Clinical research is the key to the discovery of latest diagnostic methods and to develop modern drugs for treatment of diseases. Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki and ensures that clinical trial data are credible.

It has been widely recognized that India offers unique opportunities for conducting clinical trials in view of the large patient pool, well- trained and enthusiastic investigators and premiere medical institutes available in the country along with considerable low per patient trial cost, as compared to developed countries.

A need was, however, felt to develop our own Indian Guidelines to ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population. An Expert Committee set up by Central Drugs Standard Control Organisation (CDSCO) in consultation with clinical expert has formulated this GCP guideline for generation of clinical data on drugs.

The Drug Technical Advisory Board (DTAB), the highest technical body under D&C, Act, has endorsed adoption of this GCP guideline for streamlining the clinical studies in India.

I am confident that this guideline will be immensely useful to research institutions, investigators, institutional ethics committees and regulators in providing desired direction. The guideline would also be helpful to companies who may want to locate their clinical programme in the country.

Place: New Delhi

Dr. S.P. Agarwal,

Director General of Health Services

and Chairman, DTAB

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Good Clinical Practice Guidelines

INTRODUCTION

The history of Good Clinical Practice (GCP) statute traces back to one of the oldest enduring traditions in the history of medicine: The Hippocratic Oath. As the guiding ethical code it is primarily known for its edict to do no harm to the patient. However, the complexities of modern medicine research necessitate a more elaborate set of guidelines that address a Physician's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical research.

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated.

These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

DEFINITIONS

Act

Wherever relevant, the Act means Drugs & Cosmetics Act 1940 (23 of 1940) and the Rules made thereunder.

Adverse Event (AE)

Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given. Also see *Serious Adverse Event*

Adverse Drug Reaction (ADR)

(a) In case of approved pharmaceutical products: A noxious and unintended response at doses normally used or tested in humans

(b) In case of new unregistered pharmaceutical products (or those products which are not yet approved for the medical condition where they are being tested): A noxious and unintended response at any dose(s)

The phrase ADR differs from AE, in case of an ADR there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied.

In clinical trials, an untoward medical occurrence seemingly caused by overdosing, abuse / dependence and interactions with other medicinal products is also considered as an ADR.

Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are, therefore, readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

Audit of a Trial

A systematic verification of the study, carried out by persons not directly involved, such as:

(a) Study related activities to determine consistency with the *Protocol*

(b) Study data to ensure that there are no contradictions on *Source Documents*. The audit should also compare data on the Source Documents with the interim or final report. It should also aim to find out if practices were employed in the development of data that would impair their validity.

(c) Compliance with the adopted Standard Operating Procedures (*SOPs)*

Blinding / Masking

A method of "control experimentation" in which one or more parties involved are not informed of the treatment being given. Single blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor, data analyst(s) are being unaware of the treatment assigned.

Case Record Form (CRF)

A document designed in consonance with the Protocol, to record data and other information on each trial subject. The Case Record Form should be in such a form and format that allows accurate input, presentation, verification, audit and inspection of the recorded data. A CRF may be in printed or electronic format.

Clinical Trial (Clinical Study)

A systematic study of pharmaceutical products on human subjects – (whether patients or non-patient volunteers) – in order to discover or verify the clinical, pharmacological (including pharmacodynamics / pharmacokinetics), and / or adverse effects, with the object of determining their safety and / or efficacy.

Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials is to determine the maximum tolerated dose in humans; pharmacodynamic effect, adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviour of the drug as far as possible. These studies are often carried out in healthy adult volunteers using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centres.

Exploratory trials (Phase II)

In phase II trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centres and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

Confirmatory trials (Phase III)

The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

Data on ADRs observed during clinical use of the drug should be reported along with a report on its efficacy in the prescribed format. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule 21 of the Act.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value, treatment strategies used and safety profile. Phase IV studies should use the same scientific and ethical standards as applied in pre-marketing studies.

After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

Comparator Product

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

Confidentiality

Maintenance of privacy of study subjects including their personal identity and all medical information, from individuals other than those prescribed in the Protocol. *Confidentiality* also covers the prevention of disclosure of sponsor's proprietary information to unauthorised persons.

Co-Investigator

A person legally qualified to be an investigator, to whom the Investigator delegates a part of his responsibilities.

Co-ordinating Investigator

See Principal Investigator

Clinical Research Organisation (CRO)

An organisation to which the sponsor may transfer or delegate some or all of the tasks, duties and / or obligations regarding a Clinical Study. All such contractual transfers of obligations should be defined in writing. A CRO is a scientific body – commercial, academic or other.

Contract

A written, dated and signed document describing the agreement between two or more parties involved in a biomedical study, namely Investigator, Sponsor, Institution. Typically, a contract sets out delegation / distribution of responsibilities, financial arrangements and other pertinent terms. The "Protocol" may form the basis of "Contract".

Documentation

All records (including written documents, electronic, magnetic or optical records, scans, x-rays etc.) that describe or record the methods, conduct and results of the study, and the actions taken. The Documents include Protocol, copies of submissions and approvals from the office of the Drugs Controller General of India, ethics committee, investigator(s)' particulars, consent forms, monitor reports, audit certificates, relevant letters, reference ranges, raw data, completed CRFs and the final report. Also see: Essential Documents

Escape Treatment

A supplementary treatment, usually given to alleviate pain in placebo-controlled trials, to relieve the trial subject of the symptoms caused by the investigated disease in a study.

Essential Documents

The Documents that permit evaluation of the conduct of a study and the quality of the data generated. *See Appendix V.*

Ethics Committee

An independent review board or committee comprising of medical / scientific and non-medical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.

Final Report

A complete and comprehensive description of the study after its completion. It includes description of experimental and statistical methods and materials, presentation and evaluation of the results, statistical analyses and a critical ethical, statistical and clinical appraisal. The Investigator's declaration closing the study is a part of the Final Report.

Good Clinical Practice (GCP)

It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the "Investigational Product" are properly documented.

Impartial Witness

An impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent.

Informed Consent

Voluntary written assent of a subject's willingness to participate in a particular study and in its documentation. The confirmation is sought only after information 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 subject's rights and responsibilities has been provided to the potential subject.

Inspection

An official review/ examination conducted by regulatory authority(ies) of the documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the study. The inspection may be carried out at the site of the trial, at the sponsor's / or CRO's facilities in order to verify adherence to GCP as set out in these documents.

Institution

Any public or private medical facility where a clinical study is conducted.

Investigator

A person responsible for the conduct of the study at the trial site. Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator. Also see *Principal Investigator, Sub-investigator*.

Investigational Labelling

Labelling developed specifically for products involved in the study.

Investigational Product

A pharmaceutical product (including the Comparator Product) being tested or used as reference in a clinical study. An Investigational Product may be an active chemical entity or a formulated dosage form.

Investigator's Brochure

A collection of data (including justification for the proposed study) for the Investigator consisting of all the clinical as well as non-clinical information available on the Investigational Product(s) known prior to the onset of the trial. 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 substantially relevant data is generated during the trial, the information in the Investigator's Brochure must be updated. *See Appendix IV.*

Monitor

A person appointed by the Sponsor or Contract Research Organisation (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor ensures that the trial is conducted, recorded and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

Multi-Centric Study

A clinical trial conducted according to one single protocol in which the trial is taking place at different investigational sites, therefore carried out by more than one investigator.

Non-Clinical Study

Biomedical studies that are not performed on human subjects.

Non-Therapeutic Study

A study in which there is no anticipated direct clinical benefit to the Subject(s). Such studies, unless an exception is justified, should be conducted in patient(s) having a disease or condition for which the Investigational Product is intended. Subject(s) in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Pharmaceutical Product(s)

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 who has the responsibility to co-ordinate between the different Investigators involved in a study at one site or different sites in case of a multi-center study.

Protocol

A document that states the background, objectives, rationale, design, methodology (including the methods for dealing with *AEs*, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed.

A list of items to be included in the *Protocol* is compiled in a subsequent chapter.

The content and format of the protocol should take into consideration the adopted *SOPs*, the regulatory requirements and the guiding principles of *GCP*.

The term Protocol, unless otherwise specified, relates to the latest amended version of the document, read in conjunction with all its appendices and enclosures.

Protocol Amendment(s)

Any changes or formal clarifications appended to the protocol. All Protocol Amendments should be agreed upon and signed by the persons who were the signatories to the Protocol.

Quality Assurance (QA)

Systems and processes established to ensure that the trial is performed and the data are generated in compliance with GCP. QA is validated through in-process Quality Control and in and post-process auditing of clinical trial process as well as data.

Quality Control (QC)

The operational techniques and activities undertaken within the system of QA to verify that the requirements for quality of the trial related activities have been fulfilled. QC activities concern everybody involved with planning, conducting, monitoring, evaluating, data handling and reporting.

The objective of QC is to avoid exposure of study subjects to unnecessary risks and to avoid false conclusions being drawn from unreliable data.

Randomisation

The process of assigning study subjects to either the treatment or the control group. Randomisation gives all subjects the same chance of being in either group in order to reduce bias.

Regulatory Authority

The Drugs Controller General of India or an office nominated by him is the regulatory authority for the purpose of carrying out Clinical Trials in India. The Regulatory Authority approves the study Protocol, reviews the submitted data and conducts inspections.

Raw Data

It refers to all records or certified copies of the original clinical and laboratory findings or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Also see *Source Data.*

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

An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

Schedule

Unless repugnant to the context, the Schedule means Schedule Y to the Drugs & Cosmetics Rules. (Reproduced here at Appendix II)

Source Data

Original documents (or their verified and certified copies) necessary for evaluation of the Clinical Trial. These documents may include Study Subjects' files, recordings from automated instruments, tracings, X-Ray and other films, laboratory notes, photographic negatives, magnetic media, hospital records, clinical and office charts, Subjects' diaries, evaluation check-lists, and pharmacy dispensing records.

Sponsor

An individual or a company or an institution that takes the responsibility for the initiation, management and / or financing of a Clinical Study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor.

Study Product

Any *Pharmaceutical Product* or *Comparator Product* used in a clinical study.

Sub-Investigator

See ***Co-Investigator***

Subject Files / Patient Files

A file containing demographic and medical information about a study subject. It includes hospital files, consultation records or special subject files allowing the authenticity of the information presented in CRF to be verified and where necessary allowing it to be completed or corrected. The conditions regulating the use and consultation of such documents must be honoured as prescribed under *Confidentiality*.

Study Subject (Subject)

An individual participating in a clinical trial as a recipient of the *Investigational Product*.

A *Study Subject* may be a healthy person volunteering in a trial or a person with a medical condition that is unrelated to the use of the *Investigational Product* or a person whose medical condition is relevant to the use of the *Investigational Product*.

Standard Operating Procedures (SOP)

Standard elaborate written instructions to achieve uniformity of performance in the management of clinical studies. SOPs provide a general framework for the efficient implementation and performance of all the functions and activities related to a particular study.

Subject Identification Code

A unique identification number / code assigned by the Investigator to each Study Subject to protect the Subject's identity. Subject Identification Code is used in lieu of the Subject's name for all matters related to the study.

Study Management

Steering, supervising, data management and verification, statistical processing and preparation of the study report.

Validation

Validation of Study: The process of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process equipment, material, activity or system actually leads to the expected results

Validation of Data: The procedures carried out to ensure and prove that the data contained in the final report match the original observations. The procedure is applied to Raw Data, CRFs, computer software, printouts, statistical analyses and consumption of Study Product / Comparator Product.

PREREQUISITES FOR THE STUDY

2.1. Investigational Pharmaceutical Product:

Physical, chemical, pharmaceutical properties and the formulation of the Investigational Product must be documented to permit appropriate safety measures to be taken during the course of a study. Instructions for the storage and handling of the dosage form should be documented. Any structural similarity(ies) to the other known compounds should be mentioned.

2.2. Pre-clinical supporting data

The available pre-clinical data and clinical information on the Investigational Product should be adequate and convincing to support the proposed study.

2.3. Protocol

A well designed study relies predominantly on a thoroughly considered, well-structured and complete protocol.

