وزارة الصحة والسكان

قرار رقم ٧٣٤ لسنة ٢٠١٦

بشأن المدونة المصرية للممارسة الإكلينيكية الجيدة للمستحضرات الصيدلية

وزير الصحة والسكان

بعد الاطلاع على قانون مزاولة مهنة الطب رقم ٤١٥ لسنة ١٩٥٤ ؛

وعلى قانون مزاولة مهنة الصيدلة رقم ١٢٧ لسنة ١٩٥٥ ؛

وعلى قرار رئيس الجمهورية رقم ٣٨٢ لسنة ١٩٧٦ بإنشاء الهيئة القومية للرقابة والبحوث الدوائية ولائحته التنفيذية ؛

وعلى قرار رئيس الجمهورية رقم ٢٤٢ لسنة ١٩٩٦ بتنظيم وزارة الصحة والسكان ؛

قـــرر :

مادة ١ - اعتماد المدونة المرفقة كمدونة مصرية للممارسة الإكلينيكية الجيدة للمستحضرات الصيدلية (GCP) .

مادة ٢ - يتم تحديث المدونة وفقًا للتعديلات التى تطرأ على المدونات العالمية .

مادة ٣ - ينشر هذا القرار فى الوقائع المصرية ، ويعمل به من اليوم التالى لتاريخ نشره .

صدر فى ١٥/ ١٠/ ٢٠١٦

وزير الصحة والسكان

أ.د / أحمد عماد

Egyptian Guidelines for Good Clinical Practice (GCP) on Pharmaceutical Products

2016

National Organization for Drug Control and Research

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of these Egyptian GCP Guidelines is to provide a national standard for the Egyptian medical regulatory authorities and persons who are involved in and responsible for clinical trials in Egypt to facilitate the acceptance of clinical data by the National Regulatory Authority.

The guidelines were developed with consideration of the current good clinical practices of the ICH, as well as those of the World Health Organization (WHO).

These guidelines should be followed when generating clinical trial data that are intended to be submitted to the regulatory authorities in Egypt.

The principles established in these guidelines may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

GLOSSARY

Adverse Drug Reaction (ADR)

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

Adverse Event (AE)

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Applicable Regulatory Requirement(s)

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

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit of a trial

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail

Documentation that allows reconstruction of the course of events.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

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

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report

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

Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

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

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

Coordinating Investigator

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

Contract Research Organization (CRO)

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

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

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 trial, the factors affecting a trial, and the actions taken.

Essential Documents

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

Final report

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

Good Clinical Practice (GCP)

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

Independent Data and Safety Monitoring Committee

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC)

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

Informed Consent

A process by which a subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a National Regulatory Authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the Authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the National Regulatory Authority.

Institution (medical)

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

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report

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

Investigational Product

A pharmaceutical dosage form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

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

Investigator's Brochure

A compilation of the clinical and noncinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative

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

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

National Regulatory Authority

National body having the power to regulate. In this guidelines, the expression National Regulatory Authority is the authority responsible for reviewing submitted clinical data and conducting inspections. It is sometimes referred to as competent authority.

Nonclinical Study

Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment

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

Quality Assurance (QA)

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

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Raw Data

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

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

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

Source Data

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

Source Documents

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

Sponsor

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

Sponsor-Investigator

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

Standard Operating Procedures (SOPs)

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

Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Subject/Trial Subject

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

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site

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

Unexpected Adverse Drug Reaction

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

Validation

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

Verification (Validation) of Data

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

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects)

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

GENERAL PRINCIPLES OF GCP

1. PROVISION AND PREREQUISITES FOR A CLINICAL TRIAL

1.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki (Appendix 1), and that are consistent with GCP and the applicable regulatory requirement(s).

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

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

1.4 Pre-clinical studies that provide sufficient documentation of the potential safety and eventual clinical application of a pharmaceutical product are a prerequisite for a clinical trial. The pharmaceutical, preclinical and clinical data should be adapted to the appropriate phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for the planning and conducting of subsequent trials.

