



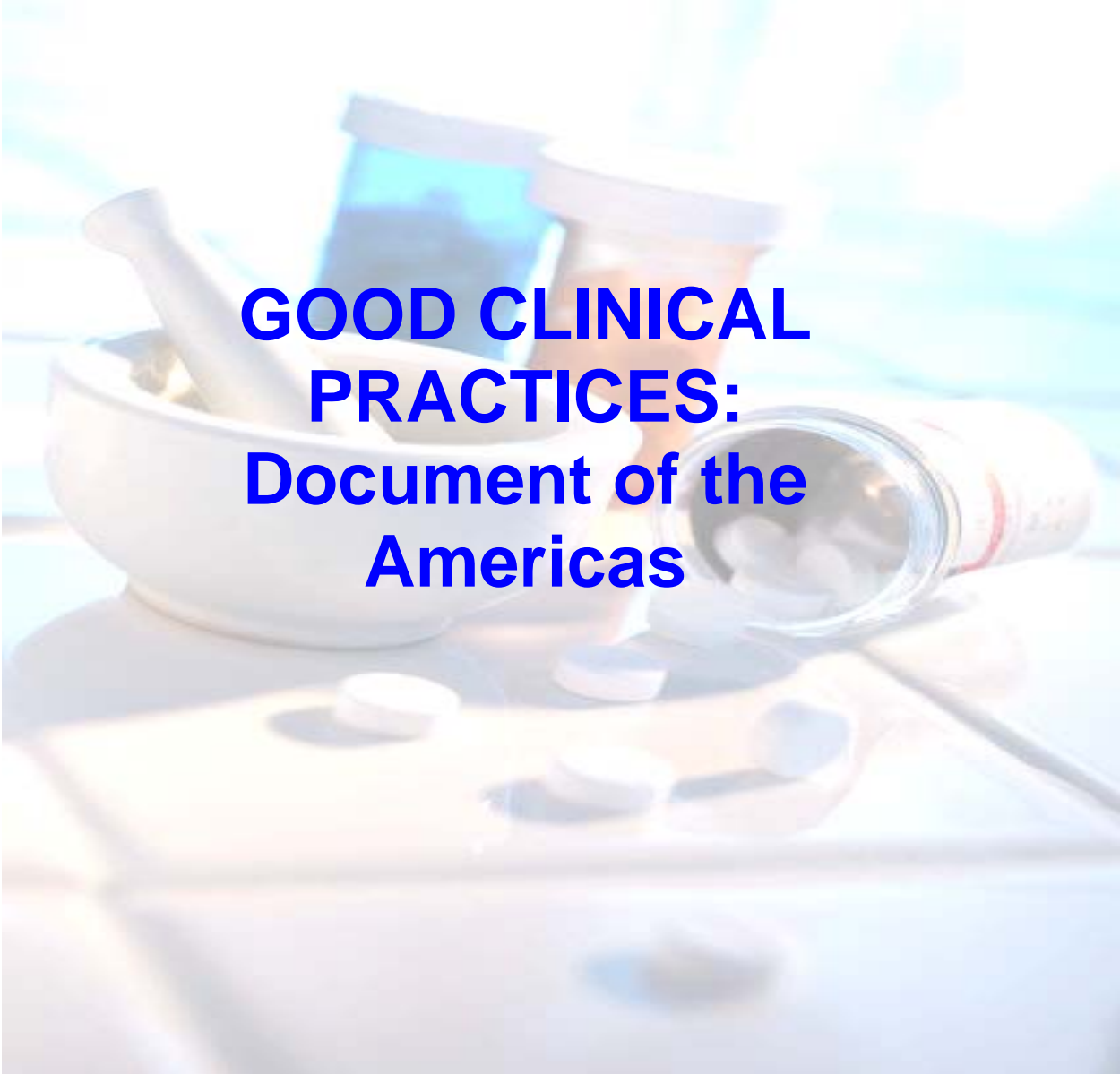
**Pan American
Health
Organization**



Regional Office of the
World Health Organization



**PAN AMERICAN NETWORK FOR DRUG
REGULATORY HARMONIZATION**



**GOOD CLINICAL
PRACTICES:
Document of the
Americas**

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ACRONYM

ADR: Adverse Drug Reaction

AE: Adverse Event

ANMAT: Administración Nacional Argentina de Medicamentos, Alimentos y Tecnología Médica (Argentina's National Administration of Drugs, Food and Medical Technology)

CRF: Case Report Form

CRO: Contract Research Organization

GCP: Good Clinical Practice

ICDRA: Conference of Drug Regulatory Authorities

ICH: International Conference on Harmonization

IEC: Independent Ethics Committee

IDMC: Independent Data Monitoring Committee

IRB: Institutional Review Board

SAE: Serious Adverse Event

Serious ADR: Serious Adverse Drug Reaction

SOP: Standard Operating Procedure

PAHO: Pan American Health Organization

PANDRH: Pan American Network for Drug Regulation Harmonization

QA: Quality Assurance

QC: Quality Control

WG/GCP: Working Group on Good Clinical Practice

WHO: World Health Organization

GOOD CLINICAL PRACTICES: Document of the Americas

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CHAPTER 1

INTRODUCCION

A clinical trial is a systematic study of drugs and/or medicinal specialties in human volunteers that strictly follows the guidelines of the scientific method. Its purpose is to discover or confirm the effects and/or identify the adverse reactions to the product investigated and/or to study the pharmacokinetics of the active ingredients, in order to determine their efficacy and safety.

Clinical trials are needed to find new therapeutic responses to diseases. Major advances in pharmacology have taken place in recent decades, made possible largely through scientific research, which in turn, is partly based on studies conducted on human subjects.

Prior demonstration of the efficacy and safety of a drug (to approve either its marketing or a new indication) is currently required in the different national regulations, as well as in the international area. However, efficacy and safety can only be demonstrated through controlled clinical trials. The results obtained in those studies are the principal factor that determines whether a drug is authorized and subsequently marketed.

These facts illustrate the need for national and international standards for clinical pharmacological research. Such standards should guarantee the scientific soundness of the study on the one hand and its ethical soundness on the other. In addition, guidelines should be established to guarantee that the data obtained from the research are adequately stored and that they can be confirmed, regardless of where the study is conducted.

In the past decade, in an effort to avoid duplication of efforts there arose the need to facilitate the acceptance of data from clinical trials, even though these were conducted in different countries. This led different regions to harmonize standards for good practice in clinical research. Recently, through the International Conference on Harmonization (ICH), the European Community, the United States, and Japan (and Canada and the World Health Organization, among others, as observers), produced guidelines standardizing criteria in different areas related to drugs. Within the framework of the International Conference on Harmonization there emerged Guidelines for Good Clinical Practice, which set forth a series of guidelines for the design, implementation, auditing, completion, analysis, and reporting of clinical trials in order to ensure their reliability.

The rest of the countries in our Hemisphere are not part of the International Conference on Harmonization. However, clinical trials in all the countries here, as in the rest of the world, should follow strict ethical and scientific principles. These principles are universal, above any differences among individuals, and their objective is to safeguard the physical and psychic integrity of the subjects involved as established in the Helsinki declaration of human rights. During the

past decade the number of patients involved in clinical trials has increased in the Region. In 1993, 2.1% of the clinical trials took place in Latin America, while in 1997 the figure was 5.1% and in 2000, 7.5% (from IMS Health).

In the Region studies of earlier phases of development are also being conducted. As a result, there has been a marked increase in the number of patients involved in the studies, along with investigators, research centers, research ethics committees, personnel in the pharmaceutical companies devoted to this subject in particular, and monitoring establishments.

Within this framework, it becomes necessary to establish harmonized criteria for good clinical practice in our Hemisphere, in which various stages of development are visible. The objective of the Document of the Americas is to propose guidelines for good clinical practice that can serve as a foundation for regulatory agencies, as well as for investigators, ethics committees, universities, and businesses.

CHAPTER 2

PRINCIPLES OF GOOD CLINICAL PRACTICES

Clinical trials are conducted aiming at obtaining evidence regarding efficacy and safety of products that, in addition to non-clinical evidence and quality data should support their registration by a regulatory authority. Ethical principles based primarily on the Declaration of Helsinki should be the basis for the approval and conduction of clinical trials. Three basic ethical principles of equal moral force, namely respect for persons, beneficence and justice, permeate all the GCP principles enumerated below

- 2.1 Clinical trials should be conducted only if the anticipated benefits for the individual trial subject and society clearly outweigh the risks involved;
- 2.2 Although the benefit of the results of the clinical trial to science and society are important and should be taken into account, the most important considerations are those related to the rights, safety and well-being of the trial subjects;
- 2.3 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion;
- 2.4 Approval of clinical trials of investigational products should be supported by adequate non-clinical and, when applicable, clinical information;
- 2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol;
- 2.6 Freely given informed consent should be obtained from every subject prior to clinical trials participation;
- 2.7 Qualified physicians (or, if appropriate, qualified dentists) should be responsible for the medical care of trial subjects, and for any medical decision made on their behalf;
- 2.8 These professionals should be adequately qualified by education, training and experience to perform their tasks regarding the trial and trial subjects;
- 2.9 Recording, handling, and storage of all clinical trial information should be appropriate to allow accurate trial reporting, interpretation and verification;

- 2.10 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);
- 2.11 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP), and should be used in accordance with the approved protocol;
- 2.12 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

CHAPTER 3 INVESTIGATIONAL ETHICS COMMITTEE / INSTITUTIONAL REVIEW BOARD (IEC /IRB)

3.1 Structure and Responsibilities of the Ethics Committee

3.1.1 The responsibility of an Ethics Committee (IEC /IRB) in the evaluation of biomedical research is to help safeguard the dignity, rights, safety, and well-being of all current and potential research subjects; with special attention to studies that involve vulnerable people;

3.1.2 A cardinal principle of research involving human subjects is to respect the dignity of the person. The goals of the research, while important, never should be placed above the health, well-being, and care of the research subjects;

3.1.3 The IEC should adhere to the principle of justice. Justice requires that the benefits and risks of the research be distributed equitably among all groups and social classes, taking age, sex, economic status, culture, and ethnicity into account;

3.1.4 The IEC should issue an independent, competent, and timely evaluation of the ethics of proposed studies;

3.1.5 The IEC is responsible for acting fully in the interests of the potential research subjects and communities involved, considering the interests and needs of the investigators, as well as the requirements of the regulatory agencies and applicable laws;

3.1.6 The IEC is responsible for evaluating the proposed research before it begins. It should furthermore see to the periodic evaluation of approved studies already in progress; these evaluations should be conducted at appropriate intervals consistent with the level of risk to the subjects, but at least once a year;

3.1.7 The IEC has the authority to approve, request changes to (prior to approval), deny permission for, or suspend a clinical trial;

3.1.8 In order to exercise its functions the IEC should receive and have at hand all documentation related to the study: the protocol, amendments to the protocol, informed consent forms and updates to them, an up-to-date résumé of the investigator, recruitment procedures, patient information, the investigator's manual, the available safety information, information on payment to patients, information on compensation to patients, and any other documents that the it might need to meet its responsibilities;

3.1.9 The IEC should determine whether the investigator is competent to conduct the proposed study, based on his résumé and any other relevant documentation that the committee requests.

3.1.10 The institutional review board/independent ethics committee (IRB/IEC) should review both the amount and method of payment to the individuals to make sure that there are no problems of coercion or improper influence on the subjects of the study. Payments to individuals must be prorated and not depend on whether the subject completes the study.

3.1.11 The IEC/IRB should make sure that the information concerning the payment of subjects, including the methods, quantities, and scheduling, is indicated in writing on informed consent form and any other written information provided to the subjects. The method for determining the prorated payment should be indicated.