2.3.1. Relevant components of Protocol

2.3.1.1. General information

a. Protocol title, protocol identifying number and date. All amendments should bear amendment number and date(s)

b. Name, address & contact numbers of the sponsor and the monitor / CRO

c. Name and title of the persons authorised to sign the protocol and the protocol amendments for the sponsor

d. Name, title, address and contact numbers of the sponsor's medical expert for the study

e. Name(s), title(s), address(es) and contact numbers of the investigator(s) who is / are responsible for conducting the study, along with their consent letter(s)

f. Name(s), address(es) and contact numbers of the institution(s) - clinical laboratories and / or other medical and technical departments along with the particulars of the head(s) of the institution(s) and the relevant department(s)

2.3.1.2. Objectives and Justification

a. Aims and objectives of the study, indicating the Phase to which the study corresponds

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

c. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical studies that are relevant to the study

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

e. Description of and justification for the route of administration, dosage regimen and treatment periods for the pharmaceutical product being studied and the product being used as control. Dose-response relationships should be considered and stated.

f. A statement that the study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements

g. Description of the inclusion & exclusion criteria of the study population

h. References to the literature and data that are relevant to the study and that provide background for the study

2.3.1.3. Ethical Considerations

a. General ethical considerations related to the study

b. Description of how patients / healthy volunteers will be informed and how their consent will be obtained

c. Possible reasons for not seeking informed consent

2.3.1.4. Study design

The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design. Description of the study design should include:

a. Specific statement of primary and secondary end points, if any, to be measured during the study

b. Description of the type of the study (randomised, comparative, blinded, open, placebo controlled), study design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), randomisation (method and procedure) and placebo controlled.

c. A schematic diagram of the study design, procedures and stages

d. Medications/treatments permitted (including rescue medications) and not permitted before and / or during the study

e. A description of the study treatments, dosage regimen, route of administration and the dosage form of the investigational product and the control proposed during the study

f. A description of the manner of packaging and labelling of the investigational product

g. Duration of the subject participation and a description of the sequence of all study periods including follow-up, if any

h. Proposed date of initiation of the study

i. Justification of the time-schedules e.g. in the light of how far the safety of the active ingredients, medicinal products has been tested, the time course of the disease in question

j. Discontinuation criteria for study subjects and instructions on terminating or suspending the whole study or a part of the study

k. Accountability procedures for the investigational products including the comparator product

l. Maintenance of study treatment randomisation codes and procedures for breaking codes

m. Documentation of any decoding that may occur during the study

n. Procedures for monitoring subjects' compliance

2.3.1.5. Inclusion, Exclusion and Withdrawal of Subjects

a. Subject inclusion criteria: specifications of the subjects (patients / healthy volunteers) including age, gender, ethnic groups, prognostic factors, diagnostic admission criteria etc. should be clearly mentioned where relevant.

b. Subject exclusion criteria, including an exhaustive statement on criteria for pre-admission exclusions

c. Subject withdrawal criteria (i.e. terminating investigational product treatment / study treatment) and procedures specifying – when and how to withdraw subjects from the treatment, type and timing of the data to be collected from withdrawn subjects, whether and how subjects are to be replaced and the follow-up on the withdrawn subjects

d. Statistical justification for the number of Subjects to be included in the Study

2.3.1.6. Handling of the Product(s)

a. Measures to be implemented to ensure the safe handling and storage of the pharmaceutical products.

b. System to be followed for labelling of the product(s) (code numbering etc.)

c. The label should necessarily contain the following information: the words - “For Clinical Studies only”, the name or a code number of the study, name and contact numbers of the investigator, name of the institution, subject’s identification code.

2.3.1.7. Assessment of Efficacy

a. Specifications of the effect parameters to be used

b. Description of how effects are measured and recorded

c. Time and periodicity of effect recording

d. Description of special analyses and / tests to be carried out (pharmacokinetic, clinical, laboratory, radiological etc.)

2.3.1.8. Assessment of Safety

a. Specifications of safety parameters

b. Methods and periodicity for assessing and recording safety parameters

c. Procedures for eliciting reports of and for recording and reporting adverse drug reactions and / or adverse events and inter-current illnesses

d. Type and duration of the follow-up of the subjects after adverse events

e. Information on establishment of the study-code, where it will be kept and when, how and by whom it can be broken in the event of an emergency

2.3.1.9. Statistics

a. Description of the statistical methods to be employed, including timing of any planned interim analysis

b. Number of study subjects needed to achieve the study objective, and statistical considerations on which the proposed number of subjects is based

c. Detailed break-up of the number of subjects planned to be enrolled at each study site (in case of multi-center studies)

d. The level of statistical significance to be used

e. Procedures for managing missing data, unused data and unauthentic data

f. Procedures for reporting any deviations from the original statistical plan (any deviations from the original statistical plan should be stated and justified in protocol and / in the final report, as appropriate)

g. Selection of the subjects to be included in the final analyses (e.g. all randomized subjects / all dosed subjects / all eligible subjects / evaluable subjects

2.3.1.10. Data handling and management

A statement should be clearly made in the protocol that "The investigator(s) / institution(s) will permit study related monitoring, audits, ethics committee review and regulatory inspection(s) providing direct access to source data / documents".

A copy of the CRF should be included in the protocol. Besides, the following details should be given:

a. Procedures for handling and processing records of effects and adverse events to the product(s) under study

b. Procedures for the keeping of patient lists and patient records for each individual taking part in the study. Records should facilitate easy identification of the individual subjects.

2.3.1.11. Quality control and quality assurance

a. A meticulous and specified plan for the various steps and procedures for the purpose of controlling and monitoring the study most effectively

b. Specifications and instructions for anticipated deviations from the protocol

c. Allocation of duties and responsibilities with-in the research team and their co-ordination

d. Instructions to staff including study description (the way the study is to be conducted and the procedures for drug usage and administration)

e. Addresses and contact numbers etc. enabling any staff member to contact the research team at any hour

f. Considerations of confidentiality problems, if any arise

g. Quality control of methods and evaluation procedures

2.3.1.12. Finance and insurance

a. All financial aspects of conducting and reporting a study may be arranged and a budget made out.

b. Information should be available about the sources of economic support (e.g. foundations, private or public funds, sponsor / manufacturer). Likewise it should be stated how the expenditures should be distributed e.g. payment to subjects, refunding expenses of the subjects, payments for special tests, technical assistance, purchase of apparatus, possible fee to or reimbursement of the members of the research team, payment of the investigator / institution etc.)

c. The financial arrangement between the sponsor, the individual researcher(s) / manufacturer involved, institution and the investigator(s) in case such information is not stated explicitly

d. Study Subjects should be satisfactorily insured against any injury caused by the study

e. The liability of the involved parties (investigator, sponsor / manufacturer, institution(s) etc.) must be clearly agreed and stated before the start of the study

2.3.1.13. Publication policy

A publication policy, if not addressed in a separate agreement, should be described in the protocol.

2.3.1.14. Evaluation

a. A specified account for how the response is to be evaluated

b. Methods of computation and calculation of effects

c. Description of how to deal with and report subjects withdrawn from / dropped out of the study

2.3.2. Supplementaries and appendices:

The following documents should be appended with the protocol:

a. Information to the Study Subjects and the mode of providing it

b. Instructions to staff

c. Descriptions of special procedures

2.4. Ethical & Safety Considerations

2.4.1. Ethical Principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki (see Appendix 1) and should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non malaficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects.

The following principles are to be followed:

a. **Principles of essentiality** whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

b. **Principles of voluntariness, informed consent and community agreement** whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby

the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by them or by someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding.

c. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born.

d. **Principles of privacy and confidentiality** whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorised on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

e. **Principles of precaution and risk minimisation** whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research subject and those affected by it are put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research or experiment.

f. **Principles of professional competence** whereby, the research is conducted at all times by competent and qualified persons, who act with total integrity and impartiality and who have been made aware of, and mindful of, the ethical considerations to be borne in mind in respect of such Study.

f. **Principles of accountability and transparency** whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner, after full disclosure is made by those associated with the Study of each aspect of their interest in the Study, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

h. **Principles of the maximisation of the public interest and of distributive justice** whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subject themselves.

i. **Principles of institutional arrangements** whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

j. **Principles of public domain** whereby, the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

k. **Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or

contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

l. **Principles of compliance** whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

2.4.2. Ethics Committee:

The sponsor and / or investigator should seek the opinion of an independent *Ethics Committee* regarding suitability of the *Protocol*, methods and documents to be used in recruitment of *Subjects* and obtaining their *Informed Consent* including adequacy of the information being provided to the Subjects. The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the Ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research

2.4.2.1 Basic Responsibilities

The basic responsibility of an IEC is to ensure a competent review of all ethical aspects of the project proposals received and execute the same free from any bias and influence that could affect their objectivity.

The IECs should specify in writing the authority under which the Committee is established, membership requirements, the terms of reference, the conditions of appointment, the offices and the quorum requirements. The responsibilities of an IEC can be defined as follows :

a. To protect the dignity, rights and well being of the potential research participants.

b. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.

c. To assist in the development and the education of a research community responsive to local health care requirements

2.4.2.2. Composition

a. IEC should be multidisciplinary and multi-sectorial in composition. Independence and competence are the two hallmarks of an IEC.

b. The number of persons in an ethical committee be kept fairly small (5-7 members). It is generally accepted that a minimum of five persons is required to compose a quorum. There is no specific recommendation for a widely acceptable maximum number of persons but it should be kept in mind that too large a Committee will make it difficult in reaching consensus opinion. 12 to 15 is the maximum recommended number

c. The Chairperson of the Committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary who generally belongs to the same Institution should conduct the business of the Committee. Other members should be a mix of medical/non-medical, scientific and non-scientific persons including lay public to reflect the differed viewpoints. The composition may be as follows :-

1. Chairperson
2. 1-2 basic medical scientists (preferably one pharmacologists).
3. 1-2 clinicians from various Institutes
4. One legal expert or retired judge

5. One social scientist / representative of non-governmental voluntary agency

6. One philosopher / ethicist / theologian

7. One lay person from the community

8. Member Secretary

d. The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. There should be adequate representation of age, gender, community; etc. in the Committee to safeguard the interests and welfare of all sections of the community/society. Members should be aware of local, social and cultural norms, as this is the most important social control mechanism. If required subject experts could be invited to offer their views.

2.4.2.3. Terms of Reference

The IEC members should be made aware of their role and responsibilities as committee members. Any change in the regulatory requirements should be brought to their attention and they should be kept abreast of all national and international developments in this regard. The Terms of References should also include a statement on Terms of Appointment with reference to the duration of the term of membership, the policy for removal, replacement and resignation procedure etc. Each Committee should have its own operating procedures available with each member.

2.4.2.4. Review Procedures

The Ethics Committee should review every research proposal on human subjects. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. **The ethical review should be done through formal meetings and should not resort to decisions through circulation of proposals.**

2.4.2.5. Submission of Application

The researcher should submit an appropriate application to the IEC in a prescribed format along with the study protocol at least three weeks in advance. The protocol should include the following:

1. Clear research objectives and rationale for undertaking the investigation in human subjects in the light of existing knowledge.

2. Recent curriculum vitae of the Investigators indicating qualification and experience.

3. Subject recruitment procedures.

4. Inclusion and exclusion criteria for entry of subjects in the study.

5. Precise description of methodology of the proposed research, including intended dosages and routes of administration of drugs, planned duration of treatment and details of invasive procedures if any.

6. A description of plans to withdraw or withhold standard therapies in the course of research.

7. The plans for statistical analysis of the study.

8. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and vernacular languages.

9. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research.

10. For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to over-dosage should be included.

11. Proposed compensation and reimbursement of incidental expenses.

12. Storage and maintenance of all data collected during the trial.

13. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.

14. A statement on probable ethical issues and steps taken to tackle the same.

15. All other relevant documents related to the study protocol including regulatory clearances.

16. Agreement to comply with national and international GCP protocols for clinical trials.

17. Details of Funding agency / Sponsors and fund allocation for the proposed work.

2.4.2.6. Decision Making Process

The IEC should be able to provide complete and adequate review of the research proposals submitted to them It should meet periodically at frequent intervals to review new proposals, evaluate annual progress of ongoing ones and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate.

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice appropriate steps. The Member Secretary should communicate the decision in writing.

2. A member must voluntarily withdraw from the IEC while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.

3. If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.

4. A negative decision should always be supported by clearly defined reasons.

5. An IEC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit/risk ratio.

6. The discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.

7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.

8. The following circumstances require the matter to be brought to the attention of IEC :

   a. any amendment to the protocol form the originally approved protocol with proper justification;

   b. serious and unexpected adverse events and remedial steps taken to tackle them;

   c. any new information that may influence the conduct of the study.

