



# FOOD AND DRUGS AUTHORITY

## GUIDELINES FOR GOOD CLINICAL PRACTICE IN GHANA

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## 1.0. INTRODUCTION

The purpose of these guidelines is to provide investigators conducting clinical trials in Ghana with clear standards of good clinical practice. The Guidelines seeks to ensure that clinical trials conducted in Ghana are designed and conducted according to sound scientific and ethical standards within the framework of good clinical practice. Compliance with these standards provides the public with assurance that the rights, safety and wellbeing of trial participants are protected and that clinical trial data are credible.

The guidelines were partly derived from the International Conference on Harmonization Good Clinical Practice (ICH GCP) and from the International Ethical Guidelines for Biomedical Research involving human subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with World Health Organization (WHO 2002).

Good Clinical Practice (GCP) is a system of shared responsibilities between clinical investigators, industry/sponsors/monitors, institutions/ethics committees, and government regulators. The Guidelines are therefore addressed to investigators, pharmaceutical, manufacturers and other sponsors of research, drug regulatory authorities, the general public and all, those who have an interest in clinical trials research in Ghana.

These Guidelines will support the regulatory requirements of the Food and Drugs Authority as stipulated in part 8, Act 851 of the Public Health Act 2012. It is therefore critical that research ethics committees, researchers, trial participants, principal investigators of trials and sponsors use these guidelines so as to ensure a standardized and ethical approach to clinical trial conducted in Ghana.

The guidelines are also applicable to academic and contract clinical research and are intended to be applied during all stages of drug development including pre and post product registration and marketing, and they are also applicable, in whole or in part to biomedical research in general. They also provide a resource for editors to determine the acceptability of reported research for publication and specifically, on any study that could influence the use or the terms of registration of a pharmaceutical product.

## 2.0. GLOSSARY

**“Adult”** A person who is eighteen (18) years of age or over that age.

**“Adverse Drug Reaction (ADR)”** All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

**“Adverse Event (AE)”** Any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product(s). An unexpected AE is an experience not reported in the current Investigators Brochure or elsewhere.

**“Amendment”** A written description of a change(s) to or formal clarification of a protocol.

**“Applicable Regulatory Requirement(s)”** Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

**“Approval(s)”** The affirmative decision of the appropriate institutions (FDA, IRB/IEC and GHS-EC) that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the appropriate institutions, Good Clinical Practice (GCP), and the applicable regulatory requirements.

**“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.

**“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), and the applicable regulatory requirement(s).

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

**“Case Report Form”** A printed, optical or electronic document designed to record all of the protocol required information. There should be assurance of accurate input and presentation and it should allow verification.

**“Certificate of Analysis (COA)”** An authenticated document issued by an appropriate authority that certifies the quality and purity of pharmaceuticals, and animal and plant products.

**“Child/Minor”** A person who is below eighteen (18) years of age or the definition of child as defined in the current Children’s Act of Ghana.

**“Clinical Trial Site”** The location(s) where trial-related activities are actually conducted.

**“Clinical Trial”** means an investigation consisting of a particular description by, or under the direction of a medical practitioner, dentist or veterinary surgeon to the patient or animal where there is evidence that a medicine, medical device or procedure or herbal medicinal product of that description has effects which may be beneficial to and safe to the patient or animal, and the medicine, medical device or procedure or herbal medicine is for the purpose of ascertaining beneficial or harmful effects.

**“Clinical Trials Technical Advisory Committee (CT-TAC)”** As established by Section 150 of the Public Health Act 2012, Act 851.

**“Contract Research Organization (CRO)”** A scientific body (commercial or academic) contracted by a Sponsor to perform some of the Sponsors trial related duties and function

**“Data Safety Monitoring Board (DSMB)”** An independent data-monitoring committee that may be established by the Sponsor to assess at intervals the progress of a clinical, the safety data, and the critical efficacy endpoints, and to recommend to the Sponsor whether to continue, modify, or stop a trial.

**“Date of Commencement”** For the purpose of the Clinical Trial Certificate and Quarterly Progress Report Form, this is defined as the date when the clinical trial site shall start to enroll participants in the clinical trial.

**“Drug/Medicine”** Includes

- 1 A substance referred to in a publication mentioned in the Fourth Schedule,
- 2 A substance or mixture of substances prepared, sold or represented for use in
  - i. Restoring, correcting or modifying organic functions in man or animal, and
  - ii. The diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal, physical state or the symptoms of it, in man or animal, or
- 3 Nutritional supplements

**“FDA”** means Food and Drugs Authority

**“Good Clinical Practice (GCP) Inspection”** The act by the FDA of conducting an official review of documents, facilities, records and any other resources that are deemed to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the FDA.

**“Good Manufacturing Practice (GMP)”** The part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorization.

**“Herbal Medicinal Product”** Includes plant-derived material preparations with therapeutic or any other human health benefits which contain raw or processed ingredients from one or more plants and materials of organic or animal origin.

**“Institutional Review Board/Independent Ethics Committee (IRB/IEC)”** An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

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

**“Investigator’s Brochure”** A collection of data consisting of all the information known prior to the clinical trial concerning the clinical and non clinical data on the investigational product(s). There should be adequate data to justify the nature, scale and duration of the proposed trial.

**“Local Monitor”** A person appointed by the Sponsor or CRO to oversee the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the SOPs, GCP and the applicable regulatory requirements.

**“Lot Release Certificate (LRC)”** An official document that authorizes the manufacturer to release a specific lot of a product.

**“Medical Device”** As defined in Part Seven, Section 149 of the Public Health Act 2012, Act 851.

**“Placebo”** A medication with no active ingredients or a procedure without any medical benefit.

**“Principal Investigator / Investigator”** The person responsible for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the Country where that clinical trial site is located.

**“Protocol Amendment”** A written description of a change(s) to or formal clarification of a protocol.

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

**“Research Institution”** Any public or private entity, agency, medical or dental facility where clinical trials are conducted.