3.2 Composition of the (IEC /IRB)

3.2.1 The (IEC /IRB) should be constituted in a way that ensures a competent evaluation and review of the scientific, medical, and ethical aspects of the study and guarantees that it can meet its goals free of any bias and influence that could affect its independence;

3.2.2 The IEC should be multidisciplinary and multisectoral and include relevant scientific experts balanced in terms of age and sex, as well as people representing community interest and concerns;

3.2.3 The IEC should have enough members to guarantee its efficiency but not so many as to make it difficult to administer. The minimum number is five;

3.2.4 The IEC should designate a chair. The chair of the (IEC /IRB) should be someone highly respected inside and outside the institution who is able to issue fair and impartial judgments, is familiar with the different areas that the IEC evaluates, and has the capacity to serve as the administrator. This individual should be independent enough to withstand pressures from the institution, the investigators, or other people or parties;

3.2.5 At least one member of the committee should not be a scientist, and, in the case of an Institutional Review Board, there should be a member from outside the institution (unrelated by blood or marriage to any staff member or personnel of the institution). It is also recommended that one of the members have knowledge of biostatistics and/or research methodology;

3.2.6 Concerning individuals from outside the institution, it is recommended that people from the community be included on the committee, e.g., lawyers, clergy, educators, and homemakers. Such members should possess an in-depth knowledge of the local community and be willing to offer their opinions from that perspective;

3.2.7 The (IEC /IRB) may have alternate members. The designation and functions of these individuals should be established in the regulations ((IEC /IRB)

Procedures). An up-to-date list of (IEC /IRB) members and their qualifications should be maintained. This list should identify the regular members and their substitutes (or alternates). To ensure a suitable quorum, alternates should possess qualifications comparable to those of the regular members. When alternates vote in a meeting, it should be documented in the minutes. The alternate should receive all the necessary documentation for reviewing the study, just as if he were the incumbent;

3.2.8 If the community in which the study will be conducted has a predominantly minority population (e.g., indigenous people), the (IEC /IRB) should include a member, alternate, or consultant from that minority group;

3.2.9 The constitution of an (IEC /IRB) should prohibit any form of discrimination based on the sex of its members (e.g., that it be made up only of men or only of women);

The (IEC /IRB) can invite experts from specific fields who are not members to serve as consultants. These individuals cannot vote in its deliberations;

3.2.10 If the (IEC /IRB) regularly evaluates studies involving vulnerable populations (e.g., the physically or mentally disabled, children, pregnant women, prisoners, etc.), it should consider including members or consultants who know or have had experience working with the group in question;

3.2.11 An investigator may be a member of an (IEC /IRB) but is not permitted to participate in the initial evaluation and subsequent review of a study in which he has a conflict of interest (for example, if he is involved with the study in some way). When selecting (IEC /IRB) members, potential conflicts of interest should be considered. Committee members should abstain from participating in the deliberations of the IEC and in voting on studies that pose a conflict of interest.

3.3 (IEC /IRB) Functions and Operations

3.3.1 The (IEC /IRB) has the authority to:

- Approve
- Deny permission for
- Request changes to, or
- Suspend a clinical trial

3.3.2 The (IEC /IRB) should inform the investigator and the institution in writing of the decision to approve, deny permission for, request changes to, or suspend a clinical trial;

3.3.3 The (IEC /IRB) should state the reason for its decisions in writing. When it decides to deny permission for a clinical trial, it should detail in writing the reasons for its decision and give the investigator the opportunity to respond personally or in writing;

3.3.4 The (IEC /IRB) should provide written procedures for appeal;

3.3.5 The review process requires that the (IEC /IRB) receive all the information necessary for its activities. It is recommended that every IEC member receive a copy of all materials. If a principal evaluator (this may be one or more individuals) is designated to review all the material and present the study to the rest of the (IEC /IRB), each member should receive a copy of the material;

3.3.6 Sufficient time should be allowed for an adequate review;

3.3.7 The majority of committee members should be involved in the review and approval process, and there should be at least one whose area of interest is not scientific and at least one from outside the research center. The necessary quorum must be obtained for the approval or denial of permission for a study (as stipulated in the (IEC /IRB) Procedures);

3.3.8 Only the members who conduct the review should participate in the decision;

3.3.9 In the case of minor changes to a protocol that has already been approved, the (IEC /IRB) can expedite the approval. The chair or members in charge of the evaluation should inform the other members of the IEC and document it in the minutes of the meeting;

3.3.10 The (IEC /IRB) has the authority to observe (directly or by means of third parties) the consent process and the conduct of the clinical trial.

3.4 Procedures

3.4.1 The IEC should adhere to written standards in the exercise of its functions. The (IEC /IRB) should establish written procedures, which should cover:

3.4.1.1 Its composition (names, training, and qualifications of its members);

3.4.1.2 The programming, notification to its members, and holding of meetings;

3.4.1.3 Initial and ongoing evaluation of the research study (this includes considering whether the investigator, his team, and the facilities are adequate for the clinical trial, and evaluation of requests to extend previously granted approvals);

3.4.1.4 Notification to the investigator and institution of the results of the initial and ongoing evaluation of the study. A written decision should be issued and the composition of the members of the (IEC /IRB) detailed (names, qualifications, and functions; who participated in the decision and final ruling, etc.);

3.4.1.5 The frequency of the ongoing review. Determination of which studies require evaluation more often than once a year and which require sources of information other than the investigator;

3.4.1.6 A provision that no subject be admitted to a study before the (IEC /IRB) issues a favorable decision in writing;

3.4.1.7 Assurance that changes (amendments) to the protocol (or any other change related to the study) will be evaluated and approved prior to implementation, except when necessary to eliminate immediate dangers to the subjects or when the changes simply involve logistical or administrative aspects of the study.

3.4.2 The investigator should inform the (IEC/IRB) of any problem involving risk to the research subjects, such as:

3.4.2.1 Serious unexpected adverse drug reactions

3.4.2.2 Deviations from or changes to the protocol to eliminate immediate dangers to research subjects

3.4.2.3 Changes that increase the risk to the subjects and/or significantly affect the way the study is conducted.

3.4.2.4 Any new information that can jeopardize the safety of the subjects or the execution of the study

3.3.2.5 Ensure that the relevant parties are informed of the cancellation of an approval granted by the IEC.

3.3.2.6 Ensure that when a study is suspended prematurely, the requesting party indicates to the (IEC/IRB) the reasons for the suspension and provides a summary of the results obtained up to that point.

3.5 Records

3.5.1 The (IEC /IRB) should keep all relevant records (e.g., written procedures, lists of its members, lists of member affiliations and occupations, documents presented, minutes of meetings, and correspondence) three years after the conclusion of the study and make them available to the regulatory authorities upon request.

CHAPTER 4 INFORMED CONSENT

4.1 Definition

Informed Consent is a process whereby a subject voluntarily confirms his desire to participate in a study, in particular after he has been informed about all aspects relevant to his decision to participate. The informed consent is documented by means of a written, signed, and dated informed consent form.

Thus, informed consent should be understood essentially as a process and, by convention, a document, with two essential purposes:

- To ensure that the subject controls the decision on whether to participate in clinical research
- To ensure that the subject participates only when the research is consistent with his values, interests, and preferences

In order to give truly informed consent, that is, in order to ensure that an individual makes a free and rational decision about whether the clinical research is consistent with his interests; emphasis should be placed on ensuring that the information is truthful, clear, precise and conveyed in a manner that can be understood by the subject, so that he can appreciate the implications for his own clinical situation, weigh all the options, ask questions, and thus, make a free and voluntary decision.

4.2 Parts of Informed Consent

Informed Consent consists of two parts:

- *Information for the research subject*

The informed consent document is a written summary of the basic information that should be communicated to the subject to comply with the substantive ethical principle of informed consent. This document serves as the basis or guide for the oral explanation and discussion of the study with the subject or his legal representative. It is understood that this document will not be the only source of the information that the subject will receive during the informed consent process.

- *Informed consent form for signature*

The informed consent form is the document that the subject or his legal representative and the witness (if applicable) will sign and date, in order leave documented evidence or proof that the subject has received sufficient information about the clinical trial, the product tested, and his rights as a research subject and that he freely and voluntarily wishes to

participate in the study. It is important to point out that some of the contents of this document may already be mandated in the country's regulations.

4.3 Guidelines for Obtaining Informed Consent

4.3.1 Voluntary informed consent should be obtained from each subject prior to his participation in the clinical trial;

4.3.2 Informed consent is a process whereby a subject voluntarily confirms his desire to participate in a particular study after he has been informed about all aspects of the study relevant to his decision;

4.3.3 Informed consent is documented by means of a written, signed, and dated informed consent form;

4.3.4 The informed consent should meet the applicable regulatory requirements and adhere to GCP and the ethical principles contained in the Declaration of Helsinki;

4.3.5 Any written information or document utilized for the consent process must have first been approved by the independent ethics committee;

4.3.6 All written information or documents should be reviewed when new information is developed that could be relevant to the subject's consent. This information should be approved by the independent ethics committee, except when it is necessary to eliminate immediate dangers to the subjects or when the changes involve only logistical or administrative aspects of the study. The new information should be communicated to the subject or his legally authorized representative in a timely manner. Communication of this information should be documented;

4.3.7 Neither the investigator nor the research staff should oblige, coerce, or improperly influence a subject to participate or continue his participation in a study;

4.3.8 The oral and written information about the study should not include language that causes the subject or his legally authorized representative to waive or appear to waive any legal right, or release or appear to release the investigator, institution, sponsor, or its representatives of any responsibility for negligence;

4.3.9 The investigator or his designated representative should fully inform the subject or his legally authorized representative of all pertinent aspects of the study;

4.3.10 The language utilized in the written and oral information on the study should be practical, not technical, and the subject, his legally authorized

representative, and the impartial witness, when applicable, should understand it. When the language of the investigator is not the language currently spoken in the country or the community, the information provided and the consent form should be in the subject's own language;

4.3.11 Before obtaining informed consent, the investigator or his designated representative should give the subject or his legally authorized representative sufficient time and opportunity to inquire about the details of the study so that he can decide whether or not to participate;

4.3.12 All questions about the study posed by the subject or his legally authorized representative should be answered to his satisfaction;

4.3.13 Before a subject participates in the study, the consent form should be signed and dated in person by the subject or his legally authorized representative and by the person who discussed informed consent with him;

4.3.14 If the subject or his legally authorized representative cannot read, an impartial witness should be present throughout the informed consent process. After the written information is read and explained and the subject or his legally authorized representative has given his oral and, if possible, signed and dated consent on the informed consent form, the witness should sign and date the form in person, certifying that the written information was explained accurately and was apparently understood by the subject or his legally authorized representative and that the subject or his legally authorized representative voluntarily gave his informed consent;

4.3.15 All oral and written information furnished to the subject or his legally authorized representative during the informed consent process should have basic content elements;

4.3.16 Before participating in the study, the subject or his legally authorized representative should receive a copy of the signed and dated informed consent form and any other written information furnished during the process. During a subject's participation in the study, he or his legally authorized representative should receive a copy of any updates to the signed and dated form and of the updated written information provided;

4.3.17 In the case of clinical trials (therapeutic and non-therapeutic) with subjects who can be included in the study only with the consent of their legally authorized representative (for example, children or patients with severe dementia), the subject should be informed about the study, insofar as he is able to understand it, and if able, should sign and date the written informed consent in person;

4.3.18 Non-therapeutic studies--that is, studies that intend no benefit to the subject--should be conducted on subjects who personally give their consent and sign and date the informed consent form;

4.3.19 In emergencies, if the subject's informed consent cannot be obtained, the consent of his legally authorized representative, if there is one, should be requested. If the prior consent of the subject or his representative cannot be obtained, the subject will be included with the documented approval of the ethics committee in order to protect his rights, safety, and well-being, pursuant to the applicable regulations. The subject or his legally authorized representative should be informed about the study as soon as possible and his consent to continue will be requested, or another type of consent obtained, as the case may be.