9. If necessary, the applicant/investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.

10. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her/his opinion must be recorded.

11. Meetings are to be minuted which should be approved and signed by the Chairperson.

2.4.2.7. Interim Review

The IEC should decide and record the special circumstances and the mechanism when an interim review can be resorted-to instead of waiting for the scheduled time of the meeting. However, decisions taken should be brought to the notice of the main committee. This can be done for the following reasons:

i) re-examination of a proposal already examined by the IEC;

ii) research study of a minor nature such as examination of case records etc.;

iii) an urgent proposal of national interest.

2.4.2.8. Record Keeping

All documentation and communication of an IEC are to be dated, filed and preserved according to written procedures. Strict confidentiality is to be maintained during access and retrieval procedures. Records should be maintained for the following :

i. the Constitution and composition of the IEC;

ii. the curriculum vitae of all IEC members;

iii. standing operating procedures of the IEC;

iv. national and international guidelines;

v. copies of the Protocol, data collection formats, CRFs, investigational brochures etc. submitted for review;

vi. all correspondence with IEC members and investigators regarding application, decision and follow up;

vii. agenda of all IEC meetings;

viii. minutes of all IEC meetings with signature of the Chairperson;

ix. copies of decisions communicated to the applicants;

x. record of all notification issued for premature termination of a study with a summary of the reasons;

xi. final report of the study including microfilms, CDs and Video-recordings.

It is recommended that all records must be safely maintained after the completion / termination of the study for at least a period of 5 years if it is not possible to maintain the same permanently.

2.4.2.9. Special Considerations

While all the above requirements are applicable to biomedical research as a whole irrespective of the speciality of research, there are certain specific concerns pertaining to specialised areas of research which require additional safe guards / protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable subjects and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances.

2.4.3. Informed Consent Process

2.4.3.1. Informed Consent of Subject :

Prior to the beginning of the Study the Investigator(s) should obtain the Ethics Committee's approval for the written informed consent form and all information being provided to the Subjects and / or their legal representatives or guardians as well as an impartial witness.

None of the oral and written information concerning the Study, including the written informed consent form, should contain any language that causes the Subject(s) or their legal representatives or guardians to waive or to appear to waive their legal rights, or that releases or appears to release the Investigator, the Institution, the Sponsor or their representatives from their liabilities for any negligence.

The information should be given to the Subjects and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the Subject(s) in both written and oral form, whenever possible.

Subjects, their legal representatives or guardians should be given ample opportunity and time to enquire about the details of the Study and all questions answered to their satisfaction.

The Investigator(s), Sponsor or staff of the Institution should not coerce or unduly influence a potential Subject to participate or to continue to

participate in the Study. Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure- such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. Persons with incurable diseases, in nursing homes, in detention, unemployed or impoverished, in emergency rooms, homeless persons, nomads, refugees and any ethnic or racial minority groups should be considered as vulnerable population whose mode of consent should be carefully considered and approved by the Ethics Committee.

Prior to the Subject's participation in the Study the written Informed Consent form should be signed and personally dated by

1. (i) The Subject *or* (ii) if the Subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Subject's legal representative or guardian *or* (iii) if the Subject and his legal representative or guardian is unable to read / write,

2. An impartial witness who should be present during the entire informed consent discussion

3. The Investigator

By signing the consent form the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the Subject or the Subject's legal representative or the guardian, and that informed consent was freely given by the Subject or the Subject's legal representative or the guardian.

The Subject's legal representative or guardian (if the subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability), the inclusion of such patients in the study may be acceptable if the ethics committee is in principle, in agreement, and if the investigator thinks that the participation will promote the welfare and interest of the Subject. The agreement of a legal representative or the guardian that participation will promote the welfare and interest of the Subject should

also be recorded with dated signature. If, however, neither the signed Informed Consent nor the witnessed signed verbal consent are possible – this fact must be documented stating reasons by the Investigator and also brought to the knowledge of Ethics Committee without any delay.

2.4.3.2. **Essential information for prospective research on subjects :** Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context :

i. the aims and methods of the research;

ii. the expected duration of the subject participation;

iii. the benefits that might reasonably be expected as an outcome of research to the subject or to others;

iv. any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected;

v. any foreseeable risk or discomfort to the subject resulting from participation in the study;

vi. right to prevent use of his/her biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;

vii. the extent to which confidentiality of records could be able to safeguard, confidentiality and the anticipated consequences of breach of confidentiality;

viii. free treatment for research related injury by the investigator / institution;

ix. compensation of subjects for disability or death resulting from such injury;

x. freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to;

xi. the identity of the research teams and contact persons with address and phone numbers;

xii. foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;

xiii. risk of discovery of biologically sensitive information;

xiv. publication, if any, including photographs and pedigree charts.

The quality of the consent of certain social groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

2.4.3.3. Informed Consent in Non-Therapeutic Study :

In case of a Non-Therapeutic Study the consent must always be given by the subject. Non-Therapeutic Studies may be conducted in subjects with consent of a legal representative or guardian provided all of the following conditions are fulfilled:

1. The objective of the Study can not be met by means of a trial in Subject(s) who can personally give the informed consent

2. The foreseeable risks to the Subject(s) are low

3. Ethics Committee's written approval is expressly sought on the inclusion of such Subject(s)

2.4.4. Essential Information on Confidentiality for Prospective Research Subjects

Safeguarding confidentiality **-** The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual subjects. Data of individual subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to drug registration authority or to health authority. Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed.

2.4.5. Compensation for Participation

Subjects may be paid for the inconvenience and time present, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. However, payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgement (inducement). All payments, reimbursement and medical services to be provided to research subjects should be approved by the IEC. Care should be taken :

i. when a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;

ii. when a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation;

iii. when a subject withdraws for any other reasons he/she should be paid in proportion to the amount of participation.

Academic institutions conducting research in alliance with industries / commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product). In cases where the review board/committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, the board should advise accordingly. Institutions need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

2.4.6. Selection of Special Groups As Research Subject

2.4.6.1. Pregnant or nursing women :

Pregnant or nursing women should in no circumstances be the subject of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be subjects of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

a. The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting fetal abnormalities and for conditions associated with or aggravated by pregnancy etc. Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant.

b. Research related to termination of pregnancy: Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made subjects for such research as per The Medical Termination of Pregnancy Act, GOI, 1971.

c. Research related to pre-natal diagnostic techniques: In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, GOI, 1994 and not for sex determination of the foetus.

2.4.6.2. Children:

Before undertaking trial in children the investigator must ensure that -

a. children will not be involved in research that could be carried out equally well with adults;

b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the

study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

c. a parent or legal guardian of each child has given proxy consent;

d. the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc;

e. research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;

f. interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;

g. the child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian;

h. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child subject as any available alternative interventions;

i. the risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained.

2.4.6.3. Vulnerable groups :

Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.

a. research on genetics should not lead to racial inequalities;

b. persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them;

c. rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected.

d. Adequate justification is required for the involvement of subjects such as prisoners, students, subordinates, employees, service personnel etc. who have reduced autonomy as research subjects.

2.4.7. Compensation for Accidental Injury

Research subjects who suffer physical injury as a result of their participation in the Clinical Trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from IEC In case of death, their dependents are entitled to material compensation.

2.4.7.1. Obligation of the sponsor to pay **:**

The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any serious sphysical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible.

RESPONSIBILITIES

3.1. Sponsor:

3.1.1. Investigator and Institution Selection:

The Sponsor is responsible for selecting the Investigator(s) / Institutions taking into account the appropriateness and availability of the study site and facilities. The Sponsor must assure itself of the Investigator's qualifications and availability for the entire duration of the Study. If organisation of a co-ordinating committee and / or selection of co-ordinating investigators are to be utilised in multi-centric studies their organisation and / or selection are Sponsor's responsibilities.

Before entering an agreement with an Investigator(s) / Institution(s) to conduct a Study, the Sponsor should provide the Investigator(s) / Institution(s) with the Protocol and an up-to-date Investigator's Brochure. Sponsor should provide sufficient time to review the Protocol and the information provided in the Investigator's Brochure.

3.1.2. Contract

The Sponsor should enter into a formal and legal agreement / contract with the Investigator(s) / Institution(s) on the following terms:

a. To conduct the Study in compliance with GCP, the applicable regulatory requirements and the Protocol agreed to by the Sponsor and given approval / favourable opinion by the Ethics Committee

b. To comply with the procedures for data recording, and reporting

c. To permit monitoring, auditing and inspection

d. To retain the study related essential documents until the Sponsor informs the Investigator(s) / Institution(s) in writing that these documents are no longer needed

The agreement should define the relationship between the investigator and the sponsor in matters such as financial support, fees, honorarium, payments in kind etc.

3.1.3. SOP

The Sponsor should establish detailed Standard Operating Procedures (SOP's). The Sponsor and the Investigator(s) should sign a copy of the Protocol and the SOPs or an alternative document to confirm their agreement.

3.1.4. Allocation of duties and responsibilities:

Prior to initiating a Study the Sponsor should define and allocate all Study related duties and responsibilities to the respective identified person(s) / organisation(s).

3.1.5. Study management, data handling and record keeping:

The Sponsor is responsible for securing agreement with all involved parties on the allocation of Protocol related and other responsibilities like:

a. Access to all Study related sites, source data / documents and reports for the purpose of inspection, monitoring and auditing by the authorised parties and inspection by national and foreign regulatory authorities

b. Data processing

c. Breaking of the Code

d. Statistical analysis

e. Preparation of the Study Report

f. Preparation and submission of materials to the Ethics Committee, Regulatory Authorities and any other review bodies

g. Reporting the ADRs, AEs to the Ethics Committee

h. Quality Assurance and Quality Control systems with written SOPs to ensure that the Study is conducted and data are generated, documented (recorded), and reported – in compliance with the Protocol, GCP and the applicable regulatory requirement(s)

It shall be the responsibility of sponsor to make arrangements for safe and secure custody of all study related documents and material for a period of three years after the completion of the study or submission of the data to the regulatory authority(ies) whichever is later.

The Sponsor may consider establishing an Independent Data Monitoring Committee (IDMC) to assess the progress of the Study. This includes the safety data and the critical efficacy endpoints at various intervals, and to recommend to the Sponsor whether to continue, modify, or stop a Study. The IDMC should have written operating procedures and should maintain written records of all its meetings.

3.1.6. Compensation for Participation

Subjects may be paid compensation for participation in accordance with the guidelines listed in 2.4.5.

3.1.7. Confirmation of review by the Ethics Committee

The Sponsor shall obtain from the Investigator(s) and / or the Institutions

a. The particulars about the members of the Investigator's / Institution's Ethics Committee including their names, addresses, qualifications and experience

b. An undertaking that the Ethics Committee is organised and operates according to the GCP and the applicable laws and regulations

c. Documented approval / favourable opinion of the Ethics Committee before the initiation of the Study

d. A copy of the recommendations in case the Ethics Committee conditions its approval upon change(s) in any aspect of the Study such as modification(s) of the Protocol, written Informed Consent Form, any other written information *and / or* other procedures

e. Ethics Committee's documents relating to re-evaluations / re-approvals with favourable opinion, and of any withdrawals or suspensions of approval / favourable opinion

3.1.8. Information on Investigational Products

As a prerequisite to planning of a Study, the Sponsor is responsible for providing the Investigator(s) with an Investigator's Brochure. The Brochure must contain the available chemical, pharmaceutical, toxicological, pharmacological and clinical data including the available data from previous and ongoing clinical studies regarding the Investigational Product and, where appropriate, the Comparator Product. This information should be accurate and adequate to justify the nature, scale and the duration of the Study. In addition, the Sponsor must bring any relevant new information arising during the period of Study to the attention of the Investigator(s) as well as the Ethics Committee.

3.1.9. Supply, storage and handling of Pharmaceutical Products

The Sponsor is responsible for supplying the Investigational Product's, including Comparator(s) and Placebo if applicable. The Products should be manufactured in accordance with the principles of GMPs and they should be suitably packaged in the manner that will protect the product from deterioration and safeguard blinding procedures (if applicable) and should be affixed with appropriate investigational labelling.

The Sponsor should determine the Investigational Product's acceptable storage conditions, reconstitution procedures and devices for product infusions if any, and communicate them in writing to all involved parties, besides stating them on the Product labels where ever possible.