**“Serious Adverse Event (SAE)”** means 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 (ICH definition 1997).

**“Sponsor”** An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a trial. This excludes an individual company, institution or organization which has been requested to provide money for a trial and does not benefit in any way from the results of the trial.

**“Vulnerable population”** An individual whose willingness to volunteer in a clinical trial may be unduly influenced by the expectations, 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 pregnant women, cognitively impaired subjects, children and prisoners.

### **3.0. RESPONSIBILITIES**

#### **3.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)**

The Ethics Committee should consist of:

3.1.1. At least 3 professionals in the medical and scientific field with sufficient qualifications and experience.

3.1.2. A legal professional

3.1.3. A consumer representative who is independent of the institution/trial site.

Only those members who are independent of the investigator/sponsor of the trial should make decisions.

3.1.4. The Ethics Committee should obtain all the information relating to the trial including, protocol, investigators brochure, patient consent forms, insurance for participants, current CV's for investigators and literature detailing rationale for the study and any other documents that the IRB/ICE may need to fulfill its responsibilities.

3.1.5. The Ethics Committee shall consider the following:

3.1.5.1. The suitability of the investigator for the proposed trial in relation to his/her qualifications, experience, supporting staff, and available facilities, on basis of the information available to the Committee.

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

3.1.5.3. The adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary legal representatives.

- 3.1.5.4. The means by which initial recruitment is to be conducted and by which full information is to be given, and by which consent is to be obtained. All written information for the subject and/or legal representative must be submitted in its final form.
- 3.1.5.5. Provision for compensation/treatment in the case of injury or death of a subject if attributed to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor.
- 3.1.5.6. The extent to which investigators and subjects may be rewarded/compensated for participation.
- 3.1.6. The Ethics Committee shall give its opinion and advice in writing clearly identifying the trial, the documents reviewed and the dates of review.

## **3.2. INVESTIGATOR**

Investigators shall satisfy the following:

- 3.2.1. The Investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications and experience through an up to date Curriculum Vitae. The Principal Investigator's qualification should be in accordance with Section 16.2.3 under the FDA's Guidelines for Conducting Clinical Trials.
- 3.2.2. The Investigator should be thoroughly familiar with the characteristics and appropriate use of the investigational product as described in the protocol, current investigator's brochure, in the product information and in other information sources.
- 3.2.3. Have a clear understanding and willingness to obey the ethical and legal requirements of the trial.
- 3.2.4. To permit monitoring and auditing of the trial and inspection by the FDA or appointed representatives.
- 3.2.5. Keep a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related duties.

- 3.2.6. The Principal Investigator shall ensure that all members of the study team have evidence of GCP training of not more than 2 years. GCP certificates shall be required for key members of the team.
- 3.2.7. The Investigator should not have been found guilty of any misconduct under the Ghana Medical and Dental Decree.
- 3.2.8. The Principal Investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in the country and who is responsible for the conduct of the clinical trial at a clinical site. A Principal Investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area.
- 3.2.9. All investigators in a clinical trial as well as the trial monitor must have had formal training in Good Clinical Practice (GCP) within the last two years.
- 3.2.10. Upon signing the application, all parties accept the responsibility that all applicable regulations and requirements will be adhered to. Furthermore, all parties are responsible for ensuring that the trial is based on and implemented according to well – founded ethical and scientific principles, which are expressed in the Helsinki Declaration and its current revisions as well as in the local and international guidelines for GCP.
- 3.2.11. Adequate Resources
- 3.2.11.1. The Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 3.2.11.2. The Investigator should have adequate number of qualified staff and adequate facilities for the duration of the trial to conduct the trial properly and safely.
- 3.2.11.3. The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, investigational product and their trial-related duties and functions.
- 3.2.12. Medical Care of Trial Subjects
- 3.2.11.1. A qualified medical practitioner should be responsible for all trial-related medical decisions. The qualified medical practitioner should also be licensed with the Medical and Dental Council of Ghana. The medical care given to, and medical decisions made on behalf of the subjects must always be the

responsibility of a qualified medical practitioner or when appropriate a qualified dentist registered with the Medical and Dental Council.

- 3.2.11.2. During and following a subject's participation in a trial, the Investigator should ensure adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the trial. The subject should be informed when medical care is needed for inter-current illness for which the Investigator becomes aware.

### 3.2.13. Other Investigator Responsibilities

- 3.2.12.1. Before initiating a trial, the Principal Investigator should have the written and dated approval from the Food and Drugs Authority (FDA) and other relevant bodies.
- 3.2.12.2. The Investigator should conduct the trial according to the approved protocol.
- 3.2.12.3. The Investigator shall not implement any deviation from or changes to the protocol and Informed Consent Form without prior review and approval of the FDA except when the changes involve only logistical or administrative aspects of the trial e.g. monitor or telephone number changes or is based on issues relating to the immediate safety of subjects already recruited into the trial.
- 3.2.12.4. The Investigator shall establish SOPs for investigational products (IP):
- 3.2.12.4.1. The IP(s) should be kept by a designated person (a pharmacist) who maintain records of the delivery process and who ensures that the product is processed and stored correctly.
  - 3.2.12.4.2. The designated person should maintain an inventory of the IP at the site, those used by each subject and the return to sponsor or alternative disposition of unused product(s).
  - 3.2.12.4.3. The Investigational product(s) should be used only on the subjects participating in the trial.
  - 3.2.12.4.4. The Investigator should ensure that the IP are used only in accordance with the approved protocol.

