



ZAMBIA MEDICINES REGULATORY AUTHORITY

**GUIDELINES ON REGULATING THE
CONDUCT OF CLINICAL TRIAL IN HUMAN
PARTICIPANTS**

First Edition

Table of contents

Page

A. Foreword.....	3
B. Acknowledgments.....	4
C. Glossary.....	5
D. GUIDELINES ON REGULATING THE CONDUCT OF CLINICAL TRIAL IN HUMAN PARTICIPANTS.....	13
When to Submit an Application to Conduct a Clinical Trial.....	13
Responsibilities Relating to Clinical Trials.....	14
Ethical Assessment.....	15
Insurance of Trial Subjects.....	15
Good Clinical Practice (GCP).....	15
The Clinical Trial Application.....	17
The Clinical Trial Protocol.....	17
The Investigator’s Brochure.....	18
Labelling and Dispensing of Trial Medications.....	18
Chemistry and Manufacturing.....	19
Requirements Concerning Informed Consent.....	20
Clinical Trial Amendments.....	22
Clinical Trial Records.....	22
Discontinuance of a Clinical Trial by a Sponsor.....	23
Reporting of Adverse Drug Reactions and Adverse Events.....	24
Submission of Progress Reports.....	24
Inspections of Clinical Trials.....	24
Withdrawal of Authorisation to Conduct a Clinical Trial.....	25
D. APPENDICES.....	25
Clinical Trial Application Form.....	27
Format for Investigator’s Curriculum Vitae.....	40
Joint Financial Declaration by Sponsor and Principle Investigator.....	41
Declaration by Principle Investigator.....	42
Declaration by Co-investigator.....	44
Clinical Trial Protocol Amendment Form.....	46
Application Form for Additional Investigators and Sites.....	49

A. Foreword

The Pharmaceutical Act (No. 14) of 2004 requires that Clinical trials intended to be conducted in Zambia meet acceptable standards of Good Clinical Practice (GCP).

These guidelines outline the information required by the Regulatory Authority from sponsors and applicants wishing to conduct clinical trials as well as to define the evaluation process for the conduct of clinical trials. These guidelines also indicate the order of the material to be submitted and the minimum requirements for conducting clinical trials.

These guidelines are not intended as a comprehensive guide on Good Clinical Practice (GCP) and should be read in conjunction with relevant international GCP guidelines. These guidelines have been prepared by the Pharmaceutical Regulatory Authority (PRA) in accordance with the WHO/SADC Guidelines.

Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the applications and subsequent approval of conduct of clinical trials.

It is therefore my sincere hope that these guidelines will provide the necessary information in preparing and submitting documents for conducting clinical trials in Zambia.

Finally, I wish to urge our esteemed readers and applicants to read this first edition of guidelines carefully and make as many suggestions as possible so that we have a version of the guidelines that are commensurate with current practices.

Dr S.M. Miti
PERMANENT SECRETARY
Ministry of Health

:

B. Acknowledgments

The Ministry of Health (MoH) and the Pharmaceutical Regulatory Authority (PRA) wish to acknowledge the immense contributions of individuals and organizations that constituted the Technical Working Group in developing these guidelines. The principal contributors for this guidance document were:

1. Professor Karashani: Ethics & Research Committee, UTH
2. Ms Esnat Mwape: Director General, PRA
3. Dr Christina Chisembele: Veterinary Surgeon, Dept. of Veterinary & Livestock Development, Lusaka
4. Dr G. Chishimba: Medical Practitioner, National AIDS Council
5. Dr K Choongo: Lecturer, UNZA School of Veterinary Medicine
6. Mrs Bernice C. Mwale: Director-Product Registration, PRA,
7. Mr. Pelekelo Mangisha: Assistant Regulatory Officer, PRA

The MoH and PRA would further like to thank the World Health Organisation (WHO) for providing financial and technical support to the development of these guidelines.

Ms E. Mwape
DIRECTOR-GENERAL
Pharmaceutical Regulatory Authority

C. GLOSSARY

The following definitions are provided to facilitate the interpretation of the guideline.

1.1 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).

1.2 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).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

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

1.5 Approval (in relation to Research Ethics Committees (REC))

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

1.6 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).

1.7 Audit Certificate

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

1.8 Audit Report

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

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 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).

1.11 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.

1.12 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.

1.13 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 Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product)

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

1.15 Compliance (in relation to trials)

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

1.16 Confidentiality

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

1.17 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.

1.18 Coordinating Committee

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

1.19 Coordinating Investigator

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

1.20 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.

1.21 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.

1.22 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.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 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.

1.25 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.

1.26 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.

1.27 Independent Research Ethics Committee (REC)

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. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 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.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) 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 regulatory authority(ies).

1.30 Institution (medical)

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

1.31 Institutional Research Ethics Committee (REC)

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.

1.32 Interim Clinical Trial/Study Report

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

1.33 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.

1.34 Investigator

A physician, dentist or other qualified person who conducts a clinical trial at a trial site. See also Sub-investigator.

1.35 Investigator / Institution

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

1.36 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.

1.37 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.

1.38 Monitor

The person responsible for ensuring that the study is performed at the agreed progression and 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).

1.39 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.

1.40 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.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

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

1.43 Principle Investigator

A person responsible for the conduct of the clinical trial at a trial site who is a physician, dentist or other qualified person, resident in the country and a member of good standing of a professional medical association. If a trial is conducted by a team of individuals at a trial site, the principle investigator is the responsible leader of the team. See also Subinvestigator.

1.44 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.

1.45 Protocol Amendment

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

1.46 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).

1.47 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.

1.48 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.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data

and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 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).

1.51 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).

1.52 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).

1.53 Sponsor

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

1.54 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.

1.55 Standard Operating Procedures (SOPs)

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

1.56 Subinvestigator

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

1.57 Subject/Trial Subject

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

1.58 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.

