formulation in the clinical trial.

5.14 *Supplying and Handling Investigational Product(s)*

5.14.1 The sponsor is responsible for supplying the investigator(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator with the investigational product(s) until the sponsor obtains documentation of all required approvals (e.g., IRB/IEC and authorities).

5.14.3 The sponsor should ensure that written procedures include the requirements that the investigator/institution follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, delivery, receipt, disposition, return, and destruction of the investigational product(s). (See ICH Guideline for ''Essential Documents for the Conduct of a Clinical Trial.'')

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and documenting this disposition.

5.14.5 Where GMP does not apply to investigational product(s), the sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of batch samples of the investigational product(s) in order to reconfirm specifications, if it appears necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, batch samples should be retained either until the statistical analyses are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 *Record Access*

5.15.1 The sponsor should ensure that it is specified in the protocol that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 *Safety Information*

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

5.17 *Adverse Drug Reaction Reporting*

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADR's) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for ''Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.''

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 *Monitoring*

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors.

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol/amendment(s), written informed consent form, written information to be provided to subjects, GCP, and the applicable regulatory requirement(s).

5.18.3 Number of Monitors

The sponsor should ensure that the trials are appropriately monitored at the trial sites.

The number of monitors needed to ensure adequate monitoring of a trial depends primarily on the complexity of the trial, the number and locations of trial sites, and the number of trial subjects.

5.18.4 Monitoring Schedule

The monitor(s) should visit the trial site(s) before, during, and after the trial. The on-site visits should be frequent enough to monitor the trial adequately.

5.18.5 Monitor's Responsibilities

The monitor(s) should ensure that the trial is conducted and documented properly by:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(*ii*) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(*iii*) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(*iv*) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(*v*) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written, informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, as per written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized or unapproved individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that accurate, complete, and current source documents and trial records are maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries against the subjects' source documents and other trial-related records. The monitor specifically should verify that:

(*i*) The data required by the protocol are reported accurately on the CRF's and are consistent with the source documents.

(*ii*) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(*iii*) Concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRF's.

(*iv*) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRF's.

(*v*) All withdrawals and dropouts are reported and explained on the CRF's.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AE's) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents. (See Guideline for ''Essential Documents for the Conduct of a Clinical Trial.'')

(q) Communicating significant deviations to the investigator and taking appropriate action to prevent recurrence of the detected deviations.

5.18.6 Monitoring Procedures

The monitor should follow established written Standard Operating Procedures.

5.18.7 Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the time, date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and followup of the monitoring report with the sponsor should be documented.

5.19 *Audit*

If or when, as part of implementing quality assurance, the sponsors performing audits should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct, protocol compliance, and GCP compliance.

5.19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals who are independent of the trial to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly.

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented in an audit report.

(d) The audit reports should not routinely be made available for inspection, but should be made available for inspection upon request by the regulatory authority(ies).

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 *Noncompliance*

5.20.1 Noncompliance with the protocol, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If monitoring and/or auditing identified serious and/or persistent noncompliance of an investigator, the sponsor should terminate the investigator's participation in the trial. When an investigator's participation is terminated because of noncompliance, the sponsor should notify promptly the responsible IRB(s)/IEC(s) and the appropriate authority(ies).

5.21 *Premature Termination of a Trial*

If a trial is prematurely terminated, the sponsor should promptly inform the investigators/institutions, the IRB(s)/IEC(s), and the appropriate regulatory authority(ies) of the termination and the reason(s) for the termination.

5.22 *Clinical Trial Reports*

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports meet the standards of the ICH guideline entitled, ''Structure and Content of Clinical Study Reports.''

5.23 *Multicenter Trials*

For multicenter trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the same protocol, or with well-documented amended protocols that are agreed to by the sponsor and approved/provided a favorable opinion by

the IRB/IEC and authorities, when required, for specific sites.

5.23.2 The CRF's are designed to capture the required data at all multicenter trial sites, with exceptions for those investigators who are collecting additional data.

5.23.3 The responsibilities of a coordinating investigator and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given sufficient instructions on how to follow the protocol and to comply with a uniform set of standards for assessment of the clinical and laboratory findings and for completing the CRF's.

5.23.5 Communication between investigators is possible.

6. *CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)*

The contents of a trial protocol should generally include the following topics:

6.1 *General Information*

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and phone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name and address of the clinical laboratory and other medical and/or technical department(s) involved in the trial.

6.1.8 Site specific information may be provided on separate protocol page(s), if not addressed in a separate agreement.

6.2 *Background Information*

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of clinically significant findings from nonclinical studies and clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 *Trial Objectives and Purpose*

A detailed description of the objectives and the purpose of the trial.

6.4 *Trial Design*

(**NOTE:** The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design). A description of the trial design, including:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

6.4.4 A description of the dosage and dosage regimen of the trial treatment(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including followup, if any.

6.4.6 A description of the ''stopping rules'' or ''discontinuation criteria'' for individual subjects, parts of trial, and entire trial. Criteria for removing subjects from the trial should be outlined.

6.4.7 Investigational product accountability procedures.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.5 *Selection and Withdrawal of Subjects*

6.5.1 Subject inclusion criteria.

6.5.2 Exclusion criteria.

6.5.3 Withdrawal criteria and procedures specifying:

(a) When and how to withdraw subjects from the trial.

(b) The type and timing of the data to be collected for withdrawn subjects.

6.6 *Treatment of Subjects*

6.6.1 The treatment(s) to be administered, including the name of the product(s), the dose(s), the dosing schedule(s), the route/mode of administration, and the treatment period(s) for the product(s).

6.6.2 Medication(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 *Assessment of Efficacy*

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analyzing of efficacy parameters.

6.8 *Assessment of Safety*

6.8.1 Specification of safety parameters.

6.8.2 Procedures for eliciting reports of and recording and reporting adverse events.

6.8.3 The duration of the followup period(s) after adverse events.

6.9 *Statistics*

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be included. In multicenter trials, the numbers of subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan.

(Any deviation(s) from the original statistical plan should be described and justified in protocol amendment(s) and/or in the final report, as appropriate.)

6.10 *Quality Control and Quality Assurance Procedures*

Monitoring and audit procedures, if not addressed in a separate agreement.

6.11 *Ethics*

Description of ethical considerations relating to the trial.

6.12 *Data Handling and Recordkeeping*

6.13 *Financing and Insurance*

Financing and insurance, if not addressed in a separate agreement.

6.14 *Publication Policy*

Publication policy, if not addressed in a separate agreement.

6.15 *Supplements*

(**Note:** Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for ''Structure and Content of Clinical Study Reports.'')

Dated: August 11, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

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