- 3.2.12.4.5. The Investigator should ensure that if there is blinding, it is maintained but there should be criteria or establishment for breaking of the code.
- 3.2.12.4.6. The Investigator or a person designated by the Investigator should explain the correct use of the IP to each subject and should check at appropriate intervals during the trial that each subject is following the instructions. In the case where the IP is administered to the subject the proper administration should be ensured.
- 3.2.12.5. The Investigator shall ensure that the subjects have signed and dated the consent form or given their consent in an acceptable form before participating in the trial.
- 3.2.12.6. The Investigator shall guarantee the confidentiality of the research data, the trial subjects' details and information provided by Sponsor.
- 3.2.12.7. The Investigator shall ensure that all data is accurately collected and recorded.
- 3.2.12.8. The Investigator shall ensure that all serious adverse events are reported promptly to the FDA within timelines specified in the FDA's Guideline for the Conduct of Clinical Trials. Proper protection procedures or treatments should be administered to trial subjects with serious adverse events.
- 3.2.12.9. The Investigator shall submit all relevant trial data to the FDA in a timely manner for validation, auditing and inspection.

### **3.3. SPONSOR**

- 3.3.1. 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, recorded and reported in compliance with the protocol, GCP and regulatory requirements.
- 3.3.2. The Sponsor is responsible for selecting Investigators according to the availability of adequate clinical trial environment facilities and resources. In addition, the Sponsor shall ensure that the investigator has sufficient training, qualifications and capability.

- 3.3.3. The Sponsor shall agree with investigator(s) on the definition, establishment and assignment of responsibilities specified in the protocol. These responsibilities include data management, unblinding of treatment codes, statistical considerations and preparation of the final clinical report.

Prior to the initiation of the clinical trial, the agreement between the Sponsor and Investigators should be in writing as part of the protocol submitted for FDA's approval or in a separate agreement. The Sponsor, in a written document, may agree to transfer all related activities of the clinical trial to designated research institutions. However, all responsibility for the trial lies with the Sponsor.

- 3.3.4. The Sponsor shall provide an up-to-date Investigator's brochure, which includes information about the products with respect to their physical, chemical, pharmacokinetic and pharmacodynamic properties obtained from animals as well as human subjects and currently available results of relevant clinical trials.

An updated Investigator's Brochure shall be submitted whenever available; at least once year.

- 3.3.5. The Sponsor shall obtain the investigator's/institutions' agreement on the following items:

3.3.5.1. The conduct of the trial in compliance with Good Clinical Practices and with the approved protocol; and to be in compliance with procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol.

3.3.5.2. The Sponsor and all investigators shall sign and date the protocol of the trial to confirm the agreement.

- 3.3.6. The Sponsor shall ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages for the duration and in the trial population to be studied.

- 3.3.7. The Sponsor shall ensure that the IP's (including active comparator(s) and placebo) is manufactured in accordance with Good Manufacturing Practices and are adequately packed and labelled in a manner that protects the blinding if applicable. In addition

- the labelling should comply with the regulatory requirements (refer to FDA's Guidelines for Labeling of Products).
- 3.3.8. The Sponsor shall determine for the IP's, acceptable storage temperature and conditions, storage times, reconstitution fluids and procedures and devices for product infusion if any.
  - 3.3.9. In blinded trials, the coding system for the IP's shall include a mechanism that permits rapid identification of the products in case of a medical emergency but does not permit undetectable breaks of the blinding.
  - 3.3.10. If formulation changes are made to the IP or comparator products during the course of the clinical development, the results of pharmaceutical and pharmacokinetic profile of the product shall be made available to the FDA prior to the use of the reformulated IP in clinical trials.
  - 3.3.11. The Sponsor shall appoint qualified and suitable trained individuals to monitor the trial.
  - 3.3.12. The Sponsor should provide insurance cover for all trial subjects. The Sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries.
  - 3.3.13. The financial aspects of the trial should be documented in an agreement between the Sponsor and the Investigator/institution.
  - 3.3.14. The Sponsor should report to the FDA and all relevant institutions, all adverse events occurring during the course of the trial. The Sponsor should expedite reporting all serious adverse events to the Ethics Committee, the FDA and the Sponsor and the Investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects. (Refer to Guidelines for the Conduct of Clinical Trials for timelines).
  - 3.3.15. When a trial is prematurely terminated or suspended by the Sponsor/Investigators, the FDA and Ethics Committee and should be informed of the decision to terminate/suspend the trial and the reasons thereof by the Sponsor/Investigators. (Refer to Guidelines for the Conduct of Clinical Trials for further details).
  - 3.3.16. When the trial is prematurely terminated, the Sponsor should submit a report to the FDA and institution within 30 (thirty) days.

- 3.3.17. When the trial is completed, the Sponsor should submit a preliminary report to the FDA and institution within 30 (thirty) days.
- 3.3.18. The external Sponsor should strengthen local capacity for ethical, scientific review, biomedical research and provide healthcare services as described in sections 20, 21 of the International Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS 2002).

Sponsors and Investigators have an ethical obligation to ensure that biomedical research projects contribute effectively to national or local capacity building. Capacity building may include, but is not limited to, the following activities:

- 3.3.18.1.1 Establishing and strengthening independent and competent ethical review processes/committees.
- 3.3.18.1.2 Developing technologies appropriate to health-care and biomedical research.
- 3.3.18.1.3 Training of research and health-care staff.
- 3.3.18.1.4 Educating the community from which research subjects will be drawn.

3.3.19. External Sponsors are ethically obliged to ensure the availability of:

- 3.3.19.1. health-care services that are essential to the safe conduct of the research
- 3.3.19.2. treatment of subjects who suffer injury as a consequence of research intervention; and
- 3.3.19.3. services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

3.3.20 The Sponsor shall appoint a Local Monitor to oversee the progress of a clinical trial and to ensure that it is conducted, recorded and reported in accordance with the SOPs, GCP and the applicable regulatory requirements.

#### **4.0. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)**

The contents of a trial protocol shall 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.

