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Government of India
Central Drugs Standard Control Organization
Directorate General of Health Services
(GCT Division)

Dated 12 SEP 2024

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Circular

Subject: Draft Guidelines on Good Clinical Practices - regarding.

Central Drugs Standard Control Organization had constituted a committee under Chairmanship of Dr. Bikas Medhi, Prof. Department of Pharmacology, PGIMER, Chandigarh for the revision of India GCP guidelines and related guidelines in-line with New Drugs and Clinical Trial Rules, 2019 and currently available international guideline.

After detailed discussion, the committee has prepared draft guidelines on Good Clinical Practices. The committee opined that the proposed draft guidelines may be circulated to various stakeholders by placing it on CDSCO website for seeking comments before finalization of the guidelines.

Accordingly, the said draft guidelines on Good Clinical Practices is being published on CDSCO website for your comments/suggestions within period of 30 days by email to dci@nic.in.

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India)

To,

1. All Stakeholders

Copy to:

1. All States/UTs Drugs Controllers.
2. All Zonal/Sub-Zonal offices of CDSCO.
3. All Port offices.
4. CDSCO-IT Cell for publication on website.

Guidelines for Good Clinical Practices (GCP)

Contents

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 an investigator's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical/clinical 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 participants. The fundamental tenet of GCP is that in research on human subject/participant, the interest of science and society should never take precedence over considerations related to the well-being of the study participant. 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, safety and well-being of participants/subjects and authenticity of biomedical/clinical data generated.

The principles of GCP are designed to be flexible and applicable to a broad range of clinical research. This guideline, along with other global guidelines encourages thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical study/research. This includes evaluation of study/research characteristics, such as the design elements, the investigational product being evaluated, the medical condition being addressed, the characteristics of the participants, the setting in which the clinical study/research is being conducted, and the type of data being collected. Careful consideration of various aspects relevant to ensuring study/research quality is needed for each clinical study/research.

The principles are intended to support efficient approaches to study/research design and conduct. For example, innovative digital health technologies, such as wearables and sensors, may expand the possible approaches to study/research conduct. Such technologies can be incorporated into existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical study/research. This will aid in keeping clinical study/research conduct in line with advancing science and technological developments. The use of technology in the conduct of clinical study/research should be adapted to fit the participant/subject characteristics and the particular study/research design.
The use of innovative clinical study/research designs and technologies may help include diverse patient populations, as appropriate, and enable wider participation. The design of the study/research, to ensure appropriate quality and meaningful study/research outcomes, may be supported by the perspectives of all stakeholders; (for example, patients, participant/subjects, healthcare providers, regulators and others). Their input can increase the likelihood of meaningful study/research outcomes, which are relevant to both study/research participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participation in the study/research does not become unduly burdensome for those involved.

These guidelines have been evolved in consideration of various national and global

guidelines and in line with NDCT Rules 2019, WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Participants 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

Academic Clinical Study/research:
Clinical study/research of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a study/research are intended to be used only for academic or research purposes and not for seeking approval of the Central Licensing Authority or regulatory authority of any country for marketing or commercial purpose;

Act

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

Adaptive Clinical Study/research:
An adaptive design is defined as a clinical study/research design that allows for prospectively planned modifications to one or more aspects of the design based on real time data generated from participants in the study/research.

Adverse Event (AE)
Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a investigational 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/medical device: A noxious and unintended response at doses normally used or tested in humans.
(b) In case of new unregistered investigational/ pharmaceutical products/medical devices (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 study/research, an untoward medical occurrence seemingly caused by overdosing, abuse / dependence and interactions with other medicinal products is also considered as an ADR.

Assent
To agree or approve after thoughtful consideration an idea or suggestion to participate in research by a young person below the age of 18 years who is old enough to understand the implications of any proposed research but not legally eligible to give consent. The assent

has to be corroborated with informed consent of parent/ LAR.

Audit
A systematic and independent examination of study/research-related activities and records performed by the sponsor, service provider (including clinical/contract research organization (CRO)) or institution to determine whether the evaluated study/research-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, applicable standard standard operating procedures (SOPs), Good Clinical Practice (GCP) guidelines and the applicable regulatory requirement(s).

