NAFDAC GOOD CLINICAL PRACTICE GUIDELINES 2016

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ACRONYMNS

AE	Adverse Events
AR	Adverse Reaction
AVAREF	African Vaccine Regulatory Forum
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DFID	UK Department for International Development
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
GCLPG	Good Clinical Laboratory Practice Guidelines
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data-Monitoring Committee
NAFDAC	National Agency for Food and Drug Administration and Control
OECD	Organization for Economic Co-Operation and Development
PATHS	Partnership for Transforming Health Systems
QC	Quality Control
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
US FDA	United States Food and Drug Administration
WHO	World Health Organization

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Director; Drug Evaluation and Research
NAFDAC.

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 humans. GCP guidelines provide unified standards for the conduct of clinical trials and acceptance of clinical data in Nigeria. The guidelines should be followed when generating clinical trial data that are intended to be submitted to the Agency.

Compliance with these guidelines provides the public assurance that the rights, safety and well-being of trial participants are protected and that data generated from clinical trials, bioavailability and bioequivalence studies of medicinal products are credible.

The GCP guidelines describe the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and ethics committees. The document is intended to provide guidance on how to comply with the provisions of the NAFDAC Good Clinical Practice Regulations. The GCP regulations contain the minimum good clinical trial requirements to ensure that clinical trials meet the ethical and scientific quality standards for designing, conducting, recording and reporting trials in humans. The GCP guidelines also provide the regulatory requirements without which clinical trials, bioavailability or bioequivalent studies cannot be commenced, participants recruited or advertisements issued to recruit trials participants.

The section on Good Clinical Laboratory Practice (GCLP) outlines the minimal requirements that trial facility should follow to assure the sponsor and the Agency that all data submitted are a true reflection of the results obtained during a study and that these data can be relied upon when making risk and/or safety assessments of study products.

The GCLP guidelines identify systems required and procedures to be followed within an organization conducting analysis of samples from clinical trials in compliance with the requirements of Good Clinical Practice (GCP). It thus provides sponsors, laboratory management, project managers, clinical research associates and quality assurance

personnel with the framework for a quality system in analysis of clinical trial samples, ensuring GCP compliance overall of processes and results.

The GCLP guidelines are intended to be applied by all trial facilities and laboratories that support clinical trials for medicinal products to be used in Nigeria. The standards will form the basis for audits and/or site visits conducted by the Agency which aims at ensuring that consistent, reproducible, auditable, and reliable results are produced in an environment conducive to study reconstruction.

This document is to be used in conjunction with other existing relevant statutes in the country. All stakeholders are encouraged to send their comments to the Agency during the use of these guidelines in order to improve future editions.

CHAPTER

1 GENERAL REQUIREMENTS

Principles of Good Clinical Practice

1.1. Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the current version of the Declaration of Helsinki (Annex 1). The basic ethical principles of equal importance, namely respect for persons, beneficence, and justice must be consistent with current good clinical practice principles.

1.2. Research involving humans should be scientifically justified and described in a clear, detailed protocol.

1.3. Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial participant and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

1.4. Research involving humans should be initiated only if the anticipated benefit(s) for the individual research participant and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial participants.

1.5. Research involving humans should receive ethics committees favourable opinion prior to initiation.

1.6. Research involving humans should be conducted in compliance with the approved protocol

1.7. Freely given informed consent should be obtained from every participant prior to research participation in accordance with national culture(s) and requirements. When a participant is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

1.8. Research involving humans should be continued only if the benefit-risk profile remains favourable.

1.9. Qualified and duly licensed medical personnel (i.e., clinician or, when appropriate, dentist) should be responsible for the medical care of trial participants, and for any medical decision(s) made on their behalf.

1.10. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

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

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

1.13. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.

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

Provisions and prerequisites for a clinical trial

Justification for the trial

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

Ethical principles

1.16. All research involving humans should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki (Annex 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-maleficence (doing no harm), as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving humans. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles (See Chapter 2 ***"Protection of trial participants"*** and sections 5.34 to 5.48**).**

Supporting data for the investigational product

1.17. Pre-clinical studies that provide sufficient documentation of the potential safety of a medicinal product for the intended investigational use are a prerequisite for a clinical trial. Information

about manufacturing procedures and data from tests performed on the actual product should establish that it is of suitable quality for the intended investigational use. The medicinal, pre-clinical and clinical data should be appropriate to the 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 the safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for planning and conducting subsequent trials.

Investigator and site(s) of investigation

1.18. Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the clinical trial, the investigator(s) and the sponsor should establish an agreement on the protocol, standard operating procedures (SOPs), the monitoring and auditing of the trial, data handling and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently.

Site of the trial, facilities and staff

1.19. Clinical trials must be carried out under conditions which ensure adequate safety for the participants.

1.20. The site selected should be appropriate to the stage of development of the product and the potential risks involved.

1.21. 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 clinical laboratory practice (GCLP) should be observed.

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

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

1.24. The investigator must notify or obtain approval for the trial from the management of relevant research facilities.

Regulatory requirements

1.25. All parties involved in a clinical trial should comply fully with the regulatory requirements of the Agency.

1.26. The pre-trial agreement between the sponsor and investigator(s)

should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application to or notification of the trial to the Agency, amendments to the trial protocol, reporting of adverse events and reactions, and notifications to the ethics committee).

Inspection of trial site

1.27. The Agency will carry out inspections at trial site(s), the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises to ensure compliance with provisions of these regulations.

1.28.

Clinical Trial Registry

1.29. The Agency requires sponsors/Investigators to register all their clinical trials (whether approved or not) in a WHO Primary Registry before commencement, and keep updating the information therein until the end of such trial.

Manufacture or import authorization of investigational products

1.30. The Agency will issue an authorisation to manufacture in whole or in part, assemble, divide, package, present, import or export any investigational medicinal product required for a clinical trial.

1.31. The authorisation will not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons under the supervision of a pharmacist and if the investigational medicinal products are intended to be used exclusively in those institutions.

1.32. The holder of marketing authorisation to manufacture, assemble or import investigational medicinal product must have at his disposal the services of at least one qualified person who is responsible for ensuring that each batch of investigational medicinal products and its comparator, where applicable, has been manufactured and checked in compliance with the requirements of good manufacturing practice.

1.33. In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies GMP. The said register or equivalent document must be kept up to date as operations are carried out and must remain at the manufacturing site and made accessible to the Agency for a period of at least five (5) years.

1.34. An authorisation will apply only to the premises, types of medicinal products specified in that application

1.35. The holder of the authorisation must at least comply with the following requirements:

a. Have at his disposal the services of staff that comply with the GMP Regulations of the Agency
b. Dispose of the investigational medicinal products only in accordance with the requirements of the Agency;
c. Give prior notice to the Agency of any changes he may wish to make to any of the particulars;
d. Allow the Agency access to his premises at any time;
e. Provide the qualified person all necessary resources to carry out his duties and to comply with principles and guidelines for good manufacturing practice for medicinal products as laid down by the Agency.

1.36. The Agency may suspend or revoke the authorisation, if the holder of the authorization fails at any time to comply with the requirements.

Labelling of investigational medicinal products

1.37. The particulars to appear on the outer packaging of investigational medicinal product(s) or, where there is no outer packaging, on the immediate packaging should be labelled as prescribed by the Agency.

1.38. An investigational medicinal product should be labelled such as to ensure protection of the participant and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.

1. -

Financial disclosure

1.39. The applicant must submit a completed financial disclosure form attesting to the absence of financial interests of the investigator and financial arrangements with the sponsor. The form should be dated and signed by the chief financial officer or other responsible corporate official or representative.

1.40. Disclosure Statement: For any investigator for whom the applicant does not submit the certification described above, the applicant should submit evidence disclosing completely and accurately the following:

a. Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial must not be influenced by the outcome of the study;

b. Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research,

compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

c. Any proprietary interest in the tested product held by any clinical investigator involved in a study;

d. Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

e. Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

1.41. The investigator must provide to the sponsor of the study sufficient and accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements as prescribed. The investigator must promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

Phase 4 studies

1.42. The Agency may request a sponsor to conduct, or a sponsor may wish to conduct post-marketing (Phase 4) studies to generate additional information about the drug's risks, benefits, and optimal use other than those used in the corresponding Phase 2 studies. These could include, but not limited to studying:

a. Different doses
b. Schedules of administration
c. Use in other patient populations
d. Use in other stages of the disease
e. Modification of the duration of use

CHAPTER

2 PROTECTION OF TRIAL PARTICIPANTS

General requirements for protection of participants

1.1. The following conditions shall apply in these guidelines:

a. The rights, safety, and well-being of the trial participants are the most important considerations and shall prevail over interests of science and society.

b. The medical care given to, and medical decisions made on behalf of participants shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.

c. Freely given informed consent shall be obtained from every participant prior to clinical trial participation as prescribed in (see sections 5.34 to 5.48).

d. The participant may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent

e. The privacy and confidentiality of records that could identify participants shall be maintained.

f. A trial shall be initiated only if an ethics committee and the Agency come to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

g. The rights of each participant to physical and mental integrity, to privacy and to the protection of the data concerning him shall be safeguarded.

h. Provision shall be made for insurance and indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial.

Exceptions

1.2. Informed consent shall be obtained before the use of any investigational medicinal product unless the provisions of section 2.3 apply and both the investigator and a physician, qualified in that area of specialization, who is not otherwise participating in the clinical investigation certify in writing all of the following:

a. The participant is confronted by a life-threatening situation necessitating the use of the investigational medicinal product.

b. Informed consent cannot be obtained from the participant

because of an inability to communicate with the participant.

c. Time is not sufficient to obtain consent from the participant's legal representative.

d. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant.

1.3. If immediate use of the investigational medicinal product is, in the investigator's opinion required to preserve the life of the participant, and time is not sufficient to obtain the independent determination required in section 2.2 in advance of using the investigational medicinal product, the determinations of the clinical investigator should be made and, within five working days after the use of the investigational medicinal product, be reviewed and evaluated in writing by a physician, qualified in that area of specialization, who is not participating in the clinical investigation.

1.4. The documentation required in section 2.2 or 2.3 should be submitted to the ethics committee within five working days after the use of the investigational medicinal product.

Clinical trial on minors

1.5. In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

a. The informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor

b. The person or legal representative has been provided with a contact point where he may obtain further information about the trial

c. The minor has received information according to his/her capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits

d. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate, the principal investigator;

e. No incentives or financial inducements to the minor or a person with parental responsibility for that minor or as the case may be, the minor's legal representative except for provision for compensation in the event of injury or loss.

f. Some direct benefit for the group of patients is obtained from

the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. In addition, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

g. The corresponding scientific guidelines of the Agency have been followed;

h. Clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored

i. The ethics committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

j. The interests of the patient shall always prevail over those of science and society.

Clinical trials on incapacitated adults

2.6. In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

a. The informed consent of the legal representative has been obtained; consent must represent the participant's presumed will and may be revoked at any time, without detriment to the participant;

b. The participant not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, its risks and its benefits.

c. The explicit wish of a participant who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator.

d. No incentives or financial inducements are given

except compensation in the event of injury or loss.

e. The clinical trial is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers.

f. Clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored

g. The Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol

h. The interests of the patient shall always prevail over those of science and society; and

i. There are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

CLINICAL TRIALS ON PREGNANT OR BREASTFEEDING WOMEN

2.7. A clinical trial on pregnant or breastfeeding women may be conducted only where, the following conditions are met:

a. The clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; or

b. If such clinical trial has no direct benefit for the pregnant woman or foetus or child after birth, it can be conducted only if:

   i. A clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;

   ii. The clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and

   iii. The clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman

concerned, her embryo, foetus or child after birth;

c. Where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; and

d. No incentives or financial inducements are given to the participant except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

Clinical trials in emergency situations

2.8. Informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the participant in the clinical trial, provided that this decision is taken at the time of the first intervention on the participant, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:

a. Due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the participant is unable to provide prior informed consent and to receive prior information on the clinical trial;

b. There are scientific grounds to expect that participation in the clinical trial will have the potential to produce a direct clinically relevant benefit for the participant resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the participant, or in the diagnosis of its condition;

c. It is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;

d. The investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the participant;

e. The clinical trial relates directly to the participant's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the participant or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;

f. The clinical trial poses a minimal risk to, and imposes a minimal burden on, the participant in comparison with the standard treatment of the participant's condition.