#### **4.1. General Information**

This shall include:

- 4.1.1. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- 4.1.2. Name and address of the Sponsor and monitor (if other than the Sponsor)
- 4.1.3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor.
- 4.1.4. Name, title, address, and telephone number(s) of the Sponsor's medical expert (or dentist when appropriate) for the trial.
- 4.1.5. Name and title of the Principal Investigator(s) who is (are) responsible for conducting the trial, and the address (both postal and location) and telephone number(s) of the trial site(s).
- 4.1.6. Name, title, address, and telephone number(s) of the other investigators designated by the PI to be responsible for some aspects of the study.
- 4.1.7. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.
- 4.1.8. Contractual agreement between the investigator and Sponsor.
- 4.1.9. A clear statement on compensation and benefits package for clinical trial participants.
- 4.1.10. Publication policy

#### **4.2. Background Information**

This shall include:

- 4.2.1. Name and description of the investigational product(s).
- 4.2.2. A summary of findings from nonclinical studies that potentially have clinical significance to the trial

- 4.2.3. Summary of findings from clinical trials that are relevant to the trial.
- 4.2.4. Summary of the known and potential risks and benefits, if any, to human subjects.
- 4.2.5. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- 4.2.6. A statement that the trial shall be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- 4.2.7. Description of the population to be studied.
- 4.2.8. References to literature and data that are relevant to the trial and that provide background for the trial.
- 4.2.9. Signed declaration by the applicant and all investigators that they are familiar with and understand the protocol and shall comply with principles of Good Clinical Practice (GCP) as determined by the Food and Drugs Authority in the conduct of the trial.
- 4.2.10. Explanation of the trial being conducted in Ghana and not in the host country of applicant or Sponsor.

### **4.3. Trial Objectives and Purpose**

- 4.3.1. A detailed description of the objectives and the purpose of the trial.
- 4.3.2. Aim of the trial and reason for its execution.

### **4.4. Trial Design**

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

- 4.4.1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- 4.4.2. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- 4.4.3. A description of the measures taken to minimize/avoid bias, including randomization and blinding.

- 4.4.4. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).
- 4.4.5. Description of the dosage form, packaging, and labeling of the investigational product(s) and sample of label to be used for investigational product.
- 4.4.6. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- 4.4.7. Quantities of investigational medicines and placebos to be used during the conduct of the study.
- 4.4.8. A detailed description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- 4.4.9. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- 4.4.10. Maintenance of trial treatment randomization codes and procedures for breaking codes.
- 4.4.11. The identification of any data to be recorded directly on the CRFs (i.e. written or electronic record of data), and to be considered to be source data
- 4.4.12. Number of human subjects to be involved in the trial and the statistical justification.
- 4.4.13. Specifications and instructions for anticipated deviations from the protocol.

#### **4.5. Selection and Withdrawal of Subjects**

- 4.5.1. Subject inclusion criteria.
- 4.5.2. Subject exclusion criteria.
- 4.5.3. Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
  - 4.5.3.1. When and how to withdraw subjects from the trial/investigational product treatment.
  - 4.5.3.2. The type and timing of the data to be collected for withdrawn subjects.
  - 4.5.3.3. Whether and how subjects are to be replaced.
  - 4.5.3.4. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

#### **4.6. Treatment of Subjects**

- 4.6.1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- 4.6.2. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- 4.6.3. Procedures for monitoring subject compliance.
- 4.6.4. Description of treatment applied to control group(s) or control period(s), placebo, and other therapy and any other treatment that may be given concomitantly including measures to be implemented to ensure the safe handling of the products
- 4.6.5. Description of diagnostic devices or kits applied to be used in the clinical trial.
- 4.6.6. Description of special analyses and/or tests or procedure to be carried out.

#### **4.7. Assessment of Efficacy**

- 4.7.1. Specification of the efficacy parameters.
- 4.7.2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.
- 4.7.3. Clear procedures for interim assessment of trial

#### **4.8. Assessment of Safety**

- 4.8.1. Specification of safety parameters.
- 4.8.2. The methods and timing for assessing, recording, and analyzing safety parameters.
- 4.8.3. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- 4.8.4. The type and duration of the follow-up of subjects after adverse events.
- 4.8.5. Provision for dealing with all adverse events. Copy of form to be used to report adverse event.
- 4.8.6. Criteria for the termination of the trial

**4.9. Statistics**

- 4.9.1. A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- 4.9.2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.
- 4.9.3. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- 4.9.4. The level of significance to be used.
- 4.9.5. Criteria for the termination of the trial.
- 4.9.6. Methods for data analyses and evaluation of results.
- 4.9.7. Procedure for accounting for missing, unused, and spurious data.
- 4.9.8. 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).
- 4.9.9. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

**4.10. Direct Access to Source Data/Documents**

- 4.10.1. 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, ethics committee review, and regulatory inspection(s), providing direct access to source data/documents.

**4.11. Quality Control and Quality Assurance**

- 4.11.1. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- 4.11.2. 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.

- 4.11.3. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements, made by the sponsor with the principal investigator and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

#### **4.12. Ethics**

- 4.12.1. General ethical consideration relating to the trial and informed consent sheet or form or otherwise should be given to patients or volunteers.
- 4.12.2. In all circumstances provisions made in the current version of ICH E6 R1 with respect to ethics and informed consent should be complied with.

#### **4.13. Data Handling and Record Keeping**

- 4.13.1. Procedure for keeping a list of participating volunteer/subjects and detailed records indicated on the case report form (CRF) for each individual taking part in the trial.
- 4.13.2. A clear statement on composition and benefit package for clinical trial participants.
- 4.13.3. All clinical and experimental data (electronic or paper) shall be kept in a secured place for a period of 5 years and 20 years for New Drug Application (NDA) after completion of the trial and be made readily available for review upon request by the Authority.

#### **4.14. Financing and Insurance**

- 4.14.1. Financing and insurance if not addressed in a separate agreement

#### **4.15. Publication Policy**

- 4.15.1. Publication policy, if not addressed in a separate agreement

With respect to issues related to protocol amendments refer to section 3.5 of the FDA Guidelines for the conduct of Clinical Trials in Ghana.