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

Audit Report
A record describing the conduct and outcome of the audit.

Audit Trail
Metadata records that allow reconstruction of the course of events by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerized systems. The audit trail should show activities, initial entry, and changes to data fields or records, by whom, when and, where applicable, why. In computerized systems, the audit trail should be secure, computer generated and timestamped.

Bioavailability study:
bioavailability study" means a study to assess the rate and extent to which the drug is absorbed from a pharmaceutical formulation and becomes available in the systemic circulation or availability of the drug at the site of action.

Bioequivalence study:
Bioequivalence study" means a study to establish the absence of a statistically significant difference in the rate and extent of absorption of an active ingredient from a pharmaceutical formulation in comparison to the reference formulation having the same active ingredient when administered in the same molar dose under similar conditions.

Bioequivalence/Bioavailability study centre:
"Bioavailability and Bioequivalence study centre" means a centre created or established to undertake bioavailability study or bioequivalence study of a drug for either clinical part or for both clinical and analytical part of such study.

Blinding / Masking
A method of "control experimentation" in which one or multiple stakeholders involved are not informed of the treatment being given.

Case Record Form (CRF)
A document designed in consonance with the Protocol, to record data and other information on each study/research participant. 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.

Certified Copy
A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information as the original, including relevant metadata, where applicable.

Clinical Study/clinical research
Research that directly involves a particular person or group of people to study the effect of interventions, or uses materials/data from humans indirectly, such as their behavior or biological samples for prevention, treatment and diagnosis of a disease condition/health disorder.

Clinical Study/research
clinical study/research" in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational new drug in human participants to generate data for discovering or verifying its, - (i) clinical or (ii) pharmacological including pharmacodynamics, pharmacokinetics or; (iii) adverse effects, with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;

Micro-dose:
The concept of micro-dosing involves the use of extremely low, non-pharmacologically active doses of a drug to define the pharmacokinetic profile of the medication in human participants.

Phase Zero
First-in-human testing of new investigational agents at subtherapeutic doses based on reduced manufacturing and toxicologic requirements, allowing the demonstration of drug-target effects and assessment of pharmacokinetic–pharmacodynamic relationships in humans earlier in clinical development.

Phase I
The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy participants or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I study/research should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the participants. Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives: -
(a) Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.
(b) Pharmacokinetics, i.e., characterization of a drug's absorption, distribution, metabolism, and excretion:
Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.
(c) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic or pharmacodynamic studies) may be conducted in healthy volunteer participants or in patients with the target disease. If there are appropriate validated indicators of activity and

potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.
(d) Early measurement of drug activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

Phase II
(i) The primary objective of Phase II study/research is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose and regimen for Phase III study/research. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I. (ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in study/research.

Phase III
(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drugs. (ii) For drugs intended to be administered for long periods, study/research involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug.

Phase IV
Phase IV or post marketing study/research of new drugs are performed after the approval of the drug and related to the approved indication. Such study/research go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Such study/research might not have been considered essential at the time of new drug approval due to various reasons such as limitation in terms of patient exposure, duration of treatment during clinical development of the drug, need for early introduction of the new drug in the interest of patients etc. Phase IV study/research include additional drug-drug interaction, dose response or safety studies and study/research design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies, etc.

Clinical study/research inspection:
Inspection of site of clinical study/research, sponsor/ CRO/ ethics committees involved in clinical study/research to verify the compliance with various regulatory provisions as per New Drugs and Clinical Trials Rules, 2019, GCP compliance to protect the rights, safety and wellbeing of the participants involved in clinical study/research and to verify the

credibility and integrity of clinical study/research data generated.

Clinical study/research protocol
Clinical study/research Protocol is a document containing the background, objective, rationale, design, methodology including matters concerning performance, management, conduct, analysis, adverse event, withdrawal, statistical consideration, and record keeping pertaining to clinical study/research.

Clinical trial registry
An official platform for registering clinical trial/study/research, such as Clinical trial Registry-India (CTRI).

Clinical Investigation
Clinical investigation means the systematic study of an investigational medical device in or on human participants to assess its safety, performance, or effectiveness.