2.9. Informed consent shall be sought to continue the participation in the

clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:

a. Regarding incapacitated participants and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information shall be given as soon as possible to the participant and to his or her legally designated representative;

b. Regarding other participants, the informed consent shall be sought by the investigator without undue delay from the participant or his or her legally designated representative, whichever is sooner and the information shall be given as soon as possible to the participant or his or her legally designated representative, whichever is sooner. For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the participant as soon as he or she is capable of giving informed consent.

2.10. If the participant or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

CHAPTER

3 ETHICS COMMITTEES

Responsibilities

3.1. An EC should safeguard the rights, safety, and well-being of all trial participants. Special attention should be paid to trials that may include vulnerable participants. The EC should operate in such a manner that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

3.2. The EC should obtain the trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, participant recruitment procedures (e.g. advertisements), written information to be provided to participants, Investigator's Brochure (IB), available safety information, information about payments and compensation available to participants, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the EC may need to fulfil its responsibilities.

3.3. The EC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

a. Favourable opinion;
b. Modifications required prior to its favourable opinion;
c. Negative opinion; and
d. Termination/suspension of any prior favourable opinion.

3.4. The EC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the EC requests.

3.5. The EC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to participants. Every ongoing trial must be reviewed at least once per year.

3.6. The EC may request more information than is outlined in section 5.41 be given to participants when, in the judgement of the EC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the participants.

3.7. When a non-therapeutic trial is to be carried out with the consent of the participant's legally acceptable representative (see sections 5.43

and 5.45), the EC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.8. Where the protocol indicates that prior consent of the trial participant or the participant's legally acceptable representative is not possible (see section 5.46), the EC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meets applicable regulatory requirements for such trials (e.g. in emergency situations).

3.9. The EC should review both the amount and method of payment to participants to assure that neither presents problems of coercion or undue influence on the trial participants. Payments to a participant should be prorated and not wholly contingent on completion of the trial by the participant.

3.10. The EC should ensure that information regarding payment to participants, including the methods, amounts, and schedule of payment is set forth in the written informed consent form and any other written information to be provided to participants. The way payment will be prorated should be specified.

Composition, functions and operations

3.11. The EC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the EC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area who can protect public interest.

c. At least one member who is independent of the institution/trial site.

d. No Ethics Committee may consist entirely of members of one gender.

e. No Ethics Committee may consist entirely of members of one profession.

f. No Ethics Committee may have a member participate in the Ethics Committee's initial or continuing review of any study in which the member has a conflicting interest, except to provide information requested by the Ethics Committee.

g. Only those EC members who are independent of the investigator and the sponsor of the trial should vote/provide

opinion on a trial-related matter. A list of EC members and their qualifications should be maintained.

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

i. An EC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

j. Only members who participate in the EC review and discussion should vote/provide their opinion and/or advice.

k. The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the EC or in the vote/opinion of the EC.

l. An EC may invite non-members with expertise in special areas for assistance.

Procedures

3.12. The EC should establish, document in writing, and follow its procedures, which should include:

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

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

c. Conducting initial and continuing review of trials.

d. Determining the frequency of continuing review, as appropriate.

e. Providing, according to the applicable regulatory requirements, expedited review and favourable opinion of minor change(s) in on-going trials that have the favourable opinion of the EC.

f. Specifying that no participant should be admitted to a trial before the EC issues its written favourable opinion of the trial.

g. Specifying that no deviations from, or changes of, the protocol should be initiated without prior written EC favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 5.22).

h. Specifying that the investigator should promptly report to the EC:
   i. Deviations from, or changes of the protocol to eliminate immediate hazards to the trial participants (see sections 3.12 (g), 5.22 and 5.23)
   ii. Changes increasing the risk to participants and/or affecting significantly the conduct of the trial (see section 4.139c).
   iii. All adverse reactions (ARs) that are both serious and unexpected.
   iv. New information that may affect adversely the safety of the participants or the conduct of the trial.

i. Ensuring that the EC promptly notify in writing the investigator concerning:
   i. Its trial-related decisions/opinions.
   ii. The reasons for its decisions/opinions.
   iii. Procedures for appeal of its decisions/opinions.

Criteria for Ethics Committee consideration of a trial

3.13. In preparing its opinion, the institutional ethics committee should consider, in particular:

a. The relevance of the clinical trial and the trial design;
b. Whether the evaluation of the anticipated benefits and risks as prescribed in section 2.1(f) is satisfactory and whether the findings are justified
c. The protocol
d. The suitability of the investigator and supporting staff
e. The investigator's brochure
f. The quality of the facilities
g. The adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions prescribed in section 2.6.
h. Provision for indemnity or re-imbursement in the event of injury or death attributable to a clinical trial;
i. Any insurance or indemnity to cover the liability of the investigator and sponsor
j. The amounts and, where appropriate, the arrangements for rewarding or reimbursing investigators and trial participants and the relevant aspects of any agreement between the sponsor and the trial site
k. The arrangements for the recruitment of participants.

Ethics Committee records

3.14. An institution, or where appropriate an Ethics Committee, should prepare and maintain adequate documentation of Ethics Committee activities, including the following:

a. Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to participants.
b. Minutes of Ethics Committee meetings which should be in sufficient detail to show attendance at the meetings; actions taken by the Ethics Committee; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or unfavourable opinion on a study; and a written summary of the discussion of controverted issues and their resolution.
c. Records of continuing review activities.
d. Copies of all correspondences between the Ethics Committee and the investigators.
e. A list of Ethics Committee members identified by name, qualification and experience including board certifications, licenses, etc., sufficient to describe each member's presence in the Ethics Committee. The employment or other relationship between each member and the institution should be indicated (e.g. full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant).
f. Written procedures for the Ethics Committee.
g. Statements of significant new findings provided to participants.

3.15. The records should be retained for at least 5 years after completion of the study, and should be accessible for inspection and copying by the Agency.

Non-Local Ethics Committee Review

3.16. Institutions or investigators engaged in a trial involving humans should have their own Ethics Committees review, provide opinion and oversee study conducted within the institution. However, Ethics Committees located in other institutions may be used where there is no competent Ethics Committee within the institution.

3.17. When non-local Ethics Committee review takes place, the reviewing Ethics Committee must document its role and responsibilities. A written agreement should be executed between the performance site

where the research is to be conducted (e.g., private practitioner's office, clinic, etc.) and the Ethics Committee or its institution. The agreement should confirm the authority of the Ethics Committee to oversee the study. While the Ethics Committee assumes responsibility for oversight and continuing review, the clinical investigator and the research site retain the responsibility for the conduct of the study.

3.18. The non-local Ethics Committee should have adequate knowledge of community attitudes, information on conditions surrounding the conduct of the study, and it's continuing status to ensure fulfilling the requirements of the Agency for each study site. The non-local Ethics Committee needs to ensure these requirements are met for each location for which it has assumed Ethics Committee oversight responsibility.

Cooperative research:

3.19. Institutions involved in multi-institutional studies may use joint review, reliance upon the review of another competent Ethics Committee, or similar arrangements aimed at avoidance of duplication of effort.

CHAPTER

4 SPONSORS

Responsibilities of the Sponsor

Quality Assurance and quality control

4.1. 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 requirements of the Agency.

4.2. 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.

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

4.4. 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.

Allocation of Responsibilities

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

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

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

Contract Research Organization (CRO)

4.8. When a sponsor transfers any or all of the sponsor's trial-related duties and functions to a CRO, 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.

4.9. Any such transfer should be described in writing. If all obligations are not transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description should be deemed not to have been transferred.

4.10. A contract research organization that assumes any obligation of a sponsor should comply with the specific requirements of the Agency and should be subject to the same regulatory action as a sponsor for failure to comply with any obligation required by the Agency.

Medical Expertise

4.11. 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.

Trial Design

4.12. 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 Case Report Forms (CRFs) and planning the analyses to analyzing and preparing interim and final clinical trial reports.

4.13. For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (*ICH E3*)

Trial Management and data handling

4.14. 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.

4.15. The sponsor may consider establishing an Independent Data-Monitoring Committee /Data Safety Monitoring Board (IDMC)/DSMB to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should

have written operating procedures and maintain written records of all its meetings.

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

a. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent with intended performance (i.e. validation).

b. Maintain SOPs for using these systems.

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

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

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

f. Any change or correction to a CRF/eCRF 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 or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to ensure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

g. Maintain adequate backup of the data.

h. Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

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

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

4.19. The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see ***Chapter 7 "Essential Documents for the Conduct of a Clinical***

Trial").

4.20. The sponsor should retain all sponsor-specific essential documents in conformance with the requirements of the Agency.

4.21. If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 5 years after formal discontinuation.

4.22. If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and the Agency.

4.23. Any transfer of ownership of the data should be reported to the Agency.

4.24. The sponsor specific essential documents should be retained until at least 5 years after the last approval of a marketing application in Nigeria or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the Agency.

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

Record keeping

4.26. A sponsor should maintain adequate records showing the receipt, supply, or other disposition of the investigational medicinal product. These records are required to include, as appropriate, the name of the investigator to whom the medicinal product is shipped, and the date, quantity, and batch or code mark of each such supply.

4.27. A sponsor should maintain complete and accurate records showing any financial interest paid to clinical investigators by the sponsor of the covered study. A sponsor should also maintain complete and accurate records concerning all other financial interests of investigators (see section 1.37).

4.28. A sponsor should retain the records and reports for 5 years after a marketing application is approved for the medicinal product; or, if an application is not approved for the medicinal product, until 5 years after shipment and delivery of the medicinal product for investigational use is discontinued and the Agency has been so notified.

Record Access

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

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

4.31. A sponsor should provide access to the Agency to copy and verify any records or reports relating to a clinical investigation conducted in relation to a trial.

Investigator Selection

4.32. The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see sections 5.1 to 5.3 and 5.8 to 5.11) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibilities.

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

4.34. The sponsor should obtain the investigators/institution's agreement:

a. To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) and with the protocol agreed to by the sponsor and given favourable opinion by the EC (see section 3.3);

b. To comply with procedures for data recording/reporting;

c. To permit monitoring, auditing and inspection and

d. To retain the trial related essential documents until the sponsor informs the investigator that these documents are no longer needed (***Chapter 7 "Trial Master File"***)

4.35. The sponsor and the investigator should sign the protocol, or an alternative document, to confirm this agreement.

Compensation to Participants and Investigators

4.36. The sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

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

4.38. When trial participants receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

Financing

4.39. The financial aspects of the trial such as financial support, fees and honorarium payments in kind must be stated in writing in the protocol or contract. The protocol or contract should be available to the ethics committee and the Agency on demand and documented in an agreement between the sponsor and the investigator.

Notification/Submission to the Agency

4.40. Before initiating the clinical trial(s), the sponsor (or the sponsor and/or the investigator should submit any required application(s) to the Agency 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.

Confirmation of Review by EC

4.41. The sponsor should obtain from the investigator:

a. The name and address of the investigator's/institution's EC.

b. A statement obtained from the National Ethics Committee that an EC is capable of reviewing the protocol and overseeing the trial.

c. Documented EC favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to participants, participant recruiting procedures, and documents related to payments and compensation available to the participants, and any other documents that the EC may have requested.

4.42. If the favourable opinion of the EC is contingent upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to participants, and/or other procedures, the sponsor

should obtain from the investigator a copy of the modification(s) made and the date favourable opinion was given by the EC.

4.43. The sponsor should obtain from the investigator documents and dates of any EC re-evaluations with favourable opinion, and of any withdrawals or suspensions of favourable opinion.

Information on Investigational Product(s)

4.44. The sponsor is responsible for supplying the investigational medicinal product(s) and, if applicable, comparator products, prepared in accordance with principles of good manufacturing practice (GMP).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.