In case any significant formulation changes are made in the Investigational Product during the course of the Study - the results of any additional studies of the new formulation (e.g. stability, bioavailability, dissolution rate) should be provided to the involved parties to enable them to determine their effects on the pharmacokinetic profile of the Product prior to the use in the Study.

The Sponsor should not supply an Investigator / Institution with the Product until the Sponsor obtains all required documentation (e.g. approval / favourable opinion from Ethics Committee and Regulatory Authorities).

The Sponsor should document procedures and lay down responsibilities for

a. adequate and safe receipt, handling, storage, dispensing of the Product

b. retrieval of unused Product from the Subjects and

c. return of unused Product to the Sponsor (or its alternative disposal procedure).

Sponsor should maintain records for retrieval of Product (e.g. retrieval after study completion, expired product retrieval etc.).

Sponsor should also maintain records of the quantities of Investigational Product with proper batch numbers. The Sponsor should ensure that the Investigator is able

to establish a system within his / her Institution for proper management of the Products as per the procedures.

The Sponsor should maintain sufficient samples from each batch and keep the record of their analyses and characteristics for reference, so that if necessary an independent laboratory may be able to recheck the same.

3.1.10. Safety Information:

Sponsor is responsible for the ongoing safety evaluation of the Product. The Sponsor should promptly notify all concerned of findings that could adversely affect the safety of the Subjects, impact the conduct of the Study or alter the Ethics Committee's approval / favourable opinion to continue the Study. The Sponsor, together with Investigator(s), should take appropriate measures necessary to safeguard the study subjects.

3.1.11. Adverse Drug Reaction Reporting:

The Sponsor should provide ADR / AE reporting forms to the Investigator(s) / Institution(s). The Sponsor should expedite the reporting to all concerned (including the Ethics Committee and the regulatory authorities) of all serious and/or unexpected adverse drug reactions.

3.1.12. Study Reports:

The Sponsor should ensure the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory and / or marketing purposes, whether or not the study has been completed. All reports prepared should meet the standards of the GCP guidelines for Format and Content of Clinical Study Reports. The sponsor should also submit any safety updates and / or periodic reports as prescribed by the regulatory authorities.

3.1.13. Monitoring

Although an extensively written guidance can assure appropriate conduct of the study, the sponsor should ensure that the studies are adequately monitored. The determination of the extent and the nature of monitoring should be based on considerations such as objective, purpose, design, complexity, blinding, size and endpoints of the study. The sponsor must appoint adequately trained monitors or CRO to supervise an ongoing study.

3.1.14. Audit:

Sponsor should perform an audit as a part of QA system. This audit should be conducted with the purpose of being independent and separate from routine monitoring or quality control functions. Audit should evaluate the study conduct and compliance with the protocol, SOPs, GCPs and applicable regulatory requirements. For the purpose of carrying out the audit – the sponsor may appoint individuals qualified by training and experience to conduct audits. The Auditors should be independent of the parties involved in the study and their qualifications should be documented.

The Sponsor should ensure that the auditing is conducted in accordance with the Sponsor's SOPs on what to audit, how to audit, the frequency of audit and the form & content of audit reports. Auditors should document their observations which should be archived by the Sponsors and made available to the Regulatory Authorities when called for.

Sponsor should initiate prompt action in case it is discovered that any party involved has not entirely complied with the GCP, SOPs, Protocol and / or any applicable regulatory requirements. If monitoring / auditing identifies serious and / or persistent non-compliance - the Sponsor should terminate the defaulting party's participation in the study and promptly notify to the regulatory authority.

3.1.15. Multicentre Studies

Since multicentre studies are conducted simultaneously by several investigators at different institutions following the same protocol, the sponsor should make special administrative arrangements for their conduct. These administrative arrangements should provide adequate assurance that the study will be planned and conducted according to GCPs.

The various tasks that may need special consideration include responsibility for commencement and overall performance of the study, supervision of the data, monitoring of the ADRs / AEs and various other policy matters. The functions, responsibilities and mandate of any special committee(s) set up or person(s) should be described in the study protocol, along with the procedure for their nomination.

A co-ordinating committee may be set up or a co-ordinator appointed with responsibility for the control of practical performance and progress of the study and maintaining contact with the regulatory authorities and the ethics committee(s).

Ideally, the studies should begin and end simultaneously at all institutions.

The sponsor should make arrangements to facilitate the communication between investigators at various sites. All investigators and other specialists should be given the training to follow the same protocol and systems. The sponsor should obtain written acceptance of the protocol and its annexes from each of the investigator and institution involved.

The CRFs should be so designed as to record the required data at all multicentre sites. For those investigators who are collecting additional data, supplemental CRFs should be provided to record the additional data.

Before initiation of multi-centre studies the sponsor should carefully define and document the following:

a. ethics committee(s), and the number of ethics committees to be consulted

b. role and responsibilities of the co-ordinating investigators

c. role and responsibilities of the CRO

d. randomisation procedure

e. standardisation and validation of methods of evaluation and analyses of laboratory and diagnostic data at various centres

f. structure and function of a centralised data management set-up

3.1.16. Premature Termination or Suspension of a Study

In case the sponsor chooses to or is required to terminate prematurely or suspend the study, then the sponsor should notify the investigator(s), institution(s), the ethics committee and the regulatory authorities accordingly. The notification should document the reason(s) for the termination or suspension by the sponsor or by the investigator / institution.

3.1.17. Role of Foreign Sponsor

If the sponsor is a foreign company, organisation or person(s) – it shall appoint a local representative or CRO to fulfil the appropriate local responsibilities as governed by the national regulations. The Sponsor may transfer any or all of the Sponsor's study related duties and functions to a CRO but the ultimate responsibility for the quality and the integrity of the Study Data shall always reside with the Sponsor. Any Study related duty, function or responsibility transferred to and assumed by a local representative or a CRO should be specified in writing. Any Study related duties, functions or responsibilities not specifically transferred to and assumed by a CRO or a local representative shall be deemed to have been retained by the Sponsor. The sponsor should utilise the services of qualified individuals e.g. bio-statisticians, clinical pharmacologists, and physicians, as appropriate, throughout all stages of the study process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical study reports.

3.2. The Monitor:

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

3.2.1. Qualifications

The monitor should have adequate medical, pharmaceutical and / or scientific qualifications and clinical trial experience. Monitor should be fully aware of all the aspects of the product under investigation and the protocol (including its annexes and amendments).

3.2.2. Responsibility

The main responsibility of the monitor is to oversee the progress of the study and to ensure that the study conduct and data handling comply with the protocol, GCPs and applicable ethical and regulatory requirements.

(a) The Monitor should verify that the investigator(s) have the adequate qualifications, expertise and the resources to carry out the study. Monitor should also confirm that the investigator(s) shall be available throughout the study period.

(b) Monitor should ascertain that the institutional facilities like laboratories, equipment, staff, storage space etc. are adequate for safe and proper conduct of the study and that they will remain available throughout the study.

(c) The Monitor should verify (and wherever necessary make provisions to ensure) that

1. the investigational product(s) are sufficiently available throughout the study and is stored properly

2. the investigational product(s) are supplied only to subjects who are eligible to receive it and at the specified dose(s) and time(s)

3. the subjects are provided with the necessary instructions on proper handling of the product(s)

4. the receipt, use, return and disposal of the product(s) at the site are controlled and documented as prescribed

5. the investigator receives the current Investigator's Brochure and all supplies needed to conduct the study as per the protocol

6. the investigator follows the protocol

7. the investigator maintains the essential documents

8. all parties involved are adequately informed about various aspects of the study and follow the GCP guidelines and the prescribed SOPs

9. verifying that each party is performing the specified function in accordance with the protocol and / or in accordance with the agreement between the sponsor and the party concerned

10. verifying that none of the parties delegate any assigned function to unauthorised individuals

(d) The monitor should promptly inform the sponsor and the ethics committee in case any unwarranted deviation from the protocol or any transgression of the principles embodied in GCP is noted.

(e) The monitor should follow a pre-determined written set of SOPs. A written record should be kept of the monitor's visits, phone calls and correspondence with the investigators and any other involved parties.

(f) The monitor should assess the institution(s) prior to the study to ensure that the premises and facilities are adequate and that an adequate number of subjects is likely to be available during the study.

(g) The monitor should observe and report the subject recruitment rate to the sponsor.

(h) The monitor should visit the investigator before, during and after the study to make assessments of the protocol compliance and data handling in accordance with the predetermined SOPs.

(i) The monitor should ensure that all staff assisting the investigator in the study have been adequately informed about and will comply with the protocol, SOPs and other details of the study.

(j) The monitor should assist the investigator in reporting the data and results of the study to the sponsor, e.g. by providing guidance on correct procedures for CRF completion and by providing data verification.

(k) The monitor shall be responsible for ensuring that all CRFs are correctly filled out in accordance with original observations, are legible, complete, and dated. The monitor should specifically verify that

1. the data required by the protocol are reported accurately on the CRFs and are consistent with the source documents

2. any dose and / or therapy modifications are well documented for each of the study subjects

3. adverse events, concomitant medications and inter-current illnesses are promptly reported on the CRFs in accordance with the protocol and the SOPs

4. visits that the subjects fail to make, tests that are not conducted and examinations that are not performed are clearly reported as such on the CRFs

5. all withdrawals and drop-outs of enrolled subjects from the study are reported and explained on the CRFs

(l) Any deviations, errors or omissions should be promptly clarified with the investigator, corrected and explained on the CRF. Monitor should also take appropriate actions designed to prevent recurrence of detected deviations. Monitor should ensure that investigator certifies the accuracy of CRF by signing it at the places provided for the purpose. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the study.

(m) The monitor should submit a written report to the sponsor after each site visit and after all telephone calls, letters and other correspondence with the investigator. Monitor's report should include the date, name of site, names of the monitor and the individuals contacted, a summary of what the monitor reviewed, findings, deviations & deficiencies observed, and any actions taken / proposed to secure compliance. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

(n) The monitor should confirm that the prescribed procedures for storage, handling, dispensing and return of investigational product are being followed and their compliance is being documented in a form as in the SOPs.

3.3. Investigator

3.3.1. Qualifications

The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the study and should have qualifications prescribed by the Medical Council of India (MCI). The investigator should provide a copy of the curriculum vitae and / or other relevant documents requested by the sponsor, the ethics committee, the CRO or the regulatory authorities. He / she should clearly understand the time and other resource demands the study is likely to make and ensure they can be made available throughout the duration of the study. The investigator should also ensure that other studies do not divert essential subjects or facilities away from the study at hand.

The investigator should be thoroughly familiar with the safety, efficacy and appropriate use of the investigational product as described in the protocol, investigator's brochure and other information sources provided by the sponsor from time to time.

The investigator should be aware of and comply with GCPs, SOPs and the applicable regulatory requirements.

3.3.2. Medical care of the study subjects

A qualified Medical Practitioner (or a Dentist, when appropriate) who is an Investigator or a Co-Investigator for the study should be responsible for all study related medical decisions. Investigator has to ensure that adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the study. Investigator should inform the subject when medical care is needed for inter-current illness(es) of which the investigator becomes aware. Investigator should also inform the subject's other attending physician(s) about the subject's participation in the study if the subject has another attending physician(s) and if the subject agrees to such other physician(s). Subsequent to the completion of the study or dropping out of the subject(s) the investigator should ensure that medical care and relevant follow-up procedures are maintained as needed by the medical condition of the subject and the study and the interventions made.

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

3.3.3. Monitoring and Auditing of Records

The investigator / institution shall allow monitoring and auditing of the records, procedures and facilities, by the sponsor, the ethics committee, CRO or their authorised representative(s) or by the appropriate regulatory authority. The investigator should maintain a list of appropriately qualified person(s) to whom the investigator has delegated study-related duties.

Investigator should ensure that all persons involved in the study are adequately informed about the protocol, SOPs, the investigational product(s) and their study related duties and functions.

3.3.4. Communication with Ethics Committee

Before initiating a study the investigator / institution must ensure that the proposed study has been reviewed and accepted in writing by the relevant ethics committee(s) for the protocol, written informed consent form, subject recruitment procedures (e.g. advertisements) and any written / verbal information to be provided to the subjects.

The investigator should promptly report to the ethics committee, the monitor and the sponsor:

1. deviations from or changes of, the protocol to eliminate immediate hazards to the subjects

2. changes that increase the risk to subject(s) and / or affecting significantly the conduct of the study

3. all adverse drug reactions and adverse events that are serious and / or unexpected

4. new information that may adversely affect safety of the subjects or the conduct of the study

5. for reported deaths the investigator should supply any additional information e.g. autopsy reports and terminal medical reports.