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

1.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

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

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

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

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

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

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

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

2. CLINICAL TRIAL PROTOCOL

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. The contents of a trial protocol should generally include the following topics:

2.1 General Information

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

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

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

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

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

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

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

2.2 Background Information

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

2.2.2 Summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

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

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

2.2.5 Statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

2.2.6 Description of the population to be studied.

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

2.3 Trial Objectives and Purpose

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

2.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

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

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

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

(a) Randomization.

(b) Blinding.

2.4.4 A description of the trial treatment(s) and the dosage, dosage regimen, dosage form, packaging and labelling of the investigational product(s).

2.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

2.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

2.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

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

2.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

2.5 Selection and Withdrawal of Subjects

2.5.1 Subject inclusion criteria.

2.5.2 Subject exclusion criteria.

2.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment)

2.6 Treatment of Subjects

2.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mod(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

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

2.6.3 Procedures for monitoring subject compliance.

2.7 Assessment of Efficacy

2.7.1 Specification of the efficacy parameters.

2.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

2.8 Assessment of Safety

2.8.1 Specification of safety parameters.

2.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

2.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

8.4 The type and duration of the follow-up of subjects after adverse events.

2.9 Statistics

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

2.9.2 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate). See Section 7

3. PROTECTION OF TRIAL SUBJECTS

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

3.1 Declaration of Helsinki

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

3.2 Independent Ethics Committee (IEC)

3.2.1 The sponsor and/or investigator must request the opinion of IEC regarding suitability of the proposed clinical trials protocols (including annexes) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

3.2.2 The IEC must be informed of all subsequent protocol amendments and of any serious or unexpected AEs occurring during the trial, likely to affect the safety the subjects or the conduct of the trial. Besides, the IEC should be asked for its opinion if a re-evaluation of the ethical aspects of the trial appears to be called for.

3.2.3 Subjects must not be entered into the trial until the IEC has issued its favourable opinion on the trial procedures and documentation. Sponsor/investigator should consider recommendations made by the IEC.

3.2.4 In submitting the clinical trial proposals to the IEC, IEC should consider the following: (a) The suitability of the investigator for the proposed trial in relation to his/her qualifications, experience, supporting staff, and available facilities, on the basis of the information available to the committee.

(b) The suitability of the protocol in relation to the objectives of the study, its scientific efficiency i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects, and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others.

(c) The adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary, legal representative.

(d) Provision for compensation/treatment in the case of injury or death of a subject if attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor.

(e) The extent to which investigators and subjects may be rewarded/ compensated for participation.

(f) IEC should give its opinion and advice in writing within a reasonable time limit, clearly identifying the trial, the documents studied and date of review.

(g) The acceptability of any proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

3.3 Informed Consent

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

3.3.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/ favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

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

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

3.3.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

3.3.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

3.3.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

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

3.3.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

3.3.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

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

(e) The subject's responsibilities.

(f) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

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

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

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

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

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

(l) That the monitor(s), the auditor(s), the IRB/IEC, and the National Regulatory Authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(m) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

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

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

(p) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

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

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

3.3.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

3.3.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

3.3.13 Except as described in 3.3.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

3.3.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

3.3.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

3.4 Confidentiality

The investigator should ensure that the confidentiality of all research data about subjects is respected by all persons involved as well as the information supplied by the sponsor.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(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 National Regulatory Authority.

4.1.2 The investigator should be thoroughly aware 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 information sources provided by the sponsor.

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

4.1.4 The investigator should permit monitoring and auditing by the sponsor, and inspection by the appropriate National Regulatory Authority.

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

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

4.2.2 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.3 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.

4.2.4 The relationship between the investigator and the sponsor in matters such as financial support, fees, and honorarium payments must be stated in writing in the protocol or contract. The protocol or contract should be available to the National Regulatory Authority and IEC on demand.