4.45. The sponsor should update the Investigator's Brochure as significant new information becomes available (see ***Chapter 8 "Investigator's Brochure"***)

Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

4.46. The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable current GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with the requirements of the Agency. The investigational label should state that the product is for clinical trial purposes only. Investigational label information should be accurate and in a language that is understandable to the participants.

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

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

4.49. In blinded trials, the package should be labelled in a way that does not

reveal the identity of the product. A coding system should be used to allow for the proper and rapid identification of the blinded products given to individual participants (in case of emergency). In addition, all study products, including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

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

4.51. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, should not promote an investigational product.

4.52. A sponsor or investigator should not market an investigational product.

Supplying and Handling Investigational Product(s)

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

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

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

4.56. The sponsor should not supply an investigator with the investigational product(s) until the sponsor obtains all required documentation (e.g. favourable opinion from EC and approval by the Agency).

4.57. 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 and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the requirements of the Agency.

4.58. The sponsor should:

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

b. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see ***Chapter 7 Essential Documents for the Conduct of a Clinical Trial***). The investigator should not supply the investigational product to any person not targeted to receive it

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

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

4.59. The sponsor should:

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

b. Maintain sufficient quantities of the investigational product(s) from each batch used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics for controlled test and validation of data as required by the Agency.

c. Provide information about the expiry date (month/year) or retest date information in a manner understandable to all staff involved in the trial.

Safety Information

4.60. The sponsor is responsible for the on-going safety evaluation of the investigational product(s).

4.61. The sponsor should promptly notify all concerned investigator(s)/institution(s) and the Agency of findings that could affect adversely the safety of participants, impact the conduct of the trial, or alter the EC's favourable opinion to continue the trial.

Adverse Reaction Reporting

4.62. The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the EC(s), where required, and to the Agency of all adverse reactions that are both serious and unexpected.

4.63. Such expedited reports should comply with the Agency's requirement(s) (see Chapter 6 "***Safety Reporting***")

4.64. The sponsor should submit to the Agency all safety updates and periodic reports, as required.

Monitoring

4.65. The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of

monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

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

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

4.68. The purposes of trial monitoring are to verify that:

a. The rights and well-being of participants are protected.

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

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

Selection and Qualifications of Monitors

4.69. Monitors should be appointed by the sponsor.

4.70. Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

4.71. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to participants, the sponsor's SOPs, GCP, and the requirements of the Agency.

Extent and Nature of Monitoring

4.72. 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. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as

investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

Monitor's Responsibilities

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

b. Verifying that the investigator has adequate qualifications and resources (see sections 5.1 to 5.3 and 5.8 to 5.11) and remain adequate throughout the trial period; that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

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

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

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

iii. That participants are provided with necessary instruction on proper use, handling, storing, and returning the investigational product(s).

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

v. That the disposition of unused investigational product(s) at the trial sites complies with the requirements of the protocol and the Agency.

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 participant's involvement 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 requirements of the Agency.

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 participants.

j. Reporting the participant 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 participants.

    iii. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

    iv. Visits that the participants 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 drop-outs of enrolled participants 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 initialled 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 EC, the sponsor, and the requirements of the Agency.

p. Determining whether the investigator is maintaining the essential documents (see ***Chapter 7 "Trial Masterfile***").

q. Communicating deviations from the protocol, SOPs, GCP, and the requirements of the Agency to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Assessment of the trial site

4.95. The monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an adequate number of trial participants is likely to be available for the duration of the trial. The monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of standard operating procedures.

Monitoring Procedures

4.96. 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.

Monitoring Report

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

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

4.99. 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.

4.100. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

Audit

4.101. If or when sponsors perform audits, as part of implementing quality

assurance, they should consider:

Purpose

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 Agency's requirements.

Selection and Qualification of Auditors

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.

Auditing Procedures

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, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants, and any identified problem(s).

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

g. To preserve the independence and value of the audit function, the Agency will not routinely request the audit reports. The Agency may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

h. When required by applicable regulation, the sponsor should provide an audit certificate.

Noncompliance

i. Noncompliance with the protocol, SOPs, GCP, and the requirements of the Agency by an investigator, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

j. If the monitoring and/or auditing identify 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's/institution's participation is terminated because of noncompliance, the sponsor should promptly notify the Agency.

Suspension, early termination and end of a clinical trial

Suspension of a trial by the Agency

4.102. The Agency may suspend or prohibit a clinical trial where it has objective grounds for considering that the conditions in the authorisation are not being met or has doubts about the safety or scientific validity of the clinical trial. Before this decision is reached, the Agency , will inform the sponsor and EC except where there is imminent risk, and ask the sponsor and/or the investigator for their opinion. The sponsor should immediately investigate the grounds for suspension or prohibition and provide a report within one week addressing the issues raised and any exceptional circumstances that might have led to those conditions not being met. The report of investigation should also be communicated to the EC.

4.103. Where the Agency has objective grounds for considering that the sponsor or investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, the Agency will require the sponsor to take steps to remedy any infringement of those obligations. The course of action should have a timetable for its implementation and a date when the sponsor should report back to the Agency on the progress and completion of its implementation.

4.104. In these circumstances the sponsor should immediately implement the course of action set and report to the Agency and the ethics committee on the progress and completion of its implementation in accordance with the timetable set.

Premature Termination or Suspension of a Trial by the Sponsor

4.105. If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, the EC and the Agency of the termination or suspension within 15 days stating the reason(s) for the termination or suspension.

4.106. A sponsor who determines that its investigational medicinal product presents an unreasonable and significant risk to participants should discontinue those investigations that present the risk, notify

the Agency, all Ethics Committees, and all investigators who have at any time participated in the trial, ensure the disposition of all stocks of the medicinal product outstanding and furnish the Agency with a full report of the sponsor's actions. The sponsor should discontinue the investigation as soon as possible, but not exceeding five (5) calendar days after determining that the investigation should be discontinued. Upon request, the Agency will confer with a sponsor on the need to discontinue an investigation

End of the clinical trial

4.107. The definition of the end of the trial should be stated in the protocol. The sponsor has to make an end of trial declaration when the complete trial has ended as described in the protocol. This declaration has to be made to the Agency and the Ethics Committee within 90 days of the end of the clinical trial.

4.108. An earlier end of the clinical trial which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as 'early termination'.

Clinical Trial Reports

4.109. Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the Agency within one year of the early termination or end of the trial. The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards for Structure and Content of Clinical Study Reports. (see ICH E3)

4.110. However, where for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results should be submitted as soon as it is available. In this case, the protocol should specify when the result are going to be submitted together with justification.

Multicentre Trials: For multicentre trials, the sponsor should ensure that:

4.111. All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, by the Agency, and given favourable opinion by the EC.

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

4.113. The responsibilities of coordinating investigator(s) and the other

participating investigators are documented prior to the start of the trial.

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

4.115. Communication between investigators is facilitated.

Inactive status

4.116. If no participants are entered into clinical studies for a period of 2 years or more after authorization to conduct an investigation or if all investigations remain on clinical hold for 1 year or more, the investigation may be placed by the Agency on inactive status. This action may be taken by the Agency either on request of the sponsor or on the Agency's own initiative. If the Agency seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the investigation should continue to remain active.

4.117. If an investigation is placed on inactive status, all investigators must be so notified and all stocks of the medicinal products must be returned or otherwise disposed of in accordance with the requirements of the Agency.

4.118. A sponsor is not required to submit periodic reports of an investigation on inactive status. An inactive investigation is, however, still in effect for purposes of the public disclosure of data and information.

4.119. A sponsor who intends to resume clinical investigation placed on inactive status should submit a protocol amendment containing the proposed general investigational plan for the coming year and ammended protocols. If the protocol amendment relies on information previously submitted, the plan should reference such information. Additional information supporting the proposed investigation, if any, should be submitted in an information amendment.

4.120. An investigation that remains on inactive status for 5 years or more must be terminated.

Clinical trial protocol and protocol amendment(s)

4.121. The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other

protocol referenced documents, such as an Investigator's Brochure.

General Information

4.122. The following should be included:

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

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

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

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

e. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the name, address (location and e-mail), and telephone number(s) of the trial site(s).

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

g. Name(s) and address (location and e-mail) of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

4.123. Provide the following:

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

b. A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

c. Summary of the known and potential risks and benefits, if any, to participants.

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

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

f. Description of the population to be studied.

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

Trial Objectives and Purpose

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

Trial Design

4.125. 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:

a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
b. 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.
c. A description of the measures taken to minimize/avoid bias, including:
    i. Randomization.
    ii. Blinding.
d. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
e. The expected duration of participant's involvement, and a description of the sequence and duration of all trial periods, including follow-up, if any.
f. A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.
g. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
h. Maintenance of trial treatment randomization codes and procedures for breaking codes.
i. 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.

4.126. Selection and withdrawal of participants

a. Participant inclusion criteria.
b. Participant exclusion criteria.
c. Participants withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying the following:
    i. When and how to withdraw participants from the

trial/ investigational product treatment.

ii. The type and timing of the data to be collected for withdrawn participants.

iii. Whether and how participants are to be replaced.

iv. The follow-up for participants withdrawn from investigational product treatment/trial treatment.

4.127. Treatment of participants

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

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

c. Procedures for monitoring participant compliance.

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

4.128. Assessment of efficacy

a. Specification of the efficacy parameters.

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

4.129. Assessment of Safety

a. Specification of safety parameters.

b. The methods and timing for assessing, recording, and analyzing safety parameters.

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

d. The type and duration of the follow-up of participants after adverse events.

4.130. Statistics

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

b. The number of participants planned to be enrolled to achieve trial objectives. In multicentre trials, the numbers of enrolled participants projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

c. The level of significance to be used. When interim analysis is carried out, the level of significance for the analysis of the final data should be adjusted accordingly.
d. Criteria for the termination of the trial.
e. Procedure for accounting for missing, unused, and spurious data.
f. 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).
g. The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, evaluable participants).

4.131. Direct Access to Source Data/Documents
The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, EC review, and the inspection(s) by the Agency, providing direct access to source data/documents.

4.132. Quality Control and Quality Assurance
The protocol should contain detailed Study Monitoring and Training Plans.

4.133. Ethics
Description of ethical considerations relating to the trial.

4.134. Data Handling and Record Keeping

4.135. Financing and Insurance
Financing and insurance if not addressed in a separate agreement.

4.136. Publication Policy
Publication policy, if not addressed in a separate agreement.

4.137. Supplements
(see ICH E3)

Substantial Protocol Amendments

4.138. Protocol amendments
If the protocol is substantially amended after initiation, then there are

certain procedures to follow.

4.139. Substantial amendments for the approval of the Agency

a. There must be arrangements for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the trial or the development of the investigational medicinal product are likely to affect the safety of the participants. In many trials, the individual best able to take these measures will be the Chief Investigator or another identified person or organisation rather than the Sponsor directly. The protocol should identify the specific individual(s) who accept(s) this responsibility. Otherwise, the Sponsor remains directly responsible.

b. These safety measures, such as temporarily halting the trial, may be taken without prior approval from the Agency but must be reported to the Agency and Ethics Committee. For all other substantial amendments, the Agency's approval must be sought before the amendment is implemented.

c. Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on:

   i. The safety or physical or mental integrity of the participants, or
   ii. The scientific value of the trial, or
   iii. The conduct or management of the trial, or
   iv. The quality or safety of any investigational medicinal product used in the trial.

d. In all cases, an amendment is only to be regarded as "substantial" when any of the above criteria are met. For each amendment, someone has to evaluate on behalf of the Sponsor whether the amendment will have a significant impact on the above issues.

e. Guidance on what may be considered a substantial amendment is listed below. The headings below are examples of aspects of a trial where amendments may need to be notified as substantial. There may be other aspects of the trial where amendments meet the criteria for substantial.