4.4 Elements of Informed Consent

- a) A statement on the study involved in the research;
- b) The objective or purpose of the study;
- c) The treatments involved in the study, how they are administered, and the probability of receiving every treatment;
- d) Procedures to be done in the study, including all invasive procedures;
- e) Responsibilities of the subject;
- f) Experimental aspects of the study;
- g) Reasonably foreseeable risks or discomforts to the subject and, when applicable, to the embryo, fetus, or infant;
- h) Reasonably expected benefits. When a clinical benefit is not intended for the subject, he will have to be aware of this;
- i) Alternative procedures or courses of treatment available to the subject and their important potential benefits;
- j) Compensation and/or treatment available for the subject in the case of a research-related injury;
- k) Advance prorated payment, if applicable, to the subject to participate in the study;
- l) Payment of the anticipated expenditures or costs, if any, to the subject to participate in the study;
- m) The subject's participation in the study is voluntary; the subject can refuse to participate or can withdraw from the study at any time without penalty or loss of the benefits to which he is otherwise entitled;

- n) Permission to give monitors auditors, the Ethics Committee, and the regulatory authorities direct access to the subject's original medical records in order to verify the procedures and/or data of the clinical trial, without violating the confidentiality of the subject insofar as the applicable laws and regulations permit. By signing the written consent form, the subject or his representative authorizes this access;
- o) The confidentiality of the records identifying the subject will remain inviolate and, insofar as the applicable laws and/or regulations permit, they will not be made public. If the results of the study are published, the subject's identity will remain confidential;
- p) Timely communication to the subject or his legally authorized representative of any new information developed that could be relevant to the subject's desire to continue participating in the study;
- q) People to contact for more information on the study and on the rights of study subjects, and whom to contact in the event of a research-related injury;
- r) Anticipated circumstances and/or reasons why a subject's participation in the study may be terminated;
- s) Expected duration of the subject's participation in the study, and
- t) Approximate number of subjects expected to participate in the study.

CHAPTER 5 INVESTIGATOR RESPONSIBILITIES

5.1 Investigator's Qualifications and Agreements

5.1.1 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 specified by applicable regulatory requirements(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority (is).

5.1.2 The investigator(s) should be thoroughly familiar with the appropriate use of the investigational product(s) as described in the protocol, in the current Investigator's Brochure, in the product information and in other relevant information source

5.1.3 The investigator should be aware of, and should comply with GCP and the applicable regulatory requirements

5.1.4 The investigator/institution should permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority (ies) and the auditing by the IEC/IRB.

5.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. Details of the names of persons, and functions and specific duties that have been delegate should be documented before the study initiation and kept updated during the study. The investigator can only delegate duties/activities but not responsibilities; and occasionally, when initiate or conduct the study with no other sponsor, the investigator can also be responsible as sponsor.

5.2 Adequate Resources

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

5.2.2 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.

5.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely. Details of person's names, functions, qualifications as well as details of facilities should be documented.

5.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5.2.5 Training of the study participants should be documented including: the name of the staff persons trained, procedures and dates.

5.3 Informed Consent

The Investigator is responsible for obtaining the informed consent (See chapter 4)

5.4 Medical Care of Trial Subjects

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

5.4.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. This care will not imply additional cost for the patient. The investigator/institution should inform a subject when medical care is needed for intercurrent illness (is) of which the investigator becomes aware.

5.4.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

5.4.4 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;

5.4.5 The investigator, through prior agreements with the sponsor, should ensure continuity of treatment for the research subjects once their involvement in the study has ended, if its interruption endangers their safety within the applicable regulatory frameworks. The national regulatory authority (NRA) must take into account that, during the course of this treatment, products that still are not officially approved will be used.

5.5 Communication with IRB/IEC

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

5.5.2 The investigator should also obtain approval for the trial protocol from the regulatory authority before initiating the study, if required by local regulations.

5.5.3 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC. During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

5.6 Compliance with Protocol

5.6.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

5.6.2 The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

5.6.3 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

5.6.4 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

5.6.5 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC Approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) To the IRB/IEC for review and approval/favorable opinion;
- (b) To the sponsor for agreement and, if required;
- (c) To the regulatory authority (ies).

5.7 Investigational Product(s)

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

5.7.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

5.7.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, 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 and reconcile all investigational product(s) received from the sponsor.

5.7.4 The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

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

5.7.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

5.8 Randomization Procedures and Unblinding

5.8.1 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 promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s)

5.9 Records and Reports

5.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

5.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

5.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained; this applies to both written and electronic changes and corrections). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

5.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

5.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However it should be retained longer as required by the regulatory requirement(s), or by agreement with the sponsor. In case of any doubts the investigator should ask the sponsor.

5.9.6 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.

5.10 Progress Reports

5.10.1 The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

5.10.2 Written summaries should be provided to the regulatory authority, if required by local regulations.

5.10.3 The investigator should promptly provide written reports to the sponsor, the IRB/IEC), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

5.11 Safety Reporting

5.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

5.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

5.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

5.12 Premature Termination or Suspension of a Trial

5.12.1 If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

5.12.2 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

5.12.3 If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution, where required by the applicable regulatory

requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

5.12.4 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

5. 13 Final Report(s) by Investigator/Institution

5.13.1 Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

5. 14 Financial Aspects

5.14.1 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution. This document is listed as an essential document in the corresponding section.

5.14.2 The agreement should include evidence of acceptance/involvement of the institution/hospital administration to the provision of facilities and services and the Sponsor's proposed payment(s).

5.14.3 Investigators should disclose financial interests as requested by IRB/IECs, sponsors, government's authorities, and journal editors. The disclosure may be required pre and end of trial and involves the investigators spouse(s) and dependent children.

CHAPTER 6 SPONSOR RESPONSIBILITIES

6.1 Quality Assurance and Quality Control

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

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

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

6.2 Contract Research Organization (CRO)

6.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control. These procedures should be documented in writing before the start of the study.

6.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

6.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

6.2.4 All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

6.3 Medical Expertise

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

6.4 Trial Design

6.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

6.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee

6.5.1 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.

6.5.2 The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings. Clinical investigators should not be included as members of the IDMC of the protocol in which they are part as investigators or any other protocol with the same product. Sponsors' employees may not serve as members; they can only assist in the activities of the IDMC.

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

- a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (eg., validation).
- b) Maintain SOPs for using these systems.
- c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (e.g., maintain an audit trail, data trail, edit 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 (e.g., maintain the blinding during data entry and processing).

6.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

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

6.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See section. "Essential Documents for the Conduct of a Clinical Trial"); 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).

6.5.7 If the sponsor discontinues the clinical development of an investigational product (i.e., 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).

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

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

6.5.10 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

6.5.11 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed

6.6 Investigator Selection

6.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to

be utilized in multicenter trials, their organization and/or selection is the sponsor's responsibility.

6.6.2 It is the responsibility of the sponsor to establish the suitability of the investigator, team and site prior to, at the initiation and during the trial. All site personnel that are involved in the trial should be involved in the trial information/training activities and trial initiation meeting

6.6.3 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.

6.6.4 The sponsor should obtain the investigator's/institution's agreement:

- a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;
- b) To comply with procedures for data recording/reporting;
- c) To permit monitoring, auditing, and inspection; and
- d) To retain the essential documents that should be in the investigator/institution files until the sponsor informs the investigator/institution these documents are no longer needed. The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

6.7 Allocation of Duties and Functions

6.7.1 Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

6.8 Compensation to Subjects and Investigators

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

6.8.2 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). When trial subjects receive

compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

6.9 Financing

6.9.1 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution. Any agreements between the sponsor and the researcher or with any other person involved in the clinical trial should be by writing as part of the protocol or by a separate agreement.

6.10 Notification/Submission to Regulatory Authority (ies)

6.10.1 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.

6.11- Confirmation of Review by IRB/IEC

6.11.1 The sponsor should obtain from the investigator/institution:

- (a) The name and address of the investigator's/institution's IRB/IEC;
- (b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations;
- (c) Documented IRB/IEC approval/favorable opinion, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

6.11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC. It is necessary to obtain favorable opinion by the local regulatory authority, if required by local regulation.

6.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

6.12 Information on Investigational Product(s)

6.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

6.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available.

6.13 Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

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

6.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), 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.

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

6.13.4 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.

6.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

6.14 Supplying and Handling Investigational Product(s)

6.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s), during the clinical trial and should, within applicable regulatory framework, provide investigational products to trial subjects after the subject participation in the trial, if the interruption can be of danger to the subject health.

6.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority (ies)).

6.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof.

6.14.4 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)).

6.14.5 The sponsor should:

- (a) Ensure timely delivery of investigational product(s) to the investigator(s);
- (b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See Section 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 for the documentation of this disposition.

6.14.6 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 the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the

extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

6.15 Record Access

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

6.15.2 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.

6.16 Safety Information

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

6.16.2 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.

6.17 Adverse drug reactions (ADRs) reports

6.17.1 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 (ADRs) that are both serious and unexpected.

6.17.2 Such expedited reports should comply with the applicable regulatory requirement(s).

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

6.18 Monitoring

6.18.1 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 applicable regulatory requirement(s).

6.18.2 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. A monitor's qualifications should be documented.
- (c) Monitors should be familiarized with the investigational products, protocol, informed consent form and any other written information provided to the subjects; also with the sponsor's SOP and GPC and with applicable regulatory requirements.

6.18.3 Extent and Nature of Monitoring

- (a) The sponsor should ensure that the trials are adequately monitored;
- (b) The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.
- (c) A written monitoring plan should be available.

6.18.4 Monitor's Responsibilities

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- (a) Acting as the main line of communication between the sponsor and the investigator;
- (b) Verifying that the investigator has adequate qualifications and resources and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these 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's authorized procedures.

(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, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and has not delegated these functions to unauthorized individuals.

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

(j) Reporting the subject recruitment rate.

(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and 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, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

- (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.
- (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
- (iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
- (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 CRFs.
- (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(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 (AEs) 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 section. "Essential Documents for the Conduct of a Clinical Trial")

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations._

6.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

6.18.6 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 date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and 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 follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

6.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

6.19.1 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 and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

6.19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

6.19.3 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 for a trial audit 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;

(d) To preserve the independence and value of the audit function, the regulatory authority (ies) should not routinely request the audit reports. Regulatory authority (ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings;

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

6.20 Noncompliance

6.20.1 Noncompliance with the protocol, SOPs, 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.

6.20.2 If the monitoring and/or auditing identify serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. The sponsor should notify promptly the regulatory authority (ies).

6.21 Premature Termination or Suspension of a Trial

6.21.1 If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6.22 Clinical Trial/Study Reports

6.22.1 Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study 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/study reports in marketing applications meet the applicable regulatory requirements.

6.23 Multicenter Trials

6.23.1 For multicenter trials, the sponsor should ensure that:
All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

6.23.2 The CRFs are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data

6.23.3 The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

6.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

6.23.5 Communication between investigators is facilitated

CHAPTER 7

GCP COMPLIANCE MONITORING PROGRAMS BY REGULATORY AUTHORITIES (RA)

7.1 Objective of the Program:

The aim of the program is to monitor compliance with GCP through inspections to all parties involved in the clinical trial

7.2-Purpose of the National GCP Compliance Program

A GCP Compliance Monitoring program is intended to ascertain whether clinical studies have been conducted in accordance with acceptable GCP standards as necessary to ensure the quality and integrity of study data and the protection of the rights and welfare of research subjects. Regulatory authority (ies) should publish the details of their (National) GCP Compliance Program. Such information should:

a- define the scope and extent of the Program

A (National) GCP Compliance Program may cover only a limited range of products, e.g. pharmaceuticals, biologicals, etc., or may include all clinical trials of medical devices, food additives and veterinary products¹. The Scope of the monitoring for compliance should be defined, both with respect to the categories of products covered and to parties subject to inspection, e.g., IRBs/IECs, Sponsors, Contract Research Organizations, clinical investigators.

b- define the authority of Inspectors for entry into trial sites and their direct access to data held by trial sites

While Inspectors will not normally wish to enter trial sites against the will of the site's management, circumstances may arise where trial site entry and access to data are essential to protect public health. The powers available to the (National) GCP Monitoring Authority in such cases should be defined.

c- describe the Inspection procedures for verification of GCP compliance.

d- describe actions that may be taken as follow-up to GCP Inspections.