1.59 Trial Site

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

1.60 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).

1.61 Vulnerable Subjects

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

1.62 Well-being (of the trial subjects)

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

D. GUIDELINES ON REGULATING THE CONDUCT OF CLINICAL TRIAL IN HUMAN PARTICIPANTS

2. When to Submit an Application to Conduct a Clinical Trial
3. Responsibilities Relating to Clinical Trials
4. Ethical Assessment
5. Insurance of Trial Subjects
6. Good Clinical Practice (GCP)
7. The Clinical Trial Application
8. The Clinical Trial Protocol
9. The Investigator's Brochure
10. Labelling and Dispensing of Trial Medications
11. Chemistry and Manufacturing
12. Requirements Concerning Informed Consent
13. Clinical Trial Amendments
14. Clinical Trial Records
15. Discontinuance of a Clinical Trial by a Sponsor
16. Reporting of Adverse Drug Reactions and Adverse Events
17. Submission of Progress Reports
18. Inspections of Clinical Trials
19. Withdrawal of Authorisation to Conduct a Clinical Trial

2. When to Submit an Application to Conduct a Clinical Trial:

- 2.1 An application for approval to conduct a clinical trial is required for the following categories of medicines:
 - a. Unregistered medicines
 - b. Registered medicines where the proposed clinical trials are outside of the conditions of approval. These may include changes to:
 - i. indication(s) and clinical use
 - ii. target patient population(s)
 - iii. route(s) of administration
 - iv. dosage regimen(s)
- 2.2 An application for authorization to conduct a clinical trial described in paragraph 2.1 above must be made on a form and accompanied by an application fee as determined by the Regulatory Authority.
- 2.3 No person may conduct a clinical trial using investigational products included in paragraph 2.1 above without prior authorisation from the Regulatory Authority.
- 2.4 A clinical trial authorised by the Regulatory Authority must be conducted in accordance with guidelines for Good Clinical Practice (GCP) as may from time to time be determined by the Authority.

- 2.5 A clinical trial authorised by the regulatory Authority may only proceed at a clinical trial site once clearance has been obtained from a recognised Research Ethics Committee.
- 2.6 Approval by the Regulatory Authority to conduct post-marketing clinical trials of a registered medicine within the approved conditions of registration of such a medicine is not required. However, approval by a recognised Research Ethics Committee is required prior to initiation of such studies.
- 2.7 Treatment of an individual patient by a medical practitioner with an unregistered medicine or with a registered medicine outside of the approved conditions of registration of such a medicine is not considered to be a clinical trial and would usually require special approval by the Regulatory Authority on a named patient basis.

3. Responsibilities Relating to Clinical Trials:

- 3.1 An application to conduct a clinical trial may be made by a pharmaceutical company (sponsor), clinical research organisation (CRO), or in the case of investigator-initiated academic research studies, by the research institution or principle investigator.
- 3.2 A statement by the applicant must be provided indicating that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading.
- 3.3 The applicant and all investigators must sign declarations that they are familiar with and understand the clinical trial protocol and will comply with Good Clinical Practice standards, as determined by the Regulatory Authority, in the conduct of the trial.
- 3.4 In the case of multicentre trials, the coordinating investigator must also sign the application form.
- 3.5 Upon signing the application, all parties accept responsibility that all applicable regulations and requirements will be adhered to. Furthermore, all parties are responsible for ensuring that the trial is based on and implemented according to well-founded ethical and scientific principles, which are expressed in the Helsinki Declaration and its current revisions as well as in international guidelines for Good Clinical Practice (GCP).
- 3.6 The principle investigator must be an appropriately qualified and competent person having practical experience within the relevant professional area, who is a resident in the country and who is responsible for the conduct of the clinical trial at a clinical trial site. A principle

investigator must have had previous experience as a co-investigator in at least two trials in the relevant professional area.

- 3.7 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 three years.
- 3.8 Multi-centre trials must have a coordinating investigator who will be responsible for coordinating all local clinical trial sites. This person does not necessarily have to be involved with any direct treatment of subjects involved in the trial.
- 3.9 If the trial is a part of an international study, information regarding the other participating countries must be provided including how large a part of the trial will be carried out locally.

4. Ethical Assessment:

- 4.1 A clinical trial that has received approval from the Regulatory Authority may only proceed once clearance has also been obtained from a recognized Research Ethics Committee for a particular trial site.
- 4.2 Ethical evaluations of clinical trials of drugs must take place in accordance with the principles of Good Clinical Practice as well as the Declaration of Helsinki and its current revisions.

5. Insurance of Trial Subjects:

- 5.1 All subjects must be satisfactorily insured against possible injuries that might arise during the conduct of the clinical trial.
- 5.2 For all sponsor-initiated trials, a valid insurance certificate for the duration of the study must be provided prior to study initiation.
- 5.3 For investigator-initiated research trials, proof of current malpractice insurance that covers clinical trials must be provided.

6. Good Clinical Practice (GCP):

- 6.1 Applicants must be able to demonstrate that clinical trials are conducted according to generally accepted principles of good clinical practice.
- 6.2 Trials must be conducted in accordance with the applicable regulatory requirement(s)

- 6.3 Before a trial is initiated, foreseeable risks and inconveniences must 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.
- 6.4 The rights, safety, and well being of the trial subjects are the most important considerations and must prevail over interests of science and society.
- 6.5 The available non-clinical and clinical information on an investigational drug must be adequate to support the proposed clinical trial.
- 6.6 Clinical trials must be scientifically sound, and described in a clear, detailed protocol.
- 6.7 A trial must be conducted in compliance with a protocol that has received regulatory and ethics approval prior to initiation.
- 6.8 The medical care given to, and medical decisions made on behalf of, subjects must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- 6.9 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 6.10 Freely given informed consent must be obtained from every subject prior to clinical trial participation.
- 6.11 All clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation and verification.
- 6.12 The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- 6.13 Investigational drugs must be manufactured, handled, and stored in accordance with applicable good manufacturing practices (GMP) and must be used in accordance with the approved protocol.
- 6.14 Systems with procedures that assure the quality of every aspect of the trial must be implemented.