4.140. Amendments related to the protocol:

a. Purpose of trial

b. Design of trial
c. Informed consent
d. Recruitment procedure
e. Measures of efficacy
f. Schedule of samples
g. Addition or deletion of tests or measures
h. Number of participants
i. Age range of participants
j. Inclusion criteria
k. Exclusion criteria
l. Safety monitoring
m. Duration of exposure to the investigational medicinal product(s)
n. Change of posology of the investigational medicinal product(s)
o. Change of comparator
p. Statistical analysis

4.141. Amendments related to the trial arrangements:
a. Change of the principal investigator or addition of new ones (i.e the lead investigator in each centre)
b. Change of the coordinating investigator
c. Change of the trial site or addition of new sites
d. Change of sponsor
e. Change of the CRO assigned significant tasks
f. Change of the definition of the end of the trial

4.142. Amendments related to the investigational medicinal product. For example:
a. Addition to stability data/change of expiry date
b. Change of formulation
c. Additional toxicology data
d. Change to route of synthesis

4.143. Addition of a new site:
Addition of a new site should be sent to the Agency as a substantial amendment but for notification only.

4.144. Changes to investigational medicinal product quality data concerning:
a. Change of name or code of investigational medicinal product
b. Immediate packaging material

4.145. Manufacturer(s) of active substance:

a. Manufacturing process of the active substance
b. Specifications of active substance
c. Manufacture of the medicinal product
d. Specification of the medicinal product
e. Specification of excipients where these may affect product performance
f. Shelf-life including after first opening and reconstitution
g. Major change to the formulation
h. Storage conditions
i. Test procedures of active substance
j. Test procedures of the medicinal product
k. Test procedures of non-pharmacopoeial excipients

4.146. Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment. For example concerning:

a. Results of new pharmacology tests
b. New interpretation of existing pharmacology tests
c. Result of new toxicity tests
d. New interpretation of existing toxicity tests
e. Results of new interaction studies

4.147. Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk: benefit assessment). For example concerning:

a. Safety related to a clinical trial or human experience with the investigational medicinal product
b. Results of new clinical pharmacology tests
c. New interpretation of existing clinical pharmacology tests
d. Results of new clinical trials
e. New interpretation of existing clinical trial data
f. New data from human experience with the investigational medicinal product
g. New interpretation of existing data from human experience with the investigational medicinal product

4.148. Non-substantial amendments:
Non-substantial amendments do not have to be reported to the Agency but should be recorded and be available upon request for inspection at the trial site.

CHAPTER

5 INVESTIGATORS

Investigator's Qualifications and Agreements

5.1. 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 Agency, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the EC, and/or the Agency.

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

5.3. The investigator should be aware of, and should comply with, GCP and the applicable requirements of the Agency.

5.4. The investigator should permit monitoring and auditing by the sponsor and the ethics committees as well as inspection by the Agency.

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

5.6. The investigator should be aware of available relevant data and literature and all information provided by the sponsor

5.7. The investigator should have access to human and other resources to assume full responsibility for the proper conduct of the trial

Adequate Resources

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

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

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

5.11. The investigator should ensure that all persons assisting with the trial are adequately informed and trained on the protocol, the

investigational product(s), and their trial-related duties and functions

Medical Care of Trial Participants

5.12. A qualified clinician (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 for a period that is dependent upon the nature of the disease and the trial and the interventions made.

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

5.14. Although a participant 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 participant's rights. The investigator should follow-up the participant for at least two weeks before taking his final decision.

Selection of trial participants

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

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

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

Communication with EC

5.18. Before initiating a trial, the investigator should have written and dated favourable opinion from the EC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements), and any other written information to be provided to participants.

5.19. As part of the investigator's written application to the EC, the

investigator should provide the EC 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 EC.

5.20. During the trial the investigator should provide to the EC all documents subject to review.

Compliance with Protocol

5.21. The investigator should conduct the trial in compliance with the protocol agreed to by the sponsor and approved by the Agency for which was given favourable opinion by the EC. The investigator and the sponsor should sign the protocol to confirm agreement. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and the sponsor.

5.22. The investigator should not implement any deviation from, or changes in the protocol without the prior consent of the sponsor, favourable opinion of the EC and approval by the Agency except in the following conditions:

a. Where changes would eliminate an immediate hazard(s) to trial participants

b. Change(s) involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)

5.23. 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 sponsor for agreement.

b. To the EC for review and favourable opinion

c. To the Agency for approval.

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

Investigational Product(s)

5.25. The investigator must be thoroughly familiar with the properties, effects and safety of the investigational medicinal 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.

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

5.27. Where required, the investigator should assign some or all of the investigator's duties for investigational product's accountability at the

trial site(s) to a pharmacist who is under the supervision of the investigator.

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

5.29. The investigational product(s) should be stored in accordance with the specifications of the manufacturer (see sections 4.47 to 4.48).

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

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

Randomization Procedures and Un-blinding

5.32. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol.

5.33. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature un-blinding (e.g., accidental un-blinding, un-blinding due to a serious adverse event) of the investigational product(s).

Informed consent of trial participants

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

5.35. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant'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.

5.36. The investigator, or a person designated by the investigator, should fully inform the participant or, if the participant is unable to provide

informed consent, the participant's legally acceptable representative, of all pertinent aspects of the trial including the written information and the favourable opinion by the EC.

5.37. 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 participant or the participant's legally acceptable representative and the impartial witness, where applicable.

5.38. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the participant or the participant'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 participant or the participant's legally acceptable representative.

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

5.40. If a participant 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. After the written informed consent form and any other written information to be provided to the participant is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's involvement in the trial and, if capable of doing so, has signed and personally dated the informed consent form or otherwise thumb printed, the witness should sign and personally date the consent form. 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 participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative.

5.41. Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants 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 participant's responsibilities.

f. The aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.

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

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

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

k. The anticipated prorated payment, if any, to the participant for participating in the trial.

l. The anticipated expenses, if any, to the participant for participating in the trial.

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

n. That the monitor(s), the auditor(s), the EC, and the Agency will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or

data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.

o. That records identifying the participant 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 participant's identity will remain confidential.

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

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

r. The foreseeable circumstances and/or reasons under which the participant's involvement in the trial may be terminated.

s. The expected duration of the participant's involvement in the trial.

t. The approximate number of participants involved in the trial.

5.42. Prior to participation in the trial, the participant or the participant'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 participants. During a participant's involvement in the trial, the participant or the participant'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 participants.

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

personally date the written informed consent form.

5.44. Except as described in 5.45, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant), should be conducted in participants who personally give consent and who sign and date the written informed consent form.

5.45. Non-therapeutic trials may be conducted in participants 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 participants who can give informed consent personally.

b. The foreseeable risks to the participants are low.

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

d. The trial is not prohibited by law.

e. The favourable opinion of the EC is expressly sought on the inclusion of such participants, and the written favourable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

5.46. In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented favourable opinion by the EC, to protect the rights, safety and well-being of the participant and to ensure compliance with applicable requirements of the Agency. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 5.41) should be requested.

5.47. The sponsor or sponsor investigator should ensure that trial participants who suffer injury as a result of their participation in a clinical investigation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap.

5.48. The sponsor should seek adequate insurance, guarantee, or similar arrangement against risks to cover compensation for possible injuries

due to the investigation.

Records and Reports

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

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

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

5.52. A basic aspect of the integrity of data is the safeguarding of "blinding" with regard to treatment assignment. It starts with the randomization of patients into treatment groups and is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

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

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

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

5.56. Any change or correction to a CRF/eCRF 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 or corrections.

5.57. For electronic data processing, only authorized persons should be

permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to ensure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

5.58. 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.

5.59. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.

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

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

5.62. The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s) as well as the responsible statistician, in accordance with the requirements of the Agency.

5.63. The investigator should maintain a confidential record to allow the translation of the unambiguous code used to conceal the identity of the individual participants in the trial (participant identification code) for a period of at least 5 years. The investigator may submit the participant identification code list to the Agency after the trial, together with the final report.

5.64. The investigator should ensure that the participation in the clinical trial is clearly marked in the participant's medical records

5.65. The investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see Chapter 7 "***Trial Masterfile***") and as required by the applicable requirement(s) of the Agency. The investigator should take measures to prevent accidental or premature destruction of these documents.

5.66. Essential documents should be retained until at least 5 years after the last approval of a marketing application in Nigeria and until there are no pending or contemplated marketing applications or at least 2 years have elapsed after the formal discontinuation of clinical

development of the investigational product. It is the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained (see sections 4.24 to 4.25).

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

5.68. The Agency may at any time conduct inspection to determine if the investigators are operating in compliance with the Agency's requirements.

5.69. The investigators should permit the Agency to access, copy, and verify any records or reports made in regards to the trial.

5.70. The Agency may conduct both announced and unannounced inspections.

Progress Reports

5.71. The investigator should submit written summaries of the trial status to the EC and the Agency annually or more frequently if requested by the Agency. The progress report should include:

a. ***Individual study information***. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

i. The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

ii. The total number of participants initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

iii. If the study has been completed, or if interim results are known, a brief description of any available study results.

b. ***Summary information***. Information obtained during the previous year of clinical and nonclinical investigations, including:

i. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

ii. A summary of all safety reports submitted during the past year.

iii. A list of participants who died during participation in the investigation, with the cause of death for each participant.

iv. A list of participants who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be product related.
v. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
vi. A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
vii. A summary of any significant manufacturing or microbiological changes made during the past year.
viii. If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.
ix. A brief summary of significant foreign marketing developments

Premature Termination or Suspension of a Trial

5.72. If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, and should inform the Agency. In addition:

a. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator should promptly inform the sponsor, the Agency and the EC, and should provide the sponsor, the Agency and the EC a detailed written explanation of the termination or suspension.
b. If the sponsor terminates or suspends a trial (see section 4.105), the investigator should promptly inform the institution where applicable and the investigator should promptly inform the EC and the Agency and provide the Agency and EC a detailed written explanation of the termination or suspension.
c. If the EC terminates or suspends its favourable opinion of a trial, the investigator should inform the institution where applicable and the investigator should promptly notify the sponsor and the Agency and provide a detailed written explanation of the termination or suspension.

CHAPTER

6 SAFETY REPORTING

Review of safety information:

6.1. The sponsor should promptly review all information relevant to the safety of the investigational medicinal product obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the Agency by the sponsor.

Written safety reports

6.2. The sponsor should notify the Agency and all participating investigators a written safety report of:

a. Any adverse experience associated with the use of the drug that is both serious and unexpected; or

b. Any finding from tests in laboratory animals that suggests a significant risk for participants including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification should be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information.

c. In each written safety report, the sponsor should identify all safety reports previously filed on the product concerning a similar adverse experience, and should analyze the significance of the adverse experience in light of the previous, similar reports.

Telephone, facsimile and email transmission safety reports.

6.3. The sponsor should also notify the Agency by telephone, by facsimile or email transmission of any unexpected fatal or life-threatening experience associated with the use of the product as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information.

6.4. The sponsor of a clinical study of a marketed medicinal product is not required to make a safety report for any adverse experience associated with use of the product that is not from the clinical study itself.

Follow up.

6.5. The sponsor should promptly investigate all safety information received

6.6. Follow up information to a safety report should be submitted as soon as the relevant information is available.

6.7. Results of a sponsor's investigation of other safety information should be submitted, as appropriate, in an information amendment or annual report.

Notification of suspected unexpected serious adverse reactions

Expedited reporting of unexpected serious adverse reactions

6.8. Conditions for expedited reporting include:

a. All adverse reactions that are both serious and unexpected are subject to expedited reporting.

b. An "unexpected" adverse reaction is one, the nature or severity of which is:

i. Not consistent with information in the investigational brochure.

ii. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be:

- Acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis
- Hepatitis with a first report of fulminant hepatitis.

6.9. The sponsor of a clinical trial (Phase I-IV) with at least one investigator site must report suspected unexpected serious adverse reactions according to the following scenarios:

a. Suspected Unexpected Serious Adverse Reactions (SUSAR) which occur within the concerned trial

b. Suspected unexpected serious adverse reactions which occur outside the concerned clinical trial as soon as the sponsor becomes aware of them.

Other safety issues requiring expedited reporting

6.10. Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to

consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance:

a. An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,
b. Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,
c. New events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the participants, such as:
    i. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
    ii. A significant hazard to the participant population such as lack of efficacy of an investigational medicinal products used for the treatment of a life-threatening disease,
    iii. A major safety finding from a newly completed animal study (such as carcinogenicity)
    iv. Any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor,
d. Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the participants.