When a GCP Inspection has been completed, the Inspector should prepare a written report of the findings. Member countries should take action where deviations from GCP Principles are found during a GCP Inspection. The appropriate actions should be described in documents from the (National) GCP Monitoring Authority. Where serious deviations are found, the action taken by (National) GCP Monitoring Authorities will depend upon the particular circumstances of each case and the legal or administrative provisions under which GCP Compliance Monitoring has been established within their countries. Examples of actions which may be taken include, but are not limited to, the following:

¹ This doc refers to trials of pharmaceutical products

- Issuance of a statement, giving details of the inadequacies or faults found which might affect the rights or welfare of subjects or the validity of studies conducted at the trial site;
- issuance of a recommendation that a study be rejected;
- suspension of a trial;
- Restriction or disqualification of a clinical investigator, sanctions against an IEC/IRB and a sponsor;
- action through the courts, where warranted by circumstances and where legal/administrative procedures so permit;
- Problems or differences of opinion, between Inspectors and inspected parties will normally be resolved during the course of an Inspection. However, it may not always be possible for agreement to be reached. A procedure should exist whereby an inspected party may make representations relating to the outcome of an Inspection for GCP Compliance Monitoring and/or relating to the action the GCP Monitoring Authority proposes to take thereon;

d-Ensure the confidentiality

Make provision for the maintenance of confidentiality, not only by Inspectors but also by any other person who gain access to confidential information as a result of GCP Compliance Monitoring activities; ensure that, unless all commercially sensitive and confidential information has been excised, reports of GCP Inspections and Study Audits are made available only to Regulatory Authorities and, where appropriate, to the trials sites inspected or concerned with Study Audits and/or to study sponsors.

7.3 Organization / Administration

7.3.1 A (National) GCP Compliance Program should be the responsibility of a properly constituted, legally identifiable body adequately staffed and working within a defined administrative framework. It is recommended that such program be under the responsibility of the existing Drug Regulatory Authority

7.3.2 Countries should:

- Ensure that the (National) GCP Monitoring Authority is directly responsible for an adequate number of inspectors having the necessary technical/scientific expertise;
- publish documents relating to the adoption of GCP Principles within their territories;

- publish documents providing details of the (National) GCP Compliance Program, including information on the legal or administrative framework within which the program operates and references to related laws and regulations, procedures, inspection manuals, guidance notes, etc.; and
- maintain records of GCP inspections and of studies audited for both national and international inspections.

7.4 Personnel and Training

7.4.1 (National) GCP Monitoring Authorities should:

- ensure that an adequate number of Inspectors is available
- ensure that Inspectors are adequately qualified and trained

7.4.2 Inspectors should have qualifications and practical experience in the range of scientific and regulatory disciplines relevant to Good Clinical Practice. GCP Monitoring Authorities should:

- ensure that arrangements are made for the appropriate training of GCP Inspectors, having regard to their individual qualifications and experience
- ensure that inspectorate personnel, including experts under contract, have no financial or other interests in the trial sites or products and studies inspected or the firms sponsoring such studies.
- provide Inspectors with a suitable means of identification (e.g., an identity card).

7.4.3 Inspectors may be:

- on the permanent staff of the (National) GCP Monitoring Authority;
- on the permanent staff of a body separate from the (National) GCP Monitoring Authority; or
- employed on contract, or in another way, by the (National) GCP Monitoring Authority to perform Inspections.

In the latter two cases, the (National) GCP Monitoring Authority should have ultimate responsibility for determining the GCP Compliance Status and the quality/acceptability of a Study inspected, and for taking any action based on the results of inspections which may be necessary.

CHAPTER 8

CLINICAL PROTOCOL

The clinical trial will follow a protocol written and signed by the investigator and the sponsor. Every change that is subsequently required should be also agreed upon and signed by both parties and annexed to the protocol as an amendment.

As a rule, the protocol of a clinical trial should include the following points:

8.1 General Information

- a) Title, identification number, and date of the protocol; any amendment should also have a number and date;
- b) Research phase;
- c) Names and addresses of both the sponsor and the monitor;
- d) Name and title of the person authorized by the sponsor to sign the protocol and the amendments;
- e) Name, title, address, and telephone number of the medical or dental experts of the sponsor of the trial;
- f) Name and résumé of the investigator responsible for conducting the trial and the address and telephone number of the place of the trial;
- g) Name, résumé, address, and telephone number of the qualified physician or dentist responsible for the medical or dental decisions related to the site of the trial (if not the same person as the investigator);
- h) Name and address of the clinical laboratory and other medical and/or technical departments and/or institutions involved in the trial;
- i) Summary of the protocol.

8.2 Background

- a) Name and description of the investigational product;
- b) Rationale of the study;
- c) Summaries of the findings of nonclinical trials that have potential clinical significance and of the clinical trials that are relevant to the current trial;

- d) Summary of the potential risks and known benefits, if any, for human subjects;
- e) Description and justification of the route of administration, dosage, and treatment periods;
- f) Statement that the trial will be carried out in accordance with the protocol, good clinical practice (GCP), and the pertinent regulatory requirements;
- g) Description of the population to be studied;
- h) References to the literature and data that are relevant to the trial and that provide background information about it.

8.3 Objectives of the Trial

A detailed description of the objectives and the purpose of the trial and of the hypotheses when appropriate.

8.4 Design of the Trial

8.4.1 The scientific integrity of the trial and the credibility of the data obtained in it depend substantially on its design. The description of the trial design should include:

- a) A description of the primary variables (and secondary variables, if any) that will be measured during the trial;
- b) A description of the type/design of the trial to be conducted (Ex.: double-blind, placebo-controlled, parallel) and an outline of the trial design, the procedures, and the stages of the study to which they correspond;
- a) A description of the measures taken to minimize or avoid bias, including:
 - Randomization
 - Blinding
- d) Descriptions of the trial treatment and of the dosage, dosage form, packaging, and labeling of the investigational product;
- e) Descriptions of the sequence and duration of all trial periods, including the follow-up, if any;

- f) A description of the rules or criteria for terminating some part of the trial or the whole trial or for withdrawing a subject from the trial;
- g) Procedures for inventory of the investigational products, including the placebo and the comparator, if any;
- h) Procedures for maintenance of the randomization codes and for opening them.
- i) Identification of any datum that might be registered in the data collection notebooks or be considered as original data (when there is no prior written or electronic record of the data).

8.5 Selection and withdrawal of subjects

8.5.1 Selection criteria

Criteria for the selection of subjects (which includes definition of diagnostic criteria).

8.5.2 Criteria for the exclusion of subjects

Criteria/procedures for the withdrawal of subjects (that is, termination of treatment with an investigational product/trial treatment) specifying:

8.5.3 When and how to withdraw subjects from the trial/treatment with the investigational product;

8.5.4 The type of data that will be collected from these subjects and the collection schedule;

8.5.5 If and how subjects are replaced;

8.5.6 The follow-up for the subjects that abandon the trial/treatment with the investigational product.

8.6 Treatment of the Subjects

8.6.1 The treatment that will be administered, including the names of all the products, dosage, method of administration, and period of treatment, along with the follow-up time, for the subjects in each branch of the trial;

8.6.2 The medication/treatments permitted (including the rescue medication) and not permitted prior to and/or during the trial;

8.6.3 Procedures for monitoring compliance by the subject.

8.7 Evaluation

Evaluation of effectiveness:

- Specification of the parameters of effectiveness
- Methods and schedule for evaluating, collecting, and analyzing the parameters of effectiveness

Safety Evaluation

- Evaluation of safety
- Specification of safety parameters
- Methods and schedule for evaluating, collecting, and analyzing safety parameters
- Procedures for recording and communicating adverse events and concomitant diseases and producing reports on them
- Type and length of follow-up of subjects after adverse events

8.8 Statistics

8.8.1 Description of the statistical methods to be used, including the schedule of any intermediate analysis that has been planned.

8.8.2 Expected number of subjects planned.

In multicenter trials, the expected number of subjects should be specified for each site where the trial is conducted. Reason for choice of sample size, including explanations (or calculations) of the power of the study and the clinical justification.

8.8.3 Level of significance that is going to be used.

8.8.4 Criteria for the conclusion of the trial.

8.8.5 Procedures to explain missing, unused, or spurious data.

8.8.6 Procedures for communicating deviation from the original statistical plan (any deviation from the original statistical plan should be described and justified in the protocol and/or in the final report).

8.8.7 Selection of the subjects that will be included in the analyses (such as all randomized subjects, all subjects treated, all subjects that meet the selection criteria, or subjects that can be evaluated).

8.9 Direct Access to the Original Data/Documents

8.9.1 The sponsor should specify in the protocol or in another written contract that the research/institution will permit monitoring, auditing, review by the ethics committee (IRB/IEC), and regulatory inspections related to the trial, and will provide direct access to the original documents/data.

8.10 Quality Control and Quality Assurance

Instructions and practical considerations for quality control will be established.

8.10.1 Ethics

- (a) Description of the ethical considerations related to the trial.
- (b) General ethical considerations of the investigation, weighing the balance between the benefits and risks to which the individual subjects are exposed and the expected impact on the society as a whole (information on the efficacy and safety of the drug under study). The potential benefits derived from the trial to the populations that suffer from the disease are related to the severity of the pathology studied or the lack of specific therapeutic solutions.
- (c) Justification of the trial design in terms of the need to conduct a scientifically and methodologically rigorous experiment that justifies the risks to which the subjects will be exposed.
- (d) Description of the reviews and approvals of the trial protocol by the IRB/IEC and, if applicable, the regulatory authority.
- (e) Description of the information given to the subjects on the characteristics of the trial and of the procedures for requesting and obtaining permission for involvement from the subjects (written informed consent).
- (f) Specification of how the confidentiality of the information obtained and the identity of the sources will be protected and who will have access to that data.

8.10.2 Data management and record maintenance

- (a) The procedures for data entry and data management will be explicitly indicated.

(b) The form of the documentation records, their storage conditions, and the mode of access to them will be explicitly indicated.

8.10.3 Financing and insurance

Financing and insurance, if these are not included in a separate contract.

8.10.4 Publication policy

Publication policy, if this is not included in a separate contract.

CHAPTER 9

GLOSSARY of TERMS ²

Adverse drug reaction (ADR)

In the clinical experiment prior to the approval of a new medicinal product or new uses for an approved one, particularly when the therapeutic dose cannot be established, all harmful unintended responses to a medicinal product related to any dose must be considered adverse drug reactions. The phrase "responses to a medicinal product" implies that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility-- that is, that the relationship cannot be ruled out. With respect to medicinal products in the market: a drug response that is harmful and unintended and that occurs at dosages normally used in humans for prophylaxis, diagnosis, or the treatment of diseases or for the modification of physiological function (see the Guidelines of the International Conference on Harmonization for Clinical Safety Data Management Definitions and Standards of an Immediate Report).

Adverse event (AE)

Any adverse medical occurrence in a patient or subject of clinical research to whom a pharmaceutical product was administered and which does not necessarily bear a causal relationship to the treatment. As a result, an adverse event (AE) can be any unfavorable and unintentional sign (including an abnormal laboratory finding), symptom, or disease associated in time with the use of a medicinal investigational product, whether or not related to it (see the Guidelines of the International Conference on Harmonization for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Amendment to the protocol

A written description of change(s) or formal clarification of a protocol.

