	Title: Good Clinical Practice Guidelines	
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PHARMACY BOARD OF SIERRA LEONE

PMB 322

CENTRAL MEDICAL STORES COMPOUND

NEW ENGLAND VILLE

FREETOWN

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TABLE OF CONTENTS

Acknowledgements

Executive Summary

1.0 . INTRODUCTION

The value of carefully constructed clinical trials as the optimum methodology for the testing and evaluation of new treatments and medicines is well recognised within the Sierra Leone. Sierra Leone provides a particularly unique research environment encompassing world class expertise in clinical trial research, modern health care facilities, a significant burden of disease, and a stable political environment.

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

The purpose of this guideline is to provide investigators conducting clinical trials in Sierra Leone with clear standards of good clinical practice. The Guidelines seeks to ensure that clinical trials conducted in Sierra Leone are designed and conducted according to sound scientific and ethical standards within the framework of good clinical practice.

The guideline was partly derived from the International Conference on Harmonization Good Clinical Practice (ICH E6(R2) GCP), World Health Organization (WHO) Guidelines for Good Clinical Practices for Trials on Pharmaceutical Products 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) and the South African GCP Guideline.

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, the general public and all, those who have an interest in clinical trials research in Sierra Leone.

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 OBJECTIVE

The purpose of this guideline is to provide Sierra Leone with clearly articulated standards of good clinical practice in research that are also relevant to local realities and contexts and to ensure that clinical trials conducted on human participants 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.

3.0 SCOPE OF THIS GUIDELINE

This guideline focuses on the management and regulation of drug trials on human participants. These guidelines have not specifically addressed clinical trials on complementary medicines, traditional medicines, non-pharmacological interventions including surgical procedures, medical devices and X-rays. However, this guideline is such that, in the absence of alternatives, the basic principles outlined in this document may be used to guide any research involving human participants, particularly research involving experimental study designs. This guideline has been guided by and based on the following documents:

- ICH GCP (R2)
- Declaration of Helsinki
- International Guidelines for Ethical Review of Epidemiological Studies, Council for International Organisations of Medical Sciences (CIOMS), 1991

- World Health Organisation, WHO Technical Report Series, No. 850, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

In the event that these Guidelines differ from any of the above texts, these Guidelines will apply. The responsibility for deviation with any of the above documents lies with the authors of these Guidelines.

4.0 REQUIREMENTS

4.0.1 PRINCIPLES

Although well-designed clinical trials will undoubtedly fit in within these modern ethical sentiments, the potential to violate the rights of trial participants particularly in vulnerable communities necessitates the need to articulate ethical guidelines for clinical trials.

The principles of GCP include:

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

requirement(s).

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

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

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

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

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

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

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

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

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

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

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

protocol.

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

The practical application of these principles requires research studies to have distinct components built into them. These include relevant and appropriate study rationale, optimal study design, investigator competence, a balance of risks and benefits for participants, transparency, patient privacy, ethical review and impartial oversight of consent procedures. To follow is a brief discussion on some of these issues as they relate to Sierra Leone.

4.0.2 Study Rationale and Motivation: A study rationale and motivation which does not ask relevant and important questions is unethical. The study rationale should demonstrate that the study question under consideration has not been substantially answered and that adequate systematic review of the subject under discussion was done. Relevant and important questions should also be problems that significantly affect local and regional populations.

Research and clinical trials however should be conducted within various settings and applied to communities with different social and economic circumstances. Research projects being undertaken in Sierra Leone should be carefully evaluated and examined as to its current and future relevancy.

The findings of the proposed study should be translatable into mechanisms for improving the health status of Sierra Leoneans. Solutions should have the potential for implementation.

4.0.3 Study Designs: Appropriate study designs are critical in contributing to answering scientific questions. The study design must therefore demonstrate a high probability for providing answers to specific research questions. Adequate supporting information and explanation on the study sample size and study population must be provided.

The social context of a proposed research population that creates conditions for possible exploitation or increased vulnerability among potential research participants should be assessed, where this is

relevant. Steps must be taken to overcome these conditions, and to promote and protect the dignity, safety and welfare of participants. It is imperative that sound study designs, and use of universally accepted ethical standards are applied in both vulnerable and non-vulnerable communities.

The design of the study should in no way prejudice the ongoing treatment and care of patients, nor should it in anyway undermine or confuse patients with respect to the best available local standard treatment practices and national policy approaches. If these are not ensured, then the design is unethical.

4.0.4 Investigator Competence: The Principal Investigator's (and other investigators') competence is assessed by two major parameters: technical and humanistic. Technical competence which includes research competence is assessed by education, knowledge, certification and experience such that the investigator is able to assume responsibility for the proper conduct of a trial, should meet all the qualifications specified by applicable regulatory requirement(s), and should provide evidence of such qualifications

through an up-to-date curriculum vitae and/or other relevant documentation requested PBSL. Humanistic parameters require compassion and empathy. This is provided by a proper clinical and research environment, encompassing good research mentoring. In all cases the Principal Investigator for each site must be a Sierra Leonean-based scientist (domicile in Sierra Leone).

4.0.5 **Balance of Harm and Benefit:** A risk benefit analysis of the study should precede the conduct of the research itself. The risk-benefit analysis should take full cognisance of benefits and harms beyond the life of the study itself, particularly in the case of chronic life-threatening conditions. Alternative ways of providing benefits to the patients might be available without research; thus, the distinction between the probability of harm and the possible benefits of the effects must be made. The principal investigator has the ethical duty of excluding participants who are at undue risk.

4.0.6 **Transparency:** Clinical trialists have an ethical obligation to honestly report a trial's existence and findings. Publication bias among other things often serves as a barrier to this and can distort

the body of evidence available for clinical decision making. That's why it is a requirement for all trials being conducted in Sierra Leone to be registered in a PBSL approved clinical trial registry preferable the Pan-African Clinical Trial Registry (PACTR).

Benefits of registering a trial are numerous. It serves to: promote collaboration among researchers, the private sector and the community through the sharing of research information; assist people to identify clinical trials they can participate in; decrease publication bias; reduce duplication of research efforts; promote best use of limited research resources; and contribute to global efforts to reduce/eliminate disease (while preserving the confidentiality of commercially valuable information regarding the medicine during the development stage). Sponsors of trials conducted in Sierra Leone are required to register their trials. Where there is no sponsor, it is the responsibility of the Principal Investigator to register the trial.

4.0.7 Privacy: Participants' right to privacy must be protected at all costs. This is maintained via the use of appropriate precautions regarding participant identifiers. This will also include

electronic/computerised records and access thereof of such information.

4.0.8 Scientific and Ethical Review: Scientific and ethical review provides an objective appraisal of the research proposal as it affects the potential participants and the general day to day functioning of the health system. The following bodies are involved in scientific and ethical review in Sierra Leone:

- **Sierra Leone Ethical and Scientific Review Committee (SLERSC):** Research Ethics Committees are usually made up of medical and non-medical professionals. SLERSC is the national ethics committee which advises the Ministry of Health and Sanitation on health research ethics in Sierra Leone. All clinical trials conducted in Sierra Leone must undergo ethical review SLERSC.
- **Data and Safety Monitoring Committees:** These committees oversee ongoing clinical trials with respect to treatment, efficacy and safety. In the advent of clear evidence of efficacy or harm,

prior to the end of the trial, premature termination can be recommended on ethical grounds.

- **The Pharmacy Board of Sierra Leone (PBSL):** Whilst the PBSL is not an ethical review committee, it is responsible for reviewing the study design, and in so doing reviews all significant ethical questions. The PBSL does thorough scientific review on all applications for clinical trials to be conducted in Sierra Leone.

4.0.9 Informed Consent: Informed consent is an essential component of ethical research. Obtaining informed consent implies the provision of information to potential participants regarding the nature of the research procedure, scientific purpose and alternatives to study participation.