7. The Clinical Trial Application:

- 7.1 The Regulatory Authority will undertake an assessment of a clinical trial only upon receiving fully completed applications.
- 7.2 The following are the requirements when submitting an application to conduct a clinical trial (6 copies of each of the following are to be submitted):
 - 7.2.1 Covering letter
 - 7.2.2 Completed Application form (CTF1)
 - 7.2.3 Cover sheet
 - 7.2.4 Checklist
 - 7.2.5 Final version of the Clinical Trial Protocol
 - 7.2.6 Patient Information leaflet and Informed Consent form
 - 7.2.7 Investigators Brochure and/or Package Insert
 - 7.2.8 Signed investigator(s) CV(s) in required format
 - 7.2.9 Signed declaration by Principal investigator(s)
 - 7.2.10 Signed joint declaration by Sponsor/National Principal investigator
 - 7.2.11 Signed declaration by Co- or Sub-investigators
 - 7.2.12 Signed declaration by regional monitor and/or study coordinator
 - 7.2.13 Indemnity and Insurance Certificate and/or
 - 7.2.14 Proof of Malpractice insurance of trialist(s)
 - 7.2.15 Ethics Committee(s) approval or
 - 7.2.16 Copy of letter submitted to Ethics Committee(s)
 - 7.2.17 Electronic copies to be submitted in Microsoft Word format
 - 7.2.18 Financial declaration by Sponsor and Principle investigator
- 7.3 Documentation must be arranged in separate folders. The extent of the documentation requirements will generally depend on the development phase of the investigational product.

8. The Clinical Trial Protocol:

- 8.1 The clinical trial protocol must contain at least the following information, consistent with the requirements of internationally accepted GCP guidelines:
 - 8.1.1 Background and purpose of the trial
 - 8.1.2 Details of the study population;
 - 8.1.3 Design and type of trial
 - 8.1.4 Criteria for selection of trial subjects
 - 8.1.5 Trial treatments
 - 8.1.6 Control groups and control treatments where applicable
 - 8.1.7 Choice of method and statistical justification for the number of trial subjects

- 8.1.8 Monitoring, assessment and reporting of effects, adverse drug reactions and adverse events
 - 8.1.9 Clinical and laboratory safety tests
 - 8.1.10 Assessment of results
 - 8.1.11 Quality assurance of data and procedures
 - 8.1.12 Drug accountability
 - 8.1.13 Ethical assessment
- 8.2 To facilitate evaluation as well as provide guidance on the relevance of the study, the protocol should clearly indicate the complete development plan for the trial and the investigational product. This should include the following:
- 8.2.1 A plan for the possible discontinuation of previous treatment
 - 8.2.2 The rationale for the use of placebo products
 - 8.2.3 Follow-up of trial subjects after the conclusion of the trial
 - 8.2.4 A plan for involvement of other personnel
 - 8.2.5 The state of readiness in case of complications
 - 8.2.6 A plan for the publication of the results (publishing plan)
 - 8.2.7 A description of how special lists of the trial subjects and forms relating to the trial subjects will be kept for each trial subject included in the trial

9. The Investigator's Brochure:

- 9.1 The investigator's brochure must contain at least following information:
- 9.1.1 The physical, chemical and pharmaceutical properties of the drug
 - 9.1.2 The pharmacological aspects of the drug, including its metabolites in all animal species tested
 - 9.1.3 The pharmacokinetics and metabolism of the drug, including the biological transformation of the drug in all animal species tested
 - 9.1.4 Toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study in respect of the drug
 - 9.1.5 Results of carcinogenicity studies in any animal species tested in respect of the drug
 - 9.1.6 Results of clinical pharmacokinetic studies of the drug
 - 9.1.7 Information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans.

10. Labelling and Dispensing of Trial Medications:

- 10.1 Investigational, comparator and /or placebo products used in a clinical trial must be properly labelled and contain the following information:

- 10.1.1 A statement indicating that the drug is an investigational drug to be used only by a qualified investigator
 - 10.1.2 The name, number or identifying mark of the drug
 - 10.1.3 The expiration date of the drug
 - 10.1.4 The recommended storage conditions for the drug
 - 10.1.5 The lot number of the drug
 - 10.1.6 The name and address of the sponsor
 - 10.1.7 The protocol code or identification
 - 10.1.8 The name and address of the premises where the clinical trial is to be carried out.
- 10.2 Registered products that are incorporated in the trial must also be labelled in accordance with 10.1 above.
- 10.3 Trial medications must be stored and dispensed by the pharmacy or the pharmaceutical department at the trial site in accordance with good dispensing practices. The general principle is that investigational products used in clinical trials should be handled in the same way as registered medicines.