3.3.5. Compliance with the protocol

The investigator / institution must agree and sign the protocol and / or another legally acceptable document with the sponsor, mentioning the agreement with the protocol, and confirm in writing that he / she has read and understood the protocol, GCPs and SOPs and will work as stipulated in them.

The investigator may implement a deviation from, or change of protocol to eliminate an immediate hazard(s) to study subjects without prior ethics committee approval / favourable opinion. The implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment(s) should be submitted by the investigator to the ethics committee (for review and approval / favourable opinion), to the sponsor (for agreement) and if required to the regulatory authority(ies).

The investigator or person designated by him/her should document and explain any deviation from the approved protocol. The Investigator should follow the study randomisation procedure, if any, and should ensure that the randomisation code is broken only in accordance with the Protocol. If the study is blinded, the Investigator should promptly document and explain to the Sponsor any premature un-blinding e.g. accidental un-blinding, un-blinding due to serious adverse event) of the Investigational Product(s).

3.3.6. Investigational Product(s)

Investigator has the primary responsibility for investigational product(s) accountability at the study site(s). Investigator should maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or the alternative disposal of the unused product(s). These records should include dates, quantities, batch / serial numbers, expiry dates if applicable, and the unique code number assigned to the investigational product packs and study subjects. Investigator should maintain records that describe that the subjects were provided the dosage specified by the protocol and reconcile all investigational products received from the sponsor. Investigator should ensure that the product(s) are stored under specified conditions and are used only in accordance with the approved protocol.

The investigator should assign some or all of his / her duties for investigational product's accountability at the study site(s) to his subordinate who is under the supervision of the investigator / institution. The investigator or subordinate should explain the correct use of the product(s) to each subject and should check at intervals appropriate for the study that each subject is following the instructions properly. The person who carries them out should document such periodic checks.

3.3.7. Selection and recruitment of study subjects:

The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects according to the protocol. It may be necessary to secure the co-operation of other physicians in order to obtain a sufficient number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or review retrospectively the availability of the subjects. Investigator should check whether the subject(s) so identified could be included in the study according to the protocol. The investigator should keep a confidential list of names of all Study Subjects allocated to each study. This list facilitates the investigator / institution to reveal identity of the subject(s) in case of need and also serve as a proof of Subject's existence. The investigator / institution shall also maintain a Subjects' screening log to document identification of Subjects who enter pre-study screening. A Subject's enrolment log shall also be maintained to document chronological enrolment of Subjects in a particular Study.

The Investigator is responsible for giving adequate information to subjects about the trial in accordance with the GCP. The nature of the investigational product and the stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Obligations of investigators regarding informed consent: The investigator has the duty to -

1. Communicate to prospective subjects all the information necessary for informed consent. There should not be any restriction on subject's right to ask any questions related to the study as any restriction on this undermines the validity of informed consent.

2. Exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the subject is not permissible However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.

3. Seek consent only after the prospective subject is adequately informed. Investigator should not give any unjustifiable subject's decision to participate in the study.

4. As a general rule obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial, and in case of incompetence to do so, a legal guardian or other duly authorised representative.

5. Renew the informed consent of each subject, if there are material changes in the conditions or procedures of the research or new information becomes available during the ongoing trial.

6. Not use intimidation in any form which invalidates informed consent. The investigator must assure prospective subjects that their decision to participate or not will not affect the patient-clinician relationship or any other benefits to which they are entitled.

As part of the information provided to the Subject, the Investigator should supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact persons who can assist in an emergency situation.

3.3.8. Records/Reports

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to the CRF should be dated, signed and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections.

Sponsor should provide guidelines to investigators and / or the investigator's designated representatives on making such corrections and should have written procedures to assure that changes in CRFs are documented and endorsed by the Investigator. The Investigator should retain records of the changes and corrections.

Progress Reports

The investigator should submit the written summaries of the study status at the periodicity specified in the protocol to the person(s) / organisation(s) to whom the investigator is reporting. All reportings made by the investigator should identify the subjects by unique code numbers assigned to the study subjects rather than by the subjects' name(s), personal identification number(s) and / or addresses.

Termination and final report:

In case the investigator and sponsor agree to prematurely terminate or suspend the study for any reason, the investigator / institution should promptly inform the study Subjects, the Ethics Committee as well as the Regulatory Authorities. The investigators should also ensure appropriate therapy and follow-up for the subjects.

However, if the investigator or the sponsor or the ethics committee decide to terminate or suspend the study without prior agreement of all parties concerned then the party initiating the suspension / termination should promptly inform all the concerned parties about such suspension / termination and suspension along with a detailed written explanation for such termination / suspension.

The Investigator should maintain documents as specified in the essential documents' list and take measures to prevent accidental or premature destruction.

The study can be closed only when the Investigator (or the Monitor or CRO – if this responsibility has been delegated to them) has reviewed both Investigator / Institution and Sponsor files and confirm that all necessary documents are in the appropriate files.

The completion of the study should be informed by the investigator to the institution, the sponsor and the ethics committee. The investigator should sign and forward the data (CRFs, results and interpretations, analyses and reports, of the study from his / her centre to the sponsor and the ethics committee. Collaborative investigators and those responsible for the analyses (including statistical analyses) and the interpretation of the results must also sign the relevant portions of the study report. Investigator should submit his signed and dated final report to the institution, the ethics committee and the sponsor verifying the responsibility for the validity of data.

In case of a multi-centre study – the signature of the co-ordinating investigator may suffice if agreed in the protocol.

In case the investigator is the sponsor then he / she assumes the responsibilities of both the functionaries.

The investigator should familiarise himself / herself with the various other responsibilities assigned to him/her under the protocol and ensure that they are carried out as expected.

RECORD KEEPING AND DATA HANDLING

The basic concept of record-keeping and handling of data is to record, store, transfer, and where necessary convert efficiently and accurately the information collected on the trial subject(s) into data that can be used to compile the Study Report.

4.1. Documentation

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of data quality and study performance for the purpose of audit. Following the SOPs facilitates documentation.

Documentation SOPs should include details of checklists and forms giving details of actions taken, dates and the individuals responsible etc.

4.2. Corrections

All corrections in the CRFs or any other study related documents should be made in a way that does not obscure the original entry. The correct data should be inserted with the reason for the correction if such a reason is not obvious. The corrections should carry the date and initials of the Investigator or the authorised person.

4.3. Electronic Data Processing

For electronic data processing only authorised person should be allowed to enter or modify the data in the computer and there should be a recorded trail of the changes and deletions made. A security system should be set-up to prevent unauthorised access to the data. If data is altered during processing the alteration must be documented and the system should be validated. The systems should be designed to permit data changes in such a way that the data changes are documented and there is no deletion of data once it has been entered. A list of authorised persons who can make changes in the computer system should be maintained. Adequate backup of the data should be maintained.

4.4. Validation of Electronic Data Processing Systems

If trial data are entered directly into the computer there must always be an adequate safeguard to ensure validation including a signed and dated printout and backup

records. Computerised systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.

4.5. Language

All written documents, information and other material used in the Study should be in a language that is clearly understood by all concerned (i.e. the Subjects, paramedical staff, Monitors etc.)

4.6. Responsibilities of the Investigator

Investigator should ensure that the observations and findings are recorded correctly and completely in the CRFs and signed by the responsible person(s) designated in the Protocol.

Laboratory values with normal reference ranges should always be recorded on a CRF or enclosed with the CRF. Values outside the clinically accepted reference range or values that differ importantly from previous values must be evaluated and commented upon by the Investigator. Data other than that requested by the Protocol may appear on the CRF clearly marked as the additional findings and their significance described by the investigator. Units of measurement must always be stated and transformation of units must always be indicated and documented.

In the medical records of the patient(s) it should be clearly indicated that the individual is participating in a clinical trial.

4.8. Responsibilities of the Sponsor and the Monitor

The sponsor must ensure that electronic data processing system conforms to the certain documented requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation). The Sponsor must maintain SOPs for using these systems. The Monitor should take adequate measures to ensure that no data is overlooked. If the computer system automatically assigns any missing values – the fact should be clearly documented.

Sponsor should safeguard the blinding, if any, particularly during data entry and processing. The Sponsor should use an explicit Subject identification code that allows identification of all the data reported for each Subject. Ownership of the data and any transfer of the ownership of data should be documented and intimated to the concerned party(ies).

QUALITY ASSURANCE

The Sponsor is responsible for the implementation of a system of Quality Assurance in order to ensure that the Study is performed and the data is generated, recorded and reported in compliance with the Protocol, GCP and other applicable requirements. Documented Standard Operating Procedures are a prerequisite for quality assurance.

All observations and findings should be verifiable, for the credibility of the data and to assure that the conclusions presented are correctly derived from the Raw Data. Verification processes must therefore be specified and justified.

Statistically controlled sampling may be an acceptable method of data verification in each Study. Quality control must be applied to each stage of data handling to ensure that all data are reliable and have processed correctly.

Sponsor's audits should be conducted by persons independent of those responsible for the Study. Investigational sites, facilities, all data and documentation should be available for inspection and audit by the Sponsor's auditor as well as by the Regulatory Authority(ies).

STATISTICS

6.1. Role of a Biostatistician

Involvement of a appropriately qualified and experienced statistician is necessary in the planning stage as well as throughout the Study. The Bio-statistician's should make a statistical model to help the Sponsor, CRO and / or the Investigator in writing the Protocol. The number of Subjects to be included in the study is determined in relation to the statistical model on which the Protocol is based.

6.2. Study Design:

The scientific integrity of a Clinical Study and the credibility of its report depends on the design of the Study. In comparative studies the Protocol should describe:

1. an “a priori” rationale for the target difference between treatments that the Study is being designed to detect, and the power to detect that difference, taking into account clinical and scientific information and professional judgment on the clinical significance of statistical differences.

2. measures taken to avoid bias, particularly methods of Randomisation.

6.2.1. Randomisation and blinding:

The key idea of a clinical trial is to compare groups of patients who differ only with respect to their treatment. If the groups differ in some other way then the comparison of treatment gets biased. Randomisation, as one of the fundamental principles of experimental design, it deals with the possible bias at the treatment allocation. It ensures that the allocation of treatment to human subjects is independent of their characteristics. Another important benefit of Randomisation is that statistical methods of analysis are based on what we expect to happen in random samples from populations with specified characteristics. The Protocol must state the method used for Randomisation.

The Study should use the maximum degree of blindness that is possible. Study subjects, investigator or any other party concerned with the study may observe and respond by knowledge of which treatment was given. To avoid such bias it is often desired that the patient or any other person involved with the study does not know which treatment was given. Where a sealed code for each individual treatment has been assigned in a blinded randomized study it should be kept both at the site of the investigation and with the sponsor.

The Protocol must state the conditions under which the code is allowed to be broken and by whom. The system of breaking the code should be such that it allows access to only one Subject’s treatment at a time. The coding system for the Investigational Product(s) should include a mechanism that permits rapid identification of the products in case of a medical emergency, but does not permit undetectable breaks of the blinding.

6.3. Statistical Analysis

The type(s) of Statistical Analyses to be used must be clearly identified and should form basis of the statistical model for the Study. Any subsequent deviation(s) should be

described and justified in the Final Report. The need and extent of an interim analysis must be specified in the Protocol. The results of the statistical analyses should be presented in a manner that is likely to facilitate the interpretation of their clinical importance, e.g. by estimates of the magnitude of the treatment effect / difference and confidence intervals rather than sole reliance on significance testing.

Missing, unused and spurious data should be accounted for during the statistical analyses. All such omissions must be documented to enable review.

SPECIAL CONCERNS

7.1 Clinical Trials of Vaccines

7.1.1 Phases of Vaccine Trials

The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a clinical trial. The phase of these trials differ from drug trials as given below:

Phase I: This refers to the first introduction of a vaccine into a human population for determination of its safety and biological effects including immunogenicity. This phase includes study of dose and route of administration and should involve **low risk subjects**. For example, immunogenicity to hepatitis vaccine should not be determined in high-risk subjects.

Phase II: This refers to the initial trials examining effectiveness (immunogenicity) in a limited number of volunteers. Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal subjects, therapeutic or curative vaccines may be given to patients suffering from particular disease.

Phase III: This focuses on assessments of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of volunteers (in thousands) in multi-centres.