Informed consent may be difficult to achieve, especially when engaging people from disadvantaged and vulnerable communities where literacy and education opportunities are inadequate and where there are language barriers. However, every effort must be carried out to achieve informed consent.

Participants' comprehension is addressed by laying out this information in a clear and simple style. In Sierra Leone, this must be achieved via the use of culturally acceptable practices including the use of the participant's language of choice. The conditions under which the consent is granted must be free of coercion, undue influence or incentives. Treatment for a given condition, which might be an attribute of the clinical trial design, should not be denied by the refusal to participate. Withdrawal from the clinical trial at any time will not result in undue clinical penalties to the participant.

4.0.10 Safety Monitoring: Safety monitoring of participants during and for defined periods after a clinical trial is an ethical requirement. This involves the prevention, appropriate monitoring, prompt reporting and appropriate management of serious adverse events.

4.0.11 Multi-centre Studies: The number of multi-centred clinical trials being undertaken in Sierra Leone is expected to increase dramatically in the coming years. There is a need to ensure that designs of such studies are appropriate for the local setting and that particular modifications are made to the local study when required

e.g. inclusion/exclusion criteria. Special attention should also be paid to the sampling strategy when reviewing multi- centred clinical trials.

Furthermore, it is unacceptable for developed country participants to have better standards of care offered in the study when compared to Sierra Leone participants. When Sierra Leone is chosen for a clinical trial while the trial is not undertaken in the country of origin an explanation should be sought about why this is the case.

4.1 GUIDELINES AND LEGISLATION

Regulations established in terms of the Pharmacy and Drugs Act of 2001 and the National Medicines Policy of 2012 enforces this guideline. Compliance with this guideline is compulsory under the direction of the Pharmacy Board of Sierra Leone.

4.1.1.REGULATORY AUTHORITIES ROLES AND RESPONSIBILITIES

This document outlines the roles and responsibilities of the various parties involved in controlling clinical trials in Sierra Leone. Specifically, these include:

4.1.1.1 The National Medicines Regulatory Authority (NMRA)/Pharmacy Board of Sierra Leone: All clinical trials of both non-registered medicinal substances and new indications of registered medicinal substances must be reviewed by the PBSL. The PBSL has a statutory obligation to ensure that the medicines available in the country fulfil the necessary requirements for safety, quality and efficacy. In the case of an ongoing trial where there are serious breaches of Good Clinical Practice (GCP), the PBSL can terminate the trial.

4.1.1.2 Research Ethics Committee: The main responsibility of Research Ethics Committee (REC) in Sierra Leone is to ensure the protection of, and respect the rights, safety and wellbeing of participants involved in a trial and to provide public assurance of that protection by reviewing, approving and providing comment on clinical trial protocols, the suitability of investigator(s), facilities, methods and procedures used to obtain informed consent. In the execution of these responsibilities, the committee should be guided

by relevant Sierra Leone ethical guidelines, professional standards and codes of practice.

4.1.1.3 The Principal Investigator (PI): The principal investigator should be Sierra Leonean- based scientist who has a sole or joint responsibility for the design, conduct, delegation of trial responsibilities, analysis and reporting of the trial. The principal investigator is accountable to the sponsor and regulatory authorities as required by this Guideline. The PI should be knowledgeable and have an understanding of the drug, its toxicology and safety. In the case of a multi-centre trial there must be a local principal investigator (PI) attached to each site. It is unacceptable to have an "absentee" PI who is based in another country. See glossary for definitions of investigator/sub-investigator.

4.1.1.4 The Sponsor: An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

4.1.1.5 The Monitor: The monitor is appointed by and reports to the sponsor. The monitor is responsible for overseeing the progress of a clinical trial and ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Pharmacy Practice (GPP), this guideline and other applicable legislation and regulations.

4.1.1.6 The Auditor: The auditors are independent individuals appointed by sponsors, local and other regulatory authority(ies) to conduct a systematic and in-depth examination of trial conduct and compliance with the protocol, SOPs, GCP, GLP, GPP and the applicable regulatory requirements. An audit is separate from routine monitoring or quality control functions.

4.1.1.7The Inspector: The inspector is a qualified employee of local and international regulatory authority(ies) whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites/sponsors/CROs/bioequivalence facilities and research ethics committees as required/instructed by the regulatory

authority(ies). Most inspectorate visits will be prearranged but some will not especially where there is suspected serious breaches of the GCP or malpractices.

4.1.2 CLINICAL TRIAL APPROVAL IN SIERRA LEONE

The following steps must be undertaken before a clinical trial can be conducted in Sierra Leone:

- PBSL Approval: A sponsor/principal investigator (PI) must apply to the PBSL for approval to conduct a trial for a non-registered drug or a registered drug for new indications etc;
- SLERSC Approval: All clinical trials to be conducted in Sierra Leone must apply for and receive ethical approval from the ethics committee

4.1.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

4.1.3.1 RESPONSIBILITIES

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

4.1.3.3 The IRB/IEC should obtain the following documents:

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

The IRB/IEC 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:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

4.1.3.4 The IRB/IEC 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 IRB/IEC requests.

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

4.1.3.6 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the

subjects.

4.1.3.7 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

4.1.3.8 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

4.1.3.9 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on

completion of the trial by the subject.

4.1.3.10 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

4.2 COMPOSITION, FUNCTIONS AND OPERATIONS

4.2.1 The IRB/IEC 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 IRB/IEC should include:

(a) At least five members.

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

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

Only those IRB/IEC 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 IRB/IEC members and their qualifications should be maintained.

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

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

4.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

4.3 RECORDS

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted

documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from PBSL.

The IRB/IEC may be asked by investigators, sponsors or PBSL to provide its written procedures and membership lists.

4.4 RESEARCH REQUIRING ADDITIONAL ATTENTION

The Sierra Leone national research ethics committee must pay special attention to protecting the welfare of certain classes of participants. Research ethics committees may impose additional measures to protect the welfare of participants requiring additional attention. For example, research ethics committees may make it mandatory to conduct post-research investigations to review whether there was compliance with the additional measures imposed. If compliance was defective, research ethics committees may withdraw approval for the research investigation concerned.

Participants whose involvement needs additional attention include:

- Minors: Children and adolescents

- Women
- People with mental disabilities or substance abuse related disorders
- Persons in dependent relationships or comparable situations
- Prisoners
- Persons highly dependent on medical care

Types of research that need additional attention include:

- Research involving collectivities
- Research involving indigenous medical systems
- Emergency care research
- Research involving innovative therapy or interventions
- Research involving vulnerable communities
- HIV and AIDS clinical and epidemiological research

4.4.1 Minors: Children and adolescents: A minor for the purposes of this guideline is defined as a person under 18 years of age. Minors should participate in research only where their participation is indispensable to the research. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. The research should investigate a problem of relevance to children. Note that all types of clinical research on minors should be scrutinized carefully.

Research involving minors should be approved only if:

- The research interventions, including those in observational research, presents the participant with no greater than minimal risk (that is, the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine medical or psychological examinations or tests – referred to as 'negligible risk' in some guidelines); or

- The research interventions present more than minimal risk but hold out the prospect of direct benefit for the participant. The risks must be justified by the anticipated benefit; or
- The research interventions, including those in observational research, present more than minimal risk and do not hold out the prospect of direct benefit to the participant, but have a high probability of yielding generalizable knowledge. That is the risk should be justified by the risk-knowledge ratio. The risk should represent a minor increase over minimal risk. The intervention or procedure should present experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or education settings.
- In all cases, the protocol must provide sufficient information to justify clearly why minors should be included as participants.