11. Chemistry and Manufacturing:

- 11.1 Clinical trial investigational medicinal products must be manufactured in accordance with the code of *Good Manufacturing Practice (GMP)* including *Good Manufacturing Practice for Investigational Medicinal Products*. This implies that the manufacture of the investigational product may be subject to control and inspection in the same way as in the case of marketed medicinal products.
- 11.2 Certificates of analysis (COAs) must be provided for all investigational and comparator products.
- 11.3 Chemistry and manufacturing information provided in the clinical trial application should be presented in a concise manner and should include the following:
- a. Drug Substance:
 - Names and Source
 - Method of Manufacture
 - Physicochemical Properties and Structure Elucidation
 - Impurities
 - Specifications and Test Methods and Batch Analyses
 - Stability and Packaging
 - b. Dosage Form:
 - Source
 - Developmental Pharmaceuticals

- Formulation and Method of Manufacture and Packaging
- Specifications and Test Methods and Batch Analyses
- Stability

- 11.4 If the pharmaceutical or chemical properties of the investigational product have been altered compared to those in use during animal testing or previous clinical trials, such alterations must be described and justified. This, for instance, applies to impurities and degradation products.
- 11.5 Pharmaceutical and/or chemical alterations in an investigational product that is used in an ongoing clinical trial, and that may affect the quality, safety and/or efficacy of the medicinal product must immediately be reported to the Regulatory Authority.
- 11.6 If the composition of the medicinal product is altered, additional bioavailability or bioequivalence studies may be required.
- 11.7 (Based on stability data, all investigation) In cases where an extension of the shelf life for the finished medicinal product is desired, an application for this must be submitted to the Regulatory Authority. In such cases stability data or certificates of analysis (COAs) from reanalysis of the relevant batches must be submitted.
- 11.8 The re-labelling of any remaining packages from previously manufactured batches must be performed in accordance with established written procedures and Good Manufacturing Practices (GMP).

12. Requirements Concerning Informed Consent:

- 12.1 It is an important principle that subjects contemplating participation in a clinical trial have access to certain basic information regarding the clinical trial.
- 12.2 A copy of the written information intended for trial subjects, as it will be set out in the informed consent form, that includes a statement of the risks and anticipated benefits arising to the health of trial subjects as a result of their participation in the clinical trial, must be submitted to the Regulatory Authority.
- 12.3 The following list of items (not exhaustive), should be included in the patient information leaflet:
- 12.3.1 An introduction including information on participation in the study
 - 12.3.2 The aims, objectives and goals of the study
 - 12.3.3 The methods to be employed and what this will involve for the trial subject

- 12.3.4 Criteria for selection that apply to the subject
- 12.3.5 Whether the trial has any direct benefit for the trial subject
- 12.3.6 Which medicines are included in the trial; whether the preparations are available on the market and if inactive substances (placebo) will be used. The patient must be informed of the fact that allocation to a specific treatment group will occur at random
- 12.3.7 Other medicines that may/may not be taken at the same time as the trial medication. Non-prescription medications and complementary products should be mentioned specifically
- 12.3.8 Pregnant and breast-feeding subjects must be excluded from participation in the study and safe contraceptives must be used by women of a childbearing age. Information concerning safe use of contraceptives for men, if this is relevant, must be provided
- 12.3.9 Practical consequences of participating (type of involvement, time required)
- 12.3.10 Risks, adverse drug reactions and any possible discomfort should be detailed
- 12.3.11 If the person does not consent to participate, details of alternative treatments available must be provided
- 12.3.12 Discontinuing current treatment as a condition of participating
- 12.3.13 Follow-up treatment, if applicable
- 12.3.14 Confidentiality
- 12.3.15 Emphasis that participation is voluntary and that consent can be withdrawn at any time and without having to provide reasons. Subjects must be informed that refusing to participate will have no effect on further treatment or the relationship to the treating physician or to the institute
- 12.3.16 Information that Regulatory Authorities and Research Ethics Committees may require access to subject identifying data. Consent for this access must be a condition for participation in the study
- 12.3.17 Information about who the trial subject can contact. This should include details of the investigator, Research Ethics Committee and Regulatory Authority
- 12.3.18 Information about indemnity, insurance and compensation in the event of trial-related injury
- 12.3.19 Information if biological fluids will be used and/or stored for pharmacogenetic sub-studies. Participation in this part of the study should be voluntary and a separate informed consent must be obtained

- 12.4 Additionally, the following issues, where applicable, must be addressed in the process of obtaining informed consent:
 - 12.4.1 Trials on under-aged subjects and subjects with reduced competence to consent
 - 12.4.2 Withdrawal of consent
 - 12.4.3 Provision of new information to subjects as these become available

13. Clinical Trial Amendments:

- 13.1 Applications for amendments to clinical trial protocols must be submitted to the Regulatory authority for approval prior to their implementation.
- 13.2 The applicant must submit the original wording, revised wording, and rationale for the change including a copy of a complete protocol incorporating all amendments.
- 13.3 These amendments must also be presented to the Research Ethics Committee for approval prior to implementation.
- 13.4 Approval must be obtained for the following amendments to the clinical trial protocol:
 - 13.4.1 Changes that affect patient selection and monitoring
 - 13.4.2 Changes that affect clinical efficacy and safety requirements (e.g. dosage adjustments, study procedures, etc)
 - 13.4.3 Changes that affect patient discontinuation
 - 13.4.4 Changes that result in the extension of the duration of the clinical trial
 - 13.4.5 Changes that result to the chemistry and manufacturing information that may affect drug safety and quality (For example: specifications for the drug where the limits of the test are relaxed or deleted; where a new impurity or degradation product has been identified; and, the addition of new raw materials, solvents, reagents, catalysts or any other material used in the manufacture of the drug substance.)

14. Clinical Trial Records:

- 14.1 The sponsor must record, handle and store all information in respect of a clinical trial in order to ensure that the clinical trial is conducted in accordance with good clinical practices and in a way that allows its complete and accurate reporting as well as its interpretation and verification.
- 14.2 The sponsor must keep all records related to the conduct of a clinical trial in a format that facilitates verification for the purpose of an inspection.

- 14.3 The sponsor must submit requested records within 48 hours if safety concerns arise.
- 14.4 Additionally, the Regulatory Authority can request the submission of additional information within seven days to facilitate an inspection of a site.
- 14.5 The sponsor must maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:
 - 14.5.1 A copy of all versions of the investigator's brochure for the drug;
 - 14.5.2 Records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change;
 - 14.5.3 Records respecting all adverse events in respect of the drug that have occurred locally or internationally, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
 - 14.5.4 Records in respect of the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the use of the drug may endanger the health of the clinical trial subjects or other persons;
 - 14.5.5 Records in respect of the shipment, receipt, disposition, return and destruction of the drug;
 - 14.5.6 For each clinical trial site, an undertaking from the principle investigator that is signed and dated by the principle investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that the principle investigator will conduct the clinical trial in accordance with good clinical practices;
 - 14.5.7 For each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Committee and Regulatory Authority for that clinical trial site.