7.1.2. Guidelines

- The sponsor and investigator should be aware of the approval process(es) involved in conducting clinical trials of vaccines. They should familiarize themselves with the guidelines provided by Drug Controller General (India), Department of Biotechnology (DBT) and Ministry of Environment and Genetic Engineering Approval Committee (GEAC) in the case of vaccines produced by recombinant DNA technology. See Appendix III.

- Some vaccines that contain active or live-attenuated microorganisms can possibly possess a small risk of producing that particular infection. The subjects to be vaccinated should be informed of the same.

- The subjects in control groups or when subjected to ineffective vaccines run a risk of contracting the disease.

- The risks associated with vaccines produced by recombinant DNA techniques are not completely known. However, for all the recombinant vaccines/products the guidelines issued by the Department of Biotechnology should be strictly followed.

- Trials should be conducted by investigator with the requisite experience and having necessary infrastructure for the laboratory evaluation of seroconversion.

- Protocols for such trials should include appropriate criteria for selection of subjects, plan of frequency of administration of the test vaccine in comparison with the reference vaccine. It should accompany detailed validation of testing method to detect the antibody titter levels.

- It should specify methodology to be adopted for prevention of centrifuged serum for the purpose of testing.

- The investigator should be provided with Quality Control data of the experimental batch of the vaccine made for the purpose of clinical trials.

- The sponsor should provide the Independent Ethics Committee approval of the nodal body (ies) to carry out clinical trials with the vaccine.

- The generic version of new vaccines already introduced in the other markets after step up clinical trials including extensive Phase III trials should be compared with the reference vaccine with regard to seroconversion in a comparative manner in a significant sample size.

- Post Marketing Surveillance (PMS) should be required following seroconversion studies. PMS data should be generated in a significant sample size sensitive to detect side effects and address other safety issues.

- Protocols for test of new vaccine should contain a section giving details of steps of manufacture, in-process quality control measures, storage conditions, stability data and a flow chart of various steps taken into consideration for manufacture of vaccine. It should also contain detailed method of quality control procedure with the relevant references.

7.2. Clinical Trials of Contraceptives

- All procedures for clinical trials are applicable. Subjects should be clearly informed about the alternative available.

- In women where implant has been used as a contraceptive for trial, a proper follow up for removal of the implant should be done, whether the trial is over or the subject has withdrawn from the trial.

- Children borne due to failure of contraceptives under study should be followed up for any abnormalities if the woman does not opt for medical termination of pregnancy.

7.3 Clinical trials with surgical procedures/ medical devices

Of late, biomedical technology has made considerable progress in the conceptualisation and designing of bio-equipments. Several medical devices and critical care equipments have been developed and many more are in various stages of development. However, only through good manufacturing practices (GMP) can the end products reach the stage of utilization by society. Most of these products are only evaluated by Central Excise testing for taxation purposes, which discourages entrepreneurs to venture in this area with quality products especially when they do not come under the strict purview of the existing regulatory bodies like ISI, BSI and Drug Controller General. This is evidenced by the very

low number of patents or propriety medical equipments manufactured and produced in the country. As the capacity of the country in this area is improving day by day the need for a regulatory mechanism/ authority is increasingly obvious. The concept of regulations governing investigations involving biomedical devices is therefore relatively new in India. At present, except for needles and syringes these are not covered by the Drugs and Cosmetics Act, 1940. The Chief Executive of the Society of Biomedical Technology (SBMT) set up under the Defence Research Development Organisation (DRDO) has drafted a proposal for the setting up of a regulatory, tentatively named as the Indian Medical Devices Regulatory Authority (IMDRA). Until the guidelines are formulated and implemented by this regulatory Authority clinical trials with biomedical devices should be approved on case to case basis by committees constituted for the specific purpose.

7.3.1. Definitions:

Medical devices: A medical device is defined as an inert diagnostic of therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic accessories.

Depending upon risks involved the devices could be classified as follows:

a. Non critical devices: An investigational device that does not present significant risk to the patients'e.g. Thermometer, B.P. apparatus.

b. Critical devices: An investigational device that presents a potential risk to the health, safety, welfare of the subject- for example, pacemakers, implants, internal catheters.

All the general principles of clinical trials described for clinical trials should also be considered for trials of medical devices. As for the drugs, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained before pre-market certification. The duration of the trial and extent of use may be decided in case to case basis by the appropriate authorities. However,

the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects.

7.3.2. Guidelines

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.

- A clinical trial of medical devices is different from drug trials, as former can not be done in healthy volunteers. Hence phase I of drug trial is not necessary for trial on devices.

- Medical devices used within the body may have greater risk potential than those used on or outside the body, for example, orthopaedic pins Vs crutches.

- Medical device not used regularly have less risk potential than those used regularly, for example, contact lens Vs intraocular lenses.

- Safety procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.

- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information on following procedures to be adopted if the patient decides to withdraw from the trial.

7.4. Clinical trials for Diagnostic Agents - Use of Radio-active Materials and X- Rays

In human beings, for investigation and treatment, different radiations- X-rays, gamma rays and beta rays, radio opaque contrast agents and radioactive materials are used. The relative risks and benefits of research proposal utilizing radioactive materials or X-rays should be evaluated. Radiation limits for the use of such materials and X-Rays should be in accordance with the limits set forth by the regulatory authority (BARC) for such materials. (BARC-Bhabha Atomic Research Centre, Mumbai).

7.4.1. Guidelines

- § Informed consent should be obtained before any diagnostic procedures.
- § Information to be gained should be gathered using methods that do not expose subjects to more radiation than exposed normally.
- § Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes.
- § Safety measures should be taken to protect research subjects and others who may be exposed to radiation.
- § The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo.
- § Information to subject about possible genetic damage to offspring should be given.
- § Non-radioactive diagnostic agents are considered as drugs and the same guidelines should be followed when using them.
- § Ultrasound to be submitted wherever possible.

7.5 Clinical trials of Herbal Remedies and Medicinal Plants

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the DCG (I) for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of Ayurveda, Siddha or Unani drugs by experts in those systems of medicine which may be used later in their own hospitals and clinics. All the general principles of clinical trials described earlier pertain also to herbal remedies. However, when clinical trials of herbal drugs used in recognized Indian systems of Medicine and Homoeopathy are to be undertaken in Allopathic Hospitals, associations of physicians from the concerned system as co-investigators/ collaborators/ members of the expert group is desirable for designing and evaluating the Study.

7.5.1. Categories of Herbal Products

The herbal products can belong to any of the three categories given below:

a. A lot is known about the use of a plant or its extract in the ancient Ayurveda, Siddha or Unani literature or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of

years. The substance is being clinically evaluated for same indication for which it is being used or as has been described in the texts.

b. When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, subacute and chronic toxicity data will have to be generated as required by the regulatory authority before it is cleared for clinical evaluation.

c. An extract or a compound isolated from a plant which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

7.5.2. Guidelines

· It is important that plants and herbal remedies currently in use or mentioned in literature of recognized Traditional System of Medicine is prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization. It may not be necessary to undertake phase I studies. However, it needs to be emphasized that since the substance to be tested is already in used in Indian Systems of Medicine or has been described in their texts, the need for testing its toxicity in animals has been considerably reduced. Neither would any toxicity study be needed for phase II trial unless there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months. It should be necessary to undertake 4-6 weeks toxicity study in 2 species of animals in the circumstances pointed out in the preceding sentence or when a larger multicentric phase III trial is subsequently planned based on results of phase II study.

· Clinical trials with herbal preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. The recommendations made earlier regarding informed consent, subject, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons with diminished autonomy, all apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. However, it is essential that such clinical trials be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator in such a clinical trial. It would neither ethically acceptable nor morally justifiable, if an allopathic physician, based on

references in ancient literature of above-mentioned traditional systems of Medicine, carries out clinical evaluation of the plant without any concept or training in these systems of medicine. Hence, it is necessary to associate a specialist from these systems and the clinical evaluation should be carried out jointly.

- When a Folklore medicine / Ethno-medicine is ready for commercialisation after it has been scientifically found to be effective, then the legitimate rights/ share of the Tribe or Community from whom the knowledge was gathered should be taken care of appropriately while applying for the Intellectual Property Rights and / Patents for the product.

APPENDICES

Appendix I:

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

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

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for

those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

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

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

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

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to

the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object

of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix II:

SCHEDULE Y

Requirements and guidelines on clinical trials for import and manufacture of new drug

1. ***Clinical Trials***

    1. *Nature of trials*: The clinical trials required to be carried out in the country before a new drug is approved for marketing depend on the status of the drug in other countries. If the drug is already approved/marketed, phase III trials as required under item 7 of Appendix I (to Sch. Y) usually are required. If the drug is not approved/ marketed, trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.

For new drug substances discovered in other countries phase I trials are not usually allowed to be initiated in India unless phase I data as required under Item 5 of the said Appendix from other countries are available. However, such trials may be permitted even in the absence of phase I data from other countries if the drug is of special relevance to the health problem of India.

For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I as required from Item 5 of the said Appendix, through phase III as required under Item 7 of the said Appendix, permission to carry out these trials is generally given in stages, considering the data emerging from earlier phase.

    2. *Permission for trials:* Permission to initiate clinical trials with a new drug may be obtained by applying in Form 12 for a test license (TL) to import or manufacture the drug under the Rules. Data appropriate for the various phases of clinical trials to be carried out should accompany the application as per format given in Appendix

I (Items I-4). In addition, the protocol for proposed trials, case report forms to be used, and the names of investigators and institutions should also be submitted for approval. The investigators selected should possess appropriate qualifications and experience and should have such investigational facilities as are germane to the proposed trials protocol.

Permission to carry out clinical trials with a new drug is issued along with a test license in Form 11.

It is desirable that protocols for clinical trials be reviewed and approved by the institution's ethical committee. Since such committees at present do not exist in all institutions, the approval granted to a protocol by the ethical committee of one institution will be applicable to the use of that protocol in other institutions, which do not have an ethical committee. In case none of the trial centres/institutions has an ethical committee the acceptance of the protocol by the investigator and its approval by the Drugs Controller (India) or any officer as authorized by him to do so will be adequate to initiate the trials.

For new drugs having potential for use in children, permission for clinical trials in the paediatric age group is normally given after phase III trials as required under item 7 of the said Appendix, in adults are completed. However, if the drug is of value primarily in a disease of children, early trials in the paediatric age group may be allowed.

3. *Responsibilities of Sponsor/Investigator:* Sponsors are required to submit to the Licensing Authority as given under Rule 21 an annual status report on each clinical trial, namely, ongoing, completed, or terminated. In case a trial is terminated, reason for this should be stated. Any unusual, unexpected, or serious adverse drug reaction (ADR) detected during a trial should be promptly communicated by the sponsor to the Licensing Authority under Rule 21 and the other investigators.

   In all trials an informed, written consent is required to be obtained from each volunteer/patient in the prescribed form (See Appendix V), which must be signed, by the patient/volunteer and the chief investigator.

2. ***Chemical and Pharmaceutical Information***

Most of the data under this heading (See Appendix I to Sch. Y, Item 2) are required with the application for marketing permission. When the application is for clinical trials only, information covered in item 2.1 to 2.3 of Appendix I will usually suffice.

3. ***Animal Toxicology***

1. *Acute toxicity:* Acute toxicity studies (See Appendix I – Sch. Y - Item 4.2) should be carried out in at least two species, usually mice and rats using the same route as intended for humans. In addition, at least two more route should be used to ensure systemic absorption of the drug, this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD 50s should be reported preferably with 95 percent confidence limits, if LD 50s cannot be determined, reasons for this should be stated.

2. *Long-term toxicity:* Long-term toxicity studies (see Appendix I – Sch. Y, Item 1.3) should be carried out in at least two mammalian species, of which one should be a non-rodent. The duration of study will depend on whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials (see Appendix III). If a species is known to metabolize the drug in the same way as humans, it should be preferred.

   In long-term toxicity studies the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e. the minimum number on which data should be available, is shown in Appendix IV to Sch. Y.

A control group of animals, given the vehicle alone, should always be included, and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it, eg: 2.5x to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.

The variables to be monitored and recorded in long-term toxicity studies include behavioral, physiological, biochemical and microscopic observations.

3. *Reproduction studies:* Reproduction studies (see Appendix I – Sch. Y, item 4.4) need to be carried out only if the new drug is proposed to be studied or used in women of childbearing age. Two species should generally be used, one of them being non-rodent if possible.