4.4.1.1 Consent Requirements: For research with minors, the following should be obtained:

- Consent from a parent or legal guardian in all but exceptional circumstances (e.g. emergencies). A caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor;
- Assent from the minor where s/he is capable of understanding;
- A child's refusal to participate in research must be respected, i.e. such refusal settles the matter

4.4.1.2 Assent Requirements: Assent means a minor's affirmative agreement to participate in research. Mere failure to object should not be construed as assent. The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the minor's assent when, in the judgement of the research ethics committee, the minor is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

4.4.2 Women: Exclusion of women as research participants has led to a lack of data needed to promote women's health. Research ethics committees should consider whether the exclusion of women is justified

in terms of research priorities and the specific research question under consideration. As part of advocating improved health for women, researchers have ethical obligations to conduct research that does not perpetuate discriminations against women by unfairly or unjustifiably excluding them from study protocols.

4.4.2.1 Women and Pregnancy: Research ethics committees must give extra attention to research that involves women who are, or may become pregnant, because of the additional health concerns during pregnancy and the need to avoid unnecessary risk to the foetus. Reasons for excluding women from research should be adequately justified both from the point of protecting the health of a foetus and from the perspective of whether such exclusion is scientifically supportable.

No research activities involving pregnant women and foetuses may be undertaken unless:

- Appropriate studies on animals and non-pregnant individuals have been completed;

- The purpose of the activity is to meet the health needs of the mother of the particular foetus, the risk to the foetus is minimal and, in all cases, presents the least possible risk for achieving the objectives of the activity.
- Individuals engaged in the activity will have no part in 1) any decision as to the timing, method and procedures used to terminate the pregnancy, and 2) determining the viability of the foetus at the termination of the pregnancy; and
- No procedural changes which may cause greater than minimal risk to the foetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

The father's informed consent need not be secured if:

- the purpose of the activity is to meet the health needs of the mother;
- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or

- the pregnancy results from rape.

4.4.2.2 Foetuses In-Utero as Participants: No foetus in utero may be involved as a participant in any research activity unless:

- the purpose of the activity is to meet the health needs of the particular foetus and the foetus will be placed at risk only to the minimum extent necessary to meet such needs; or
- the risk to the foetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent.

The father's informed consent need not be secured if:

- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or

- the pregnancy resulted from rape.

4.4.2.3 Foetuses Ex Utero, including Nonviable Foetuses, as Participants: Until it has been ascertained whether or not a foetus ex utero is viable, a foetus ex utero may not be involved as a participant in any research activity unless:

- there will be no added risk to the foetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or
- the purpose of the activity is to enhance the possibility of survival of the particular foetus to the point of viability.

No nonviable foetus may be involved as a participant in any research activity unless:

- vital functions of the foetus will not be artificially maintained; ☐ experimental activities which of themselves would terminate

the heartbeat or respiration of the foetus will not be employed; and

- the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if:

- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or
- the pregnancy resulted from rape.

Individuals engaged in the activity will have no part in (1) any decision as to the timing, method and procedures used to terminate the pregnancy, and/or (2) determining the viability of the foetus at the termination of the pregnancy.

No procedural changes, which may cause greater than minimal risk to the foetus or the pregnant woman, will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

Any activity permitted above may be conducted only if the mother is legally competent and has given informed consent after having been fully informed about the possible impact on the foetus.

4.4.3 People with Mental Disabilities or Substance Abuse Related Disorders: People with mental disabilities include those people with psychiatric, cognitive or developmental disorders. The issue with these groups of people as far as research is concerned, is their capacity for reason regarding participation and comprehension of information provided. This issue is also applicable to research on persons with substance abuse related disorders. Institutionalisation may also further compromise a person's ability to make a truly voluntary decision to participate in a study.

Research in people with mental disabilities or with substance abuse related disorders must therefore:

- Be relevant to mental disabilities or substance abuse related disorders so that it is necessary to involve people who have a mental disability and/or a substance abuse related disorder/s;
- Justify the involvement, as the study population, of institutionalised people with mental disabilities;
- Ensure appropriate evaluation procedures for ascertaining participants' ability to give informed consent. If participants are deemed unable to understand and to make a choice, then an appropriate individual, able to consent on their behalf must be sought;
- Ensure that consent is free from coercion and risk to participants; and
- Ensure that only minimal risk is involved, and that the risk is outweighed by the anticipated benefits for the participants and by

the importance of the knowledge that will emanate from the research.

Persons with intellectual or mental impairment should not participate in research that might equally well be conducted with persons without those impairments.

Consent to research must be obtained from:

- the person with the intellectual or mental impairment, wherever he or she is competent to give informed consent;
- the person's legal guardian where the person is deemed not competent to do so; or
- an authority, organisation or person having that responsibility by law.

Consent cannot be given for participation in research that is contrary to the interests of the person with the intellectual or mental impairment.

The intellectually or mentally impaired person's refusal to participate in research must always be respected.

4.4.4 Persons in Dependent Relationships or Comparable Situations: Persons whose proposed involvement in research arises from dependent or comparable relationships need additional attention and the research ethics committee must be satisfied that their consent is both adequately informed and voluntary.

It is not possible to define such relationships exhaustively, but they include persons who are in junior or subordinate positions in hierarchically structured groups and may include relationships between:

- older persons and their caregivers;
- persons with chronic conditions or disabilities and their caregivers;
- wards of State and guardians;
- patients and health-care professionals;
- students and teachers;
- prisoners and prison authorities;
- persons with life-threatening illnesses;

- employees and employers, e.g. farm workers and their employers, members of the uniformed services and hospital staff and their employers.

4.4.5 Prisoners: Ethical review must take cognisance of the impact of a prisoner's incarceration on their ability to make a voluntary decision, without coercion, on whether or not to participate in research. Research studies in Sierra Leone may involve prisoners as participants only when the ethics committee has ensured that the clinical trial involves:

- the study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided;
- no more than minimal risk and inconvenience to the participants;
- the study of prisons as institutional structures or of prisoners as incarcerated persons,
- research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on diseases that may be more prevalent in prisons and research on social and psychological problems such as alcoholism, drug addiction, and

sexual assaults) only after appropriate experts have been consulted; and

- research on practices, both innovative and accepted, that have the intent and probability of improving the health or wellbeing of prisoners.

Where some prisoners may be assigned to control groups that may not benefit from the research, the research may proceed only after appropriate experts have been consulted. Research that could be conducted on a population other than prisoners should not be permitted, unless cogent motivation is presented to the research ethics committee, and the committee is satisfied that the motivation does not represent exploitative research. Research ethics committees should take into consideration the extent to which research facilitates the empowerment of prisoners as a vulnerable group.

In addition, when reviewing research involving prisoners, research ethics committees must meet the following requirements:

- A majority of the research ethics committee, other than prison members, shall have no association with the prison(s) involved, apart from their membership of the research ethics committee;
- At least one member of the research ethics committee shall be a prisoner, or a prisoners' representative with appropriate background and experience to serve in that capacity. Where a research project is reviewed by more than one ethics committee, only one research ethics committee need satisfy this requirement of a prisoners' representative.

4.4.6 Persons Highly Dependent on Medical Care: The involvement in research of participants who are highly dependent on medical care raises ethical issues that deserve special attention. The gravity of their medical condition may require invasive measures carrying increased risk. Researchers need to acknowledge that informed consent may be compromised by the effect of the medical condition on the participant's capacity to form an opinion or to communicate. Additionally, there may be a perception of coercion if a participant is reluctant to refuse consent for fear that it may compromise his or her medical treatment.

Researchers need to consider whether an unfair burden of participation is being placed on groups such as those referred to below.

4.4.6.1 Intensive Care Research: Characteristic features of intensive care research are the difficulties in communicating with patients receiving ventilatory assistance and the impairment of cognition in heavily sedated individuals. Whenever possible, information regarding intensive care research should be obtained from potential participants before their admission to that care. Because of their extreme vulnerability such persons should be excluded from all but minimally invasive observational research.

4.4.6.2 Neonatal Intensive Care Research: Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out in the section entitled Research Involving Children. These principles do not permit research that is contrary to the child's best interests.

The small size and vulnerability of some infants are unique features of this research, which renders all but minimal intrusion likely to be contrary to the child's best interests. The collection of even small

blood samples additional to those required for diagnostic purposes, or the handling of a low birth-weight infant to make observations will demand careful scrutiny.