Clinical Investigation Plan
Clinical investigation plan means a document which contains the information about the rationale, aims and objective, design and the proposed analysis, conduct, methodology including performance, management, adverse event, withdrawal and statistical consideration and record keeping pertaining to clinical investigation.

Clinical performance evaluation
Clinical performance evaluation means the systematic performance study of a new *in vitro* diagnostic medical device on a specimen collected from human participants to assess its performance.

Controlled Human Infection studies (CHIS):

Controlled Human Infection studies (CHIS) refers to the research methodology that involves intentionally exposing healthy human volunteers to a specific pathogen or infectious agent under controlled conditions. These studies aim to understand disease pathophysiology & immune responses, develop vaccines, test treatment modalities, and evaluate the safety and efficiency of potential New Chemical Entities (NCE)

Comparator Product:
A pharmaceutical product (including placebo) used as a reference in clinical study/research.

Compensation:
Provision of financial payment to the research participants or their legal heirs when temporary or permanent injury or death occurs due to participation in biomedical and health research.

Confidentiality:
Maintenance of privacy of study participants 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.

Confidentiality agreement:

Secrecy or non-disclosure agreements designed to protect trade secrets, information, and expertise from being misused by those who have learned about them.

Clinical Research Organization/Contract Research Organization (CRO)
Clinical/Contract Research organization means a body commercial or academic or of other category owned by an individual or an organization having status of legal entity by whatsoever name called to which the sponsor may delegate or transfer some or all of tasks, duties and/or obligations regarding clinical study/research or bioavailability or bioequivalence study, such transfer or delegation of contractual transfers or obligations must be in writing.

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".

Computerized Systems Validation
A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect study/research participant's protection and the reliability of study/research results.

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

See **Principal Investigator**

Data Acquisition Tool (DAT)
A paper or electronic tool designed to collect data and associated metadata from a data originator in clinical study/research according to the protocol and to report the data to the sponsor. The data originator may be a human (e.g., the participant/subject or study/research staff), a machine (e.g., wearables and sensors) or an electronic transfer of data from one system to another (e.g., extraction of data from an electronic health record or laboratory system). Examples of DATs include but are not limited to CRFs, interactive response technologies (IRTs), patient-reported outcomes (PROs), clinical outcome assessments (COAs) and wearable devices, irrespective of the media used.

Decentralized clinical study/research
Decentralized clinical study/research (DCT) are study/research where some or all of a clinical study/research's activities occur at locations other than a traditional clinical study/research site. These alternate locations can include the participant's home, a local health care facility, or a nearby laboratory.

Direct Access
Permission to examine, analyse and verify records that are important to the evaluation of a clinical study/research and may be performed in person or remotely. Any party (e.g.,

domestic, and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of participants' identities and their data and sponsor's proprietary information.

Data Monitoring Committees (DMCs)/ Data and Safety Monitoring Boards (DSMBs)/ Data and Safety Monitoring Committees (DSMCs)

A clinical study/research DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical study/research. The DMC advises the sponsor regarding the continuing safety of study/research participants and those yet to be recruited to the study/research, as well as the continuing validity and scientific merit of the study/research. When a single DMC is responsible for monitoring multiple study/research, the considerations for establishment and operation of the DMC are generally similar to those for a DMC monitoring a single study/research, but the logistics may be more complex. For example, in case of multiple conflict of interest determinations may be needed for each DMC member.

Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (e.g., data safety monitoring board) that may be established by the sponsor to assess at intervals the progress of a clinical study/research, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop study/research.

Development Safety Update Report (DSUR)

DSUR prepared by the sponsor presents a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by: (1) examining whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety; (2) describing new safety issues that could have an impact on the protection of clinical study/research participants; (3) summarizing the current understanding and management of identified and potential risks; and (4) providing an update on the status of the clinical investigation/development program and study results. A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR.

Documentation

All records (including physical records (dry & wet – like pathological slides/blocks, as applicable)/electronic data 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.

e-Consent

electronic informed consent refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey

information related to the study and to obtain and document informed consent.

Electronic Case Record Form (e-CRF)
The eCRF is an auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.

Escape/rescue medicine /treatment
A supplementary treatment, usually given to alleviate pain in placebo-controlled study/research, to relieve the study/research participant/subject of the symptoms caused by the investigated disease in a study.

