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Introduction

According to article number 21 of proclamation number 176/91 of Drug Administration and Control Authority with regard to Clinical trial, the Authority is responsible to protect the safety and rights of the subjects participating in a trial and to ensure that trials are adequately designed to meet scientifically sound objectives. These aims may be met by several means, including the specification of investigator qualifications and requirement of protocol review and approval by relevant scientific/ethics committees. The mandate of the Authority is to review protocols, and where necessary to protect the safety of subjects, to require protocol revisions and/or termination of trials. The Authority has also a right for on-site inspection of the quality of the data obtained, with due concern for subject confidentiality, comparison of the procedures and practices of the clinical investigator with the commitments set out in the protocols and reports submitted to the Authority by the investigator or the sponsor.

Any clinical trial conduction in the country on human beings and/or on animals other than laboratory animals should have got prior permission before the commencement of the trial. This guideline is established to assist applicants for clinical trial. The information indicated under item number 1 to 8 is to be completed and submitted by the investigator(s) and/or the sponsor prior to commencement of the trial. After the termination of the trial the findings of the trial should be submitted as indicated under item number 9. Any findings from the trial need to be approved by the Authority before it is published elsewhere.

The responsibilities of each party involved in the trial i.e. the sponsor, the investigator and the monitor should have to be stated clearly in the protocol accordingly.

The guideline is subject to revision and proposal for changes are welcomed and can be sent to the Drug Administration and Control Authority P.O. Box 5681, Addis Ababa, Ethiopia

Definition

Definitions given below apply specifically to the terms used in this guide. They may have different meanings in other contexts.

Adverse event
Any untoward medical occurrence that may present itself during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

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

Case report form (CRF)

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

Clinical Trial
Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Comparator product
A pharmaceutical or other product (including placebo) used as a reference in a clinical trial.

Confidentiality
Maintenance of the privacy of trial subjects including their personal identity and all personal medical information.

Contract Research Organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

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

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

Good Clinical Practice (GCP)
Good Clinical Practice is a standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the diagnostic/therapeutic/prophylactic product under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled in conformity with quality standards appropriate for their intended use and as required by the product specification. Any reference to GMP in this document should be understood as a reference to the current WHO GMP Guidelines.

Informed consent
A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subjects rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

Investigator
A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence which could be evidenced by an up-to-date curriculum vitae and other credentials. The medical/dental care and decisions must always be the responsibility of a clinically-competent person legally allowed to practice medicine/dentistry.

Investigational labelling
Labelling developed specifically for products involved in a clinical trial.

Investigational product
Any pharmaceutical product (see definition) or placebo being tested or used as reference in a clinical trial.

Investigators brochure
A collection of data for the investigator consisting of all the relevant information on the investigational product(s) known prior to the onset of a clinical trial including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data in animals as well as in man and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the information must be updated.

Monitor
A person appointed by the sponsor or Contract Research Organization (CRO), and responsible to the sponsor or CRO, for the monitoring and reporting of progress of the trial and for verification of data.

Patient/subject files
Hospital files, consultation records or special subject file allowing the authenticity of the information presented in case record forms to be verified and, where necessary, allowing them to be completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

Pharmaceutical product
Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.

Principal investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

Protocol
A document which states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator/institution involved and the sponsor. It can, in addition,
function as a contract.

Raw data
Raw data refer to all records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and valuation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, recorded data from automated instruments or exact, verified copies in the form of photocopies, microfiches etc. The term can also include photographic negatives, microfilm or magnetic media.

Sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

Study product
Any pharmaceutical product (see definition) or placebo being tested or used as reference in a clinical trial.

Trial subject
An individual participating in a clinical trial and may be:
a) a healthy person volunteering in a trial,
b) a person with a condition unrelated to the use of the investigational product,
c) a person (usually a patient) whose condition is relevant to the use of the investigational product; who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control.

1. Application form for Clinical Trial Conduction

Complete the application form as indicated in Annex I in two copies. One copy of the Application is to be returned to the applicant after evaluation of the application.