4.4.6.3 Terminal Care Research: Research in terminal care is distinguished by the short remaining life expectancy of participants and potential vulnerability to unrealistic expectations of benefits.

Researchers must take care that the prospect of benefit from research participation is neither exaggerated nor used to justify a higher risk than that involved in the patient's current treatment.

Researchers must respect the needs and wishes of participants to spend time as they choose, particularly with family members

4.4.6.4 Research Involving Persons with Impaired Capacity to Communicate: The distinguishing features of research involving persons with impaired capacity to communicate include acute impairment states requiring medical care, as well as non-acute states. In the former, the condition and medical care may mask the person's degree of cognition and require different means of

expression. In the latter, the condition may be such as to prevent the person expressing wishes at all.

4.4.6.5 Research Involving Unconscious Persons: The distinguishing feature of research with unconscious persons is that, because of their incapacity for cognition or communication, it is impossible for them to be informed about the research or for a researcher to determine their wishes about it. Consent to participation in research by an unconscious person must be given by others, including relevant statutory authorities, on that person's behalf. Because of their extreme vulnerability unconscious persons should be excluded from all but minimally invasive observational research.

When research procedure precludes conformity to the principle of consent, and neither the prospective participant nor the participant's representative is able to give consent in advance, a research ethics committee may approve a research project without prior consent if it is satisfied that:

- inclusion in the research project is not contrary to the interest of the patient;
- the research is intended to be therapeutic and the research intervention poses no more of a risk than that inherent in the patient's condition and alternative methods of treatment;
- the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care; and
- as soon as reasonably possible, the participant and the participant's relatives or legal representatives will be informed of the participant's inclusion in the research, and will be advised of their right to withdraw from the research without any reduction in quality of care.

In the case of research proposals in which it is practicable to obtain consent before including in the research a participant who is highly dependent on medical care, a research ethics committee must be satisfied that:

- adequate provision will be made for informing patients and their relatives about the research, to ensure that stress and other emotional factors do not impair their understanding of it; and
- the dependency of patients and their relatives on the medical personnel providing treatment does not affect any decision to participate.

4.4.7 Emergency Care Research: The benefits of emergency care research include improved effective treatment for life-threatening conditions and improving therapies for survival and quality of life. Research into emergency medical treatment needs to involve participants who are experiencing medical emergencies.

The distinguishing feature of emergency care research however is that consent to commence a project usually has to be obtained rapidly, when the vulnerability of patients and families is likely to be greatest. Because of their extreme vulnerability, such persons should be excluded from all but minimally invasive observational research. Research ethics

committee must therefore take great care when assessing emergency care research.

Moreover, the circumstances surrounding emergency care research are such that it may not always be possible to obtain consent for inclusion without delaying the initiation of treatment, and so risking a reduction of potential benefits. As such there may be circumstances in which it is not possible to obtain consent for inclusion in emergency care research. After a protocol has been presented by a researcher giving clear reasons to justify the initiation of the emergency care research without consent, a research ethics committee may approve the research without consent provided it is satisfied that:

- reasonable steps are being taken to ascertain the religious and cultural sensitivities of patients experiencing medical emergencies;
- the condition of the patient precludes the giving of consent;
- inclusion in the trial is not contrary to the interests of the patient;

- the research is intended to be therapeutic and poses no more risk than is inherent to the patient's condition or would be caused by alternative methods of treatment;
- the patient and the patient's next of kin or legal representatives will be informed as soon as is reasonably possible of the patient's inclusion in the study and of the option to withdraw from the research project at any time;
- the patient will be informed, and consent obtained, once the patient who has undergone the necessary emergency procedures has regained consciousness; and
- the research is based on valid scientific hypotheses and offers a realistic possibility of benefit over standard care.

4.4. INVESTIGATOR

4.4.1 Investigator's Qualifications and Agreements

4.4.1.1 The investigator(s) 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 3.2 sub-section 3.2.3 under the PBSL Guidelines for Conducting Clinical Trials.

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

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

4.4.1.4 The investigator should permit monitoring and auditing by PBSL.

4.4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant

trial-related duties.

4.4.1.6 The Investigator should not have been found guilty of any misconduct under the Pharmacy and Drugs Act and Sierra Leone Medical and Dental Council Act.

4.4.1.7 The Principal Investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is resident in Sierra Leone 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.

4.4.1.8 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.

4.4.1.9 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 (see Appendix 3) and its current revisions as well as in the local and international guidelines for GCP.

4.6 Adequate Resources

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

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

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

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

4.6.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.6.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.7 Medical Care of Trial Subjects

4.7.1 A medical practitioner (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. The qualified medical practitioner should also be licensed with the Sierra Leone Medical and Dental Council or the Pharmacy Board of Sierra Leone. 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.

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

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

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

4.8 Communication with PBSL

4.8.1 Before initiating a trial, the principal investigator should have the written and dated approval from the PBSL

4.8.2 As part of the investigator written application to PBSL, the investigator should provide PBSL 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 PBSL.

4.8.3 During the trial the investigator should provide PBSL all documents subject to review.

4.9 Compliance with Protocol

4.9 .1 The investigator should conduct the trial in compliance with the protocol agreed to by the sponsor and, which was given approval by PBSL. The investigator and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.9.2 The investigator should not implement any deviation from, or changes of the protocol without prior review and approval from

PBSL of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

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

4.9.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior PBSL approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

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

(c) to PBSL review and approval.

4.10 Investigational Product(s)

4.10.1 Responsibility for investigational product(s) accountability at the

trial site(s) rests with the investigator.

4.10.2 The investigator should assign some or all of the investigator's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist who is under the supervision of the investigator.

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

4.10.4 The investigational product(s) should be stored as specified by the sponsor (see 4.13.2 and 4.14.3) and in accordance with

applicable regulatory requirement(s).

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

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

4.11 Randomization Procedures and Unblinding

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

4.12 Informed Consent of Trial Subjects

4.12.1 In obtaining and documenting informed consent, the

investigator should comply with the applicable regulatory requirement(s) such as PBSL requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki(see Appendix 3 of this Guideline). Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

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

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

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

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

4.12.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the

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

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

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

4.12.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or

the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, 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 subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

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

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random

assignment to each treatment.

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

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

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

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

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

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

(k) The anticipated prorated payment, if any, to the subject for

participating in the trial.

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

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

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

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of

the trial are published, the subject's identity will remain confidential.

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

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

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

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

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

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

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

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

4.12.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

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

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

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

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

(d) The trial is not prohibited by law.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.12.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or

elsewhere, with documented approval/favourable opinion by the IRB/IEC and PBSL approval, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.13 Records and Reports

4.13.1 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

4.13.2 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.

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

4.13.4 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 4.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.13.5 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 11.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures

to prevent accidental or premature destruction of these documents.

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

4.13.7 Upon request of the PBSL the investigator/institution should make available for direct access all requested trial-related records.

4.14 Progress Reports

4.14.1 The investigator should submit written summaries of the trial status to the PBSL as specified in section 3.5 sub-section 3.4.1 of PBSL guideline for conducting clinical trial., or more frequently, if requested by the PBSL.

4.14.2 The investigator should promptly provide written reports to PBSL on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.15 Safety Reporting

4.14.1 All serious adverse events (SAEs) should be reported

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

4.14.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the PBSL according to the reporting requirements and within the timelines specified PBSL.

4.14.3 For reported deaths, the investigator should supply PBSL with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.16 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and also inform PBSL. In addition:

4.16.1 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/institution should promptly inform the sponsor and PBSL and should provide the sponsor and PBSL a detailed written explanation of the termination or suspension.

4.16.2 If the sponsor terminates or suspends a trial (see sub-section 4.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform PBSL and provide PBSL a detailed written explanation of the termination or suspension.