(a)Fertility studies: The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy. The highest dose used should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans. The control and the treated group should be of similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.

(b)Teratogenicity studies: The drugs should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be the proposed dose for clinical use in humans or multiple of it. The route of administration should be the same as for human therapeutic use. The control and the treated groups should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites, resorptions if any; and the number of fetuses with their sexes, weights and malformations if any.

(c) Perinatal studies: The drug should be administered throughout the last third of pregnancy and then through lactation and weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observations should include macroscopic autopsy and where necessary, histopathology.

4.Local toxicity: These studies (see Appendix I, Sch. Y, Item 4.5) are required when the new drug Is proposed to be used typically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.

5.*Mutagenicity and Carcinogenicity :* These studies (see Appendix I, Sch. Y Item 4,6) are required to be carried out if the drug or its metabolite is related to a known carcinogen or when the nature and action of the drug is such as to suggest a carcinogenic/mutagenic potential. For carcinogenicity studies, at least two species should be used. These species should not have high incidence of spontaneous tumors and should preferably be known to metabolize the drug in the same manner as humans. At least three does levels should be used; the highest does should be sub-lethal but cause observable toxicity; the lowest does should be comparable to the intended human therapeutic does or a multiple of it, eg: 2.5x; to make allowance for the sensitivity of the species; the intermediate does to be placed logarithmically between the other two doses. A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Observations should include macroscopic changes observed at autopsy and detailed histopathology.

4. Animal Pharmacology

Specific pharmacological actions (see Appendix I to Sch. Y, Item 3.2) are those with therapeutic-potential for humans. These should be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s should be given. Special studies to elucidate mode of action may also be described.

General pharmacological action (see Appendix I to Sch. Y, Item 3.3) are effects on other organs and systems, especially cardiovascular, respiratory and central nervous systems.

Pharmacokinetic data help relate drug effect to plasma concentration and should be given to the extent available.

5. Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials (see Appendix I, Sch. Y, Item 5) is to determine the maximum tolerated dose in humans; pharmacodynamic effects, adverse reactions, if any,

with their nature and intensity; and pharmacokinetic behaviors or the drug as far as possible. These studies are carried out in healthy adult males, using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centers.

6. Exploratory trials (Phase II)

In phase II trial (see Appendix I to Sch. Y, Item 6) a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

7. Confirmatory trials (Phase III)

The purpose of these trials (see Appendix I to Sch. Y, Item 7) is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

If the drug is a new drug substance discovered in India and not marketed in any other country, phase III data should be obtained on at least 500 patients distributed over 10-15 centers. In addition, data on adverse drug reactions observed during clinical use of the drug as recommended and to provide a report on its efficacy and adverse drug reactions in the treated patients. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule-21 of Drugs & Cosmetics Rules.

8. Special Studies

(A) These include studies on solid oral dosage forms, such as, bioavailability and dissolution studies. These are required to be submitted on the formulations manufactured in the country. (See Appendix I, Items 8.1 and 8.2)

(B) These include studies to explore additional aspects of the drug, eg: use in elderly patients or patients with renal failure, secondary or ancillary effects, interactions, etc. (See Appendix I to Sch. Y, Item 8.1 and 8.2).

9. Submission of Reports (Appendix II to Schedule Y)

The reports of completed clinical trials shall be submitted by the applicant duly signed by the investigator within a stipulated period of time. The applicant should do so even if he is no longer interested to market the drug in the country unless there are sufficient reasons for not doing so.

10. Regulatory status in other counties

It is important to state if any restrictions have been placed on the use of the drug in any other country, eg: dosage limits, exclusion of certain age groups, warnings about adverse drug reaction, etc. (See Appendix I, Sch. Y, Item 9.2)

Likewise, if the drug has been withdrawn from any country especially by a regulatory directive such information should e furnished along with reasons and their relevance, if any, to India (See Appendix I, Item 9.1(d)).

11. Marketing Information

The product monograph should comprise the full prescribing information necessary to enable a physician to use the drug properly. It should include description, actions, indications, dosage precaution, drug interactions, warnings and adverse reactions.

The drafts of label and carton texts should comply with provisions of Rules 96 and 97 of the said rules.

Appendix I to Schedule Y

Data required to be submitted with application for permission to market a new drug

1. Introduction

A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information

1. Chemical name; code name or number, if any; non-proprietary or generic name, if any; physio-chemical proportion.

2. Dosage form and its composition.

3. Specifications of active and inactive ingredients.

4. Tests for identification of the active ingredient and method of its assay.

5. Outline of the method of manufacture of the active ingredient.

6. Stability data.

3. Animal pharmacology

1. Summary.

2. Specific pharmacological actions.

3. General pharmacological actions.

4. Pharmacokinetics, absorptions, distribution, metabolism, excretion.

4. Animal toxicology (See Appendix III and IV to Sch. Y)

1. Summary

2. Acute toxicity

3. Long term toxicity

4. Reproduction studies

5. Local toxicity

6. Mutagenicity and carcinogenicity

5. Human/clinical pharmacology (Phase I)

1. Summary.

2. Specific pharmacological actions.

3. General pharmacological actions.

4. Pharmacokinetics, absorptions, distribution, metabolism, excretion.

6. Exploratory clinical trials (Phase II)

1. Summary

2. Investigator wise reports.

7. Confirmatory clinical trials (Phase III)

1. Summary
2. Investigator wise reports.

8. Special studies

1. Summary
2. Bioavailability and dissolution studies.
3. Investigator wise reports.

9. Regulatory status in other countries

1. Countries where

    (a) Marketed

    (b) Approved

    (c) Under trial, with phase

    (d) Withdrawn, if any, with reasons

2. Restrictions on use, if any, in countries where marketed/approved.
3. Free sale certificate from country of origin.

10. Marketing information

1. proposed product monograph
2. Drafts of labels and cartons
3. Sample of pure drug substance, with testing protocol

Notes I: All items may not be applicable to all drugs, for explanation, see text of Schedule Y.

II: For requirements of data to be submitted with application for clinical trials see text of Schedule Y, Section I and also Appendices II and III to Sch. Y.

APPENDIX I to Schedule YI

Format for submission of Clinical Trial Reports

….Title of the trial

….Name of the investigator and institution

….Objectives of the trial

….Design of study: open, single-blind or double-blind, non-comparative or comparative; parallel group or crossover.

….Number of patients, with criteria for selection and exclusion; whether written informed consent, was obtained.

….Treatments given: drugs and dosage forms: regimens; method of allocations of patients to the treatments; method of verifying compliance, if any.

….Observations made before, during and at the end of the treatment, for efficacy and safety , with methods used.

….Results: exclusions and dropouts, if any, with reasons; description of patients with initial comparability of groups where appropriate; clinical and laboratory observations on efficacy and safety; adverse drug reactions.

….Discussions of results: relevance to objectives, correlation with other reports data, if any; guidance for further study, if necessary.

….Summary and conclusion.

APPENDIX III to Schedule Y

Animal toxicity requirements for clinical trials and marketing of a new drug

Route of administration	Duration of Human administration	Phase	Long term toxicity requirements
Single dose or several doses in one Day		I-III, MP	2sp; 2 wk
Oral or Parenteral or Transdermal	Up to 2 wk	I, II	2sp; Up to 4 wk
		III, MP	2sp: Up to 3 mo
	Up to 3 wk	I, II	2sp; 4 wk
		III	2sp; 3 mo
		MP	2sp; up to 6 mo
	Over 3 mo	I,II	2sp; 3 mo
		III, MP	2sp; 6 mo
Inhalation (general anaesthetics)		I:III, MP	4sp; 5d (3h/d)
Aerosol	Repeated or Chronic use		I:II 1-2 sp; 3h/exp.
		III	1-2 sp; Up to 6wk, (2 exp/d)
		MP	1-2 sp; 24wk (2 exp/d)
Dermal	Short term or Long term application	I,II	1 sp; single 24th exp; then 2 wk observation
		III:MP	1 sp; **
Ocular or Otic or Nasal	Single or Multiple application	I:II	Irrigation test; graded doses
		III	1 sp; 3 wk; daily applications as in clinical use.
			1 sp; **

		MP	
Vaginal or Rectal	Single or Multiple application	I, II, III, MP	1 sp; **

** Number and/or duration of application commensurate with duration of use

Abbreviations: sp- species; wk- week; d- day; h- hour; mo- month; MP – Marketing Permission; exp- exposure I, II, III – Phases of clinical trial (see Appendix I, item No. 5-8).

Note : (1) Animal toxicity data available from other countries are acceptable and do not need to be repeated/duplicated in India. (2) Requirements for fixed dose combinations are given in Appendix VI.

APPENDIX IV to Schedule Y

Number of animals for long term toxicity studies

2-6 Weeks					7-26 Weeks			
Group	Rodents (rats)		Non-Rodents (dogs)		Rodents (rats)		Non-Rodents (dogs)	
	M	F	M	F	M	F	M	F
Control	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Low dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Interme-diate dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
High dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6

APPENDIX V to Schedule Y

Patient consent form for participation in a Phase I Clinical Trial

This clinical trial involves the study of a new …….. agent in volunteers/patients suffering from ……..

The drug which will be administered to volunteers/patients has been found to be safe in animal toxicity tests and other experimental data. The volunteers/patients will be required to undergo, if necessary, all routine examinations including taking of X-ray, ECG, EEG etc. at intervals. The volunteers/patients may be asked to collect stool and urine, and there may be need to draw blood or any other body fluid on several occasions to test the effects of concentrations of the drugs. The volunteers/patients are free to withdraw from the trial at any stage.

Authorisation

I have read/been briefed on the above project summary and I voluntarily agree to participate in the project. I understand that participation in this study may or may not benefit me. Its general purpose, potential benefits, possible hazards, and inconveniences have been explained to my satisfaction. I hereby give my consent for this treatment.

Signature or thumb impression

Name of the volunteer/patient

Date: Signature of Chief Investigator

Patient consent form for participation in Phase II and Phase III Clinical Trial

I …… exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of a new drug, namely ……. for the treatment of …….. . I understand that I may be treated with this drug for the diseases. I am suffering from …….. . I have been informed to my satisfaction, by the attending physician the purpose of the clinical trial and the nature of drug treatment and follow up including the laboratory investigation to monitor and safeguard my body function.

I am also aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so.

Signature of the patient

Date:

Signature of the attending physician

APPENDIX VI to Schedule Y

Data requirements of Fixed Dose Combinations

Fixed Dose combinations (FDC) fall into four groups and their data requirements accordingly

(a) The first group of FDC includes those in which one or more of the active ingredients is a new drug. Such FDC are treated in the same way as any other new drug , both the clinical trials and for marketing permission (see Rule 122-E, Item (a)).

(b) The second group of FDC includes those in which active ingredients already approved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature (see Rule 122-E, item (c)). For permission to carry out clinical trials with such FDC, a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredient as well as their combinations in the proposed ratio. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. (See Appendix I, Item 9).

For marketing permission, the reports of clinical trials carried out with the FDC in India should be submitted. The nature of trials depending on the claims to be made and the data already available.

(c) The third group of FDC includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim.

(d) The fourth group of FDC includes those whose individual active ingredients have been widely used in particular indication for years, there concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

No additional animals or human data are generally required for these FDC, and marketing permission may be granted if the FDC has an acceptable rationale.

APPENDIX III

FORMAT FOR SUBMISSION OF PRECLINICAL AND CLINICAL DATA*

FOR r-DNA BASED VACCINES, DIAGNOSTICS AND OTHER BIOLOGICALS

(Reproduced from Guidelines for Generating Preclinical and Clinical Data for r-DNA based vaccines, diagnostics and other biologicals issued by Department of Biotechnology, Ministry of Science and Technology, Govt. of India)

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*For details to generate these data, please consult the document entitled " Guidelines for generating preclinical and clinical data for r-DNA based vaccines, diagnostics and other biologicals".

A : SPECIFICATION AND CHARACTERIZATION INFORMATION ON r-DNA VACCINES AND BIOLOGICAL PRODUCTS

1. **Description in details of the method of r-DNA products:**

   (a) host cells,

   (b) gene construct,

   (c) vector construction including a description of the source and function of the component parts of the vectors,

   (d) source and diagram of the plasmid(s) used,

   (e) all intermediate cloning procedures, and

   (f) transfection methods.