15. Discontinuance of a Clinical Trial by a Sponsor:

- 15.1 If a clinical trial is discontinued by the sponsor in its entirety or at a clinical trial site, the sponsor must inform the Regulatory Authority no later than 15 days after the date of the discontinuance; and must:
 - 15.1.1 Provide the Regulatory Authority with the reason/s for the discontinuance and its impact on the proposed or ongoing

- clinical trials in respect of the drug conducted by the sponsor;
- 15.1.2 As soon as possible, inform all investigators of the discontinuance and of the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;

16. Reporting of Adverse Drug Reactions and Adverse Events:

- 16.1 The term adverse drug reactions is understood as adverse events where the connection to the trial medication cannot be excluded (possible or probable connection).
- 16.2 The sponsor must report serious adverse drug reactions that emerge during trials as individual reports (one report per patient).
- 16.3 During the course of a clinical trial, the sponsor must inform the Regulatory Authority and the Research Ethics Committee of any serious unexpected adverse drug reaction in respect of the drug that has occurred locally or internationally as follows:
- 16.3.1 If it is fatal or life threatening, immediately but no later than seven days after becoming aware of the information
- 16.3.2 If it is neither fatal nor life threatening, within 15 days after becoming aware of the information.
- 16.4 The potential connection to the study drug must be clarified, and updated reports sent to the Regulatory Authority as soon as these are available.
- 16.5 With regard to adverse drug reaction that are serious and already known (described in Investigator's Brochure or the Summary of Product characteristics (SPC)) there are no fixed time limits. These cases must be reported as soon as the necessary information is available.

17. Submission of Progress Reports:

- 17.1 The applicant conducting the clinical trial must submit progress reports to the Regulatory Authority on a six monthly basis from the date of initiation of the clinical trial and within 30 days of the completion or termination of the clinical trial

18. Inspection of Clinical Trials:

- 18.1 The Regulatory Authority may inspect clinical trial sites and trial sponsors to ensure that the generally accepted principles of good clinical practice are met.

- 18.2 The objectives of the inspection will be to ensure that participants in clinical trials are not subjected to undue risks, to validate the quality of the data generated or to investigate complaints.
- 18.3 The Regulatory Authority may use the information collected as a result of these inspections to ensure compliance with the regulatory framework and may take enforcement action, when deemed necessary.

19. Withdrawal of Authorisation to Conduct a Clinical Trial

- 19.1 The Regulatory Authority may request additional information on a clinical trial or withdraw the authorisation to conduct a clinical trial if the Authority is of the opinion that the safety of the subjects in the trial is compromised, or that the scientific reasons for conducting the trial have changed.

E. APPENDICES

1. Clinical Trial Application Form
2. Format for Investigator's Curriculum Vitae
3. Joint Financial Declaration by Sponsor and Principle Investigator
4. Declaration by Principle Investigator
5. Declaration by Co-investigator
6. Clinical Trial Protocol Amendment Form
7. Application Form for Additional Investigators and Sites
8. Clinical Trial Adverse Event Report form

**APPLICATION TO CONDUCT
A CLINICAL TRIAL**

APPLICATION TO CONDUCT A CLINICAL TRIAL

The following are the requirements when submitting an application to conduct a clinical trial:

- i. Covering letter
- ii. Cover sheet
- iii. Checklist
- iv. Completed Application form
- v. All documents and electronic copies to be submitted in duplicate
- vi. Final version of the Clinical Trial Protocol
- vii. Patient Information leaflet and Informed Consent form
- viii. Investigators Brochure and/or Package Insert
- ix. Signed investigator(s) CV(s) in required format
- x. Signed declaration by Principal investigator(s)
- xi. Signed joint declaration by Sponsor/National Principal investigator
- xii. Signed declaration by Co- or Sub-investigators
- xiii. Signed declaration by regional monitor and/or study coordinator
- xiv. Indemnity and Insurance Certificate and/or
- xv. Proof of Malpractice insurance of trialist(s)
- xvi. Ethics Committee(s) approval or
- xvii. Copy of letter submitted to Ethics Committee(s)
- xviii. Diskettes to be submitted in Microsoft Word format
- xix. Financial declaration by Sponsor and Principle investigator

CLINICAL TRIAL APPLICATION

SECTION 1 – CHECKLIST OF REQUIRED DOCUMENTATION

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title:

Protocol No:

Version No:

Date of Protocol:

Study Drug:

Ref number (if applicable):

Ref number(s) of comparator drug(s) (if applicable):

Ref number(s) of concomitant drug(s) (if applicable):

Date(s) MCC approval of previous protocol(s):

Sponsor:

Applicant:

Contact Person:

Address:

Telephone Number:

Fax Number:

Cell Number:

E-mail address:

FOR OFFICIAL USE

Date original application received:

Tracking No:

Application fee paid:

Signature:

Date:

ACKNOWLEDGEMENT OF RECEIPT OF APPLICATION (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.

Contact Details: Name:

Fax No.:

Receipt of new application is hereby acknowledged.