4.16.3 If the PBSL terminates or suspends its approval of a trial (see subsections 3.1.2 and 3.3.9), the investigator should inform the

institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.17 Final Report(s) by Investigator

Upon completion of the trial, the investigator s should provide the PBSL with a summary of the trial's outcome. See PBSL guidelines for conducting clinical trial for format.

4.18 SPONSOR

4.18.1 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the

information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent. The quality management system should use a risk-based approach as described below.

4.18.1.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

4.18.1.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

4.18.1.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk

controls by considering:

(a) The likelihood of errors occurring.

(b) The extent to which such errors would be detectable.

(c) The impact of such errors on human subject protection and reliability of trial results.

4.18.1.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations

from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

4.18.1.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

4.18.1.6 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

4.18.1.7 Risk Reporting The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

4.19 Quality Assurance and Quality Control

4.19.1 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 PBSL regulatory requirement(s).

4.19.2 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.

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

4.19.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol submitted

to PBSL or in a separate agreement

4.20 Contract Research Organization (CRO)

4.20.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

4.20.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing. The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

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

4.20.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and

functions of a sponsor.

4.21 Medical Expertise

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

4.22 Trial Design

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

4.22.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see Section 6 of this guideline).

4.23 Trial Management, Data Handling, and Record Keeping

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

4.23.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

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

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

performance (i.e. validation). The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

(b) Maintains SOPs for using these systems. The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

(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 (see subsections 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

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

(h) Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

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

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

4.23.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see section 11. Essential Documents for the Conduct of a Clinical Trial).

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

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

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

4.24 Investigator Selection

4.24.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see subsections 4.1, 4.2) 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 responsibility.

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

4.24.3 The sponsor should obtain the investigator's/institution's agreement on the following:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see subsection 4.1.3), and with the protocol agreed to by the sponsor and approved by PBSL.

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see subsection 4.1.4) and

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

4.25 Allocation of Responsibilities

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

4.26 Compensation to Subjects and Investigators

4.26.1 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 as stipulated by PBSL

guidelines for conducting clinical trial.

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

4.26.3 When trial subjects receive compensation, the method and manner of compensation should comply with PBSL regulatory requirement(s).

4.27 Financing

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

4.28 Notification/Submission to PBSL

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, should submit any required application(s) to PBSL for review and PBSL approval before commencement of the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

4.30 Confirmation of Review by IRB/IEC

4.30.1 The sponsor should obtain from the investigator/institution:

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

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

4.31 Information on Investigational Product(s)

4.31.1 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.

4.31.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see section 7. Investigator's Brochure of this guideline).

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

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

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

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

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

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

4.33 Supplying and Handling Investigational Product(s)

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

4.33.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains PBSL approval.

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

4.33.4 The sponsor should:

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

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see Section 11. Essential Documents for the Conduct of a Clinical Trial).

(c) Maintain a system for retrieving investigational products and

documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

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

4.33.5 The sponsor should:

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

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the PBSL regulatory requirement(s), whichever represents the longer retention period.

4.34 Record Access

4.34.1 The sponsor should ensure that it is specified in the protocol or

other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, PBSL review and regulatory inspection.

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

4.35 Safety Information

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

4.34.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and PBSL of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the PBSL approval to continue the trial.

4.36 Adverse Drug Reaction Reporting

4.36.1 The sponsor should expedite the reporting to PBSL, all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s),of all adverse

drug reactions (ADRs) that are both serious and unexpected.

4.36.2 Such expedited reports should comply with the PBSL regulatory requirement(s) as specified in PBSL guidelines for conducting clinical trials.

4.36.3 The sponsor should submit to PBSL all safety updates and periodic reports, as required by PBSL regulatory requirement(s).

4.37 Monitoring

4.37.1 Purpose

The purposes of trial monitoring are to verify that:

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

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

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

4.37.2 Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

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

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the PBSL regulatory requirement(s).

4.37.3 Extent and Nature of Monitoring

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.

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g.,

data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

(a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

(b) examine data trends such as the range, consistency, and variability of data within and across sites.

(c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems. (d) analyze site characteristics and performance metrics.

(e) select sites and/or processes for targeted on-site monitoring.

4.37.4 Monitor's Responsibilities

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

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

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 4.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

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

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

(ii) That the investigational product(s) are supplied only to

subjects who are eligible to receive it and at the protocol specified dose(s).

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

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

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

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

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

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies

needed to conduct the trial properly and to comply with the PBSL regulatory requirement(s).

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

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

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

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

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

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

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

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

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

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

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate

corrections, additions, or deletions are made, dated, explained (if necessary), and 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 IRB/IEC, the sponsor, and PBSL regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see section 11. Essential Documents for the Conduct of a Clinical Trial).

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

4.37.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as

well as those procedures that are specified by the sponsor for monitoring a specific trial.

4.37.6 Monitoring Report

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

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

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

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

(e) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management

and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

4.37.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

4.38 Audit

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

4.38.1 Purpose

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

4.38.2 Selection and Qualification of Auditors

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

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

4.38.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's

written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

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

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

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

4.39 Noncompliance

4.39.1 Noncompliance with the protocol, SOPs, GCP and PBSL regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. If noncompliance that significantly affects or has the potential to significantly affect human subject protection

or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

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

4.40 Premature Termination or Suspension of a Trial

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

4.42 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to PBSL as required by PBSL regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

4.43 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

4.43.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and approvals of PBSL and IEC.

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

are designed to capture the additional data.

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

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

4.43.5 Communication between investigators is facilitated.

4.44. The external sponsor should strengthen local capacity for ethical, scientific review, biomedical research and provide healthcare services as described in guidelines 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:

4.44.1 Establishing and strengthening independent and competent ethical review processes/committees.

4.44.2 Developing technologies appropriate to health-care and biomedical research.

4.44.3 Training of research and health-care staff.

4.44.4 Educating the community from which research subjects will be drawn.

4.44. External sponsors are ethically obliged to ensure the availability of:

4.44.1. health-care services that are essential to the safe conduct of the research

4.44.2. treatment of subjects who suffer injury as a consequence of research intervention; and

4.44.3. 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.

4.46. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

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.

4.47 General Information

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

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

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

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

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

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

4.47.7 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.

4.48 Background Information

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

4.48.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to

the trial.

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

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

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

4.48.6 Description of the population to be studied.

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

4.49 Trial Objectives and Purpose

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

4.50 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:

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

4.50.2 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.

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

(a) Randomization.

(b) Blinding.

4.50.4 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).

4.50.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including

follow-up, if any.

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

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

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

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

4.51 Selection and Withdrawal of Subjects

4.51.1 Subject inclusion criteria.

4.51.2 Subject exclusion criteria.

4.51.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

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

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

4.52 Treatment of Subjects

4.52.1 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.

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

4.52.3 Procedures for monitoring subject compliance.

4.53 Assessment of Efficacy

4.53.1 Specification of the efficacy parameters.

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

4.54 Assessment of Safety

4.54.1 Specification of safety parameters.

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

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

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

4. 55 Statistics

4.54.1 A description of the statistical methods to be employed, including

timing of any planned interim analysis(ses).

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

4.54.3 The level of significance to be used.

4.54.4 Criteria for the termination of the trial.

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

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

4.54.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

4.56 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, IRB/IEC review, and PBSL regulatory inspection(s), providing direct access to source data/documents.

4.57 Quality Control and Quality Assurance

4.57.1. 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 PBSL regulatory requirement(s).

4.57.2. 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.

4.57.3. 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.

4.58 Ethics

Description of ethical considerations relating to the trial.

4.58.1. General ethical consideration relating to the trial and informed consent sheet or form or otherwise should be given to patients or volunteers.

4.58.2. In all circumstances provisions made in this guideline with respect to ethics and informed consent should be complied with.

4.59 Data Handling and Record Keeping

4.59.1. 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.

4.59.2. A clear statement on composition and benefit package for clinical

trial participants.

4.59.3. 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 PBSL.

4.60 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

4.61 Publication Policy

Publication policy, if not addressed in a separate agreement.