Expedited reporting

6.11. Expedited reporting is not usually required:

a. For reactions which are serious but expected,
b. For non-serious adverse reactions whether expected or not.
c. It is generally not necessary to report events that are considered unrelated to the investigational medicinal product.

Managing SUSARs associated with active comparator or placebo

6.12. The sponsor must report to the Agency, the Ethics Committee and marketing authorization holder all SUSARs associated with a comparator product in the concerned clinical trial even if this product is authorised.

6.13. Where SUSARs are associated with placebo (e.g. reaction due to an excipient), it is recommended that the sponsor report such cases.

Fatal or life-threatening SUSARs

6.14. The Agency and the Ethics Committee should be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the Agency and the Ethics Committee within an additional eight calendar days.

Non fatal and non life-threatening SUSARs

6.15. All other SUSARs and safety issues must be reported to the Agency and the Ethics Committee as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

Minimum criteria for initial expedited reporting of SUSARs

6.16. Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria defining a valid case report are met:

a. A suspected investigational medicinal product,
b. An identifiable participant (e.g. participant code number),
c. An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d. An identifiable reporting source,
e. Clinical trial authorization number of the Agency,
f. A study protocol number

Follow-up reports of SUSARs

6.17. In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.

6.18. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

Format of the SUSARs reports

6.19. Save in exceptional circumstances electronic reporting should be the expected method for expedited reporting of SUSARs according to the

format prescribed by the Agency.

Form and format of the reports about other important safety issues also qualifying for expedited reporting

6.20. Other important safety issues also qualifying for expedited reporting should be notified by a letter under the heading of safety report. The first page of the report should reference the Clinical trial number issued by the Agency,

a. The title
b. The Protocol number (current version)
c. Points of concern summarised in a short section.
d. Registry number

Informing the EC

6.21. The concerned EC should only receive expedited individual reports of SUSARs that occurred in participants who have been recruited in the concerned trial and in other countries are periodically reported at least every 6 months.

6.22. The summary report should highlight the main points of concern which occurred within the period covered by the report. A copy of the report should be sent to the Agency.

Managing adverse reactions/events in blinded trials

6.23. As a general rule treatment codes should be broken by the sponsor before reporting a SUSAR to the Agency and the concerned EC

6.24. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse event may be a serious adverse reaction unexpected or otherwise judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind.

6.25. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for data-analysis and interpretation of results at the study's conclusion. The unblinding of single cases by investigators in the course of a clinical trial should only be performed if relevant for the safety of the trial participant.

6.26. It is recommended that in case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship assuming that the tested investigational medicinal product caused the reaction. If the case appears to be a SUSAR, then the blinding should be broken. Then three possibilities resulting from the procedure of unblinding

must be considered:

a. If the product administered to the participant is the tested investigational medicinal products, the case would be reported as a SUSAR to the relevant competent authorities and the relevant Ethics Committees.

b. If the product administered to the participant is a comparator with a marketing authorisation, the adverse reaction should be reassessed for expectedness according to the summary of product characteristics as identified in the study protocol. If the adverse reaction is unexpected then the SUSAR should be reported; otherwise it is an expected serious adverse reaction and not reportable on an expedited basis.

c. Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where after unblinding SUSARs are associated with placebo, it is the sponsor's responsibility to report such cases.

6.27. Managing blinding in high morbidity and high mortality disease and where efficacy endpoints could also be SUSARs

6.28. However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with the Agency in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

6.29. For such trials, sponsors should appoint an Independent Data Monitoring Committee in order to review Safety Data on the trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and procedures of the Data Monitoring Committee must be described in the protocol. The sponsor should notify the Agency and the concerned EC the opinion and recommendations of the Data monitoring Committee as soon as possible. However, cases of SUSARs in these same studies that are not efficacy endpoints should be reported as usual.

Informing investigators and ethics committees of new safety information

6.30. International standards regarding such communication are discussed within the NAFDAC GCP Guidelines, including the addendum on "Guideline for the Investigator's Brochure." In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in

accordance with the regulatory requirements, so as to keep the description of safety information updated.

Key data elements for inclusion in expedited reports of serious adverse drug reactions

6.31. The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

6.32. Patient Details

a. Initials
b. Other relevant identifier (clinical investigation number, for example)
c. Gender
d. Age and/or date of birth
e. Weight
f. Height

6.33. Suspected Medicinal Product(s)

a. Brand name as reported
b. International Non-Proprietary Name (INN)
c. Batch number
d. Indication(s) for which suspect medicinal product was prescribed or tested
e. Dosage form and strength
f. Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)
g. Route of administration
h. Starting date and time of day
i. Stopping date and time, or duration of treatment

6.34. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

6.35. Details of Suspected Adverse Drug Reaction(s)

a. Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.
b. Start date (and time) of onset of reaction
c. Stop date (and time) or duration of reaction
d. Dechallenge and rechallenge information
e. Setting (e.g., hospital, out-patient clinic, home, nursing home)
f. Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

6.36. Details on Reporter of Event (Suspected ADR)

a. Name
b. Address
c. Telephone number
d. Profession (speciality)

6.37. Administrative and Sponsor/Company Details

a. Source of report: was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other?
b. Date event report was first received by sponsor/manufacturer
c. Country in which event occurred
d. Type of report filed to authorities: initial or follow-up (first, second, etc.)
e. Name and address of sponsor/manufacturer/company
f. Name, address, telephone number, and email address of contact person in reporting company or institution
g. Identifying regulatory code or number for marketing authorization dossier or clinical investigation process for the

CHAPTER

7 TRIAL MASTER FILE

Essential documents for the conduct of a clinical trial

7.1. Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with the requirements of the Agency.

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

7.3. The minimum list of essential documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

a. Before the clinical phase of the trial commences,
b. During the clinical conduct of the trial, and
c. After completion or termination of the trial.

7.4. A description is given of the purpose of each document, and whether it should be filed in either the investigator or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

7.5. Trial master files should be established at the beginning of the trial, both at the investigator's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator and sponsor files and confirmed that all necessary documents are in the appropriate files.

7.6. Any or all of the documents addressed in these guidelines may be subject to, and should be available for audit by the sponsor's auditor and inspection by the Agency.

Before the Clinical Phase of the Trial Commences

Title of Document	Located in Files of	
	Investigator	Sponsor
Investigator's brochure	X	X
Signed protocol and amendments, if any, and sample Case Report Form (CRF)	X	X
Informed consent form (including all applicable translations)	X	X
- Any other written information e.g. Patient Information Leaflet	X	X
- Advertisement for participant recruitment (if used)	X	
Financial aspects of the trial	X	X
Insurance cover for all trial participants	X	X
Signed agreement between involved parties, e.g.: - Investigator and sponsor - Investigator and CRO - Sponsor and CRO - Investigator and authority(ies) (where required)	 X X X	 X X(where required) X X
Dated, documented favourable opinion of Ethics Committee (EC) of the following: - Protocol and any Amendments - CRF(if applicable) - Informed consent form(s) - Any other written information to be provided to the participant(s) - Advertisement for participant recruitment (if used) - Participant compensation (if any) - Any other documents of given favourable opinion	X	X
EC composition	X	X
Evidence of accreditation of Ethics Committee (EC) with National Health Research Ethics Committee	X	X
Clinical trial authorization by the Agency	X	X
Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)	X	X

Normal value(s)/range(s) for medical/ laboratory/technical procedure(s) and/or test(s) included in the protocol	X	X
Medical/laboratory/technical procedures /tests Certification or Accreditation or Established quality control and/or external quality assessment or - Other validation (where required)	X	X
Sample of label(s) attached to investigational product container(s)		X
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or investigator's brochure)	X	X
Shipping records for investigational product(s) and trial-related materials	X	X
Certificate(s) of analysis of investigational product(s)		X
Decoding procedures for blinded trials	X	X
Master randomisation list		X
Pre-trial monitoring report		X
Trial initiation monitoring report	X	X
Evidence of GCP training of the Investigators in the last 2 years	X	X
Declaration of conflict of interest, financial disclosure by the investigators	X	X
Names and qualifications of monitors	X	X
List of members of Data Safety Monitoring Board (DSMB)	X (where applicable)	X (where applicable)
Evidence of registration in an WHO Clinical Trial Primary Registry	X	X

6.1. During the clinical conduct of the trial

Title of Document	Located in Files of	
	Investigator	Sponsor
Investigator's brochure updates	X	X
Any revision to:	X	X

- Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to participants - Advertisement for participant recruitment (if used)		
Dated, documented favourable opinion of EC of the following: - Protocol amendment(s) - Revision(s) of informed consent form - Any other written information to be provided to the participant Advertisement for participant recruitment (if used) Any other documents given favourable opinion continuing review of trial (where required)	X	X
Authorisations/approvals/notifications of the Agency	X	X
Curriculum vitae for new investigator(s) and/or sub-investigator(s)	X	X
Updates to normal value(s)/range(s) for medical/ laboratory/ technical procedure(s)/test(s) included in the protocol	X	X
Updates of medical/laboratory/ technical procedures/tests Certification or Accreditation or Established quality control and/or external quality assessment or Other validation (where required)	X (where required)	X
Documentation of investigational product(s) and trial-related materials shipment	X	X
Certificate(s) of analysis for new batches of investigational products		X
Monitoring visit reports		X
Relevant communications other than site visits Letters Meeting notes Notes of telephone calls	X	X
Signed informed consent forms	X	
Source documents	X	

Signed, dated and completed Case report forms (CRF)	X (copy)	X (original)
Documentation of CRF corrections	X (copy)	X (original)
Notification by originating investigator to sponsor of serious adverse events and related reports	X	X
Notification by sponsor and/or investigator, where applicable, to the Agency and EC(s) of unexpected serious adverse drug reactions and of other safety information	X (where required)	X
Notification by sponsor to investigators of safety information	X	X
Interim or annual reports to EC and the Agency	X	X(where required)
Participant screening log	X	X (where required)
Participant identification code list	X	
Participant enrolment log	X	
Investigational products accountability at the site	X	X
Signature sheet	X	X
Record of retained body fluids/ tissue samples (if any)	X	X

6.2. After completion or termination of the trial

Title of Document	Located in Files of	
	Investigator	Sponsor
Investigational product(s) accountability at site	X	X
Documentation of investigational product destruction	X (if destroyed at site)	X
Completed participant identification code list	X	
Audit certificate (if available)		X
Final trial close-out monitoring report		X
Treatment allocation and decoding documentation		X
Final report by investigator to EC where required, and where applicable, to the Agency	X	
Clinical study report	X	X

Archiving

6.1. All essential documents relating to the clinical trial should be retained by the Sponsor and should be made available upon request by the Agency

6.2. The sponsor and the investigator should retain the essential documents relating to a clinical trial for at least 25 years after its completion.

6.3. They should retain the documents for a longer period, where so required by the Agency or by an agreement between the sponsor and the investigator.

6.4. Essential documents should be archived in a way that ensures that they are readily available, upon request, to the Agency.

6.5. The medical files of trial participants should be retained in accordance with requirements of the Agency and with the maximum period of time permitted by the hospital, institution or private practice.

6.6. Any transfer of ownership of the data or of documents should be documented. The new owner should assume responsibility for data retention and archiving in accordance with (see also sections 4.23 to 4.25; 5.49 to 5.70).

6.7. The sponsor should appoint individuals within its organization who are responsible for archives.

6.8. Access to archives should be restricted to the named individuals responsible for the archives.

6.9. The media used to store essential documents should be such that those documents remain complete and legible throughout the required period of retention and can be made available to the Agency upon request.

6.10. Any alteration to records should be traceable.

CHAPTER

8 INVESTIGATOR'S BROCHURE

8.1. The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in participants. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides insight to support the clinical management of the study participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

8.2. These guidelines delineate the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by the Agency, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures.

More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the ECs and the Agency before it is included in a revised IB.

8.3. Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible ECs and the Agency. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in these guidelines.

General Considerations

Title Page:

8.4. This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. (see Appendix 1).

Confidentiality Statement:

8.5. The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the EC.

Contents of the Investigator's Brochure

8.6. The IB should contain the following sections, each with literature references where appropriate:

Table of Contents

a. An example of the Table of Contents is given in Appendix 2.