4.3 Selection of Trial Subjects

The investigator is responsible for ensuring the unbiased selection of adequate number of suitable subjects according to the protocol.

4.4 Medical Care of Trial Subjects

4.4.1 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.

4.4.2 During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.4.3 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.

4.4.4 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.

4.5 Communication with IRB/IEC

4.5.1 Before initiating a trial, the investigator should have written and dated approval/favourable 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.

4.5.2 As part of the investigator's written application to the IRB/IEC, the investigator should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator should supply a copy of the updated Investigator's Brochure to the IR/IEC.

4.6 Compliance with Protocol

4.6.1 The investigator should conduct the trial in compliance with the protocol agreed to by the sponsor which is required by the National Regulatory Authority and which was given approval/ favourable opinion by the IEC. The investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.6.2 The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any change or deviation in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject.

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

4.6.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable 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/favourable opinion,

(b) to the sponsor for agreement and, if required,

(c) to the National Regulatory Authority.

4.7 The Investigational Product

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

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

4.8 The Trial Site

4.8.1 The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial and to deal with all reasonable foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

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

4.9 Submission to the National Regulatory Authority

4.9.1 The investigator, sponsor, or investigator jointly with the sponsor, should give obtain approval from the National Regulatory Authority. Any submission to the national regulatory authority should be in writing and dated, and contain sufficient information to identify the protocol.

4.9.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC and National Regulatory Authority on any changes significantly affecting the conduct of the trial and/or increasing the risk to subjects.

4.10 Review by an Independent Ethics Committee (IEC)

Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by IEC. Any submission to and acceptance by the IEC should be in writing and dated, and contain sufficient information to identify the protocol or other submitted documents.

4.11 Serious Adverse Events(AEs)/Reactions

The investigator should notify (with documentation) the sponsor, IEC and the National Regulatory Authority immediately in case of the serious AEs and to take appropriate measures to safeguard subjects.

4.12 Monitoring, Auditing and Inspection

The investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits. In addition, the investigator must accept inspection and/or auditing by the National Regulatory Authority and by persons appointed by the sponsor for quality assurance.

4.13 Records and Reports

4.13.1 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 (see Section 6.1).

4.13.2 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/corrections. The investigator should retain records of the changes and corrections.

4.13.3 The investigator should maintain the trial documents as specified and required by the applicable National Regulatory Authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

4.13.4 Essential documents should be retained a period of time defined by the National Regulatory Authority.

4.13.5 Upon request of the monitor, auditor, IRB/IEC, or National Regulatory Authority, the investigator should make available for direct access all requested trial-related records.

4.14 Safety Reporting

4.14.1 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 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.

4.14.2 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.

4.14.3 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).

4.15 Termination of Trial

In the case of premature termination of the clinical trial, the investigator must inform the National Regulatory Authority, the IEC and, where applicable, the sponsor. Reasons for termination must be stated in writing.

4.16 Final Report

4.16.1 After completion of the trial, a final report must be drawn up and submitted to the National Regulatory Authority. The report should be dated and signed by the investigator in accordance with requirements to verify responsibility for the validity of the data.

4.16.2 The investigator should agree and sign the final report of the trial. For multicentre trials, the signature of the coordinating investigator may suffice in the protocol.

5. SPONSOR

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

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

The sponsor should obtain confirmation of review by IRB/IEC and documented approval/favourable opinion.

5.1 Selection of the Investigator(s)

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

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

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

5.1.4 The sponsor should obtain the investigator's agreement 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/favourable opinion by IRB/IEC.

5.1.5 Both the sponsor and investigator must agree on and sign the protocol as an agreement of the details of the clinical trial and the means of data recording (e.g CRF). Any such agreement must be documented.

5.2 Delegation of Responsibilities

5.2.1 The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a contract research organization (CRO) which should be specified in writing. 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.

5.3 Medical Expertise

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

5.4 Financing and Insurance

5.4.1 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator.