4.62 INVESTIGATOR'S BROCHURE

4.62.1 Introduction

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 human subjects. 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 subjects 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.

This guideline delineates 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. PBSL may permit 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, to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and to PBSL before it is included in a revised IB.

4.62.2 General Considerations

The IB should include:

4.62.2.1 Title Page

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. An example is given in Appendix 1.

4.62.2.2 Confidentiality Statement

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 IRB/IEC.

4.62.3 Contents of the Investigator's Brochure

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

4.62.3.1 Table of Contents

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

4.62.3.2 Summary

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.

4.62.3.3 Introduction

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 performing research 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.

4.62.3.4 ***Physical, Chemical, and Pharmaceutical Properties and Formulation***

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.

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.

Any structural similarities to other known compounds should be mentioned.

4.62.3.5 Nonclinical Studies

Introduction:

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.

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

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

– Duration of effects

– Dose response

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

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.

(a) Nonclinical Pharmacology

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).

(b) Pharmacokinetics and Product Metabolism in Animals

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.

(c) Toxicology

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

– Single dose

– Repeated dose

– Carcinogenicity

– Special studies (e.g. irritancy and sensitisation)

– Reproductive toxicity

– Genotoxicity (mutagenicity)

4.62.3.6 Effects in Humans

Introduction:

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 in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

– A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

– Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

– Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

– Population subgroups (e.g., gender, age, and impaired organ function).

– Interactions (e.g., product-product interactions and effects of food).

– Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

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 drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug 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).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

4.62.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The PBSL 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 PBSL's monitoring activities.

4.63.1. 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.

4.63.2. The inspections may be carried out randomly, and/or for specific reasons and shall be either announced or unannounced.

4.63.3. 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 PBSL by the investigator or the sponsor.

4.63.4. During the inspection PBSL shall assure itself that:

4.63.4.1. The facilities used by the investigator continue to be acceptable for the purposes of the study.

4.63.4.2. The approved study protocol for the investigation is being followed.

4.63.4.3. Any changes to the protocol have been approved by respective Ethics Committees and the Board

4.63.4.4. Accurate, complete and current records are being maintained.

4.63.4.4. Serious adverse events (SAEs) are reported to the sponsor and to the PBSL and institutional review board(s) within the stipulated time as specified in these guidelines.

4.63.4.6. The investigator is carrying out the agreed-upon activities, and has not delegated them to other previously unspecified staff.

4.63.4. During an inspection, inspectors:

4.63.4.1. Should be given easy access to the trial sites and laboratories at all times

4.63.4.2. 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.

4.63.6. 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.

4.63.7. Before an inspection, the principal investigator (or the co-investigator) shall be informed of the impending inspection either in writing, by phone or electronically.

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

4.64. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

4.64.1 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 PBSL 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 PBSL 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 PBSL.

The sponsor and investigator/institution should maintain a record of the location(s) of their

respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval. Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

1.	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X correct	X
2.	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X correct	X

3.	**INFORMATION GIVEN TO TRIAL SUBJECT** **- INFORMED CONSENT FORM** (including all applicable translations) **- ANY OTHER WRITTEN INFORMATION** **- ADVERTISEMENT FOR SUBJECT RECRUITMENT** (if used)	To document the informed consent To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent To document that recruitment measures are	X	X

		appropriate and not coercive		
4.	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

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

NO.	Title of Document	Purpose	Located in File	
			Investigator/Institution	**Sponsor**
4.	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
6.	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.: - investigator/institution	To document agreements	X	X

	and sponsor - investigator/institution and CRO -sponsor and CRO -investigator/institution and authority(ies) (where required)		X X	X (where required) X X
7.	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X correct	X

	-Protocol and any amendments -CRF (if applicable) -Informed consent form(s) -Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) -Subject compensation (if any) - Any other documents given approval/ favourable opinion			

			Investigator/Institution	**Sponsor**
8.	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X Correct	X
9.	**PBSL AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval /notification by PBSL has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X correct	X

10.	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X (where required)	X (where required)
11.	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X
12.	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS**	To document competence of facility to perform required	X	X

	- certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	test(s) , and support reliability of results	(where required)	

			ion	
13.	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
14.	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
14.	**SHIPPING RECORDS**	To document shipment	X	X

	FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	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		
16.	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
17.	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind	X	X(third party if applicable)

		for the remaining subjects' treatment		

NO.	Title of Document	Purpose	Located in File	
			Investigator/Institution	**Sponsor**
18.	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable
19.	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 20)		X
20.	**TRIAL INITIATION**	To document that trial	X	X

	MONITORING REPORT	procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 19)		
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.				
21.	**INVESTIGATOR'S BROCHURE UPDATE**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

NO.	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
22.	**ANY REVISION TO:** -Protocol/amendment(s) and CRF -Informed consent form any other written -Information provided to subjects -Advertisement for subject recruitment used)	To document revisions of these trial related documents that take effect during trial	X	X
23.	**DATED, DOCUMENTED APPROVAL/FAVOURAB**	To document that the amendment(s) and/or	X	X

	LE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: -Protocol amendment(s) e -Revision(s) of: ✓ informed consent form ✓ any other written information to be provided to the subject ✓ advertisement for subject recruitment if used)	revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).		

	-Any other documents given approval/favourable opinion - Continuing review of trial (where required)			

NO.	Title of Document	Purpose	Located in File	
			Investigator/Institution	**Sponsor**
24.	**PBSL AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:**	To document compliance with applicable regulatory requirements	X (where required)	X

	- Protocol amendment(s) and other documents			
24.	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 10)	X	X
26.	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST (S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 11)	X	X

27	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** **-C**ertification or -Accreditation or -Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period (see 12)	X (where required)	X
28.	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 14.)	X	X

NO.	**Title of Document**	**Purpose**	**Located in File**	
			Investigator/ Institution	**Sponsor**
29.	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see .16)		X
30.	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
31.	**RELEVANT**	To document any	X	X

	COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes -notes of telephone calls	agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting		
32.	**SIGNED INFORMED CONSENT FORMS**	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.	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial	X	

		data collected. To include original documents related to the trial, to medical treatment, and history of subject		

NO.	**Title of Document**	**Purpose**	**Located in File**	
			Investigator/ Institution	**Sponsor**
34.	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
34.	**DOCUMENTATION OF**	To document all	X	X

	CRF CORRECTIONS	changes/additions or corrections made to CRF after initial data were recorded	(copy)	(original)
36.	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11of this Guideline for GCP and 3.4 of PBSL Guideline for Conducting Clinical Trials.	X	X
37.	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO PBSL AND**	Notification by sponsor and/or investigator, where applicable, to PBSL and IRB(s)/IEC(s) of unexpected serious adverse drug	X (where required)	X

	IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	reactions in accordance with 4.17 and 4.11.1 and of other safety information in accordance with 4.16.2 and 4.11.2 of this GCP Guideline.		
38.	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 4.16.2 of this Guideline.	X	X
39.	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND PBSL**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to PBSL) in accordance with 4.17.3 of this Guideline.	X	X (where required)

NO.	**Title of Document**	**Purpose**	**Located in File**	
			Investigator / Institution	**Sponsor**
40.	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
41.	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to	X	

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

	SAMPLES (IF ANY)	be repeated		

After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified before and during the trial should be in the file together with the following

NO.	**Title of Document**	**Purpose**	**Located in File**	
			Investigator/ Institution	**Sponsor**
46.	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final	X	X

		accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor		
47.	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed site)	X
48.	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	

49.	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
50.	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
51.	**TREATMENT ALLOCATION AND DECODING DOCUMENTAT ION**	Returned to sponsor to document any decoding that may have occurred		X

NO.	**Title of Document**	**Purpose**	**Located in File**

			Investigator/ Institution	**Sponsor**
52.	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial. See 3.4.3 of PBSL Guideline for Conducting Clinical Trial.	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial.See PBSL 3.4.of PBSL Guideline for Conducting Clinical Trial.	X (if applicable)	X

4.7 GOOD CLINICAL AND LABORATORY PRACTICE

GCLP standard is expected in the analysis of samples from clinical trials and provides a framework for organisations regarding facilities, systems and procedures to ensure the reliability, quality and integrity of the work and results to satisfy GCP expectations.