Summary

b. A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

c. A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for conducting the trial with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

Physical, Chemical, and Pharmaceutical Properties and Formulation:

d. A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

e. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

f. Any structural similarities to other known compounds should be mentioned.

Nonclinical Studies **:**

g. The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the

results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

h. The information provided may include the following, as appropriate, if known/available:

a. Species tested
b. Number and sex of animals in each group
c. Unit dose (e.g., milligram/kilogram (mg/kg))
d. Dose interval
e. Route of administration
f. Duration of dosing
g. Information on systemic distribution
h. Duration of post-exposure follow-up
i. Results including the following aspects:
    i. Nature and frequency of pharmacological or toxic effects
    ii. Severity or intensity of pharmacological or toxic effects
    iii. Time to onset of effects
    iv. Reversibility of effects
    v. Duration of effects
    vi. Dose response

i. Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

j. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Nonclinical Pharmacology

k. A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that

assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

Pharmacokinetics and Product Metabolism in Animals

l. A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Toxicology

m. A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

i. Single dose
ii. Repeated dose
iii. Carcinogenicity
iv. Special studies (e.g. irritancy and sensitisation)
v. Reproductive toxicity
vi. Genotoxicity (mutagenicity)

Effects in Humans

n. A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.

Pharmacokinetics and Product Metabolism in Humans

o. A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
   i. Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
   ii. Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
   iii. Population subgroups (e.g., gender, age, and impaired organ function).
   iv. Interactions (e.g., product-product interactions and effects of food).
   v. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

Safety and Efficacy

p. A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse reaction patterns/incidences across indications or subgroups should be discussed.

q. The IB should provide a description of the possible risks and adverse reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

Investigator's Brochure Cover Page

Appendix 1:

TITLE PAGE (Example)

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:
Release Date:

Replaces Previous Edition Number:

Date:

Appendix 2

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

Confidentiality Statement (optional)

Signature Page (optional)

Table of Contents

Summary

Introduction

Physical, Chemical, and Pharmaceutical Properties and Formulation

Nonclinical Studies

Nonclinical Pharmacology
Pharmacokinetics and Product Metabolism in Animals
Toxicology

Effects in Humans

Pharmacokinetics and Product Metabolism in Humans
Safety and Efficacy
Marketing Experience

Summary of Data and Guidance for the Investigator

References on 1. Publications
2. Reports

These references should be found at the end of each chapter
Appendices (if any)

CHAPTER

9 GOOD CLINICAL LABORATORY PRACTICE (GCLP)

Organization and personnel

Trial Facility Management Responsibilities

9.1. The individual(s) who performs the role of laboratory management should be named.

9.2. Trial facility management should ensure that the principles of GCLP as defined in these guidelines are complied with in their laboratory, ensuring overall compliance with GCP.

At a minimum the trial facility management should:

9.3. Ensure that qualified personnel, appropriate facilities, equipment, and materials are available

9.4. Maintain a record of the qualifications, training, relevant experience and job description for each individual working within the trial facility and to ensure these records are maintained, current and up to date

9.5. Ensure that personnel clearly understand the functions they are to perform and where necessary, provide training for these functions. This should include training and competence to perform the techniques required by the clinical protocol, analytical plan or associated analytical methods. The trial facility management should provide all personnel involved in the analysis or evaluation of clinical trial materials with GCP and GCLP training commensurate with their roles and responsibilities

9.6. Ensure that Health and Safety precautions within the trial facility are applied according to national regulations

9.7. Ensure that appropriate standard operating procedures (SOPs) are established and followed and a historical record of all SOPs is maintained

9.8. Ensure there is a quality audit programme with designated personnel

9.9. Ensure a programme of QC is operated within the laboratory and where appropriate, membership of external proficiency schemes

9.10. Ensure an analytical plan exists which defines the work to be performed at the trial facility

9.11. Ensure that any amendments to the analytical plan are agreed and

documented

9.12. Maintain copies of the clinical trial protocol and analytical plan, including any amendments to these documents

9.13. Ensure that a sufficient number of personnel are available for the timely and proper conduct of the work

9.14. Before the work is initiated in the laboratory for each trial, designate an individual with the appropriate qualifications, training, and experience as the analytical project manager. If it is necessary to replace the analytical project manager during a trial, this should be documented

9.15. Ensure that an individual or organisation is identified as having responsibility for the management of the archives used for the retention of trial and laboratory records

9.16. For any work sub-contracted by the facility, the management is responsible to the sponsor for its conduct.

Analytical Project Manager Responsibilities

9.17. The analytical project manager has the responsibility for the overall conduct and reporting of the analyses being performed by the trial facility

9.18. These responsibilities should include, but not be limited to, the following functions:

a. Agree to the analytical plan by dated signature prior to initiation of the work

b. Ensure that procedures specified in the analytical plan are followed, and that authorisation for any modification is obtained and documented together with the reasons for change

c. Ensure that all results of the analyses are fully documented and accurately reported

d. Sign and date the analytical report, if issued, to indicate acceptance of responsibility for the validity of the results

e. When analytical results are issued, the analytical project manager should ensure that these results are only issued under the dated signature of an authorised signatory

f. Ensure that after completion of the analyses, the analytical plan, the analytical report and/or analytical results, raw data and any supporting study documentation are archived and retained

g. Prior to the initiation of analytical work, lines of communication should be established and documented between the sponsor, or their representative, and the analytical project manager.

Trial personnel responsibilities

9.19. All personnel involved in the conduct of a trial should be familiar with GCLP, those parts of GCP that apply to their work and be fully familiar with the function they are to perform.

9.20. All personnel are responsible for recording raw data promptly, accurately and in compliance with GCLP and are responsible for the quality of their data.

9.21. All personnel are responsible for following the instructions given in the clinical protocol, analytical plans and SOPs.

FACILITIES

Trial Facilities

9.22. The trial facility should be of suitable size, construction and location to meet the requirements of the trial and minimize any disturbances that might interfere with the validity of the trial.

9.23. The trial facility should have appropriately designed areas of sufficient size for the type of work being performed and provide an adequate degree of separation and security to assure the integrity of trial materials at all times.

9.24. Suitable facilities should be available for the preparation of trial supplies in order to ensure accurate preparation of such materials.

9.25. There should be appropriate storage areas as needed for samples and supplies. Storage areas should be separated as appropriate to prevent contamination or mix up of trial materials.

Archive Facilities

9.26. Appropriate space should be provided for the safe and secure archive storage of data, reports, samples and specimens.

9.27. These facilities should be suitable to accommodate the types of material that will be archived and to protect contents from untimely deterioration.

9.28. Archive facilities must be secure to prevent unauthorised access to the retained materials.

9.29. If suitable facilities cannot be provided for the storage of trial records, alternative arrangements should be made. This could include the use of third-party contract archive facilities.

Waste Disposal

9.30. The handling and disposal of wastes generated during the

performance of a trial should be carried out in a manner that is consistent with regulatory requirements.

Equipment, materials and reagents

Equipment

9.31. Equipment used in the analysis of trial materials and operation of the trial facility should be suitably located and of appropriate design and adequate capacity.

9.32. Equipment used should be periodically inspected, cleaned, maintained, and calibrated, as appropriate. Records of such maintenance and any unscheduled maintenance or calibration should be retained.

9.33. An equipment service schedule listing all relevant equipment and the schedule of planned service and calibration activities should be maintained.

9.34. Any equipment that is out of service for any reason should be clearly identified as such.

9.35. Equipment users should be suitably qualified and trained in the operation of the equipment.

9.36. In all cases equipment used should be demonstrably fit for purpose.

Materials

9.37. Materials used in the analysis of trial materials should be demonstrably fit for purpose and appropriately stored.

Reagents

9.38. Reagents should be suitably labelled and indicate the identity, concentration, specific storage instructions and stability. Stability information should include the preparation date and expiration date.

STANDARD OPERATING PROCEDURES (SOPS)

General

9.39. A trial facility should have documented standard operating procedures approved by trial facility management. These are intended to ensure the quality and integrity of the work performed and the data generated.

9.40. These SOPs must be of uniform format as determined by the management.

9.41. A Document Control Plan must exist to facilitate the review for

accuracy and relevance of all SOPs.

9.42. A list of current standard operating procedures which includes the version number should be maintained current and up to date.

9.43. Standard operating procedures should be periodically reviewed to ensure that they remain current and up to date.

9.44. Published textbooks, articles and manuals may be used as supplements to these standard operating procedures provided that these are also retained.

9.45. Personnel within the trial facility should have immediately available standard operating procedures relevant to the activities they perform.

Application

9.46. Standard operating procedures should be available for, but not be limited to, the following types of activities. The details given under each heading are to be considered as illustrative examples:

- ***a. Trial supplies***
  Supply, preparation, labelling, handling, shipment and storage
- ***b. Equipment***
  Operation, maintenance, cleaning, calibration of equipment
- ***c. Record keeping, reporting, storage, and retrieval***
  Coding of trials, data collection, preparation of reports, indexing systems, handling of data, the use of computerized data systems and the operation of the archive.
- ***d. Trial materials (where appropriate)***
  Storage, retrieval and chain of custody of samples
- ***e. Preparation of trial packs (sample kits).***
- ***f. Procedures for receipt, transfer, sampling, storage, identification and care of trial materials and samples***.
- ***g. Procedures for the analysis of trial materials and the conditions and criteria under which any repeat assays are performed***
- ***h. Procedures linked to patient safety and confidentiality*** such as expedited reporting of results, unblinding and blinding of samples and procedures for dealing with the receipt of unexpected, unscheduled or poorly labelled samples
- ***i. The retention of trial and laboratory records, and the operation of the archive***
- ***j. Quality control procedures***
  The quality control procedures operated by the trial facility to ensure the quality and accuracy of results.
- ***k. Management of deviations***
- ***l. Quality audit procedures***

Operation of quality audit personnel in performing and reporting trial audits, inspections, and analytical report reviews

m. ***Contracts and agreements***.

PLANING OF THE WORK

9.47. ***Analytical Plan***

a. For each trial, there should be a written analytical plan prior to the initiation of the work and it should be available to the personnel involved in the work.
b. This plan should be agreed to by the dated signature of the analytical project manager and sponsor, and as appropriate the investigator.
c. The analytical plan may form part of the contractual agreement with the sponsor or be contained within the trial protocol.
d. The analytical plan should be retained as part of the records for the trial.
e. All changes, modifications, or revisions to the agreed analytical plan should be documented, including justification(s). Agreement by the analytical project manager and sponsor should be indicated by dated signatures. Copies of all such amendments should be maintained with the original analytical plan.

Content of the Analytical Plan

9.48. The analytical plan should be sufficiently detailed to provide clear instruction to those undertaking the work and contain, but not be limited to, the following information:

9.49. ***Identification of the work***

a. A descriptive title.
b. A statement that indicates the nature and purpose of the work.
c. A unique identifier that will link the work within the analytical plan to the trial protocol while retaining the chain of custody and identity of all trial materials.

9.50. ***Information Concerning the Sponsor and the Trial Facility***

a. Name and address of the sponsor.
b. Name and address of the investigator.
c. Name and address of the trial facility.
d. Name of the analytical project manager.

9.51. ***Dates***

a. The date of agreement to the analytical plan by signature of

the Analytical Project Manager and the Sponsor.

b. The proposed starting and completion dates for the work.

9.52. Analytical Process

a. The methods to be used during the analysis of trial materials. Reference to published analytical methods may also be made. This should include detailed information on the analytical design, methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed.

b. The preparation and shipment of materials such as sample kits to be used in the collection of trial materials must be covered by an analytical plan. A separate plan for the preparation of trial packs could be produced or such logistics could be included in the analytical plan.

c. The type and number of trial materials to be received by the trial facility.

d. The method and condition under which trial materials are transported from one location to another.

e. For "blinded" or "coded" trials the conditions of blinding and the unblinding procedures to be followed.

9.53. Records

a. A list of the records to be retained and their location on completion of the work.

b. Method of reporting results.