Approval (with regard to the IRB/IEC)

The affirmative decision of the institutional review board/independent ethics committee (IRB/IEC) that states that the clinical trial was reviewed and can be conducted in the institution within the guidelines established by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

Applicable regulatory requirement

Any law or regulation that governs the conduct of clinical studies of investigational products.

Audit

An examination that is systematic and independent of the activities and documents related to the study to determine if the evaluated activities were carried out and the data were recorded, analyzed, and reported accurately in

² The documents that have not been prepared by the group (Operational Guides for Ethics Committees and Surveying and Evaluating Ethical Review Practices (WHO)) have been incorporated with their original glossaries

keeping with the protocol, the standard operating procedures of the sponsor, good clinical practices (GCP), and the applicable regulatory requirements.

Audit of the study data

A comparison of the source data and records associated with the interim or final report to determine whether the source data were accurately reported, to determine whether tested was carried out in accordance with the study protocol and applicable GCP, to obtain additional information not provided in the report, and to establish whether practices were employed in the development of data that would impair their validity.

Audit document

Documentation that makes it possible to reconstruct the events.

Audit report

The auditor's written evaluation of the results of the audit for the sponsor.

Blinding

A procedure in which one or more parties of the study is prevented from knowing the assignment to treatment. Simple blinding usually refers to the subject(s) not knowing the assignment and double blinding to the subject(s), investigator(s), monitor(s) and, in some cases, the analyst, not knowing the assignment to the treatment.

Case report form (CRF)

A printed, optical, or electronic document designed to record all the information on each subject of the study that, under the protocol, must be reported to the sponsor.

Certified audit

Audit accompanied by a declaration of the auditor confirming that the audit was conducted.

Clinical trial

Any research conducted on human subjects for the purpose of discovering or confirming the clinical and/or pharmacological effects and/or any other pharmacodynamic effect of investigational product(s) and/or identifying any adverse reaction to investigational product(s) and/or studying the absorption, distribution, metabolism, and excretion of investigational product(s) to verify its/their safety and/or efficacy.

Clinical study report

A written description of a study of any therapeutic, prophylactic, or diagnostic agent conducted on human subjects, in which the clinical and statistical description, presentations, and analysis are fully integrated into a single report (see the Guideline of the International Conference on Harmonization on the Structure and Contents of Clinical Study Reports)

Coordinating committee

A committee that the sponsor can organize to coordinate the management of a multicenter study.

Comparator/comparator drug

A research or commercial product (for example, active control) or placebo used as reference in a clinical trial.

Confidentiality

The privacy or secrecy of information or data, maintained through refraining from revealing to others information that is the property of the sponsor or the identity of a subject, unless personally authorized.

Compliance (with regard to the studies)

Adherence to all the requirements related to the study, the requirements for good clinical practice (GCP), and applicable regulatory requirements.

Contract

A written agreement, dated and signed, between two or more parties that establishes any arrangement of the delegation and distribution of tasks and obligations, including financial matters, if applicable. The protocol can serve as the basis for a contract

Coordinating investigator

An investigator in a multicenter study who is assigned responsibility for coordinating the investigators in the different participating centers.

Contract research organization (CRO)

A person or organization (commercial, academic, or other) contracted by the sponsor to carry out one or more of the tasks and functions of the sponsor related to the study.

Direct access

Authorization to examine, analyze, confirm, and reproduce any record and report that is significant for the evaluation of a clinical trial. Any of the parties (for example, authorities and auditors of the sponsor) that have direct access must take all reasonable precautions within what is stipulated in the applicable regulatory requirements, in order to maintain the confidentiality of the identity of the subjects and of the information that is the property of the sponsor.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records and scans, X-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a study, the factors that affect a study, and the actions taken.

Essential documents

Documents that individually and collectively permit evaluation of the conduct of a study and of the quality of the general data (see Section 8: Essential Documents for the Conduct of a Clinical Study).

Good clinical practice (GCP)

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

GCP compliance status

The level of adherence of a trial to the GCP principles as assessed by the national authority for GCP monitoring compliance.

GCP compliance monitoring

The periodic inspection of any of the parties involved in conducting a clinical trial (such as the IRB/IEC, investigators, sponsors) for the purposes of confirming compliance with GCP and the corresponding regulations.

Identification code of the subject

A unique identifier that the investigator assigns to each subject of the study in order to protect his or her identity, which is used instead of the name of the subject when the investigator reports adverse events and/or some other datum related to the study.

Impartial witness

An individual independent of the study who cannot be influenced by the bad faith of the personnel involved in the study, who is present during the acquisition of the informed consent if the subject or legally accepted representative of the subject cannot read and who reads the informed consent form and any other written information provided to the subject.

Independent ethics committee (IEC)

An independent organization (a review board or an institutional, regional, national, or international committee), made up of medical/scientific professionals and nonscientific/nonmedical members, whose responsibility is to guarantee protection of the rights, safety, and well-being of the human beings involved in a study and to provide a public guarantee of that protection, through, among other means, the review and approval/favorable opinion of the study protocol, the capability of the investigator(s), and the adequacy of the installations, methods, and materials that will be used upon obtaining and documenting the informed consent from the subjects of the study. The legal status, composition, function, regulatory requirements, and operation of independent ethics committees can differ among the countries, but they should make it possible for the independent ethics committee to act in accordance with GCP as described in this guide.

Independent data monitoring committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee)

An independent committee for monitoring data that the sponsor can establish to evaluate at intervals the progress of a clinical trial, the safety data, and the critical points for evaluation of effectiveness and to recommend to the sponsor whether a study should be continued, modified, or stopped.

Institutional review board (IRB)

An independent entity made up of medical, scientific, and nonscientific members whose responsibility is to guarantee protection of the rights, safety, and well-being of the human beings involved in a study through, among other things, continuous review and approval of the study protocol and amendments and the documentation of the informed consent of the subjects of the study.

Interim clinical study report (“Interim Analysis”)

A report on interim results and their evaluation based on analyses conducted during the course of a study.

Informed consent

A process whereby a subject voluntarily confirms his or her desire to participate in a particular study, having been informed of all the aspects of it that are relevant to making the decision to participate. The informed consent is documented by means of a written consent form that is signed and dated.

Investigator’s brochure

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

Investigational product

A dosage form of an active ingredient or placebo that is being tested or used as reference in a clinical trial, including a product authorized for sale when it is used or prepared (formulated or packed) differently than the approved manner or when it is used to obtain more information about a previously approved use.

Inspection

The act by a regulatory authority(ies) of conducting an official review of the documents, facilities, records, and any other resource that are deemed by the authority(ies) to be related to the clinical study and that may be located at the site where the study is conducted, at the facilities of the sponsor and/or of the contract research organization (CRO), or at other sites that the regulatory authority(ies) considers appropriate.

Institution (medical)

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

Investigator

A person responsible for the conduct of a clinical trial at the site where the study is conducted. If a study is conducted by a group of individuals, the investigator is the head of the group and will be called the principal investigator.

Investigator/institution

Expression that means: "The investigator and/or the institution, when the applicable regulatory requirements so stipulate."

Inspector

A person who conducts inspections and audit study on behalf of the national authority for GCP monitoring compliance.

Legally accepted representative

An individual, legal representative, or other entity authorized under the applicable laws to accept on behalf of a probable candidate that person's involvement in the clinical trial.

Monitoring

The act of continuously reviewing the process of a clinical trial and making sure that it is conducted, recorded, and reported according to the protocol, standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirements.

Monitoring report

A written report submitted by the monitor to the sponsor after each visit to the study site and/or any other study-related communication, according to the SOPs of the sponsor.

Multicenter study

A clinical trial conducted that follows a single protocol but conducted in more than one place and, consequently, by more than one investigator.

Nonclinical trial

Biomedical studies that do not involve human subjects.

National GCP compliance program

The particular program established by a country to monitor compliance with good clinical practice within its territory through inspections.

National GCP monitoring authorities

A body established in a country charged with monitoring compliance with good clinical practice within its territory and with carrying out other functions related to good clinical practice, as determined nationally.

Opinion (with regard to the independent ethics committee)

The ruling and/or advice provided by an independent ethics committee (IEC).

Original medical record

See "Source document."

Protocol

A document that describes the object(s), design, methodology, statistical considerations, and organization of a study. The protocol also usually provides the background and foundations for the study but these may be provided in other documents referenced in the protocol. In the guidelines for GCP the term "protocol" refers to the original protocol and the amendments to the protocol.

Protocol amendment

See "Amendment to the protocol."

Quality assurance (QA)

All planned systematic actions established to guarantee that the study is being conducted and that the data are generated, documented (recorded), and reported in compliance with good clinical practice (GCP) and the applicable regulatory requirements.

Quality control (QC)

The operational techniques and activities carried out within the quality assurance system to confirm that the quality requirements of the activities related to the study have been met.

Regulatory authorities

The authorities responsible for drug regulation. These can be agencies with the power to regulate. In the guidelines for good clinical practice of the International Conference on Harmonization, the term "regulatory authority" is used to designate the authorities that review the clinical data submitted and those that conduct inspections. Such organizations are sometimes referred to as responsible authorities.

Randomization

The process of assigning the subjects in a study to treatment or control groups by chance in order to reduce bias.

Source data

The information in original records and certified copies of the original records of clinical findings, observations, or other activities in a clinical trial that is necessary for the reconstruction and evaluation of the study. The source data are contained in the source documents (original records or certified copies).

Source documents

Documents, data, and original records (for example, hospital records, clinical files, laboratory notes, memoranda, diaries of the subjects or evaluation checklists, records of delivery from the pharmacy, recorded data from automated instruments, copies or transcriptions certified after being confirmed

as exact copies, microfiches, photographic negatives, magnetic or microfilm media, X-rays, files on the subjects, and records maintained in the pharmacy, in the laboratories, and in the technical medical departments involved in the clinical study).

Serious adverse event (SAE) or serious adverse drug reaction (serious ADR)

Any unfavorable occurrence that at any dose:

- (a) results in death,
- (b) threatens life, requires or extends hospitalization of the patient,
- (c) involves hospitalization that results in persistent or significant disability, or is a birth defect or birth anomaly.

Sponsor

An individual, company, institution, or organization responsible for initiating, administering/controlling, and/or financing a clinical study.

Sponsor-investigator

An individual who initiates and leads, alone or in conjunction with others, a clinical study and under whose immediate direction the investigational product is administered to, delivered to, or used by the subject. This term excludes any entity that is not an individual person (that is, corporations or agencies are not included). The obligations of a sponsor-investigator include those of both a sponsor and an investigator.

Standard operating procedures (SOPs)

Detailed written instructions to achieve uniformity in the execution of a specific function.

Site where the study is conducted

The place(s) where the activities related to the study are carried out.

Subinvestigator

Any individual member of the clinical trial group who is designated by the investigator at a study site to perform critical procedures related to the study and/or make important decisions related to it (for example, associates, residents, research fellows). The investigator also oversees these actions.

Study subject³

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

³ In this document Subject, Individual or Person may be used as the same.

Unexpected adverse drug reaction

An adverse reaction whose nature or severity is not consistent with the applicable information on the product (for example, the investigator's brochure for an unapproved investigational product, or package insert/summary of the characteristics of an approved product). See the Guidelines of the International Conference on Harmonization for the Clinical Safety Data Management: Definitions and Standards of an Immediate Report.

Trial site

Location(s) where the trial related activities are actually conducted.

Vulnerable subjects

Individuals whose desire to participate in a clinical trial can be unduly influenced by the expectation, justified or not, of the benefits associated with their involvement, or of retribution by people in higher positions of authority if they refuse to participate. Some examples are members of a group with a hierarchical structure, such as medical, dental, chemistry, pharmacy, biology, and nursing students, subordinate personnel in a hospital or laboratory, employees of the pharmaceutical industry, members of the armed forces, and individuals who are arrested or imprisoned. Other vulnerable subjects include patients with incurable diseases, people in convalescent homes, the unemployed or indigent, patients in emergency situations, ethnic minorities, homeless people, seasonal workers, refugees, minors, and those who cannot give their consent.