## **5.0. INVESTIGATOR'S BROCHURE**

- 5.1. Investigators Brochure containing information on the following but not limited to:
  - 5.1.1. Chemical, physical and pharmaceutical properties and formulations,
  - 5.1.2. Preclinical, pharmacological and toxicological data,
  - 5.1.3. Human pharmacological and clinical data with the substance concerned and any other supporting documentation sufficient to establish quality, safety and efficacy where applicable.
  - 5.1.4. Marketing experience in countries where the investigational product is being marketed or approved. Where appropriate there should be discussions of published reports.
- 5.2. Sample of label to be used for the investigational products.
- 5.3. Clear instructions on storage and handling of investigational products.
- 5.4. An updated investigator's brochure should be submitted whenever updated or at least once a year. Additional information and any changes that have been incorporated in the updated investigator's brochure should be highlighted for ease of review and evaluation
- 5.5. Good Manufacturing Practice (GMP) certificate/statement from the country of manufacture for the product/ placebo issued by the competent recognized Authority.

## **6.0. GOOD CLINICAL PRACTICE INSPECTIONS**

The FDA reserves the right to interrupt and inspect any trial for which authorization has been given, as and when necessary for a good cause. An inspection of the conduct of a clinical trial by on-site visits forms part of the Authority's monitoring activities.

- 6.1. Periodic Good Clinical Practice (GCP) Inspections of the trial sites shall be conducted to ensure that the facilities used continue to be acceptable throughout the clinical investigation.

- 6.2. The inspections may be carried out randomly, and/or for specific reasons and shall be either announced or unannounced.
- 6.3. An inspection would consist of a comparison of the procedures and practices of the principal investigator with the commitments set out in the protocol and reports submitted to the Authority by the investigator or the sponsor.
- 6.4. During the inspection the FDA shall assure itself that:
  - 6.4.1. The facilities used by the investigator continue to be acceptable for the purposes of the study.
  - 6.4.2. The approved study protocol for the investigation is being followed.
  - 6.4.3. Any changes to the protocol have been approved by respective Ethics Committees and the Authority.
  - 6.4.4. Accurate, complete and current records are being maintained.
  - 6.4.5. Serious adverse events (SAEs) are reported to the sponsor and to the FDA and institutional review board(s) within the stipulated time as specified in these guidelines.
  - 6.4.6. The investigator is carrying out the agreed-upon activities, and has not delegated them to other previously unspecified staff.

To facilitate the above the Authority may require the submission of specific data listing before or during the conduct of a GCP inspection.

- 6.5. During an inspection, inspectors:
  - 6.5.1. Should be given easy access to the trial sites and laboratories at all times
  - 6.5.2. Should have easy access to all patient files and raw data utilised for and generated during the trial. All site data and documents including participant files must be available for verification.
- 6.6. All observations and findings shall be verified in order to ensure the credibility of data and to assure that the conclusions that would be presented are derived correctly from the raw data.
- 6.7. Before an inspection, the principal investigator (or the co-investigator) shall be informed of the impending inspection either in writing, by phone or electronically.

- 6.8. An unannounced inspection may however be conducted, if the FDA has reasonable cause to believe that the approved protocol is being violated.

Refer to Appendix I for details of an inspection by the FDA.

## **7.0. CONDUCT OF CLINICAL TRIALS IN VULNERABLE POPULATIONS**

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

### **7.1. Research involving children (including infants).**

Before undertaking research involving children, the investigator must ensure that:

- 7.1.1. The research might not equally well be carried out with adults;
- 7.1.2. The purpose of the research is to obtain knowledge relevant to the health needs of children;
- 7.1.3. A parent or legal representative of each child has given permission;
- 7.1.4. The agreement (assent) of each child has been obtained to the extent of the child's capabilities; and,
- 7.1.5. A child's refusal to participate or continue in the research will be respected.

### **7.2. Research involving individuals who are cognitively impaired subjects by reason of mental or behavioral disorders are not capable of giving adequately informed consent.**

Before undertaking research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- 7.2.1. Such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;

- 7.2.2. The purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioral disorders;
- 7.2.3. The consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,
- 7.2.4. In cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.

**7.3. Pregnant women as research participants:**

- 7.3.1. Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research.
- 7.3.2. Pregnant women should be presumed to be eligible for participation in biomedical research.
- 7.3.3. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her foetus is a prerequisite for the woman's ability to make a rational decision to enroll in a clinical study.
- 7.3.4. In this discussion, if participation in the research might be hazardous to a foetus or a woman if she becomes pregnant, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.
- 7.3.5. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus and their subsequent offspring, and to their fertility.

- 7.3.6. Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her foetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.

## **APPENDIX I:**

### **DETAILS OF AN INSPECTION BY THE FOOD AND DRUGS AUTHORITY**

#### **1.0. SELECTION OF CLINICAL TRIALS FOR INSPECTION**

Selection of approved clinical trials for GCP inspection shall be based on benefit to risk ratio considering but not limited to the underlisted:

- 1.1. The phase of the clinical trial
- 1.2. The nature of the investigational product.
- 1.3. The market authorization status of the investigational product
- 1.4. The population under study
- 1.5. Capacity of trial site
- 1.6. Previous experience of FDA with sponsor/principal investigator with respect to compliance to GCP requirements.

#### **2.0. WHAT DOES AN INSPECTION INVOLVE?**

The inspection may involve:

- 2.1. A comparison of the practices and procedures of the clinical investigator with the commitments made in the application to conduct a clinical trial;
- 2.2. A comparison of the data submitted to the authority with the source data; and/or
- 2.3. A system inspection of the sponsor, clinical laboratory or CRO generating data for submission to regulatory authorities. This may include inspection of both the clinical facility and analytical facility.