2. Description of the method of sequence verification (such as restriction enzyme mapping, PCR etc.).

3. **Description on Identity-Physical, Chemical, Immunological and Biological wherever applicable**

(a) Description on recombinant DNA products :

(1) Primary structure (Amino acid sequences)

(2) Secondary structure (disulfide linkages etc.)

(3) Post-translation modification (glycosylation etc.)

(b) Monoclonal antibodies (if applicable) :

- identity by rigorous immunochemical and physicochemical characterization.

4. **Potency.**

(a) Production of specific antigen in transfected cell line,

(b) Immune response in mice,

(c) Hypersensitivity (Guinea pig maximization test), and

(d) Permissible limits of potency.

5. **General Safety Test.**

6. **Data on sterility tests as per Indian Pharmacopia guidelines.**

7. **Data on purity of recombinant product.**

(a) Limits of purity,

(b) Characterization of minor impurities like RNA, protein and genomic DNA,

(c) Permissible limits of moisture, if lyophilized, and

(d) Pyrogenicity

8. **Description of constituent materials like preservatives etc.**

9. **Data on stability of finished formulation as per IP (Indian pharmacopia) guidelines.**

B : DATA ON PRECLINICAL TESTING

1. Biological activity/ pharmacodynamics *in vitro* and in appropriate animal models.
2. Safety Pharmacology (Functional indices of toxicity).
3. Toxicology and pharmacokinetics (Absorption, Distribution, Metabolism, Excretion-ADME)
4. Immunogenicity/Immunotoxicity
5. Reproductive and developmental toxicity
6. Genotoxicity studies
7. Carcinogenicity studies

C: RECOMBINANT IMMUNODIAGNOSTIC REAGENTS

1. Specification and characterization of r-DNA diagnostic products (Please provide information as per column1-9 under Section A of this format).
2. The data on the sensitivity / specificity / predictive positive value/ predictive negative value / overall diagnostic accuracy of recombinant product in diagnostic assay.
3. Data on (1) “in-house” validation and (2) independent validation.
4. Data using indigenous / internationally available panel of sera / clinical materials.

D: CLINICAL TRIALS

1. **Phase I : Human/Clinical Pharmacology Immunogenic Potency**

    (a) Details on level of specific antibodies including its kinetics in healthy subjects.

    (b) Details on cytokine profiles in healthy subjects.

    (c) Details on T-cell responses in healthy subjects.

    (d) Data on auto-antibodies and immune complexes in healthy subjects.

    (e) Details on haematological and clinical chemistry.

2. **Phase II: Exploratory Clinical Trials- Preventive/Therapeutic Efficacy (Data to be generated in subjects residing in endemic/ non-endemic areas)**

    (a) Protective / therapeutic potentials of r-DNA vaccines.

    (b) Details of the haematological data.

    (c) Details on the clinical chemistry.

    (d) Data on experiments on minimum protective / therapeutic dose vis-à-vis immune response (both T&B cells).

3. **Phase III: Confirmatory Trials**

    (a) Preventive / therapeutic effects.

    (b) Immunological / clinical chemistry parameters in some subjects belonging to different ethnic and socio-economic groups.

APPENDIX IV

INVESTIGATOR'S BROCHURE (IB)

Introduction

The Investigator's Brochure is a compilation of the clinical and non-clinical data on the Investigational Product(s) that are relevant to a study of the product(s). It provides the investigator(s) and others involved in the study with the information on the rationale to facilitate compliance with the key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides background material to support the clinical management of the study subjects. The information contained in the IB should be in a concise, simple, objective, balanced, and non-promotional form to enable an understanding unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data. The IB should be revised whenever necessary in compliance with the sponsor's written procedures, the stage of development and the generation of relevant new information. However, any relevant new information that is considered important should be communicated to the Investigator(s), Ethics Committee and the Regulatory Authorities immediately, even before it can be methodically included in the IB.

Contents of the Investigator's Brochure

The IB should include Sponsor's name, the reference number allocated to the study, the identity of each investigational product (ie. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor). The IB should bear an edition number and date. Besides, wherever applicable it also bears a reference to the number and date of the edition it supersedes.

The Sponsor may wish to include a statement instructing the readers to treat the IB as a confidential document for the sole purpose of the Study for which it has been prepared.

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

1 Table of Contents

2 Introduction: This section includes information relevant to the stage of clinical development including the significant physical properties , chemical properties, pharmaceutical, pharmacological (pharmacological class, advantages over other substances in that class and rationale for performing the proposed study), toxicological, pharmacokinetic, metabolic, and clinical information (anticipated prophylactic/ therapeutic or diagnostic indication(s)) of all active ingredients. The introductory statement should necessarily provide the general approach to be followed in evaluating the Investigational Product.

3 Physical, Chemical, and Pharmaceutical Properties and Formulation parameters: A description should be provided of the Investigational Product substance(s), including the chemical and / or structural formula(e), and a brief summary of the relevant physical, chemical and pharmaceutical properties. Any structural similarities to other known compounds should be mentioned. Information should also be provided on the excipients.

Appropriate storage and dosage handling instructions should also be given.

4 Non-clinical Studies: Information provided should include data relating to non-clinical pharmacology, pharmacokinetics, metabolism profile in animals and toxicology. The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and the Investigational Product metabolism studies should be provided in summary form, stating the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic effects besides the possible unfavourable effects in humans.

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

- Species used
- Number and sex of animals in each group
- Unit dose (mg/kg)
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution

· Duration of post-exposure follow-up

· Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects

- Severity or intensity of pharmacological or toxic effects

- Time to onset of effects

- Reversibility of effects

- Duration of effects

- Dose response

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

(a) Non-clinical Pharmacological (Pharmacodymanics)

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (eg. special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

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

(c) Toxicology

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

- Single dose

- Repeated dose

- Carcinogenicity

- Special studies (eg. irritancy and sensitisation)

-Reproductive toxicity

- Genotoxicity (mutagenicity)

5 Effects in Humans:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Brief summaries of other clinical studies conducted on the same product should be provided if available.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational

product(s) should be presented, including the following, if available:

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

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

Population subgroups (eg. gender, age, and impaired organ function).

Interactions (eg. Product-product interactions and effects of food).

Other pharmacokinetic data (eg. results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

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

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

(c) Regulatory & Post-marketing Experiences

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

6 Summary of Data and Guidance for the Investigator

7 Bibliography

This section should provide an overall discussion of the non-clinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. Available published reports on related products should be discussed.

The information given in this section should provide the investigator with a clear understanding of the possible risks and adverse reactions.

Guidance should also be provided on the recognition and treatment of possible overdose and adverse drug reactions.

APPENDIX V

ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

Essential Documents are those documents which individually and collectively allow the evaluation of the conduct of a study and the quality of the data generated. These documents demonstrate the compliance (or otherwise) of the Investigator, Sponsor and Monitor with the Good Clinical Practice and with other applicable regulatory requirements.

Essential Documents are needed for Sponsor's independent audit function and inspection by the Regulatory Authority.

The various Essential Documents needed for different stages of the study are classified under three groups:

1. before the clinical phase of the study commences,

2. during the clinical conduct of the study, and

3. after completion or termination of the study.

The documents may be combined but their individual elements should be readily identifiable.

Master files containing all documents pertaining to the study should be created at the beginning of the study, at the Investigator / Institution site, Sponsor's office, Ethics committee's office and the CRO's office.

Legend :

I - Investigator / Institute, S - Sponsor, C - CRO,

E - IEC, · - Yes, ° - Not applicable

Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
Before the Clinical Phase of the Trial Commences During this planning stage the following documents should be generated and should be on file before the trial formally starts.						
1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has	·	·	·	·

		been provided to the investigator				
2	Signed protocol and amendments, if any, and sample case report form(CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	·	·	·	·
3	Information given to trial subject - informed consent form (including all applicable translations)	To document the informed consent	·	·	·	·
4	- Any other written information	To document that subjects will be given appropriate information (content and wording) to support their ability to give fully informed consent	·	·	·	·
5	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	·	·	·	·
6	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	·	·	·	·
7	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	·	·	·	·
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**

8	Dated, documented approval / favourable opinion of independent ethics committee (IEC) of the following: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - Subject compensation (if any) - any other documents given approval / favourable opinion	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s)	·	·	·	·
9	Independent ethics committee composition	To document that the IEC is constituted in agreement with GCP	·	·	·	·
10	Regulatory authority(ies)	To document appropriate authorisation / approval /	·	·	·	·

	authorisation / approval / notification of protocol (where required)	notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)				
11	Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator(s) and Co-Investigator / Sub-Investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	·	·	·	·
12	Normal value(s) / range(s) for medical / laboratory / technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	·	·	·	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	·	·	·	°
14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	·	·	·	°
15	Shipping records for investigational product(s) and	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related	·	·	·	°

	trial-related materials	materials. Allows tracking of product batch, review of shipping conditions, and accountability				
16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	·	·	°
	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subject's treatment	·	·	·	°
17	Master randomisation list	To document method for randomisation of trial population	°	·	·	°
18	Pre-trial monitoring report	To document that the site is suitable for trial (may be combined with Trial initiation monitoring report)	°	·	·	°
19	Trial initiation monitoring report	To document that the trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with Pre-trial monitoring report)	·	·	·	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available						
20	Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	·	·	·	·

21	Any revision to: - protocol amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment(if used)	To document revisions of these trial related documents that take effect during trial	·	·	·	·
22	Dated, documented approval / favourable opinion of Independent ethics committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information provided	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s).	·	·	·	·

	to subject - advertisement for subject recruitment(if used) - any other documents given approval / favourable opinion - continuing review of trial (where required)					
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
23	Regulatory authority(ies) authorisations / approvals / notifications where required for: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	·	·	·	·
24	Curriculum vitae for new investigator(s) and / or sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	·	·	·	·

25	Updates to normal value(s) / range(s) for medical / laboratory / technical procedure(s) / test(s) included in the protocol	To document normal values and ranges that are revised during the trial	·	·	·	°
26	Medical / laboratory / technical procedures / tests - certification or - accreditation or - established quality control and / or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period	·	·	·	°
27	Documentation of investigational product(s) and trial-related material shipment	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	·	·	·	°
28	Certificate(s) of analysis for new batches of investigational products	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	·	·	°
29	Monitoring visit reports	To document site visits by, and findings of, the monitor	°	·	·	°
30	Relevant communications other than site visits - letters	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	·	°	·	°

	- meeting notes - notes of telephone calls					
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
31	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	· (Original)	· (Copy)	· (Copy)	°
32	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trials, to medical treatment, and history of subject	· (Original)	· (Copy)	· (Copy)	°
33	Signed, dated and completed case report forms (CRF)	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	· (Copy)	· (Copy)	· (Copy)	°
34	Documentation of CRF corrections	To document all changes / additions or corrections made to CRF after initial data were recorded	· (Original)	· (Copy)	· (Copy)	°
35	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports	·	·	·	·
36	Notification by sponsor	Notification by sponsor and/or investigator, where	·	·	·	·

	and/or investigator, where applicable, to regulatory authority(ies) and IEC(s) of unexpected serious adverse drug reactions and of other safety information	applicable, to regulatory authorities and IEC(s) of unexpected serious adverse drug reactions and of other safety information				
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
37	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	·	·	·	·
38	Interim or annual reports to IEC and authority(ies)	Interim or annual reports provided to IEC and to authority(ies)	·	·	·	·
39	Subject screening log	To document identification of subjects who entered pre-trial screening	·	· (Where required)	· (Where required)	°

40	Subject identification code list	To document that investigator / Institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ Institution to reveal identity of any subject	·	·	·	°
41	Subject enrolment log	To document chronological enrolment of subjects by trial number	·	·	·	°
42	Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol	·	·	·	°
43	Signature sheet	To document signatures and initials of all persons authorised to make entries and / or corrections on CRFs	·	·	·	°
44	Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	·	·	·	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	E
After Completion or Termination of the Trial After completion or termination of the trial, all of the documents identified should be in the file together with the following						
45	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, return by the subjects, and returned to sponsors	·	·	·	°
			·	·	·	°

46	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site	(if destroyed at site)			
47	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	·	·	·	°
48	Audit certificate (if available)	To document that audit was performed	°	·	·	°
49	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	°	·	·	°
50	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	°	·	·	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
51	Final report by investigator to IEC where required, and where applicable,	To document completion of the trial	·	·	·	·

	to the regulatory authority(ies)					
52	Clinical study report	To document results and interpretation of trial	·	·	·	·