Welfare (of the subjects of the study)

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

ANNEX 1
OPERATIONAL GUIDELINES FOR ETHICS COMMITTEES THAT REVIEW
BIOMEDICAL RESEARCH⁴

1) PUB: TDR/PRD/ETHICS/2000.1

Operational Guidelines for Ethics Committees that Review Biomedical Research

<http://www.who.int/tdr/publications/publications/pdf/ethics.pdf>

2) PUB: TDR/PRD/ETHICS/2002.1

Surveying and Evaluating Ethical Review Practices: a complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research

<http://www.who.int/tdr/publications/publications/pdf/ethics2.pdf>

⁴ WHO Documents

ANNEX 2

A SELF-EVALUATION QUESTIONNAIRE FOR IEC's (CHECK LIST)

This questionnaire may be useful when defining the procedures of an IEC that are being set up or for an IEC that wishes to review/reconsider its organization and operation. Most items listed are applicable also to ethics committees that are not affiliated to a particular institution (independent). The written procedures can be audited to verify appropriate compliance.

There are three possible options for each item, regarding the existence of written procedures: **YES, NO or not applicable (NA)**, as appropriate.

DOES THE ETHICS COMMITTEE HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE THE FOLLOWING ITEMS?

1) Institutional authorization for the establishment of the ethics committee:

Yes **No** **NA**

2) The definition of the purpose(s) of the ethics committee (e.g., the protection of patients participating in clinical research):

Yes **No** **NA**

3) The principles which govern the ethics committee in assuring that the right and welfare of research patients are protected:

Yes **No** **NA**

4) The authority of the ethics committee:

a) the scope of authority (e.g., what types of clinical trials are reviewed)

Yes **No** **NA**

b) authority to disapprove, modify or approve clinical trials based upon protection of human subjects:

Yes **No** **NA**

c) authority to require progress reports from the investigators and oversee the conduct of the study:

Yes **No** **NA**

d) authority to suspend or terminate approval of a study:

Yes **No** **NA**

e) authority to place restrictions on a study
Yes No NA

5) The ethics committee's relationship to:

a) the administration of the institution
Yes No NA

b) the other committees and department chairpersons
Yes No NA

c) the research investigators
Yes No NA

d) regulatory agencies
Yes No NA

6) The membership of the ethics committee:

a) number of members
Yes No NA

b) qualification of members
Yes No NA

a) diversity of members
c.1) at least one non-scientific member
Yes No NA

c.2) men and women
Yes No NA

c.3) at least one member independent of the institution where the study will be conducted
Yes No NA

b) alternate members
Yes No NA

7) Management of the ethics committee:

a) The chairperson of the ethics committee
a.1) Selection and appointment process
Yes No NA

a.2) Length of service
Yes No NA

a.3) duties / responsibilities
Yes No NA

- a.4) removal process:
Yes **No** **NA**
- b) the members of the ethics committee
- b.1) selection and appointment process
Yes **No** **NA**
- b.2) length of service
Yes **No** **NA**
- b.3) duties / responsibilities
Yes **No** **NA**
- b.4) attendance requirements
Yes **No** **NA**
- b.5) removal process
Yes **No** **NA**
- c) Training of the committee's Chair and members
- c.1) orientation or initial indications
Yes **No** **NA**
- c.2) continuing education
Yes **No** **NA**
- c.3) consults/reference materials (committee's library)
Yes **No** **NA**
- d) compensation of the members of the committee
Yes **No** **NA**
- e) liability coverage for members of the committee
Yes **No** **NA**
- f) use of consultants
Yes **No** **NA**
- g) secretarial/administrative staff duties
Yes **No** **NA**
- h) available resources (e.g., meeting area, filing space, equipment, computers, **etc.**)
Yes **No** **NA**
- i) conflict of interest policy:
- i.1) no selection of members of the ethics committee by investigators
Yes **No** **NA**
- i.2) prohibition of participation in deliberations and voting by investigators
Yes **No** **NA**

8) Functions of the ethics committee:

- a) conducting initial and continuing study review,
Yes **No** **NA**
- b) reporting, in writing, findings and actions to the investigator and the institution
Yes **No** **NA**
- c) determining which studies require review more often than annually
Yes **No** **NA**
- d) determining which studies need verification from sources other than the investigators to verify changes that have occurred since previous review by the ethics committee.
Yes **No** **NA**
- e) ensuring changes in approved research are not initiated without IEC/IRB review and approval except where necessary to eliminate apparent immediate hazards,
Yes **No** **NA**
- f) prompt reporting to the IEC and regulatory agencies of:
 - f.1) unanticipated problems involving risks to research subjects,
Yes **No** **NA**
 - f.2) serious noncompliance with applicable regulations or the requirements of the IEC
Yes **No** **NA**
 - f.3) suspension or finalization of IEC approval
Yes **No** **NA**
 - f.4) determining which device studies pose significant or non-significant risks
Yes **No** **NA**

9) Operations of the ethics committee

- a) scheduling of meetings,
Yes **No** **NA**
- b) distribution to members, of, for example, place and time of meeting, agenda, and study material to be reviewed
Yes **No** **NA**
- c) the review/assessment process. Description of the process ensuring that:
 - c.1) all members receive study documentation for the study to be reviewed
Yes **No** **NA**Or

- c.2) one or more "primary reviewers"/"secondary reviewers" receive the complete documentation for review, report to committee and lead discussion. If other members review summary information, these members must have access to complete study documentation.
Yes **No** **NA**
- c.3) role of any subcommittees of the IEC
Yes **No** **NA**
- c.4) emergency notification and reporting procedures
Yes **No** **NA**
- c.5) expedited review procedure for approval of studies or modifications (already approved studies) involving minimal risks
Yes **No** **NA**
- d) Criteria for approval of the ethics committee containing all requirements
Yes **No** **NA**
- e) Voting requirements:
- e.1) quorum required
Yes **No** **NA**
- e.2) diversity requirements of quorum (e.g. requiring at least one physician member when reviewing studies of developing articles)
Yes **No** **NA**
- e.3) percent needed to approve or disapprove a study
Yes **No** **NA**
- e.4) full voting rights of all reviewing members
Yes **No** **NA**
- e.5) no written or telephone votes
Yes **No** **NA**
- e.6) prohibition against conflict-of-interest voting
Yes **No** **NA**
- f) Further review/approval by others within the institution
Yes **No** **NA**
- g) Communications from the IEC to the investigator for additional information,
Yes **No** **NA**
- g.1) to the investigator conveying IEC decision,
Yes **No** **NA**
- g.2) to institution administration conveying IEC decision,
Yes **No** **NA**
- g.3) to sponsor of research conveying IEC decision
Yes **No** **NA**

- h) Appeal of IEC decisions
- h.1) criteria for appeal
Yes **No** **NA**
- h.2) to whom appeal is addressed
Yes **No** **NA**
- h.3) how appeal is resolved (override of disapprovals is prohibited),
Yes **No** **NA**

10) IEC documentation / record requirements

- a) Membership roster showing qualifications,
Yes **No** **NA**
- b) Written procedures and guidelines,
Yes **No** **NA**
- c) Minutes of meetings,
Yes **No** **NA**
- c.1) members present (any consultants and guests shown separately)
Yes **No** **NA**
- c.2) summary of discussion on debated issues - record of IEC decisions,
Yes **No** **NA**
- c.3) record of voting (showing votes for, against and abstentions)
Yes **No** **NA**
- d) Retention / file of protocols reviewed and approved consent documents.
Yes **No** **NA**
- e) Communications to and from the IEC,
Yes **No** **NA**
- f) Adverse reactions reports, and documentation that the IEC reviews such reports.
Yes **No** **NA**
- g) Records of continuing review by the IEC
Yes **No** **NA**
- h) Record retention requirements
Yes **No** **NA**
- i) Budget and accounting records
Yes **No** **NA**
- j) Emergency use reports
Yes **No** **NA**
- k) Statements of significant new findings provided to subjects / patients,
Yes **No** **NA**

11) Information the investigator provides to the IEC

a) Professional background / qualifications to do the research (including a description of necessary support services and facilities)

Yes **No** **NA**

b) Clinical study protocol which includes:

b.1) title of the study

Yes **No** **NA**

b.2) purpose of the study (including the expected benefits obtained from the study conducted)

Yes **No** **NA**

b.3) sponsor of the study

Yes **No** **NA**

b.4) results of previous related research

Yes **No** **NA**

b.5) subject inclusion/exclusion criteria

Yes **No** **NA**

b.6) justification for use of any special / vulnerable subject populations (e.g. decisionally impaired persons or children)

Yes **No** **NA**

b.7) study design (including as needed, a discussion of the appropriateness of research methods)

Yes **No** **NA**

b.8) description of study procedures

Yes **No** **NA**

b.9) provisions for managing adverse events

Yes **No** **NA**

b.10) the circumstances surrounding consent procedure, including setting, subject autonomy concerns, language difficulties, vulnerable populations

Yes **No** **NA**

b.11) the procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators and document storage

Yes **No** **NA**

b.12) compensation to subjects for their participation

Yes **No** **NA**

b.13) any compensation for injured research subjects

Yes **No** **NA**

- b.14) provisions for protection of patient/subject's privacy
Yes **No** **NA**
- b.15) extra costs to patients / subjects for their participation in the study
Yes **No** **NA**
- c) Investigator's Brochure (when one exists)
Yes **No** **NA**
- d) The case report form, CRF (when one exists)
Yes **No** **NA**
- e) The proposed informed consent document
- e.1) containing all requirements.
Yes **No** **NA**
- e.2) translated consent documents, as necessary, considering likely subject population(s)
Yes **No** **NA**
- f) Requests for changes in study after initiation,
Yes **No** **NA**
- g) Reports of unexpected adverse events,
Yes **No** **NA**
- h) Progress reports
Yes **No** **NA**
- i) Final report
Yes **No** **NA**
- j) Institutional forms / reports
Yes **No** **NA**

12) Emergency research consent exception

- a) Ensure compliance with requirements defining the disapproval of this kind of studies in the institution,
Yes **No** **NA**
- b) The ethics committee shall promptly notify in writing when it determines it cannot approve a study (including reasons)
Yes **No** **NA**
- c) In order to approve a consent waiver, the committee must find and document,
- c.1) That subjects are in a life-threatening situation, that there are no available or satisfactory treatments for such condition and that collection of scientific evidence is necessary,
Yes **No** **NA**
- c.2) That obtaining informed consent is not feasible because:

- c.2.1) medical condition precludes consent,
Yes **No** **NA**
- c.2.2) there is no time to get consent from a legally authorized representative,
Yes **No** **NA**
- c.2.3) identification of legal representative is not reasonable,
Yes **No** **NA**
- c.3) That there is prospect of direct benefits to study subjects because,:
- c.3.1) life-threatening situation needs treatment
Yes **No** **NA**
- c.3.2) previous data support potential for benefit to subjects
Yes **No** **NA**
- c.3.3) the risk/benefit of both standard and proposed treatments are reasonable
Yes **No** **NA**
- c.4) That a waiver situation is needed to carry out the study
Yes **No** **NA**
- c.5) That a therapeutic window is defined, during which investigator will seek consent rather than starting without consent. Summary of efforts will be documented and given to the ethics committee at time of continuing review of the study (by the IEC).
Yes **No** **NA**
- c.6) That the IEC reviews and approves consent procedures and document. IEC reviews and approves family member objection procedures.
Yes **No** **NA**
- c.7) Additional protections, including at least:
- c.7.1) consultation with community representatives
Yes **No** **NA**
- c.7.2) public disclosure of plans, risks and benefits
Yes **No** **NA**
- c.7.3) public disclosure of study results
Yes **No** **NA**
- c.7.4) assure an independent Data Monitoring Committee is established
Yes **No** **NA**
- c.7.5) objection of family member summarized for continuing review
Yes **No** **NA**
- c.8) Ensure implementation of procedures to inform at earliest feasible opportunity of subject's inclusion in the study (in these cases, participation

may be discontinued). Procedures to inform family the subject was in the study if subject dies.