Date:

Signature (of recipient):

Name:

CHECKLIST

- COVERING LETTER
 - FULLY COMPLETED APPLICATION (SECTIONS 1–3)
 - PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES, ETC.)
 - PATIENT INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)
 - INVESTIGATORS BROCHURE AND / OR ALL PACKAGE INSERT(S)
 - INVESTIGATOR'S CV(S) IN REQUIRED FORMAT
 - SIGNED DECLARATION(S) BY INVESTIGATOR(S)
 - CV(S) AND SIGNED DECLARATION(S) BY STUDY CO-ORDINATOR AND/OR MONITOR
 - CERTIFICATE(S) OF ANALYSIS
 - INSURANCE CERTIFICATE
- AND IF NECESSARY:**
- LETTER ENDORSING GENERIC INSURANCE CERTIFICATE
 - ETHICS APPROVAL
- OR**
- COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL
 - COPY/IES OF RECRUITMENT ADVERTISEMENT(S) (IF APPLICABLE)
 - FINANCIAL DECLARATION (SPONSOR AND NATIONAL PI)

Electronic versions of the application form (Sections 1 –3), the protocol, the investigator's brochure and/or other relevant documents:

- LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT)

List of files submitted on diskette/CD-ROM:

**NB: INCOMPLETE APPLICATIONS WILL NOT BE
PROCESSED**

--

Declaration by applicant:

We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

We, the undersigned, hereby declare that all information contained in, or referenced by, this application is complete and accurate and is not false or misleading.

We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and all applicable legal, ethical and regulatory requirements.

Applicant (local contact)

Date

National Principal Investigator /
National Co-coordinator /
Other (state designation)

Date

SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title:

Protocol Number/identification:

Date of final protocol:

Part 1: CONTACT DETAILS (NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)

1.1 Applicant: (as in Section 1)

1.2 Sponsor: (as in Section 1)

1.3 If no sponsor, person or organisation initiating, managing, and / or funding the clinical trial:

1.4 Local Contact Person for correspondence:

1.5 National Principal Investigator/Coordinator: (or equivalent person)

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor:

1.8 Study Coordinator:

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(S)

2.1 Name(s) and details of investigational product(s) to be used in trial:

[A summary of the chemistry and manufacturing data, formulation, composition, excipients and strength should be provided. Complete chemistry and manufacturing data should be included in the investigator's brochure. Product(s) registration number(s) and date(s) of registration, if applicable, should be included]

- 2.2 Name(s) and details (as above) of comparator product(s) and product registration number(s) and date(s) of registration if applicable:

[As in 2.1, where applicable. Package inserts for registered comparator products should be included]

- 2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and product registration number(s) if applicable:

[As in 2.1, where applicable. Package inserts for registered products should be included]

- 2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required:

- 2.5 If any of the above drugs are marketed locally, explain whether locally-sourced products will be used in the trial:

- 2.6 Details of receipt of drugs from supplier, packaging, storage and shelf-life and dispensing:

- 2.7 Date (or envisaged date) of application for registration of trial medication:

*[Provide an explanation if registration is **not** envisaged]*

- 2.8 Registration status of trial medication, for the indication to be tested in this trial, in other countries:

[i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority] [Attach as an appendix if necessary]

Part 3: DETAILS OF TRIALIST(S) AND TRIAL SITE(S)

- 3.1 Details of Investigator(s):

[Designation and title of principal investigators / investigators) Include Name/Address/Tel/Cell/Fax/E-Mail]

- 3.2 Current work-load of Investigator(s):

[Number of studies currently undertaken by trialist(s) as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work and non-trial work]

Recommended format for Investigator work-load:

Investigator (Name and designation):			
Total number of current studies (all stages) on specified date	Number	Date	
Total number of patients / participants for which responsible on specified date	Number	Date	
ESTIMATED TIME PER WEEK [168 hours denominator]	Hours	%	
<u>Clinical trials</u>	Clinical work (patient contact)		
	Administrative work		
<u>Organisation</u> (Practice / university / employer)	Clinical work		
	Administrative work		
<u>Teaching</u>	Preparation / evaluation		
	Lectures / tutorials		
<u>Writing up</u> work for publication / presentation			
<u>Reading</u> / sourcing information (e.g. internet searches)			
<u>Other</u> (specify)			

3.3 Details of Trial Site(s):

[Name of site, physical address, contact details, contact person, etc]

3.4 Capacity of Trial Site(s):

[Number of staff, names, qualifications, experience -- including study coordinators, site facilities, emergency facilities, other relevant infrastructure]

Part 4: PARTICIPANTS (TRIAL SUBJECTS)

- 4.1 Number of local participants:
- 4.2 Total number of participants worldwide:
- 4.2 Total enrollment in each local site/centre:
[If competitive enrollment, state minimum and maximum number per site.]
- 4.3 Volunteer base from which local participants will be drawn:
- 4.4 Retrospective data indicating potential of each site to recruit required number of participants within envisaged duration of trial:
[Attach as an appendix if necessary]

Part 5: OTHER DETAILS

- 5.1 Provide an explanation if the trial is to be conducted locally only and not in the host country of the applicant / sponsor:
- 5.2 Estimated duration of trial:
- 5.3 Details of other Regulatory Authorities to which applications to conduct this trial have been submitted, but approval has not yet been granted. Include date(s) of application:
- 5.4 Details of other Regulatory Authorities which have approved this trial. Include date(s) of approval and number of sites per country:
- 5.5 Details of other Regulatory Authorities or Research Ethics Committees which have rejected this trial, if applicable, and provide reasons for the rejection:
- 5.6 Details of and reasons for this trial having been suspended at any stage by other Regulatory Authorities, if applicable:

- 5.7 Details if this trial is being undertaken in other SADC countries, any other country in Africa, or any country where there is no regulatory control of clinical trials:
- 5.8 Previous studies using this agent which have been approved by the Regulatory Authority:
Approval number:
Study title:
Protocol number:
Date of approval:
Principal Investigator:
Date(s) of progress report(s):
Date of final report:
- 5.9 If any sub-studies are proposed as part of this protocol, indicate whether these will also be conducted locally. If not, please explain:

Part 6: ETHICS

- 6.1 *Research Ethics Committee responsible for each site, date of approval or date of application:*
- [Attach copy of response(s) made by, and/or conditions required by Research ethics Committee(s) if available]
- 6.2 *State which Good Clinical Practice (GCP) guidelines are being followed:*
- 6.3 Details of capacity building component of the trial, if any:
- 6.4 Details of GCP training of investigators, monitors, study co-coordinators in terms of conducting this trial:
- 6.5 *Detailed safety and monitoring plan for each site:*
- [Attach as an appendix if necessary]
- 6.6 *Details of trial insurance:*
- [e.g. insurer, policy holder, policy number, insurance cover, period of validity]

6.7 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial:

6.8 *Remuneration to be received by investigators, trial participants or others:*

[Indicate breakdown of costs to be covered, if applicable. Indicate compensation to be received by participants for travel and incidental expenses.]