9.54. Quality Audit

a. The quality audit to be performed to assure the quality and integrity of the data generated and the accuracy of its reporting.

SUB-CONTRACTING

9.55. No analytical or other study related work should be subcontracted without the prior approval of the sponsor.

9.56. When a sponsor approves or consents to subcontract work, the approval should be communicated to the Agency in writing by the Sponsor

9.57. When work is sub-contracted by the trial facility, trial facility management are responsible to the sponsor for the conduct of this work.

9.58. Prior to placement of sub-contracted work, assurance should be obtained to confirm the subcontractor will work in accordance with

Good Clinical Laboratory Practice and any trial requirements.

9.59. A contract for subcontracted work should clearly provide that the contract acceptor is subject to inspection by the Agency and the subcontracted work should be in accordance with the Agency's regulation and guidelines

9.60. The agreement for sub-contracted work (contract/service level agreement, protocol and/or analytical plan) should clearly specify the role and responsibilities, the detail of the analyses to be performed and the retention of trial data.

TRIAL MATERIALS

Receipt

9.61. Procedures for the receipt, handling, storage, retrieval and management of trial materials should be designed to prevent mix-ups and maintain their integrity. Trial materials should be adequately identified at all times.

9.62. Trial materials should be transported in such a way that their integrity and viability remain unaffected, ensuring safety for the carrier and the public.

9.63. Trial materials should be checked on receipt to confirm their identification.

9.64. Records of identity, source, date of arrival, and condition on arrival should be maintained.

Chain of Custody

9.65. Facilities and procedures should be designed and operated to maintain trial materials identification and traceability at all times.

9.66. Records should be maintained to allow the reconstruction of the chain of custody of trial materials received and to allow the retrospective evaluation of material storage.

9.67. Trial material storage areas should be monitored where controlled conditions are required to maintain the integrity of trial materials. Contingency plans that define the actions to be taken in the case of malfunction of such equipment or facility should be in place. Such plans should ensure the integrity of the stored trial materials.

Logistics

9.68. When a trial facility prepares sample kits or materials used for the collection of trial materials, the systems used for the preparation,

distribution, sample collection and return of such materials to the trial facility should be documented and the systems and procedures used, validated.

9.69. Details of the logistics required on a given trial should be documented in the analytical plan.

9.70. The type of material required, the type and design of the package, the timing and means of distribution both from the trial facility to the Investigator site and return, the checks performed and storage requirements should be detailed in the analytical plan.

9.71. The processes involved in these logistics should be subject to quality control procedures to confirm conformance of practice with defined requirements.

CONDUCT OF THE WORK

General

9.72. The work should be conducted in accordance with the trial protocol and the analytical plan.

9.73. All data generated during the conduct of the analytical phase should be recorded directly, promptly, accurately, and legibly. These entries should be signed or initialled and dated.

9.74. All analysis or evaluation of trial materials must be performed in accordance with the clinical trial protocol and patient informed consent. Consequently, a check should be made to ensure that the analytical plan does not conflict with or exceed the requirements detailed in the clinical trial protocol.

9.75. The analytical method used should be selected to ensure it is suitable and will provide reliable results. Such methods should be validated to ensure results generated are accurate and reproducible.

9.76. Trial materials should be uniquely identified at every stage of the analysis.

9.77. Trial materials should be analysed within the defined timeframe as determined at the time of method validation. Workflows in the laboratory should be such that a trial material should not be overlooked and therefore not analysed in the correct timeframe.

9.78. Any change in the data should be made so as not to obscure the previous entry, and should indicate the reason for the change and should be identified by date and signed or initialled by the individual making the change.

Additional work

9.79. Any additional work to that agreed in the analytical plan should be

sanctioned by the sponsor and not compromise informed consent, unless there are urgent patient safety implications.

Computer systems

9.80. Computerized systems should meet the general requirements for equipment as described in this document. Due to the nature of computerized systems and their key role in operations, further requirements apply to their use. In all cases computer systems should be appropriately validated and maintained and be demonstrably fit for purpose.

9.81. When a computer system is used to capture raw data, a definition of what constitutes the raw data should be documented. This is usually documented within the SOP for that system.

9.82. Computerized systems used to receive, capture, process or report data should be acquired, developed, tested, released, used, maintained and retired according to established guidelines. These may include the OECD monograph *"The application of GLP principles to computerized systems*" and the FDA guidelines for the use of computer systems in the conduct of clinical trials.

9.83. Procedures that address the security and operation of the computer systems should exist. These should include the maintenance of a data audit trail, the date/time and individual responsible for the collection of the data, system change control procedures, maintenance and system security procedures that ensure the integrity of trial data.

9.84. Access to computer systems should be restricted to authorized personnel.

9.85. If data is retained electronically means should exist to ensure the data held can always be retrieved.

Method validation

9.86. The selection of instrument platforms and analytical methodologies should take into account current regulatory guidelines and sponsor expectations, where appropriate.

9.87. Each analytical method used in the analysis of trial materials should be appropriately documented, validated, controlled and approved. Changes to a method should be controlled and validated and result in the issue of a further version of the method.

9.88. Each analytical method should be appropriately validated to establish and demonstrate its fitness for purpose.

9.89. Records to demonstrate the validity and suitability of such methods within the trial facility should be retained.

9.90. Analytical platforms/methods should not be changed during the course of a trial, without prior consultation and agreement with the sponsor. Such changes must be controlled, documented and appropriately authorized and may result in the need for further method validation.

Processing trial materials

9.91. Trial material should be analysed and reported within a time frame consistent with patient safety issues and trial protocol, analytical plan, standard operating procedure and any contractual requirements.

Repeat analysis

9.92. The laboratory should have documented procedures governing rules for repeat analysis consistent with pharmaceutical industry standards. These may be included within the analytical plan.

9.93. Specific rules covering the performance of repeat analysis may also be covered in the trial protocol or analytical plan.

9.94. It is not acceptable to selectively report data. Consequently, the rationale for performing repeat analysis and the reason for the selection of the data to be reported should be documented.

Deviations

9.95. The impact of any deviations from the analytical plan or the laboratory's SOPs or documented policies should be assessed and documented. Where there is potential for a deviation to impact on the integrity or reliability of trial data, patient confidentiality, patient consent or patient safety; appropriate procedures should be implemented to ensure the issue is reported to the sponsor or their representative immediately.

Safety

9.96. Laboratory procedures should take account of local legislation and standard practice in addressing the safe handling of hazardous substances and trial materials.

REPORTING RESULTS

General

9.97. There are two basic types of report that might be produced when reporting results from analytical work.

a. *Analytical Report*: a formal report which may be issued on

completion of the work detailed in the analytical plan.

b. *Analytical Results*: a document(s) containing just the results which is usually issued rapidly on completion of sample analysis on a given day.

9.98. The analytical plan should indicate the type of reporting mechanism to be followed and the timeline for issuance of any such documents.

9.99. The decision as to the type of document produced should be agreed upon by the sponsor and analytical project manager and, when appropriate, the investigator.

Issue of reports

9.100. All results should be subject to a quality control review to ensure the accuracy of the information produced.

9.101. Copies of analytical reports or analytical results should be provided to the sponsor and investigator, as appropriate.

9.102. A copy of all issued analytical reports and analytical results should be retained by the trial facility.

Analytical Report

9.103. The analytical report should be signed and dated by the analytical project manager to indicate acceptance of responsibility for the validity of the data reported. The extent of compliance with these principles should be indicated.

Content of the Analytical Report

9.104. An analytical report should contain, but not be limited to, the following:

a. Identification of the analytical work by a descriptive title and identification number;
b. The clinical trial number;
c. Name and address of the sponsor;
d. Name and address of the investigator(s);
e. Name and address of any trial facilities and any investigator sites involved; including identity of any investigators;
f. Name and address of the analytical project manager;
g. The start and completion dates of the laboratory work;
h. A quality audit certificate;
i. Description of methods and materials used including data manipulation techniques and any statistical methods used;
j. Presentation of the results;
k. All information and data required by the analytical plan;
l. The location(s) where the analytical plan, any specimens

required to be retained, data and the final analytical report are to be stored.

9.105. Corrections or additions to a final analytical report once issued should be in the form of an amendment. Amendments should clearly state the reasons for corrections or additions and should be authorized by the dated signature of the analytical project manager.

Analytical results

9.106. Analytical results should be appropriately and accurately reported. Such reports should include but not necessarily be limited to the following:

a. Identification of the analytical work by unique identification number.
b. The clinical trial number.
c. Identity of the sponsor.
d. Identity of the trial facilities and the investigator to whom the results are directed.
e. Name of the analytical project manager.
f. Presentation of the results.

9.107. The analytical results should be issued under the dated signature of an authorized signatory.

9.108. Analytical results may be reissued when corrections or additions are required. In such circumstances the amended document must clearly indicate that the results have been amended and the reason for any such change.

QUALITY CONTROL

9.109. The trial facility should maintain appropriate quality control procedures to ensure the quality and accuracy of all aspects of the work performed and reported.

9.110. QC procedures may apply, but are not limited, to the following aspects of the work:

a. Within analytical batch acceptance criteria
b. External proficiency scheme results
c. Production of analytical plans and consistency with clinical protocol
d. Creating criteria for acceptability of materials and reagent supplied
e. Secondary tube labelling or aliquoting
f. Sample kit preparation
g. Sample receipt, handling and storage
h. Results/reports reflect raw data accurately.

9.111. Documenting and trending of QC sample results to indicate drift in the analytical performance should be maintained. Defined acceptance criteria should be established and documented.

9.112. Where appropriate, the laboratory should subscribe to membership of appropriate external accreditation/performance/proficiency schemes. Such schemes can provide useful indicators as to the competency of the laboratory to accurately perform such work.

QUALITY AUDIT

9.113. Independent auditing of the trial facility should be conducted to assure compliance with the trial protocol, analytical plan, standard operating procedures and these principles.

9.114. Facilities, systems, equipment, methods, quality control procedures, personnel, reports and documentation should be audited at intervals following a prearranged programme.

9.115. Audits should be conducted by a competent person(s) designated by trial facility management. This person(s) should be independent of the work being audited. Independents audits by external experts may also be utilized.

9.116. All audit results should be recorded. Reports of the audits should contain all the observations made during the audit and, where applicable, any corrective actions.

9.117. Analytical project managers and trial facility management should respond to these audit reports in a timely manner.

9.118. Any corrective actions indicated should be tracked to ensure appropriate implementation.

9.119. On the satisfactory completion of an audit, an audit report/certificate should be produced, which identifies the activities audited, and an indication of the compliance of those activities with these guidelines.

STORAGE AND RETENTION OF RECORDS

9.120. The following should be retained for the period specified by the Agency or as defined by the trial protocol:

a. The analytical plan, data, samples/specimens (where appropriate), analytical results and if issued the final analytical report;

b. Records of all audits performed by the quality audit function;

c. Records of the qualifications, training, experience and job descriptions of personnel;

d. Records and reports of the maintenance and calibration of

equipment;

e. Records of storage conditions (temperature, humidity) for trial materials

f. The historical file of standard operating procedures including the index, plus any operating manuals used as part of an SOP;

g. The records and results of all the quality control tests performed to confirm the accuracy of the work including results from proficiency tests.

9.121. If a trial facility does not have appropriate facilities for the storage of such materials in the manner defined the use of commercial contract archive facilities should be used.

9.122. If a trial facility goes out of business and has no legal successor, the archive material should be transferred to a suitable archive designated by the sponsor of the trial.

9.123. Controls should be in place to ensure that any retrieval or loan from the archive is authorised by laboratory management and that the material is returned promptly after use.

Electronic records

9.124. If any records, be they trial or laboratory, are to be retained and archived electronically then they should be retained in such a way as to ensure they remain retrievable and in human-readable format.

Retention of samples and specimens

9.125. Samples may be retained for further analysis outside of the original aims of the trial, provided this is defined in the clinical protocol and approved by the Ethics Committee.

9.126. Samples and specimens should be retained as required by GCP but only as long as the quality of the preparation permits evaluation.

9.127. Trial materials should be retained in such a way as to ensure the integrity and accessibility to the material retained and permit meaningful evaluation.