Yes

No

NA

c.9) IEC disapproval must be documented in writing and sent to the study investigator and sponsor. The sponsor must promptly disclose to the regulatory authority, other investigators and other IEC's involved.

Yes

No

NA

ANNEX 3

OPERATIONAL GUIDELINES FOR INFORMED CONSENT

Purpose of the Guidelines

This Guideline will serve as a model for the preparation of the Model Informed Consent (MIC), comprised of an Informed Consent Document for the Subject, the Model Consent for Signature, and guidelines for obtaining this consent for the responsible clinical investigator and research team.

Preparation of the Informed Consent Document for the Subject and the Model Consent for Signature

Language, drafting, and presentation of the Model Informed Consent (MIC):

The language utilized shall be practical, simple, direct, and understandable to subjects with any level of schooling, to their legal representatives, if applicable, and to the witnesses. Technical medical terminology shall not be used, unless it is indispensable, in which case the investigator should explain its meaning to the subject. Scientific and legal terms, as well as language that make the subject optimistic or pessimistic about the research shall be avoided. Efforts shall be made to ensure that the wording of the MIC does not cause the subject or his legal representatives to waive any legal right, or release the investigator, institution, or sponsor of its obligations. The MIC should be printed on letterhead containing the name of the institution and hospital where the study is being conducted.

Contents of the MIC:

The MIC should consist of two parts that make up a single document: the Model Informed Consent Document for the subject and the Consent Form for signature

Information to the subject

1. Title of the study

The title should be explicit enough for the people to whom it is directed. If it does not meet this requirement, it should be simplified.

2. Invitation to participate in the study

The document shall explain that the subject is invited to participate in a clinical trial and that, before agreeing he should understand what it is about. It should suggest that he take his time before agreeing to participate and that, if he so desires, he discuss it with his family, friends, and general practitioner or family physician.

3. Clear and concise description of the study's objectives

The document should provide information about the investigative nature of the study and the objectives of the research.

4. Selection of patients

It should explain to the subject how study participants are selected and indicate how many subjects will participate.

5. Statement of intent to participate in the study and to withdraw from it at will

The document shall state the right of the subject to participate voluntarily in the trial and to withdraw from it when he desires, without explanation and without the loss of subsequent adequate medical care.

6. Description of the study's characteristics and methodology

The document shall indicate the duration of the study and how long the subject's participation is expected to last. It should also describe the circumstances of the treatment (inpatient, outpatient etc.) and the number, frequency, and type of tests (invasive and non-invasive) that he will be subjected to. In the case of invasive tests, it shall explain the procedures involved. The document shall also state the number of visits or consultations required and indicate that they may be more frequent than in ordinary medical practice. It shall use non-technical language to explain the methodology of the trial and, if applicable, the need for comparisons to reach a conclusion about which treatment or diagnostic method is superior. It shall also explain to the subject that study groups and control groups will be formed, that he may be assigned to one or the other, and that this decision is random; this means that the determination of which group he will be assigned to will not depend on the investigator but the process, a methodology that makes it possible to obtain results with rigor and accuracy. If the research involves a blind study involving the use of a placebo for the control group, the subject should be informed of this fact in terms that he or his legal representatives can understand.

7. Restrictions, limitations, and concomitant treatments

The document shall detail any restrictions or limitations on the subject during the study, e.g., if he will have to alter his lifestyle or some habit or if certain drugs and/or food can influence the outcome of the study and therefore cannot be consumed with the treatment in question. With regard to tobacco, alcohol, or other substances, the subject or his representative shall be told how frequently they can be used or informed about the need to abandon any habit that interferes with the study.

8. Procedures or drugs that will be evaluated

The document shall provide a brief description of the procedure or the characteristics of the drug to be evaluated and its current stage of development.

9. Therapeutic Alternatives

The document shall describe the therapeutic alternatives to the treatment under study.

10. Description of the benefits

The document shall inform the subjects or their legal representatives about the potential individual and social benefits that the investigator expects to obtain with the use of the product being tested. It shall make a real and fair assessment of what the product is expected to accomplish. When placebos are used, it should explain their use and state the probabilities of receiving them.

11. Description of the side effects and/or discomforts and/or risks of the tests

The document shall note the potential adverse events that may occur during and after the research, based on the results of previous trials of both the product being tested and the product used as the control, if the protocol requires one. It shall indicate the steps that will be taken in this regard if necessary. It should indicate the risks and drawbacks of the tests to be performed, if relevant. With regard to adverse events, the document shall furnish a list of all the people to whom the subject or his representative could recur and how to locate them, so that steps can be taken as quickly as possible on behalf of the subject if such an event occurs; or, so that the subject can ask questions and obtain information beyond what is provided in the consent form.

12. Development of new information during the study

There should be a statement that subject shall be informed throughout the trial of any event that occurs or any new relevant information developed during the course of the research that could affect the decision to continue participating in the trial.

13. Withdrawal from the trial or termination of the research

The document should explicitly state that the investigator can decide to terminate the subject's participation or the study itself, indicating the circumstances that will warrant this termination and the provisions that will be made for the patient.

14. Precautions with women during pregnancy

The document shall provide specific instructions for women of reproductive age involved in the consent process. It shall explain that the drug to be administered during the trial is under study and that, as a result, the risk and results of its administration during pregnancy are not fully known.

15. Confidentiality

The document shall inform the subject that all personal data obtained during the trial will be properly handled; guaranteeing discretion and confidentiality with regard to his identity and that, to ensure this, documents generated in the clinical trial will use only his initials. Monitors, people in charge of quality control, auditors, if applicable, the members of the review board and ethics committee, and the health authorities shall have free access to the subject's original clinical history to verify the procedures and/or data of the clinical trial without violating the confidentiality of the subject, insofar as the applicable laws and regulations permit; and it shall be stated that by signing a written informed consent form, the subject or his legal representative is authorizing this access.

16. Sponsor and Organizations and Institutions involved in the Study

The document shall indicate who sponsors the study and who finances it. It should also mention whether the principle clinical investigator receives remuneration for conducting the clinical trial.

17. Approval of the protocol

A record will be kept of who approved the protocol for the clinical trial: e.g., the ethics committee, the regulatory authorities, etc.

18. Contacts or people to recur to in the event of questions or dissatisfaction

The document should clearly identify whom to contact for further information regarding the study and the rights of research subjects or in the event of some research-related injury.

Model for basic structure of the informed consent document for the research subject and the informed consent form

I. General information

- 1-[Title of the Study]
- 2-[Protocol Number]
- 3-[Sponsor/Address]
- 4-[Principal Investigator]
- 5-[Telephone]
- 6-[Participating Centers/ Address]
- 7-[Introduction]

II- Specific information (on the study)

- 8- [Purpose of the Study]
- 9-[Background]
- 10-[Duration of the Study]
- 11-[Expected Number of Subjects Participating]
- 12-[Exclusions]
- 13-[Design of the Study]
- 14-[Treatment provided in the Study]
- 15-[Procedures done in the Study]
- 16-[Additional/Optional Studies (Sub studies)]
- 17-[Possible Risks and Discomfort]
- 18-[Precautions]
- 19-[Women of Reproductive Age]
- 20-[Potential Benefits]

III -Rights of the subject

- 21-[Notification of New Findings]
- 22-[Alternative Treatments]
- 23-[Options at the Conclusion of the Study]
- 24-[Confidentiality]
- 25-[Payment for Participation]
- 26-[Costs]
- 27-[Compensation for Study-related Harm or Injuries]
- 28-[Voluntary Participation and Withdrawal]
- 29-[Questions/ Contacts]

IV -Consent to participate

- 30-[General Information]
- 31-[Subject's Declaration of Consent]
- 32-[Additional Declarations]
- 33-[Signature Requirements]

Proposal on checklist of requirements for the informed consent document for the research subject and the informed consent form

Protocol No.: _____

Required:

- A statement that the study involves research
- Explanation of the purposes of the research
- Treatments provided in the study and probability of random assignment for every treatment
- Expected duration of subject's participation
- Description of the procedures to be done, including all invasive procedures
- Responsibilities of the subject
- Identification of any experimental procedures
- Details of any experimental aspects of the study
- Description of any reasonably foreseen risks or discomforts to the subject and, when applicable, to an embryo, fetus, or infant
- When no clinical benefit is intended for the subject, the subject should be aware of this.
- Description of any reasonably foreseeable benefits to the subject or others
- Disclosure of specific, appropriate alternative procedures or treatments for the subject and their important potential benefits and risks
- Any anticipated expenditures for the subject while participating in the study
- The expected prorated payment, if any, for the subject's participation in the study
- Explanation of the circumstances under which the investigator can terminate subjects' participation in the study without their consent.
- Inform the subject about who will have access to his medical records (monitor, auditor, and institutional review board, regulatory authorities) to confirm the study's procedures and data, indicating that confidentiality will be maintained to the extent allowed by the applicable laws and regulations. If the results of the study are published, the subject's identity will remain confidential.
- By signing the informed consent form, the subject authorizes access to his medical records.
- The subject's medical files will be kept strictly confidential, will be protected by the applicable local and federal regulations, and will not be made public.

- Compensation and/or treatment available to the subject in the event of a research-related injury
- People to contact:
 - for questions about the study
 - for questions about the rights of the research subject
 - in the event of a research-related injury
- Statement that the participation is voluntary and that the subject can withdraw from the study at any time without penalty or loss of the benefits to which he is otherwise entitled
- Explanation of the anticipated circumstances under which the investigator can suspend the subject's participation without his consent
- Additional costs to the subject that may arise from participation in the study
- The subject or his representative will be notified in a timely fashion if significant new findings are developed during the course of the research that might affect the subject's willingness to continue participating.
- Approximate number of subjects
- Consequences of the subject's decision to withdraw from the research and termination procedures
- Statement that the particular treatments or procedures may involve risks to the subject (or the embryo/t fetus) that is currently unforeseeable.

ANNEX 4

A Guide to Clinical Investigator Inspections

This document provides a guide to inspectors and regulatory authorities for planning, conducting and reporting clinical investigator inspections. The objectives of these inspections are to assure the quality and integrity of clinical trial data relied upon by regulatory authorities and to assure that the rights and welfare of research subjects are protected.

1. Planning the inspection

1.1 Selection of the studies

Inspections can be conducted before, during or after a study is completed. Considering that it is not possible to inspect all studies being conducted in a given country, the first step in the inspection process is to decide which studies are to be inspected. Each country should establish written criteria for selecting studies to be inspected.

These criteria may include, for example:

- importance of the trial for regulatory decision-making;
- nature of the study;
- vulnerability of subjects;
- data irregularities;
- complaints.

1.2 - Identification of inspectors

The regulatory authority should identify a qualified inspector or team of inspectors and ensure that they are provided all the information needed to conduct the inspection of the selected study. This information may include, for example, protocol, amendments, informed consent form, samples of case report forms (CRF), study reports etc.

1.3- Preparing for inspection

The inspector(s) should thoroughly review the information provided for the inspection assignment and develop a plan to be used for conducting the inspection. The inspection plan should be specific for the site and study to be inspected under the regulatory authorities GCP compliance monitoring program. In planning the inspection, the inspector must understand the precise scientific objectives of the study and be able to identify significant study endpoint data supporting the study objectives. This endpoint data will be the principal focus of the subjects' records review (see section 2.b.3). To develop an effective plan the inspector must read and become familiar with the protocol. This should include familiarity with inclusion/exclusion criteria, allowed and disallowed concomitant medications, required visit and test procedures, any special test article handling or storage requirements, and known information about the test drug such as its adverse event profile.