Essential document/Record
Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical study/research that facilitate the ongoing management of the study/research and collectively allow the evaluation of the methods used, the factors affecting a study/research and the actions taken during the study/research conduct to determine the reliability of the study/research results produced and the verification that the study/research was conducted in accordance with GCP guidelines and applicable regulatory requirements (Annexure/checklist)

Ethics Committee (EC)
An ethics committee is an multi displiniary/ multi sectorial committee responsible to undertake scientific and ethical review of clinical research. Ethics committee could be an institutional ethics committee (EC) or an independent (Ind EC) (with no institutional affiliation). The EC 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 participants involved in a study. The EC ensures an independent fair and un-biased review 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 participants and adequacy of confidentiality safeguards. The legal status, composition, function, operations and regulatory requirements pertaining to ECs is defined in New Drugs and Clinical Trials Rules 2019 which allow the EC to act in agreement with GCP as described in this guideline.

Interim analysis
An interim analysis is any examination of data obtained from participants in study/research while that study/research is ongoing and is not restricted to cases in which there are formal between-group comparisons. The observed data used in the interim analysis can include one or more types, such as baseline data, safety outcome data, pharmacokinetic, pharmacodynamic or other biomarker data, or efficacy outcome data.

Final Report
A complete and comprehensive written description of the study/research/study of any therapeutic, prophylactic, or diagnostic agent conducted in human participants, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report 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 study/research 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 participants 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
A literate person, who is independent of the research and would not be unfairly influenced by people involved with the study, who attends the informed consent process if the participant and/or
their LAR cannot read, and understand the informed consent form and any other written information supplied to the participant.

Informed Consent
Written signed and dated paper confirming a participant's willingness to voluntarily participate in a particular research, after having been informed of all aspects of the research that are relevant for the participant's decision to participate.

Inspection –
See **Clinical study/research inspection**

Institution/ Clinical study/research site
"Clinical study/research site" means any hospital or institute or any other clinical establishment having the required facilities to conduct clinical study/research.

Interim clinical study/research report: - see interim analysis.

Investigator
A person responsible for the conduct of the study at the study/research site. Investigator is responsible for the rights, health and welfare of the study participants. 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.

See **co-investigator**

Investigational product 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 or placebo.

Investigational new drug
"Investigational new drug" means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country.

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 study/research. There should be adequate data to justify the nature, scale and duration of the proposed study/research and to evaluate the potential safety and need for special precautions. If new substantially relevant data is generated during the study/research, the information in the Investigator's Brochure must be updated.

Legally authorized representative (LAR)/Legally acceptable representative (LAR)
A person who, under applicable law or judicial authority, can give consent on behalf of a prospective participant/subjectwho, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the ethics committee.

Medical Device
Medical device means substances used for in vitro diagnosis and surgical dressings, surgical bandages, surgical staples, surgical sutures, ligatures, blood and blood component collection bag with or without anticoagulant covered under subclause (i) of Medical Device Rules 2017; substances including mechanical contraceptives (condoms, intrauterine devices, tubal rings), disinfectants and insecticides notified in the Official Gazette under sub-clause (ii) of medical device rules 2017; (C) devices notified from time to time under sub-clause (iv), of clause (b) of section 3 of the Act and medical device rules

Medical Management
medical management" means treatment and other necessary activities for providing the medical care to complement the study/research treatment.

Metadata
The contextual information required to understand a given data element. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data. For this guideline, relevant metadata are those needed to reconstruct the study/research conduct.

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

Monitoring Plan
A document that describes the strategy, methods, responsibilities and requirements for monitoring the clinical study/research.

Monitoring Report

A documented report following site and/or centralized monitoring activities.

Multi-Centre Study

Clinical study/research conducted according to one single protocol in which the study/research is taking place at different investigational sites, therefore carried out by more than one investigator.

Global clinical study:

Global clinical study means any clinical study which is conducted as part of a clinical development of a drug in more than one country.

Non-Clinical Study

Biomedical studies that are not performed on human participants.

Non interventional studies

Non-interventional studies are defined as studies, in the context of which findings resulting from individuals' treatment with medicinal products are analysed using epidemiological methods; the treatment, including the diagnosis and monitoring, does not follow a predetermined study/research protocol but results exclusively from current medical practice.