#### **3.0. THE INSPECTION**

Details of the various phases of an inspection, including pre-inspection contact; the opening meeting and the actual inspection are outlined below:

### 3.1. **Pre-Inspection Contact:**

Where appropriate, appointments for inspection of an investigational site should be made by a telephone call and/or an e-mail. A written confirmation of the inspection date, time and program (if applicable) may be forwarded to the site, the sponsor company or the CRO.

The Local Monitor responsible for the monitoring of the study needs to be present during the inspection. The time span between initial contact and actual inspection shall be as short as possible. Any undue delay of the inspection on the part of the clinical investigator will be investigated.

### 3.2. **Opening Meeting:**

The purpose of this meeting is for the Inspector(s) to,

- 3.2.1. explain the purpose of the inspection, i.e. routine or for -cause,
- 3.2.2. outline the scope of the inspection
- 3.2.3. and to obtain a brief review of the organization of the site being inspected.

### 3.3. **The Inspection Purpose:**

The overall purpose of the conduct of the inspection should be to establish whether the investigator has fulfilled his/her GCP responsibilities. This includes the following:

- 3.3.1. To ascertain whether the investigator is thoroughly familiar with the properties of the investigational product(s) as described in the investigator's brochure.
- 3.3.2. To ensure that investigator has sufficient time to conduct and complete the clinical study,
- 3.3.3. To ensure that the investigator has adequate staff and appropriate facilities (including laboratories) available for the duration of the study, and
- 3.3.4. To ensure that other studies do not divert essential participants or facilities away from the study in hand.
- 3.3.5. To establish whether the investigator has studied the protocol and whether the assisting personnel have been adequately informed of their responsibilities.

- 3.3.6. To determine if the Authority's and Ethics Committee and other relevant approvals has been obtained with stipulated conditions adhered to.
- 3.3.7. To determine in what manner the investigational products are handled and stored, and that investigational products are dispensed to study participants in accordance with the protocol and that any unused products are returned to the Sponsor. Reconciliation of trial medication must be provided.
- 3.3.8. To ensure that the confidentiality of all information about participants is respected (by all persons involved).
- 3.3.9. To ensure that the investigator observes the following points particularly related to medical care:

In addition, the investigator needs to provide retrospective data on numbers of participants who would have satisfied the proposed entrance criteria during preceding time periods in order to assure an adequate recruitment rate for the study. The investigator also needs to provide an up-to-date curriculum vita.

The Investigator is medically responsible for those participants who are under his/her care for the duration of the study and must ensure that appropriate medical care is maintained after the study. Where appropriate, fully functional resuscitation equipment should be immediately available in case of emergency. Clinical significant abnormal laboratory values or clinical observations must be followed up after completion of the study.

#### **4.0. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

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 in addition to other functions not herein mentioned serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

The minimum list of essential documents which has been developed are outlined below. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (Refer to Appendix II for more details):

- 4.1. Before the clinical phase of the trial commences,
- 4.2. During the clinical conduct of the trial, and
- 4.3. After completion or termination of the trial.

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

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

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the FDA.

## **5.0. TRIAL PROCEDURES**

This part identifies the nature of the information that shall be obtained during each inspection to determine if the clinical investigator is meeting his/her obligation as trialist. This outline provides only the minimal scope of the inspection and the inspector shall extend the inspection as the facts evolve. The inspection conducted shall be sufficient in scope to determine compliance with Good Clinical Practice.

Scientific data shall not be evaluated during the inspection, but only verify documentation and validate data. An inspection may include the following checks:

- 5.1. The protocol, included amendments must be signed by the investigator.
- 5.2. Ethics Committee and regulatory approval documentation.
- 5.3. Validation of signed informed consent documents. Signatures shall be checked against evidence on patient files. It would be determined whether written informed consent was obtained for all participants prior to the entry into the study and whether this was recorded in the participants medical records. A copy of the information presented orally may also be obtained.
- 5.4. Participant records shall be verified.
- 5.5. The condition, organization, completeness and legibility of the investigator's raw data files may need to be described.

- 5.6. Necessary processes would be put in place to determine whether there is adequate documentation to assure that all inspected participants did exist and were available for the duration of their stated participation in the study.
- 5.7. The raw data in the clinical investigator's records would be compared with the completed case record forms.

The following shall also be determined:

- 5.8. Whether the number and type of participants entered into the study were confined to the protocol limitations
- 5.9. Whether the inclusion and exclusion criteria as specified in the protocol were followed
- 5.10. Observations, information, and data condition of the participants at the time of entering into the trial.
- 5.11. Observations and data on the condition of the participant throughout participation in the investigation, including results of lab tests, development of unrelated illness and other factors which might alter the effects of the test article
- 5.12. Records of exposure of the participant to the test article.
- 5.13. Whether clinical laboratory testing (including ecgs x-rays and other special investigations), as noted in the case reports, can't be evaluated by the presence of completed laboratory reports in the source documents.
- 5.14. The occurrence of adverse reactions would be determined. The reporting of these events to FDA and the Ethics Committee shall be documented.
- 5.15. All persons obtaining raw data or involved in the collection or analysis of such data would be identified.

## **6.0. TRIAL MEDICATION**

With regard to trial medication the following are considered as important in an inspection:

- 6.1. Determination of accounting procedures for the test and comparator drugs.
- 6.2. Dates and quantity of trial medication dispensed as well as the recipients must be available as well as corroboration by raw data notations.
- 6.3. The blinding of medication, if appropriate, must be validated to ensure protection of the study from bias.

- 6.4. It shall be determined whether distribution of the article was limited to those persons under the investigator's direct supervision.
- 6.5. The storage area may be inspected.
- 6.6. It would be determined whether the test article is a controlled substance and whether it is securely locked
- 6.7. Access to the controlled substance must be restricted to the investigator and the responsible pharmacist.