5.4.2 The sponsor should provide insurance for subjects in the event of trial-related injury or death, and provide indemnity for the investigator, except in the case of claims resulting from malpractice and/or negligence.

5.5 Trial Design Management, Data Handling, and Record Keeping

5.5.1 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 reports.

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

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

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

5.5.5 The sponsor must maintain a list of individuals who are authorized to make data change, and prevent unauthorized access to the data by appropriate security systems (see Section 6.2).

5.5.6 When electronic data handling or remote electronic data entry systems are employed, the sponsor must use validated, data processing programs with adequate user documentation. A predetermined set of standard operating procedures (SOP) for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file (see Section 6.2).

5.6 Investigational Product(s)

5.6.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.6.2 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical 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.

5.6.3 If any significant new information becomes available, the sponsor should update the Investigator's Brochure.

5.6.4 The sponsor is responsible for supplying the investigator(s)/ institution(s) with the investigational product(s).

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

5.7 Quality Assurance and Quality Control

5.7.1 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).

5.7.2 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.

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

5.7.4 Agreements, made by the sponsor with the investigator and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.8 Safety Information and Adverse Drug Reaction Reporting

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

5.8.2 The sponsor should promptly notify all concerned investigator(s)/ institution(s) and the National Regulatory Authority of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.8.3 The sponsor should expedite the reporting to all concerned investigator(s), to the IRB/IEC(s) and to the National Regulatory Authority of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.8.4 The sponsor should submit to the National Regulatory Authority all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.9 Termination of Trial

If the sponsor decides or is required to terminate the clinical trial prematurely, then the investigator(s), IEC and National Regulatory Authority must be notified of this decision, and of the reasons for termination.

5.10 Monitoring

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

5.10.2 The sponsor should ensure that the trials are adequately monitored. 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.

5.10.3 The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments.

5.10.4 Responsibilities of the monitor:

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 remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying that storage times and conditions are acceptable and that supplies are sufficient throughout the trial.

(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, and have 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 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 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 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 as required by regularity Authority.

(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.

5.10.5 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.

5.10.6 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 with the sponsor should be documented by the sponsor's designated representative.

5.11 Audit

5.11.1 The sponsor is responsible for performing audits as part of implementing quality assurance, they should consider:

(a) 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.

(b) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

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

(d) 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.

(e) 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).

(f) The observations and findings of the auditor(s) should be documented.

5.12 Noncompliance

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator participation is terminated because of noncompliance, the sponsor should notify promptly the National Regulatory Authority.

5.13 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

(a) All the investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, by the National Regulatory Authority, and given approval/favourable opinion by the IRB/IEC.

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

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

(d) All the 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.

(e) Communication between investigators is facilitated.

6. HANDLING AND ARCHIVING OF DATA

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

The allocation of responsibilities for handling of data and record-keeping should be specified in the protocol or other written agreement(s) between the sponsor and investigator(s).

6.1 Responsibilities of the Investigator

6.1.1 The investigator must ensure that the observations and findings are recorded correctly and completely in the case-report forms (CRFs) and signed by the responsible person designated in the protocol.

6.1.2 If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated print-out and back-up records. Computerized systems should be validated and a detailed description for their use be produced and kept up-to-date.

6.1.3 All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions.

6.1.4 Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.

6.1.5 Data other than those requested by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.

6.1.6 Units of measurement must always be stated, and conversion of units must always be indicated and documented.

6.1.7 The investigator should maintain a confidential record to allow the identification of the individual subjects in the trial (subject identification code).

6.1.8 The investigator must arrange for the retention of the subject identification codes for at least 5 years after the completion or discontinuation of the trial. Subject files and other source data must be kept for the maximum period of time but not less than 5 years.

6.2 Responsibilities of the Sponsor and the Monitor

6.2.1 The sponsor must use validated, data processing programs with adequate user documentation. A predetermined set of standard operating procedures (SOP) for such systems must be available.