Periodic Safety Update Report (PSUR)

A Periodic Safety Update Report (PSUR) is a systematic review of the safety data of an approved medicine which include all relevant new information from appropriate sources, patient exposure data and summarizes marketing authorization status of product.

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.

Phytopharmaceutical drug

Phytopharmaceutical drug includes purified and standard fraction with defined minimum four bio-active or phyto-chemical compound (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route as specified in Rule 2 (eb) of the Drugs & Cosmetics (D&C) Rules, 1945.

Post marketing surveillance

PMS is practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market. PMS can be active or by way of spontaneous reporting.

Post marketing surveillance study or observational or non-interventional study for active surveillance:

Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licencing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert. In such studies the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs are already approved for marketing.

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)
The systematic and independent examination of all study/research-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted, and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard standard operating procedures (SOPs), applicable regulations and GCP guideline.

Quality Control (QC)
Periodic operational examination of the study/research related processes carried out proactively by the process owners to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, SOPs, applicable regulation and GCP guideline.

Randomisation
The process of assigning study participants to either the treatment or the control group. Randomisation gives all participants the same chance of being in either group 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 Study/research 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 study/research. Also see Source Data.

Real-world data
RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.

Real-world evidence
RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

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.

Sever adverse event:
The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Service Provider
A person or organisation (commercial, academic or other) providing a service used during the conduct of a clinical study/research to either the sponsor or CRO or the investigator or any other related entity to fulfil one or more of their study/research-related activities.

Source Data
Original documents or data (which includes relevant metadata) or certified copies of the original documents or data, irrespective of the media used. This may include study/research participants' medical/health records/notes/charts; data provided/entered by study/research participants (e.g., electronic patient-reported outcome (ePROs)); healthcare providers' records from pharmacies, laboratories and other facilities involved in the clinical study/research; and data from automated instruments, such as wearables and sensors.

Sponsor
An individual or a company or an institution that takes the responsibility for the initiation, management of a Clinical Study.

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

Sub-Investigator
See **Co-Investigator**

Participant/subjectFiles / Patient Files
A file containing demographic and medical information about a study participant. It includes hospital files, consultation records or special participant/subjectfiles 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 Participant/subject(Participant)
An individual participating in clinical study/research as a recipient of the *Investigational Product*.

A *Study Participant/subject*may be a healthy person volunteering in study/research 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 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.

Participant/subjectIdentification Code
A unique identification number / code assigned by the Investigator to each Study Participant/subjectto protect the Participant's identity. Participant/subjectIdentification Code is used in lieu of the Participant'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.

Suspected unexpected serious adverse reactions (SUSARs)
Adverse reactions due to medicines administered in clinical study/research that are unexpected and serious.

Treatment Emergent Adverse Event
An event that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.

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.

Vulnerable participants

Vulnerability in research pertains to individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens or social injustice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so.

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 participants
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 participant/subjectparticipation 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 participants 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 participants' compliance

2.3.1.5 Inclusion, Exclusion and Withdrawal of Participants

a. Participant/subject inclusion criteria: specifications of the participants (patients / healthy volunteers) including age, gender, ethnic groups, prognostic factors,

diagnostic admission criteria etc. should be clearly mentioned where relevant.

b. Participant/subject exclusion criteria, including an exhaustive statement on criteria for pre-admission exclusions.
c. Participant/subject withdrawal criteria (i.e. terminating investigational product treatment / study treatment) and procedures specifying – when and how to withdraw participants from the treatment, type and timing of the data to be collected from withdrawn participants, whether and how participants are to be replaced and the follow-up on the withdrawn participants
d. Statistical justification for the number of Participants to be included in the Study
e. justification for placebo, benefit–risk assessment, If standard therapies are to be withheld, to be included in justification
f. justification of inclusion/exclusion of vulnerable populations

2.3.1.6 Handling of the Investigational 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.)
   The label should necessarily contain the following information: the words – clinical trial supply, containers bearing labels, indicating the name of the Investigational Product or code number, batch or lot number, wherever applicable, date of manufacture, use before date, storage conditions, name of the institution or organisation or the centre where the clinical trial or bioavailability or bioequivalence study is proposed to be conducted, name and address of the manufacturer, and the purpose for which it has been manufactured.