2. Agreement between the investigator and the sponsor

Prior to the trial, the investigator(s) and the sponsor should establish an agreement on the protocol, the monitoring, the auditing and on standard operating procedures (SOP), and the allocation of trial-related responsibilities. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial. An agreement made on the basis of this principle between the investigator(s) and the sponsor should be submitted as indicated in Annex II

3. The investigator

3.1. The investigator should

3.1.1. 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 up to date curriculum vitae

3.1.2. have clear understanding and willingness to obey the ethical and legal requirements of the trial

3.1.3. permit monitoring and auditing of the trial and inspection by the Authority

3.1.4. have sufficient time to properly conduct and complete the trial within the agreed trial period

3.1.5. have adequate number of qualified staff and adequate facilities for the duration of the trial to conduct the trial properly and safely.

3.2. Responsibility of the investigator

3.2.1. Proper and safe handling of the investigational products during and after the conduct of the trial, preferably in cooperation with a hospital pharmacy or pharmacy.

3.2.2. That the investigational product is used only in accordance with the protocol, which implies only for subjects included in the trial and by designated staff responsible to the investigator, and that this use is documented in such a way that reconciliation is possible to assure appropriate dosage.

3.2.3. That dosage and instructions for use are correct and that every subject involved understands them properly.

3.2.4. That unused investigational products are returned in accordance with the protocol to the pharmacy or sponsor or are destroyed, and that records of these activities are kept according to the protocol.

4. The Sponsor

The responsibilities of the sponsor(s) are:

4.1. Supplying the fully characterized investigational and comparator product(s) prepared in accordance with principles of Good Manufacturing Practice, properly coded, suitably packaged in such a way as to provide protection against deterioration during transport and storage at intermediate destinations, and affixed with appropriate investigational labeling.

4.2. Ensuring that the package of investigational product(s) is of a size suitable for the trial and adequate for the trial subjects;

4.3. Keeping sufficient samples from each batch used in the trial as a reference for future re-checking

4.4. Providing expiry date (month/year) or retest date information of the investigational and/or comparator product in a manner understandable to clinical study staff.

4.5. to provide an up to date investigator's brochure

4.6. Obtain the investigator's/institutions agreement on

4.6.1. the trial to be conducted in compliance with Good Clinical Practice with the protocol agreed to by the sponsor; and to be in compliance with procedures for data recording/reporting and to permit monitoring, auditing and inspection according to the protocol

4.6.2. The sponsor and all investigators should sign and date the protocol of the trial to confirm the agreement

4.7. Ensure sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human and/or target animal exposure by the route, at the dosages for the duration and in the trial population to be studied

4.8. Ensure that the investigational product (including active comparator(s) and placebo) are manufactured in accordance with GMP and are adequately packed and labeled in a manner that protects the blinding if applicable.

5. The Monitor

The monitor is responsible:

5.1. That all study products for the trial are used exclusively within the limits defined by the protocol;

5.2. That inventory records of study products are in order and that there are sufficient supplies;

5.3. That the expiry dates will not be, or have not been, exceeded;

5.4. Adequacy of storage conditions for study products;

5.5. Procedures and records of returned and/or unused pharmaceutical products.

5.6. That assist the investigator with respect to all the required reports

5.7. That all staff members of the trial are adequately informed of and understand the detailed procedures of the trial, and are willing to comply with the protocol

5.8. That the space and facilities, including laboratories, equipment, and staff at the investigator's site are adequate; and that the number of the trial subjects recruited are sufficient throughout the trial

5.9. Should verify the accuracy and completeness of CRF entries against the raw data, and inform the Investigator of any CRF entry error, omission or illegibility.

6. Site of the trial (medical institution), facilities and staff

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical, and clerical staff to support the trial. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

Facilities should be available to meet all reasonably foreseeable emergencies.