CONFIDENTIALITY

9.128. Procedures for the handling of trial materials, collection of data and reporting of results should be designed to maintain participant confidentiality and study blinding/coding arrangements within the requirements of Good Clinical Practice, Declaration of Helsinki and the trial protocol.

9.129. The trial facility should be aware of any blinding and unblinding conditions that apply to a trial and take care not to inadvertently

REFERENCES

1. Draft Harmonized Good Clinical Practice (GCP) Guidelines for AVAREF countries published in 2009

2. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) April 1996 ICH

3. EudraLex - Volume 10 Clinical trials guidelines.http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

GLOSSARY

The definitions given below apply specifically to the terms used in these guidelines. Theymay have different meanings in other contexts.

Adverse Event	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which may or may not have a causal relationship with this treatment. 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 an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	All untoward and unintended responses to an investigational medicinal product related to any dose administered.
Analytical plan	A formal document describing all aspects of the work to be performed by the trial facility.
Analytical project manager	The individual responsible for the overall conduct of the work defined by the analytical plan.
Applicable Regulatory Requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.
Approval	The affirmative decision of the Agency that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the ethics committee, the institution and Good Clinical Practice (GCP)
Audit	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), Good Clinical Laboratory Practice (GCLP) and the Agency's 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
Bioavailability	The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug, bloodstream bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.
Bioequivalence	The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
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 participant(s) being unaware, and double-blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).
Case-report form (CRF)	A document (printed, electronic or optically designed) that is used to record data on each trial participant during the 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	Any investigation in participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites

Clinical trial phases	Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of medicinal products, is given below: **Phase I**: These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of the safety, and the pharmacokinetic and, where possible, pharmacodynamic profile of the active ingredient in humans. **Phase II**: These trials are performed in a limited number of participants 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 the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose response relationships in order to provide an optimal background for the design of extensive therapeutic trials. **Phase III:**Trials in larger (and possibly varied) patient groups, with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

	Phase IV: Studies performed after marketing of the medicinal product. Trials in phase IV are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration, new combinations, etc. are normally considered as trials on new medicinal products.
Clinical Trial Register:	The formal record of an internationally agreed minimum amount of information about a clinical trial
	(trial registration data set). This record is usually stored in and managed using a database.
Clinical Trial Registry:	The entity that houses the clinical trial registers. It is responsible for ensuring the completeness and accuracy of the information the register contains, and that the registered information is used to inform health care decision making.
Clinical trial/study	A systematic study on medicinal products in participants (including patients and other volunteers) in order to discover or verify 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 objective of ascertaining their safety and efficacy.
Clinical trial/study report	A written description of a trial/study of any medicinal product agent conducted in participants, 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

Computerised system	A system (consisting of one or more hardware components and associated software) that is involved with the direct or indirect capture of data, processing or manipulation of data, reporting and storage of data, and may be an integral part of automated equipment. Examples include a programmable analytical instrument or a personal computer linked to a Laboratory Information Management System (LIMS).
Confidentiality	Maintenance of the privacy of trial participants, including their personal identity and all personal medical information
Container	In relation to investigational medicinal product, a container is a bottle, jar, box, packet or other receptacle which contains or is to contain the investigational medicinal product, not being a capsule, cachet or other article in which the product is or is to be administered, and where any such receptacle is or is to be contained in another such receptacle, includes the former but not the latter receptacle.
Contract	A written document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation or distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.
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. Any such transfer should be defined in writing.
Coordinating Committee	A committee that a sponsor may organize to coordinate the conduct of a multicenter trial
Coordinating Investigator	An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.
Declaration of Helsinki	A declaration adopted by the World Medical Assembly in June 1964, as amended by the General Assembly of the Association in its current version.

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 to maintain the confidentiality of participants' identities and sponsor's proprietary information.
Essential Documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 7. Essential Documents for the Conduct of a Clinical Trial).
Ethics committee opinion	The judgment or the advice provided by an Ethics Committee (EC) in relation to clinical trial which maybe favourable or unfavourable.
Ethics Committee (EC)	An independent body, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of participants involved in clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and also on the methods and documents to be used to inform trial participants, obtain their informed consent, initiate and conduct periodic review of such research.
Good Clinical Laboratory Practice (GCLP)	Applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.
Good Clinical Practice (GCP)	A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the reporting of clinical trials provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected

Good Laboratory Practice (GLP)	Is intended to promote the quality and validity of test data. It is a managerial concept covering the organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported
Good Manufacturing Practice (GMP)	That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by NAFDAC, WHO or other relevant regulatory guidelines.
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 participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the participant.
Independent Data Monitoring Committee (IDMC))	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.
Informed consent	A process by which a participant voluntarily confirms willingness to participate in a particular clinical trial after having been informed of all aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Inspection	The act by which the Agency conducts an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the Agency 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 organizations' facilities, or at other establishments which the Agency deems fit to inspect.
Institution (medical)	Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

	is the principal communication link between the sponsor and the investigator and is appointed by the sponsor.
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), Good Clinical Laboratory Practice (GCLP) 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.
Multicenter Trial	A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located within and outside the country.
Nonclinical Study	Biomedical studies not performed on participants.
Original medical record	See Source Documents.
Packaging	All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product.
Packaging material	Any material employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
Participant	An individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control. A participant may either be a healthy human or a patient.
Participant Identification Code	A unique identifier assigned by the investigator to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial related data

Patient/participant file	A collection of data consisting of all relevant information on the patient or participant (such as a hospital file, consultation record or special participant file) that permits the authenticity of the information presented in the case report form to be verified and, where necessary, completed or corrected. The conditions regulating the use and consultation of such documents must be respected.
Primary Clinical Trial	Clinical Trial Registry found in the WHO Registry
Registry:	Network that meets specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary Registries must also meet the requirements of the International Committee of Medical Journal Editors (ICMJE).
Protocol	A document that states the background, rationale and objectives of the clinical trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the principal investigator, the institution involved and the sponsor. It is a contract and binds the signatories.
Protocol Amendment	A written description of a change(s) to or formal clarification of a protocol.
Qualified person	The holder of a certificate or other evidence of formal qualifications awarded on completion of a university or other higher education course of study in pharmacy, chemistry, medicine, biology or a related life science, which the Agency has stated to be qualifications sufficient for the purpose of performing the functions of a qualified person;
Quality Assurance (QA)	Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and the applicable regulatory requirement(s). These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting, and professional or personnel qualifications.

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 participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Raw data	All original records and documentation, or verified copies thereof, which are the result of the original observations and activities during the conduct of the work and are necessary for the reconstruction and evaluation of the reported results. For the purposes of GCLP, 'source data' and 'raw data' are regarded as equivalent.
Regulatory Authorities	Bodies having the power to regulate and may include the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.
Rescue Medication	Medication which is provided to a patient in case the study drug is not effective in controlling some symptoms of the patient's illness.
Sample kit	The necessary components required to collect clinical trial materials prior to their analysis or evaluation in a laboratory.
Serious Adverse Event (SAE) or Serious Adverse Reaction	Any untoward medical occurrence that at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
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, participants' 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, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Sponsor	An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial.
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 participant. 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 (SOP)	Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.
Study product / investigational product	Any medicinal product 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.
Sub-investigator	Any individual member of the clinical trial team designated and supervised by the principal 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). See also Investigator Chapter 5.
The Agency	National Agency for Food and Drug Administration and Control (NAFDAC)

Trial facility	The persons, premises and facilities necessary for conducting the work.
Trial facility management	The individuals within an organization performing the analysis who are responsible for ensuring that the facility operates according to Good Clinical Laboratory Practice.
Trial material	Any material from a trial which is to be analysed. This may include, but is not limited to: samples (plasma, serum, urine, faeces, tissues and cells), specimens, data, results, ECG traces or x-ray plates.
Trial participant	An individual who participates in a clinical trial, either as a recipient of the medicinal product under investigation or as a control. The individual may be: a healthy person who volunteers to participate in a trial; a person with a condition unrelated to the use of the investigational product; a person (usually a patient) whose condition is relevant to the use of the investigational product.
Trial Site	The location(s) where trial-related activities are actually conducted.
Unexpected Adverse 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	The 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.
Validation of a computerised system	A documented process that demonstrates that a computerised system is suitable for its intended purpose.
Verification (validation) of data	The procedures carried out to ensure that the data contained in the final report match the original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer printouts and statistical analyses and tables.

Vulnerable Participants	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 medicinal industry, members of the armed forces, and persons kept in detention. Other vulnerable participants 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 participants)	The physical and mental integrity of the participants involved in a clinical trial
Witness	A person who will not be influenced in any way by those who are involved in the clinical trial, who is present and may provide assistance if required when the participant's informed consent is obtained, and documents that this consent is given freely by signing and dating the informed consent form.

ANNEX

1 DECLARATION OF HELSINKI[1]

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving participants, 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 be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving participants to adopt these principles.

General Principles

3. 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 should act in the patient's best interest when providing medical care."

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

5. Medical progress is based on research that ultimately must include studies involving participants.

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[1] Adopted by the 18th WMA General Assembly, Helsinki, Finland, **June 1964** and amended by the:
29th WMA General Assembly, Tokyo, Japan, **October 1975**
35th WMA General Assembly, Venice, Italy, **October 1983**
41st WMA General Assembly, Hong Kong, **September 1989**
48th WMA General Assembly, Somerset West, Republic of South Africa, **October 1996**
52nd WMA General Assembly, Edinburgh, Scotland, **October 2000**
53rd WMA General Assembly, Washington DC, USA, **October 2002** (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, **October 2004** (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, **October 2008**
64th WMA General Assembly, Fortaleza, Brazil, **October 2013**

6. The primary purpose of medical research involving participants is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

1. Medical research is subject to ethical standards that promote and ensure respect for all participants and protect their health and rights.

2. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research participants.

3. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research participants. The responsibility for the protection of research participants must always rest with the physician or other health care professionals and never with the research participants, even though they have given consent.

4. Physicians must consider the ethical, legal and regulatory norms and standards for research involving participants 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 participants set forth in this Declaration.

5. Medical research should be conducted in a manner that minimises possible harm to the environment.

6. Medical research involving participants must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

7. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

8. Physicians who combine medical research with medical care should

involve their patients in research only to the extent that this 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 participants.

9. Appropriate compensation and treatment for participants who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

10. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving participants may only be conducted if the importance of the objective outweighs the risks and burdens to the research participants.

11. All medical research involving participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

12. Physicians may not be involved in a research study involving participants unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

13. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

14. Medical research with a vulnerable group is only justified if the research

is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

15. Medical research involving participants 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.

16. The design and performance of each research study involving participants must be clearly described and justified 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, potential conflicts of interest, incentives for participants and information regarding provisions for treating and/or compensating participants who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

17. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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 participants 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 amendment

to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

18. Every precaution must be taken to protect the privacy of research participants and the confidentiality of their personal information.

Informed Consent

19. Participation by individuals capable of giving informed consent as participants in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

20. In medical research involving participants capable of giving informed consent, each potential participant 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, post-study provisions and any other relevant aspects of the study. The potential participant must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential participants as well as to the methods used to deliver the information.

After ensuring that the potential participant has understood the information, the physician or another appropriately qualified individual must then seek the potential participant'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.

All medical research participants should be given the option of being informed about the general outcome and results of the study.

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

relationship.

22. For a potential research participant who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 group represented by the potential participant, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

23. When a potential research participant who is deemed incapable of giving informed consent 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 authorised representative. The potential participant's dissent should be respected.

24. Research involving participants 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 group. In such circumstances the physician must seek informed consent from the legally authorised 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 participants 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 must be obtained as soon as possible from the participant or a legally authorised representative.

25. The physician must fully inform the patient which aspects of their 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 adversely affect the patient-physician relationship.

26. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after

consideration and approval of a research ethics committee.

Use of Placebo

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

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

28. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

29. Every research study involving participants must be registered in a publicly accessible database before recruitment of the first participant.

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

publication.

Unproven Interventions in Clinical Practice

31. In the treatment of an individual patient, where proven interventions do not exist or other known interventions 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 judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.