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

6.2.3 The sponsor must ensure the greatest possible accuracy when processing data. It should always be possible to compare the data printout with the original observations and findings.

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

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

6.2.6 The sponsor or subsequent owner, must retain all other documentation pertaining to the trial for the lifetime of the product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that hard copy be obtained from it if required.

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

6.2.8 The final report must be retained by the sponsor or subsequent owner for five years beyond the lifetime of his product. Any change of ownership of the data should be documented.

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

7. STATISTICS AND CALCULATIONS

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

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

7.1 Experimental Design

The scientific integrity of a clinical trial and the credibility of the data produced depend mainly

on the design of the trial. In the case of comparative trials, the protocol should therefore describe:

(a) A priori rationale for the targeted difference between treatments that the trial is designed to detect, and the statistical power to detect that difference, taking into account clinical and scientific information and professional judgment on the clinical significance of statistical differences.

(b) Measures taken to avoid bias, particularly with regard to the randomization, when relevant, and selection of patients.

7.2 Randomization and Blinding

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

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

7.3 Statistical Analysis

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

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

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

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

8. Role of National Regulatory Authority

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

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

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

8.1 General Responsibilities

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

The National Regulatory Authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor (see Section 5.10). In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

8.2 On-site Inspections

The National Regulatory Authority should carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the National Regulatory Authority by the investigator or the sponsor.

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

Inspections may include data audit. The National Regulatory Authority should have easy access to all patient files and raw data used for and generated during the trial.

9. Clinical Trial

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

Clinical trials are commonly classified into different Phases (I to IV). It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description on each phase, depending on purposes as related to clinical development of pharmaceutical products, are shown below:

9.1 Phase I

It presents the first trials of a new active ingredient or new formulations in human beings which are often carried out in healthy volunteers. Their purpose is to perform a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamics of the active ingredient in humans,

9.2 Phase II

These trials are executed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

9.3 Phase III

The trials of this phase are done in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The outline and profile of any frequent adverse reactions must be investigated and special characteristics of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age).

These trials should rather be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

9.4 Phase IV

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

9.5 Financial of the Trial

All financial aspects involved in conducting and reporting a trial should be clearly arranged and a budget made out. Information should be available about the sources of economic support (e.g. foundations, private or public funds, sponsor/manufacturer). Likewise it should be clearly apparent how the expenditures are distributed, e.g. refunding expenses of the patients, payment for special tests, technical assistance, purchase of apparatus, possible fees to or reimbursement of the members of the research team, payment of the University/Clinic..etc.

9.6 Insurance and Liability

Healthy/Patient volunteers taking part in a clinical trial should be satisfactorily insured against any injury caused by the trial. The liability of the involved patients must be clearly understood before the start of a trial of a medicinal product containing an active substance.

9.7 Pre-Trial Data

Chemical, Pharmaceutical, animal pharmacological and toxicological data on the substance and/or the pharmaceutical dosage form in question must be available and professionally evaluated before a new product is subjected to clinical trials. The sponsor's responsibility for providing exhaustive, complete and relevant material, e.g. by means of an investigator's Brochure, is emphasized.

REFERENCES

1. Guidelines for Good Clinical Practice, E6(R1), ICH Harmonized Tripartite Guideline, June 1996.
2. WHO Technical Report Series, No. 850, 1995, Annex 3, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.
3. International Ethical Guidelines for Biomedical Research Involving Human Subjects, WHO, Geneva, CIOMS, 2002.

Appendix 1

DECLARATION OF HELSINKI A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol maybe made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he/or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at anytime without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissents hould be respected.

29 Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

* The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

* Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

طبعت بالهيئة العامة لشئون المطابع الأميرية

رئيس مجلس الإدارة

مهندس / عماد فوزى فرج محمد

رقم الإيداع بدار الكتب ٢٦٨ لسنة ٢٠١٦

٢٠١٦/٢٥٢٤٥ - ٢٠١٦/١١/٢ - ١٤٠٦