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

7. Ethical principles and The Ethics Committee

All research involving human subjects should be conducted in accordance with the ethical principles contained in the Declaration of Helsinki and should respect three basic ethical principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and laws and regulations of the Authority. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles. The approved ethical principle by Ethics Committee should contain but not limited to the following information:

7.1. Indicate the number and type of subjects and criteria used for subject selection
7.2. Indicate the benefits and any known risks or inconveniences to the subjects involved in the study
7.3. Describe precisely the information, which will be conveyed to potential subjects of the study and the manner by which this information is to be conveyed.
7.4. The name and status of the project staff member(s)
7.5. Indicate any special incentives or treatment the subjects receive for their participation
7.6. Indicate any special confidentiality of all information obtained during the course of the study, relating to participants included in the study, will be maintained
7.7. The suitability of the investigator for the proposed trial in relation to his/her qualifications, experience, supporting staff, and available facilities, on the basis of the information available to the committee.
7.8. The suitability of the protocol in relation to the objectives of the study.
7.9. The opinion and advice of the Ethics Committee should be stated clearly in writing by identifying the trial, the documents reviewed and the dates of review

NOTE: In case where the Ethics committee is other than the National Ethics Committee the Ethics committee should consist of at least a) Four professionals in the medical and scientific field with sufficient qualifications and experience, b) A legal professional c) a religious or community representative who is independent of the institution/trial site

8. The Consent

8.1. A written informed consent should be signed and personally dated by the subject. A wittiness should sign the consent form to attest that the subject/legal representative gave consent freely. A copy of the signed and dated consent form should be given to the subject/representative before trial commences.

8.2. The written informed consent should at least contain the following information (such a sample should be submitted during the submission of trial application)

8.2.1. That the trial involves research

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

8.2.3. The subjects responsibility

8.2.4. The expected duration of the trial

8.2.5. The reasonably foreseeable risks or inconveniences to the subject

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

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

8.2.8. 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

8.2.9. That the subject's identity will remain confidential whether results of the trial are published or not published.

8.2.10. The contact persons for further information about the trial or whom to contact in the event of trial-related injury.

8.2.11. That the subject may be requested to terminate participation in the trial

9. Supporting data for the investigational product

Preclinical studies that provide sufficient documentation of potential safety and eventual clinical application of a pharmaceutical product are a necessary prerequisite for a clinical trial. The pharmaceutical, preclinical and clinical data should be adapted to the appropriate phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial.

9.1. Product Description

9.1.1. Name, strength, dosage form, doses to be administered, route of administration and the source of the drug

9.1.2. Name and address of the manufacturer

9.1.3. Complete composition of the product(s)

9.2. Certificate of pharmaceutical product and GMP certificate

9.3. Information about manufacturing procedures

9.4. Tests performed on the actual product to establish that the product is of suitable quality for the intended investigational use (Attach Certificate of Analysis).

9.5. Information on safety and efficacy collected in previous and ongoing clinical trials elsewhere with the investigational product

9.6. For chemical or biological methods to control disease vectors state clearly any potential risks involved to both human populations and other environmental components. Indicate the measures planned to evaluate possible environmental changes.

9.7. Handling and Accountability of pharmaceutical products

The sponsor is responsible for ensuring that the pharmaceutical product(s) supplied for the trial (investigational product, or comparator products) are of appropriate quality and subject to quality assurance Procedures. If significant formulation changes are made in the investigational or comparator product during the course of the trial, the results of additional studies (e.g. stability, comparative dissolution rate or, as appropriate, comparative bioavailability) demonstrating that these changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product should be available prior to the use of the new formulation in the clinical trial.

9.8. Supply and storage

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

Good Manufacturing Practice has not only to be considered by the supplier of the pharmaceutical product(s), but also for temporary storage by intermediaries.

Records should contain information about the shipment, delivery, receipt, disposition, return and destruction of any remaining pharmaceutical products. The investigator must not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the hospital should assume responsibility for storage, delivery, and the return and keeping of records of the investigational pharmaceutical product(s). If it does, the procedure in the pharmacy must be documented to make auditing possible

9.9. Investigational labelling and packaging -The sponsor is responsible for the proper packaging and investigational labelling of the pharmaceutical products used. Study products should be labelled in compliance with the protocol. The investigational label should state that the product is for clinical research purposes only. Investigational label information should be accurate and in a language which is understandable to the subject.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. A coding system should be implemented to allow for the proper identification of the blinded products on an individual subject basis in an emergency.