GCLP covers the entire laboratory involvement within a trial and not just what happens within the laboratory. It focuses on the accuracy in the performance of an individual measurement but also considers the Integrity of the sample prior to analysis. GCLP also covers method validation to ensure the methods are fit for the purpose for which it is intended.

The main benefits for trial laboratories that comply with GCLP include:

- Ensuring the quality, reliability, consistency and integrity of the laboratory data.

- Comparability of laboratory data across different laboratories
- Archiving records to enable the documented reconstruction of the study after the study has been completed
- Uniformity of the performance of specific functions across all laboratories worldwide
- Efficiently managed resources and minimised waste
- Confidence in the abilities of the laboratory and personnel involved

Organisation and personnel is the first key principle of GCLP and is critical to the implementation of GCLP within a clinical trial laboratory. Each laboratory may be organised in slightly different ways but should consist of laboratory management, an analytical project manager and laboratory staff.

Designated storage areas for the safe and secure archival, storage and retrieval of data, reports, and samples shall be provided. Security measures for this area must be in place and must be adequate to 'prevent the unauthorised access to the retained materials. Suitable archive facilities can be provided by a third party if required.

Periodic inspections, cleaning, routine and preventative maintenance, calibration and repair shall be carried out as appropriate, and this must be recorded and retained. A service schedule should be in place for all relevant equipment. Equipment used should be 'demonstrably fit for purpose' and only operated by suitably qualified and trained individuals.

SOPs should be periodically reviewed and an up to date list of current SOPs (including version numbers) should be maintained. Laboratory staff should have immediate access to relevant SOPs for the activities being performed. The diagram below provides some examples of processes that should be described in written SOPs:

All laboratory personnel are responsible for complying with the instructions given in each SOP and must document and communicate any deviation from SOP instructions to the laboratory management. The laboratory management must ensure that each SOP is understood and followed by the relevant laboratory staff. Where required the Laboratory management should provide training for the activities outlined in the SOPs.

Prior to the initiation of the work for each specific trial the laboratory shall produce a written analytical plan that describes the work to be performed by the laboratory. This plan should be an exact reflection of the requirements detailed in the clinical protocol and only include work that is covered by the informed consent given by the trial subjects'.

The analytical plan shall be:

- agreed, signed and dated by the sponsor and laboratory manager
- made available to the staff involved in that work
- retained as part of the laboratory records for the trial

The plan may be:

- a controlled document or
- form part of the contractual agreement with the sponsor or
- be contained within the clinical protocol

All changes, modifications or revisions to the agreed analytical plan should be documented, including justification(s)', and be agreed to by the dated signature of the analytical project manager and the sponsor.

'Copies of all such amendments should be maintained with the original analytical plan'.

The analytical plan shall contain enough detail to provide clear instruction to the laboratory staff undertaking the work. At a minimum it shall include the following:

- Identification of the work – title, nature and purpose of the work.
- Information concerning the sponsor and the laboratory – name, address and contact details of the sponsor, investigator and laboratory.
- Dates – date of agreement to the analytical plan and proposed starting and completion dates for the laboratory work.
- Analytical Process – methods to be used including analytical design, methods, materials and conditions, type and frequency of analysis etc. Preparation and shipment of materials used for sample collection.
- Records – list of the records to be retained and archive location.
- Quality Audit – quality audits to be performed to assure the quality and integrity of the data and the accuracy of the reported results.

All 'work should be conducted in accordance with the Trial Protocol and the Analytical Plan' and all the data produced must be recorded:

- directly,
- promptly,
- accurately,
- legibly

The data produced (including any changes to the data) should be signed or initialled and dated and this can be done manually or using a computer system. When choosing and utilising a computer system for the trial there are many considerations to take into account such as:

- The computer system used should be appropriately validated and demonstrably fit for purpose
- The system needs to be well maintained throughout the trial.
- When used to receive, capture, process or report data the system should be developed, tested and operated within the established guidelines/laws.

- Procedures should be outlined to ensure system security including establishing a data audit trail
- Computer access should be limited to authorised personnel only
- Data retained electronically should be adequately backed up to ensure the data can always be accessed/retrieved

'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'. Decisions about the most appropriate choice of method(s) to use should be based on current guidelines, regulations and the expectations of the sponsor. Methods used in sample analysis should always be:

- documented
- validated
- controlled
- approved

The laboratory should retain records demonstrating the validity and suitability of all analytical methods. Analytical methods should remain

unchanged throughout the duration of the trial; however, if changes are required, they must be approved by the sponsor, documented and revalidated.

Once the methods are validated and the trial is underway the samples should be analysed and reported within a set timeframe and in accordance with the relevant SOPs, the clinical protocol and the analytical plan, taking into account local legalisation and standards of practice for safety.

For more details go to British Association of Research Quality Assurance (BARQA) (2003) Good Clinical Laboratory Practice Version 1 (available as World Health Organization (2009) Good Clinical Laboratory Practice) Web 19 March 2015

5.0 GLOSSARY

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be

established: 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 untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational)

product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adult

A person who is eighteen (18) years of age or over that age.

Amendment (to the protocol)

See Protocol Amendment.

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 PBSL or the national ethics committee that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the PBSL or the national ethics committee, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

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).

Audit Certificate

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

Audit Report

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

Audit Trail

Documentation that allows reconstruction of the course of events.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of

the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

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

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.

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Child/Minor A person who is below eighteen (18) years of age.

Clinical Trial/Study

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

Phase I refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness.

Phase II investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.

Phase III trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.

Phase IV trials are conducted after the national drug regulatory authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect, to establish the incidence of adverse reactions, or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the pre-marketing phases (such as children or the elderly) or to establish a new clinical indication for a drug. Such research is to be distinguished from marketing research, sales promotion studies, and routine post-marketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees (see Guideline 2 of CIOMS International Ethical Guidelines for Biomedical research in human subjects).

Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH E3 Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product)

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

Compliance (in relation to trials)

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

Confidentiality

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

Contract

A written, dated, and signed agreement between two or more involved

parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee

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

Coordinating Investigator

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

Contract Research Organization (CRO)

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

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and

auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

"Drug/Medicine" Includes

1. 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

2. Nutritional supplements

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and

electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see Essential Documents for the Conduct of a Clinical Trial).

Good Clinical Practice (GCP)

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

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the

safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Impartial Witness

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

Independent Ethics Committee (IEC)

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

Informed Consent

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

Inspection

The act by PBSL of conducting an official review of documents, facilities, records, and any other resources that are deemed by the Board 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 Board.

Institution (medical)

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

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and

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

Interim Clinical Trial/Study Report

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

Investigational Product

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

Investigator

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

Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see section7. Investigator's Brochure).

Legally Acceptable Representative

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

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.

Monitoring

The act of overseeing the progress of a clinical trial either by PBSL or an independent monitor selected by the sponsor to ensure that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

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

Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than

one site, and therefore, carried out by more than one investigator.

Nonclinical Study

Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee)

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

Original Medical Record

See Source Documents.

PBSL means Pharmacy Board of Sierra Leone

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

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

Protocol Amendment

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

Quality Assurance (QA)

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

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the

trial-related activities have been fulfilled.

Randomization

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

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

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

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Source Data

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

Source Documents

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

Sponsor

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

Sponsor-Investigator

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

Standard Operating Procedures (SOPs)

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

Sub investigator

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

Subject/Trial Subject

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

Subject Identification Code

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

Trial Site

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

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Validation of Computerized Systems

A process of establishing and documenting that the specified

requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Vulnerable Subjects/population

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

nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects)

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

Prepared by	Reviewed by	Approved by
Head of PVG & CT	Head, Quality Assurance	Registrar

6.0 REFERENCES

1.ICH GCP

2. International Guidelines for Ethical Review of Epidemiological Studies, Council for International Organisations of Medical Sciences (CIOMS), 1991

3. World Health Organisation, WHO Technical Report Series, No. 850, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995.