The inspector should also be aware of any data irregularities or special issues of concern that have been observed during in-house review of the marketing application (or protocol submission) by the drug regulatory authority. This information must be communicated to and understood by the inspector. If possible the inspector should have access to data listings.

The inspection plan may be as formal or informal as the inspector wishes but at a minimum should identify what specific source data and source documents will need to be examined and ,if applicable, which facilities should be visited

1.4. Scheduling the inspection

Routine inspections should be announced to the clinical investigator in advance to ensure his/her availability and the availability of the study records at the time of the inspection. When an inspection is announced the inspector should inform the clinical investigator of the documents that should be available for inspection and the facilities that should be visited if applicable. In certain circumstances unannounced inspections may be necessary, for example when there is suspicion of misconduct in a trial.

2- Conducting the inspection

2.1- Opening Interview

The inspector should meet with the principal investigator at the outset of the inspection and present his/her official identification and any official notice that may be required. The inspector should explain the nature and the scope of the inspection, and provide a short verbal summary of the methods and procedures to be used to conduct the inspection.

During the opening interview, it is imperative to find out who did what, when, where and how with respect to the following:

- Screening and admissions of patients to study
- Obtaining informed consent
- Collection and analysis of study data
- Recording, transcribing and reporting of data to sponsor
- Receipt, return and administration of the test drug

Other interviews with key study personnel and, if applicable with study subjects, may take place during the inspection and as questions arise.

2.2 Study Records Review

This part of the inspection includes an examination of essential documents. The purpose of the review is to determine whether the trial activities were conducted according to the protocol, applicable regulatory requirements and GCP and ensure that the data were both recorded and accurately reported. The study

records review includes a study data audit, which involves a comparison of source data with the information provided to the sponsor or regulatory authority. The study data audit provides for obtaining additional information not provided in the report, and establishing whether practices were employed in the development of the data that would impair their validity.

2.2.1 Records inventory and format

Because of the complexity and volume of records found at a clinical site, and limited time available for the on site inspection, it may not be possible to easily examine, in detail, all of study records during the audit. However, even if all records cannot be examined in detail, the inspector should be able to identify and account for all study records quickly by taking an inventory of the records. This should be done before starting the in-depth review of specific subjects' records. This can be facilitated by first having someone familiar with the study files explain their organization and location. The inspector should then verify, at a minimum, that there is a case file for each subject reported at the site. Other essential documents (see chapter 5 of this document) should also be accounted for (e.g. ethics committee approvals, test drug receipt records, etc.) Any records, which are missing should be accounted for and verified by direct examination before conclusion of the audit.

2.2.2 Protocol

The inspector should compare a copy of the protocol provided to the regulatory authorities and the protocol in the clinical investigator's file to determine if there are any differences with respect to the following:

- Subject selection (inclusion/exclusion criteria)
- Number of subjects
- Frequency and nature of subject observations
- Dosage
- Route of administration
- Frequency of dosage
- Blinding procedures

If there are differences determine if these were documented by a protocol amendment or amendments and were approved in accordance with applicable regulatory requirements.

2.2.3 Subjects' records

Compare original source data in subjects' files against the CRFs and/or final report to the sponsor to verify that the source data is accurately and completely reported. If time permits audit 100% of the subjects' records, otherwise select a representative sample of subjects enrolled at intervals during the beginning, middle, and end of the study. However, if a significant problem in one particular area (for example failure to take the test drug as required) is observed, audit

this particular aspect of the study for all of the subjects. It is virtually impossible to audit 100% of all data for each subject. Therefore it is important to have an audit plan as discussed in section 1.c and focus the on significant endpoint data identified in the plan. There should be source data to support the following critical points:

- Did subjects exist and did they show up for their visits as reported?
- Did subjects admitted to and/or completing the study meet protocol inclusion/exclusion criteria?
- Did subjects receive the test medication according to protocol with respect to dose and frequency?
- Was significant endpoint data collected and reported fully and correctly in accordance with the protocol?
- Were adverse events reported to the sponsor and the regulatory authority?

2.2.4 Human subject protection documentation

The review of study records should include verification that human subject protection measures and rules were implemented and followed. The following documentation should be reviewed:

- Material submitted to the IEC/IRB for approval prior to study initiation
- Documentation of IEC/IRB approval
- Signed and dated informed consent forms for each study subject
- Reports to and correspondence between the investigator and IRB/IEC as required by national law

2.2.5 Drug accountability

The inspector should review individual subject study records to verify correct dose administration with respect to quantity, frequency, duration and route of administration. Additionally the inspector should examine drug shipping and distribution records to reconstruct the pathway of test drug distribution and verify receipt dates, quantity and identity of the test drug and compare test drug usage with amounts shipped and returned to the sponsor at the end of the study. If unused supplies were not returned to the sponsor, the inspector should verify alternate disposition was handled appropriately and documented. The inspector should verify the test drug was stored under appropriate conditions.

2.2.6 Other records and site facilities

In addition to the subject records addressed above, the inspector should review general study records in the study file as necessary to verify the details of study conduct. Such records may include correspondence with the sponsor,

investigator brochure, regulatory authorization documentation, monitoring reports, etc.

The inspector may also inspect the site facilities as appropriate to determine if they are adequate to fulfill protocol requirements. (i.e. presence of specialized equipment such as EEG, EKG, treadmills, etc.)

2.3. Concluding the inspection

The inspector should conclude the inspection by conducting a final discussion with the clinical investigator. The inspector should explain and discuss the inspection findings. Findings should be described in terms of their nature and scope (i.e. how many records reviewed and to what extent). Findings should be strictly objective based on the records and information available during the inspection. Depending upon the national inspection program requirements, the inspector may issue a list of inspectional observations at the conclusion of the inspection.

3. Documenting and reporting the inspection

The inspection should be documented thoroughly in writing both during and after the inspection. The only tangible outcome of an inspection is the written report and the inspector's notes. The report may be used to support scientific and regulatory decisions. For example, the drug regulatory authority may base marketing approval decisions for new products on the inspection reports. Also, where serious noncompliance is observed, legal or administrative sanctions against the clinical investigator will be based on the documented results of the inspection.

3.1 - Documentation during the inspection-

The inspector should keep notes of the inspection while it is underway. These notes will ensure the accuracy of the inspection report after the inspection. Such notes should include information provided verbally and through examination of study records during the inspection. The inspector should record the name(s) and position(s) of the individual(s) providing study records and key details of the study conduct. Notes should document which subject files and study records were examined during the audit. The opening and closing interviews should be thoroughly documented in the inspector's notes. The inspector should verify and document adverse findings during the inspection. Findings should be documented by collecting copies of pertinent study records as necessary. The inspector should, however, avoid collecting highly sensitive medical records with patient identifying information unless absolutely necessary. The inspector must respect applicable national laws regarding maintaining confidentiality of records.

3.2 Reporting after the inspection

The inspector should prepare a narrative inspection report detailing inspection findings, as soon as possible after the inspection. The inspection report should fully describe the nature and scope of the inspection. The report should explain the reason for the inspection, for example, was it routine or conducted for a special purpose? It should also describe the scope of the inspection, for example, was it limited to a narrow record review to address a specific concern or was it a comprehensive inspection of the study conduct? In describing the scope of the inspection, the report should state what records were covered and the number of files or case histories covered relative to the number of subjects on the study. The report should also include the name of the test drug, study sponsor, protocol title and number, dates of the study and number of subjects. It should identify individuals who performed significant study functions as well as those providing information during the inspection.

The most important part of the report is the description of the inspection findings. The inspector should describe each of the significant findings in detail. This description should be specific and quantify what was observed in terms of the total number of records examined. Inspection observations should be objective and the report should include, as exhibits, copies of records taken to document objectionable findings. All exhibits should have all pages numbered and be specifically referenced in the report.

The report should include a discussion of the exit interview with the clinical investigator at which inspection findings were discussed. The clinical investigator's response to the observations should be reported.

ANNEX 5

ESSENTIAL DOCUMENTS FOR CLINICAL TRIALS

Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable. Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority (ies).

1- Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
Signed protocol and amendments, if any, and sample of case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
Information given to trial subject: - Informed consent form (Including all applicable translations) - Any other written information - Advertisement for subject recruitment (if used)	- To document the informed consent - To document that subjects will be given appropriate information (content and wording) to support their ability to give fully informed consent - To document that recruitment measures are appropriate and not coercive	X X X	X X
Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
Signed agreement between involved parties, e.g. : - Investigator/institution and sponsor - Investigator/institution and CRO - Sponsor and CRO required - Investigator/institution and authority(ies) (Where required)	To document agreements	X X X	X X (Where required) X X
Dated, documented approval/favorable opinion of IRB/IEC of the following: - Protocol and any amendments -CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s)	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)	X	X

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
<ul style="list-style-type: none"> - Advertisement for subject recruitment(if used) - Subject compensation (if any) - Any other documents given approval/favorable opinion 			
Institutional review board/independent ethics committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
Regulatory authority(ies) authorization/approval/ / notification of protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to the initiation of the trial in compliance with the applicable requirement(s)	X (where required)	X (where required)
Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub investigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
Medical/laboratory/technical procedures/tests <ul style="list-style-type: none"> - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required) 	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects		X
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
Certificate(s) of analysis of investigational product(s) shipped.	To document identity, purity, and strength of investigational products to be used in the trial		X

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
Master randomization list	To document method for randomization of trial population		X (third party if Applicable)
Pretrial monitoring report	To document that the site is suitable for the trial		X
Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff	X	X

2- During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
Any revisions to: - protocol/amendments(s) and CRF - Informed consent form (Including all applicable translations) - Any other written information provided to subjects - Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents to take effect during trial	X	X
Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following: - Protocol amendment(s) - Revision(s) of Informed consent form(s) - Any other written information to be provided to the subject(s) advertisement for subject recruitment (if used) - Any other documents given - Approval/favorable opinion - Continuing review of trial (where required)	To document that the amendments and/or revision(s) have been subjects to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X
Regulatory authority(ies) authorization/approval/ notification where required for: - Protocol amendment(s) and other documents -	To document compliance with applicable regulatory requirement(s)	X (where required)	X
Curriculum vitae of new investigator(s) and/or subinvestigator(s)		X	X
Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges that are revised during the trial	X	X

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Updates to normal values of medical/laboratory/ technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required) -	To document that tests remain adequate throughout the trial period	X (where required)	X
Documentation of investigational product(s) and trial related materials shipment		X	X
Certificate(s) of analysis for new batches of investigational product(s)			X
Monitoring visit reports	To document the visits at the site where the study is conducted		X
Relevant communications other than site visits -Letters -Meeting notes -Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
Signed informed consents form	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	X	
Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports	X	X
Notification by sponsor and/or investigator, where applicable, to regulatory authority (ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authority (ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	X (where required)	X

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	X	X
Interim or annual reports to IRB(s)/IEC(s) and authority(ies)	Notification by sponsor to investigators of safety information	X	X (where required)
Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
Investigational product (s) accountability at the site	To document that investigational product(s) have been used according to the protocol	X	X
Signature sheet	To document signatures and initials of all persons authorized to make entries and/or Corrections on CRFs	X	X
Record of retained body fluids / tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

3- After completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in the sections 1 and 2 should be in the file together with the following

Title of Document	Purpose	Located in File of Investigator/ Institution	Located in file of Sponsor
Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
Audit certificate (if required)	To document that audit was performed (if required)		X
Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
Final report by investigator/institution to IRB/IEC where required, and where applicable , to the regulatory authority (ies)	To document completion of the trial	X	
Clinical Study Report	To document results and interpretation of trial	X (if applicable)	X