In blinded trials all study product(s), including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

9.10. Sample of investigational product-**Four samples of investigational product must be submitted with application for clinical trial**

10. ITEMS TO BE CONTAINED IN A CLINICAL TRIAL PROTOCOL

The trial protocol should, where relevant, be required to cover the following points:

a) Title and justification for the trial.
b) Statement of rationale, objectives and purpose of the trial.
c) Site of the trial, name and address of the sponsor.
d) Name, address and qualifications of each investigator.
e) Description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double- blind, single-blind), and randomization (method and procedure).
f) Description of trial subjects. Criteria for inclusion and exclusion of potential trial subjects and process of recruitment, types, methods and time of allocation of subjects.
g) Number of trial subjects needed to achieve the trial objective based on statistical considerations.
h) Description of and justification for route of administration, dosage, dosage interval and treatment period for the pharmaceutical product being tested and the product being used as a control. Dose-response relationships should be considered.
i) Any other treatment that may be given or permitted concomitantly.
j) Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.
k) Description of how responses are recorded. Description and evaluation of methods of measurement, times of measurements, follow-up procedures.
l) Measures to control patients' compliance with the treatments.
m) Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.
n) Methods of recording and reporting adverse events/reactions, provisions for dealing with complications.
o) Procedures for the maintenance of subject identification code lists, treatment records, randomization list and/or case report form (CRF). Records should permit easy identification of individual patients/participants and permit auditing and construction of data.
p) Information on establishment of the trial code, where it will be kept and when, and how and by whom it can be broken in the event of an emergency.
q) Measures to be implemented to ensure the safe handling and storage of pharmaceutical products, and to promote and control compliance with the prescribed and other instructions.
r) Description of methodology on the evaluation of results (e.g. statistical methods) and on the report on patients/participants withdrawn from the trial.
s) Time schedule for completion of the trial.
t) Information to be presented to the trial subjects including how they will be informed about the trial and how and when consent will be obtained.
u) Staff instructions, i.e. statement of how the staff involved are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

v) Ethical considerations and measures relating to the trial.
w) Medical care after the trial and modalities of post-trial treatment should be defined.
x) Statements regarding financing, insurance, liability, delegation/distribution of responsibilities,
y) List of literature referred to in the protocol.

11. Termination of trial and final report

11.1. In the case of premature termination of the trial, the investigator must inform the Authority, the ethics committee and, where applicable, the sponsor. Reasons for termination must be stated clearly in writing.

11.2. After completion of the trial, a final report must be drawn up and submitted to the Authority. The report should be dated and signed by the investigator and by the monitor (where applicable). Before approval of the report by the authority, any publication in any manner is strictly prohibited.

11.3. Case Report Form

11.3.1. The investigator should ensure that collection procedures, storage and retrieval of data meet minimum requirements for quality and facilitate verification, validation, audit and inspection. The CRF should be signed and dated by the authorized individuals.

11.3.2. Any change or correction to a CRF, as well as the process of duplicating raw data, should not obscure the original data and corrections should be initiated and dated by responsible person.

Annex I

Application form for Clinical Trial

1. Name of the Scientific working group _____
2. Project Title _____
3. Objective and relevance of the Project _____
4. Duration of Project _____
5. Funds requested and source of funds _____
6. Principal investigator _____
7. Position or post presently held _____
8. Institution responsible for the research project _____
9. Department(s) and investigator(s) collaborating with and or accommodating the project _____
10. Statements on the capacity of the institution _____

Signature of the principal investigator _____

Date _____

For official use only

Date Approved _____

Signature of person to Sign on behalf the Authority

Name _____

Position _____

Signature _____

Date Rejected and Reasons (if)

_____

Annex II

AGREEMENT MADE PRIOR TO COMMENCEMENT OF CLINICAL TRIAL

Name of scientific working group

1. The Sponsor _____
2. The Investigator(s) _____
3. The Monitor _____
4. Other (if any) _____
5. Name of the project _____

We hereby agree, in the capacity of principal investigator, the sponsor, the monitor and the site of the clinical trial in the above named project to conduct the investigation in accordance with the statements and procedures stipulated in the clinical investigation protocol agreed up on by the Drug Administration and Control Authority and our self. We also agree to submit a copy of our findings to the Authority prior to its being published elsewhere in any manner or form.

Signature of principal investigator _____
Date: _____

Signature of the sponsor _____

Date _____

Signature of the Monitor _____

Date: _____