7.0 APPENDIX

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).....

1 Table of Contents .....

2. Reports

These references should be found at the end of each chapter

Appendices (if any)

APPENDIX 3: DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to

a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country i which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests

of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and

potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or mayconsent under duress. In that case the informed consent should be obtained by a physician who Is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor,permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the

minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

4. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (Non-clinical

biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental designed is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 4: DOCUMENTS/INFORMATION THAT MAY BE USED FOR REVIEW PRIOR TO THE START OF THE INSPECTION

1. PBSL documents

   PBSL Procedures

   Assessment Reports

2. Overview of the conduct of the study:

total number of sites/locations/countries

inclusion rate, screening, randomisation, etc.

SAEs, ADRs

drop out frequency

time frame of trial

annual reports,

3. Sites

investigator(s)/co-investigator(s) CVs and qualifications

information on sites involved/selected (including e.g. pharmacy, clinical departments, X-ray, MRI, Echo, ECG, CT, CROs)

4. Lab

local/central

type of labs involved

type of examinations/tests

special equipment/procedures

5. Sponsor

responsibilities defined in contracts

CRO(s) involved

protocol, amendments, investigator's brochure

CRFs

patient information and consent

printout (of parts) of the clinical database

quality management (QC, QA)

sponsor SOPs related with the scope of the inspection

6. Trial Medication

GMP

manufacturing

labelling

blinding procedures

randomisation list

quality documentation

7. Ethics

patient information/informed consent

patient recruitment

insurance

updates of safety information

IEC opinion

8. Local legal regulations

applicable GCP and legal requirements

notification/approval of protocol

importation of investigational products

insurance

trial medication:

import license, labelling, storage,

SAE reporting

Appendix 5: ELEMENTS FOR AN INSPECTION PLAN

1. General aspects

Items

Support

Timelines

Expertise

SOP

Legalities

2. General Content

Agenda, Dates

Sites, Facilities

Team Members

Systems

Specifics

3. Layout

options

Linear Modules

Agenda with Addenda

4. Situational Aspects

Prospective

Flexible

APPENDIX 6: MODEL LETTERS FOR ANNOUNCEMENT

1. Template for the announcement of the inspection to the sponsor

<Headed paper, and name and address of inspector carrying out the inspection>

<Date>

<Local sponsor contact, name>

<Address>

PBSL Reference No.,

Application for <product name>

GCP Inspection

Subject: GCP Inspection of <sites and protocol name/number>

Dear <Local sponsor contact>,

The above-mentioned clinical study has been included in the marketing authorisation application for <product name>.

In connection with the examination of the above application, PBSL has asked for an inspection to be carried out of the conduct of the clinical study <protocol number.

Your facility has been selected as part of this inspection process. The PBSL is conducting this inspection. The lead inspector at your site will be <name> who will be accompanied by <names of other inspector/experts and their affiliation>. The inspection will be carried out at your facility at the following address: <sponsor site address>

We propose to conduct the inspection at your site on <dates>. We anticipate the inspection will last for <number> days. We will want to have an opening meeting of approximately 1½ hours at the beginning of the inspection with you and key members of your study team. There will also be a closing meeting of approximately 1½ hours with you and your team. During the inspection you and/or designated members of your

team should be available, on occasions, to explain details of the study conduct or to assist in locating documents and data.

You will need to ensure that all relevant departments and personnel are notified. They should be ready for inspection and have relevant documentation (including the local Trial Master File, Standard Operating Procedures, Case Report Forms) and facilities available and accessible. We will require direct access to these records. We will also need to interview members of the clinical study team, in particular the monitors responsible for the sites during the study, and to visit facilities involved including <monitoring, data management, clinical safety – include as required>. We will also be inspecting the following clinical investigators/<other facilities as appropriate> monitored/managed by your site. We may require access to relevant databases and/or printouts from these during the inspection.

Please ensure that there is a room where we can work, reviewing records and interviewing members of the study team. There should be a desk/table and chairs and we will need access to a phone, fax and photocopier. There will be <number of inspectors> inspectors present.

Please confirm your availability on these dates and that the address for the inspection is the appropriate one for the activities to be inspected. If there are any difficulties with the availability of the relevant personnel, documents or facilities please notify us immediately.

If you need any further information about the procedure to be followed for the inspection please contact me at the above address. We look forward to meeting you and your team.

2. Template for the announcement of the inspection to investigators

<Headed paper, and name and address of inspector carrying out the inspection>

<Date>

<Principal Investigator, name>

<Address>

PBSL Reference No.

Application for <product name>

GCP Inspection

Subject: GCP Inspection of < protocol name/number>

Dear <Principal Investigator name>,

The above-mentioned clinical study, including the work of your centre has been included in the marketing authorisation application for <product name>.

In connection with the examination of the above application, PBSL has asked for an inspection to be carried out of the conduct of the clinical study <protocol number>.

Your site has been selected as part of this inspection process. The < inspectorate name> is conducting this inspection on behalf of the PBSL. The lead inspector at your site will be <name> who will be accompanied by <names of other inspectors and their affiliation>. The inspection will be carried out at your site at the following address: <site address>

We propose to conduct the inspection at your site on <dates>. We anticipate the inspection will last for <number> days. We will want to have an opening meeting of approximately 1½ hours at the beginning of the inspection with you and key members of your study team. There will also be a closing meeting of approximately 1½ hours with you and your team. During the inspection you and/or designated members of your team should be available, on occasions, to explain details of the study conduct or to assist in locating documents and data.

You will need to ensure that all relevant departments and personnel are notified. They should be ready for inspection and have relevant documentation (including study related files, procedures, Case Report Forms, source documents and medical records) and facilities available and accessible. We will require direct access to these records. We will also need to interview members of the clinical study team and to visit facilities involved in this clinical study including the pharmacy, clinical laboratory <include departments/personnel as relevant>.

Please ensure that there is a room where we can work, reviewing records and interviewing members of the study team. There should be a

desk/table and chairs and we will need access to a phone, fax and photocopier. There will be <number of inspectors> present.

Please confirm your availability on these dates and that the address is the address of the site where the study was conducted. If there are any difficulties with the availability, at this site, of the relevant personnel, documents or facilities please notify us immediately.

If you need any further information about the procedure to be followed for the inspection please contact me at the above address. We look forward to meeting you and your team.

Yours sincerely,

<Lead Inspector>

cc: <names> Inspection team members, <name(s) Sponsor/Applicant contact>.

Appendix 7– Suggested covering letter text for submission of individual inspection report to the inspectee and sponsor

Address

With regard to the GCP inspection conducted DD/MM/YY to DD/MM/YY at <inspectee>, please find enclosed the inspection report.

The following advice is provided regarding report responses.

1. One person should assume overall responsibility for the responses. This individual should sign and date the document that includes the responses.

2. You should respond to the inspection findings. The inspection report will be clear on those findings that concern the application and these must be responded to otherwise the application may not be progressed. Inspection responses should cross-reference the finding number detailed in the report.

3. Responses should detail a brief summary of planned corrective and preventive actions and estimated timeframe for completion.

4. Indicate clearly if there is any major disagreement or factual errors with any inspection finding. 6. Photocopies of documentary evidence should NOT be submitted unless specifically requested in the report.

4. Please provide the responses in electronic format (by e-mail to PBSL or on CD) and a paper copy (inspector to amend this as required).

We look forward to receiving responses to the findings listed in the report by DD/MM/YY. (Amend date as appropriate)

Yours sincerely

Name

Appendix 8– Grading of inspection findings

Critical

Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or legal action required

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Comments

The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

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