SECTION 3 – APPLICANT’S REPORT / PRESENTATION

[Please use Black 12 point Arial Font, using MSWord for the electronic version]

[The following section should be fully completed]

1. Title:
2. Protocol Number/Identification:
3. Summary of the Rationale for study:
[Provide a brief description of the rationale and relevance of the study, e.g. why should this trial be undertaken at all?]
4. Summary of the Background Information:
[Provide a brief statement on each of the following:]
Disease / problem
Local relevance (e.g. local epidemiology)
Properties of trial drug (e.g. pharmacological / chemical / pharmaceutical)
Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity, etc)
Clinical findings (e.g. pharmacokinetics, safety, tolerability, efficacy)
5. Objectives of study:
[These should be clearly listed and justified]
6. Study design:
[These should be clearly described and each component justified. Include study phase, use of placebo, dosages, randomisation, blinding, duration of treatment, etc.]
7. Trial Participants:
[Number of participants; ability to enrol required number within stated time, etc]
8. Criteria for selection, eligibility and enrolment:
[Inclusion and exclusion criteria listed and justified]

9. Treatment modalities and regimens, drug accountability:
[These should be clearly explained and justified for all participant groups/arms, e.g. route of administration, dose, etc. Clearly describe drug accountability]
10. Outcome measurements/variables:
[These should be clearly stated and justified]
11. Adverse events:
[Measures to monitor assess and report all adverse events should be clearly stated and justified]
12. Statistical measures:
[Provide a clear and justified description of the following:]
Determination of sample size
Statistical method(s) and analysis of quantitative measures
Statistical method(s) and analysis of qualitative measures
Data processing (e.g. how, where, when, who)
Interim analysis and stopping rules if applicable
13. Ethical Issues:
[The following additional information, in respect of the proposed trial, is required:]
 - *Comment on which GCP guidelines are being followed*
 - *Comment on choice of investigators*
 - *Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial*
 - *Comment on capacity building element of trial*
 - *Comment on resources of sites and sponsor*
 - *Comment on monitors and monitoring plan*
 - *Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements*
 - *Comment on insurance and indemnity measures*
 - *Comment on appropriateness of Patient Information Leaflet and Informed Consent*
 - *Comment on availability and completeness of separate Patient Information leaflets and Informed Consent forms for any proposed archiving of biological specimens for later research or for genetics research.*
 - *Comment on ethics of the publication policy*
 - *Comment on treatment and/or management of participants and their disease condition(s) after completion of trial*
 - *Comment on ethics committee capacity to monitor site and conduct of trial*

- Provide an explanation if minimum recommended compensation for participants is not being provided.

14. Other relevant information not included above:

- Are references adequate and dates of references current?
- Are there discrepancies between the protocol and investigator's brochure or package inserts? Are there specific explanation(s) for these discrepancies?
- Other comments on this trial.

For office use:

Reviewer's questions and concerns to be considered and/or forwarded to applicant:

Reviewer's recommendation:

Declaration of conflict of interests by reviewer (if applicable):

Signature of reviewer:

Date:

Appendix 2

Recommended Format for CVs of Individuals Participating in Clinical Trials

1. Study Title:
2. Protocol Number:
3. Designation:
[e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Co-ordinator, Regional Monitor, Local Monitor, Clinical Research Associate]
4. Personal Details
Name:
Work Address:
Telephone Number:
Fax Number:
Cell-phone Number:
e-mail address:
5. Academic and Professional Qualifications
6. Professional registration number
7. Current personal medical malpractice insurance details
8. Relevant related work experience (brief) and current position
9. Participation in clinical trials research in the last three years
[Study title, protocol number, designation. If multiple trials, only list those with relevance to this application, or in the last year]
10. Peer-reviewed publications in the past 3 years
11. Date of last GCP training
[As a participant or presenter]
12. Any additional relevant information supporting abilities to participate in conducting this trial
[Briefly]

Signature:

Date:

Appendix 3

Joint Declaration by Sponsor (or representative) and Principal Investigator (or National Principal Investigator) concerning sufficient funds to complete study

Title:

Protocol:

I, <full name>, representing <sponsor or representative>

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.

Signed _____ Date _____

SPONSOR (or alternative)

Name

Address

Contact details

Signed _____ Date _____

PRINCIPAL INVESTIGATOR (or National PI)

Name

Address

Contact details

Appendix 4

Declaration by Principal Investigator

Name:

Title of Trial:

Protocol:

Site:

1. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Principle Investigator within the context of this study.
2. I have notified the regulatory authority of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
3. I have thoroughly read, understood, and critically analysed the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).
4. I will conduct the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the Regulatory Authority have been obtained.
7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons), shall at all times be treated in a dignified manner and with respect.
9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
*[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal associations with other persons or organizations that may inappropriately influence (bias) his or her actions.]**
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
12. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

Appendix 5
Declaration by Co- and Sub-Investigators

Name:

Title of Trial:

Protocol:

Principal Investigator's Name:

Site:

Designation:

13. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the Investigator within the context of this study.
14. I will carry out my role in the trial as specified in the protocol and in accordance with Good Clinical Practice (GCP).
15. I will not commence with my role in the trial before written authorisations from the relevant Research Ethics Committee(s) as well as the Regulatory Authority have been obtained.
16. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.
17. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
18. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
*[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]**
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
19. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.
20. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

Appendix 6
Declaration by Regional Monitor

Name:

Title of Trial:

Protocol:

Site:

21. I am familiar with internationally accepted standards of Good Clinical Practice (GCP) and understand the responsibilities and obligations of the clinical trial Monitor within the context of this study.
22. I have notified the regulatory authority of any aspects of the above with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)
23. I will carry out my responsibilities as specified in the trial protocol and accordance with Good Clinical Practice (GCP)
24. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
*[Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.]**
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
25. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)
26. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)
27. I will submit all required reports within the stipulated time-frames.

Signature:

Date:

Witness:

Date:

APPLICATION FOR CLINICAL TRIAL PROTOCOL AMENDMENT

REFERENCE/TRACKING NUMBER FOR THIS CORRESPONDENCE: _____

APPLICATION FOR APPROVAL OF:

- PROTOCOL AMENDMENT**
- INCREASE IN NUMBER OF PATIENTS PARTICIPATING**
- CHANGES IN DOSE / REGIMENT OF STUDY DRUG**

STUDY TITLE:

PROTOCOL NUMBER:

DATE:

1. APPLICANT

- 1.1 Name/address/telephone/fax number of Applicant wishing to conduct trial:
- 1.2 Name/address/telephone/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable):
- 1.3 Name, designation and qualifications of person representing the Applicant (**Local Contact Person for all further correspondence**)
- 1.4 National Coordinator name, address, telephone/fax number

1.5 International Principal Investigator name, address, telephone/fax number

1.6 Name of sponsor

2. TRIAL PARTICULARS (original application)

2.1 Trial Approval Number:

2.2 Date of Approval of original protocol:

2.3 Number of local Investigators approved for this trial:

2.4 Number of local sites approved for this trial:

2.5 Number of participants approved for this trial:

3. AMENDMENT PARTICULARS

(Please list requests for approval)

Does the applicant wish to increase the number of local subjects participating in this trial?

Yes

No

Does the applicant wish to change the dose / regimen of the study drug?

Yes

No

Does this amendment request require a new consent form to be signed by the participant?

Yes

No

If "Yes" please submit new PIL together with this application.

3.1 Protocol Amendment Number:

3.2 Version Number and Date of Protocol Amendment (for each document submitted):

3.3 General motivation for the proposed Amendment: [List all of the issues included in the amendment and provide the rationale for each amendment]

3.4 Details of the proposed Protocol Amendment: [For each amendment, provide a brief motivation and clearly **highlight changes to the original protocol**; this can be done either as “**old text**” replaced with “**new text**” or with the **old text deleted** with a line through it and the **new text in bold and underlined**]

3.5 Will this Amendment apply to all approved investigators/sites:

YES
NO

If NO: Specify the investigator(s) / site(s) for which the Amendment will apply:

4. ETHICS COMMITTEE APPROVAL

4.1 Have the Research Ethics Committee(s) responsible for each centre to which this amendment applies been notified?

4.2 Research Ethics Committee(s) responsible:

4.3 Date of application to Ethics Committee:

4.4 Date of approval by Ethics Committee:

I/We, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

Applicant (local contact)

Date

APPENDIX 8

**APPLICATION FOR ADDITIONAL
INVESTIGATOR(S), CHANGE OF
INVESTIGATOR(S) OR
ADDITIONAL CLINICAL TRIAL
SITES**

REFERENCE/TRACKING NUMBER FOR THIS CORRESPONDENCE: _____

APPLICATION FOR APPROVAL OF:

- CHANGES IN INVESTIGATOR (S) AT APPROVED SITE (includes additional investigators)**
- ADDITIONAL SITE(S)**

STUDY TITLE:

PROTOCOL NUMBER:

DATE:

--

1. APPLICANT

- 1.1 Name/address/telephone/fax number of Applicant wishing to conduct trial

- 1.2 Name/address/telephone/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable)
- 1.3 Name, designation and qualifications of person representing the Applicant (**Local Contact Person for all further correspondence**)
- 1.4 National Coordinator name, address, telephone/fax number
- 1.5 International Principal Investigator name, address, telephone/fax number
- 1.6 Name of sponsor

2. TRIAL PARTICULARS (original application)

- 2.1 Trial Approval Number:
- 2.2 Date of Approval of original protocol:
- 2.3 Number of local investigators approved for this trial:
- 2.4 Number of local sites approved for this trial:
- 2.5 Number of participants approved for this trial:

3. INVESTIGATOR DETAILS

- 3.1 Name and address of additional Investigator(s) / Changes to Investigators: *[Proof of GCP training must be provided for investigators who have not previously participated in clinical trials]*
- 3.2 Summarise other ongoing/planned studies at this site involving this investigator: *[Provide details of studies, including numbers of subjects, whether the investigator is involved in research in a full-time or part-time capacity, and any other detail that may effect the capacity of the site at any one time]*
- 3.3 Details of Ethics Committee(s) who will approve investigator(s):
- 3.4 Date of application to Ethics Committee:
- 3.5 Date of approval by Ethics Committee:
- 3.6 Is CV for additional Investigator(s) attached? YES / NO

3.7 Is the Declaration of Intent attached? **YES / NO**

4. CAPACITY OF THE SITE

4.1 Describe how the site is structured so as to be able to take on the work for which this application is being made: [Give details of support staff, facilities, back up and any other relevant infrastructure]

5. RATIONALE FOR APPLICATION

5.1 Briefly explain the reason for the new investigator/s or site(s):

I/We, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

Applicant (local contact)

Date