## **7.0. LABORATORY**

The FDA during an inspection would determine the systems and procedures that are followed within an organization that is conducting analysis of samples from clinical trials in compliance with the requirements of Good Clinical Practice (GCP).

Inspections of a laboratory being used to analyze samples from a clinical trial shall be in accordance with provisions outlined in the *Good Clinical Laboratory Practice Guidelines* published by WHO/TDR.

### **7.1 Transfer of Biological Samples**

No person shall make arrangements to receive or ship biological samples from a clinical trial without prior approval from the Authority.

Persons who wish to import or export any biological samples from a clinical trial shall submit an application and a suitable Material Transfer Agreement for approval by the Authority. The application must be accompanied with the appropriate clearance from a reputable Ethics Committee or Institutional Review Board in Ghana.

## **8.0 COMPUTER ELECTRONIC DATA SYSTEMS**

If electronic data systems are involved in gathering data, storing data, or transmitting data to the sponsor, these would be identified and their capabilities established. The following are important:

- 8.1 The source of data entered into the computer

- 8.2 The qualification of the personnel to enter data
- 8.3 At which time/stage should the entering be done
- 8.4 Provision for access to data and computer
- 8.5 Security codes
- 8.6 Procedure and persons responsible for changes and audit trail.
- 8.7 Procedure for submission of data to sponsor? (hard disk, floppy disk, fax, modern network, mail, messenger)
- 8.8 Procedures for corrections (errors, omissions, etc.) in the data received and documentation

## **9.0. EXIT MEETING / INSPECTION REPORT**

At the post inspection meeting the inspectors would convey the findings of the inspection to the investigator and the representative of the pharmaceutical company or contract research organization and other key members of the study team. The inspection reports shall eventually reflect discussions had at the exit meeting

The matters discussed at this meeting shall be in line with the report written by the inspectors.

Important matters include:

When significant violations of GCP are observed, reports shall contain sufficient narrative and accompanying documentation to support the findings. When it is apparent that the study has been conducted in substantial compliance with the guidelines, an abbreviated report may contain the following shall be compiled:

- 9.1 The comparison of raw data recorded in the case report forms to that of the source data, including the number of records compared and what was compared (patient charts, hospital records, lab slips and etc.)
- 9.2 A statement about the trial medication accountability records
- 9.3 A statement about protocol adherence, which should be characterized and quantified.
- 9.4 A statement about the obtaining of informed consent from each participant.
- 9.5 A statement identifying the specific individual responsible for each significant aspect of the study.
- 9.6 A statement on follow-up of adverse experiences (including death) if any occurred.

If deficiencies were found during the inspection in any of these or in any of the areas it needs to be explained and documentation attached as exhibits.

Inspections conducted 'for-cause' would have full reporting. (A for-cause inspection may be the result of prior knowledge or suspicion of alleged violations of Act 851 of the Public Health Act, 2012 and/or guidelines. A for-cause inspection may concentrate the data verification on specific areas of the study or may expand the data verification to cover multiple studies. This inspection may also result when a study is of singular importance to the approval of registration of a medicine, i.e. one of two adequate and well controlled studies.)

## **APPENDIX II**

### **ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

#### **1.0. Introduction**

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 all applicable regulatory requirements.

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

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable

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

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

**2.0. Before the Clinical Phase of the Trial Commences**

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

	Title of Document	Purpose	Located in Files of	
			Investigator	Sponsor
1.	<b>INVESTIGATOR’S BROCHURE</b>	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
2.	<b>SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)</b>	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
3.	<b>INFORMATION GIVEN TO TRIAL SUBJECT</b>			
i.	<b>- INFORMED CONSENT FORM</b> (including all applicable translations)	To document the informed consent	X	X



	<p><b>APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b></p> <ul style="list-style-type: none"> <li>- Protocol and any amendments</li> <li>- CRF (if applicable)</li> <li>- Informed consent form(s)</li> <li>- Any other written information to be provided to the subject(s)</li> <li>- Advertisement for subject recruitment used)</li> <li>- Subject compensation (if any)</li> <li>- Any other documents given approval/ favourable opinion</li> </ul>	<p>IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)</p>	
8.	<p><b>INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE COMPOSITION</b></p>	<p>To document that the IRB/IEC is constituted in agreement with GCP</p>	<p>X X (where required)</p>
9.	<p><b>REGULATORY AUTHORITY(IES)</b></p>	<p>To document appropriate authorization /approval /notification by the regulatory authority(ies) has</p>	<p>X X (where required)</p>

	<b>AUTHORISATION/ APPROVAL/ NOTIFICATION OF PROTOCOL</b> (where required)	been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)		
10.	<b>CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB- INVESTIGATOR(S)</b>	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
11.	<b>NORMAL VALUE(S) /RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and/or ranges of the tests	X	X
12.	<b>MEDICAL/ LABORATORY/ TECHNICAL PROCEDURES /TESTS - Certification or</b>	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X

	<ul style="list-style-type: none"> <li>- Accreditation or</li> <li>- Established quality control and/or external quality assessment or</li> <li>- Other validation (where required)</li> </ul>			
13.	<b>SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</b>	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
14.	<b>INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b> (if not included in protocol or Investigator’s Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
15.	<b>SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b>	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
16.	<b>CERTIFICATE(S) OF ANALYSIS OF</b>	To document identity, purity, and strength of investigational product(s) to be used in the trial		X

	<b>INVESTIGATIONAL PRODUCT(S) SHIPPED</b>			
17.	<b>DECODING PROCEDURES FOR BLINDED TRIALS</b>	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (a third party if applicable)
18.	<b>MASTER RANDOMISATION LIST</b>	To document method for randomization of trial population		X (a third party if applicable)
19.	<b>PRE-TRIAL MONITORING REPORT</b>	To document that the site is suitable for the trial (may be combined with 20)		X
20.	<b>TRIAL INITIATION MONITORING REPORT</b>	To document that trial procedures were reviewed with the investigator and the investigator's trial staff ( may be combined with 19)	X	X

**3.0. During the Clinical Conduct of the Trial**

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

	<b>Title of Document</b>	<b>Purpose</b>	<b>Located in Files of Investigator /Sponsor</b>	
21.	<b>INVESTIGATOR'S BROCHURE UPDATES</b>	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

<p>22.</p>	<p><b>ANY REVISION TO:</b></p> <ul style="list-style-type: none"> <li>- Protocol/amendment(s) and CRF</li> <li>- Informed consent form any other written</li> <li>- Information provided to subjects</li> <li>- Advertisement for subject recruitment (if used)</li> </ul>	<p>To document revisions of these trial related documents that take effect during trial</p>	<p>X</p> <p>X</p>
<p>23.</p>	<p><b>DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b></p> <ul style="list-style-type: none"> <li>-Protocol amendment(s)</li> <li>-Revision(s) of: <ul style="list-style-type: none"> <li>- informed consent form</li> <li>- any other written information to be provided to the subject</li> </ul> </li> <li>- advertisement for subject recruitment if used)</li> <li>-Any other documents given approval/favourable opinion</li> </ul>	<p>To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion.</p> <p>To identify the version number and date of the document(s).</p>	<p>X</p> <p>X</p>

<p>24.</p>	<p>-Continuing review of trial (where required)</p> <p><b>REGULATORY AUTHORITY(IES) AUTHORISATIONS/ APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR:</b></p> <p>- Protocol amendment(s) and other documents</p>	<p>To document compliance with applicable regulatory requirements</p>	<p>X  (where required)</p>	<p>X</p>
<p>25.</p>	<p><b>CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB- INVESTIGATOR(S)</b></p>	<p>(see 10)</p>	<p>X</p>	<p>X</p>
<p>26.</p>	<p><b>UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) ) INCLUDED IN THE PROTOCOL</b></p>	<p>To document normal values and ranges that are revised during the trial (see 11)</p>	<p>X</p>	<p>X</p>
<p>27.</p>	<p><b>UPDATES OF MEDICAL/LABORATO RY/ TECHNICAL</b></p>	<p>To document that tests remain adequate throughout the trial period (see 12)</p>	<p>X  (where required)</p>	<p>X</p>

	<p><b>PROCEDURES/TESTS</b></p> <ul style="list-style-type: none"> <li>- Certification or</li> <li>- Accreditation or</li> <li>- Established quality control and/or external quality assessment or</li> <li>- Other validation (where required)</li> </ul>			
28.	<p><b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT</b></p>	(see 15)	X	X
29.	<p><b>CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</b></p>	(see 16)		X
30.	<p><b>MONITORING VISIT REPORTS</b></p>	To document site visits by, and findings of, the monitor		X
31.	<p><b>RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</b></p> <ul style="list-style-type: none"> <li>- Letters</li> <li>- Meeting notes</li> </ul>	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X

	- Notes of telephone calls			
32.	<b>SIGNED INFORMED CONSENT FORMS</b>	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 3)	X	
33.	<b>SOURCE DOCUMENTS</b>	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
34.	<b>SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</b>	To document that the investigator or authorized member of the investigator’s staff confirms the observations recorded	X (copy)	X (original)
35.	<b>DOCUMENTATION OF CRF CORRECTIONS</b>	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
36.	<b>NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</b>	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 3.4 of FDA Guidelines for Conducting Clinical Trials in Ghana	X	X
37.	<b>NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE,</b>	Notification by Sponsor and/or Investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information in	X (where required)	X

	<b>TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION</b>	accordance with 3.3.14 and 3.2.12.8 of FDA Guidelines for GCP in Ghana and 3.4 of FDA Guidelines for Conducting Clinical Trials in Ghana.		
38.	<b>NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION</b>	Notification by sponsor to investigators of safety information of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.	X	X
39.	<b>INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)</b>	Interim or annual reports provided to IRB/IEC in accordance with approving IRB/IEC requirements and to authority(ies) in accordance with 3.5.1.2 and 3.5.1.3 of FDA Guidelines for Conducting Clinical Trials in Ghana	X	X (where required)
40.	<b>SUBJECT SCREENING LOG</b>	To document identification of subjects who entered pre-trial screening	X	X (where required)
41.	<b>SUBJECT IDENTIFICATION CODE LIST</b>	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows	X	

42.	<b>SUBJECT ENROLMENT LOG</b>	investigator/institution to reveal identity of any subject  To document chronological enrolment of subjects by trial number	X	
43.	<b>INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE</b>	To document that investigational product(s) have been used according to the protocol	X	X
44.	<b>SIGNATURE SHEET</b>	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
45.	<b>RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)</b>	To document location and identification of retained samples if assays need to be repeated	X	X

**4.0. After Completion or Termination of the Trial**

After completion or termination of the trial, all of the documents identified in sections 2.0 and 3.0 of Appendix II should be in the file together with the following

	<b>Title of Document</b>	<b>Purpose</b>	<b>Located in Files of</b>	
			<b>Investigator/</b>	<b>Sponsor</b>
46.	<b>INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE</b>	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X

47.	<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</b>	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
48.	<b>COMPLETED SUBJECT IDENTIFICATION CODE LIST</b>	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
49.	<b>AUDIT CERTIFICATE</b> (if available)	To document that audit was performed		X
50.	<b>FINAL TRIAL CLOSE-OUT MONITORING REPORT</b>	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
51.	<b>TREATMENT ALLOCATION AND DECODING DOCUMENTATION</b>	Returned to sponsor to document any decoding that may have occurred		X
52.	<b>FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)</b>	To document completion of the trial	X	

53.	<b>CLINICAL STUDY REPORT</b>	To document results and interpretation of trial	X  (if applicable)	X
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