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 participants 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 participants needed to achieve the study objective, and statistical considerations on which the proposed number of participants is based
c. Detailed break-up of the number of participants 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 participants to be included in the final analyses (e.g. all randomized participants / all dosed participants / all eligible participants / evaluable participants

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 participants.

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 participants, refunding expenses of the participants, 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 Participants 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 participants 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 Participants and the mode of providing it
b. Instructions to staff
c. Descriptions of special procedures

2.3.1 Academic clinical study/research

(1) No permission for conducting an academic clinical study/research shall be required for any drug from the Central Licensing Authority where,
   (i) the clinical study/research in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and
   (ii) the clinical study/research referred to in clause (i) has been initiated after prior approval by the Ethics Committee for clinical study/research; and
   (iii) the observations generated from such clinical study/research are not required to be submitted to the Central Licensing Authority; and
   (iv) the observations of such clinical study/research are not used for promotional purposes.

(2) In the event of a possible overlap between the academic clinical study/research and clinical study/research or a doubt on the nature of study, the Ethics Committee concerned shall inform the Central Licensing Authority in writing indicating its views within thirty working days from the receipt of application to that effect.

(3) The Central Licensing Authority shall, after receiving the communication from the Ethics Committee examine it and issue necessary clarification, in writing, within thirty working days from the date of receipt of such communication; provided that where the Central Licensing Authority does not send the required

communication to such Ethics Committee within thirty working days from the date of receipt of communication from the said Ethics Committee, it shall be presumed that no permission from the Central Licensing Authority is required.

(4) The approved academic clinical study/research shall be conducted in accordance with the approved clinical study/research protocol, ethical principles specified in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the Indian Council of Medical Research with a view to ensuring protection of rights, safety and wellbeing of study/research participant/subjectduring conduct of clinical study/research of licenced and approved drug or drug formulation for any new indication or new route of administration or new dose or new dosage form for academic research purposes.

An "academic clinical study/research" means a clinical study/research of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a study/research are intended to be used only for academic or research purposes and not for seeking approval of regulatory authority of any country for marketing or commercial purpose. No permission for conducting an academic clinical study/research shall be required for any drug from the regulatory agency provide — (i) the clinical study/research in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and (ii) the clinical study/research has been initiated after prior approval by the Ethics Committee for clinical study/research; and (iii) the observations generated from such clinical study/research are not required to be submitted to the regulatory authority; and (iv) the observations of such clinical study/research are not used for promotional purposes. However, in the event of a possible overlap between the academic clinical study/research and clinical study/research or a doubt on the nature of study, the Ethics Committee concerned shall inform the DCG (I) in writing indicating its views within thirty working days from the receipt of application to that effect. The academic clinical study/research shall be required to be conducted in accordance with the approved clinical study/research protocol, ethical principles specified in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the ICMR with a view to ensuring protection of rights, safety and wellbeing of study/research participant/subjectduring conduct of such clinical study/research. Therefore, ethical principles including compensation, medical management in case of injury or death etc. as prescribed in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the ICMR are applicable for academic clinical study/research.

2.4 Ethical & Safety Considerations

2.4.1 Ethical Principles

1.0 Statement of General Principles

Research on human participants pertains to a broad range of scientific enquiry aimed

at developing generalizable knowledge that improves health, increases understanding of disease and is ethically justified by its social value. Every research has some inherent risks and probabilities of harm or inconvenience to participants/communities. Therefore, protection of participants should be built into the design of the study. Do no harm (non-maleficence) has been the underlying universal principle guiding health care in all systems of medicine around the world. While conducting biomedical and health research, the four basic ethical principles namely; respect for persons (autonomy), beneficence, non-maleficence and justice have been enunciated for protecting the dignity, rights, safety and well-being of research participants. These four basic principles have been expanded into 12 general principles described below, and are to be applied to all biomedical, social and behavioural science research for health involving human participants, their biological material and data.

1.1. General Principles

1.1.1 Principle of essentiality whereby after due consideration of all alternatives in the light of existing knowledge, the use of human participants is considered to be essential for the proposed research. This should be duly vetted by an ethics committee (EC) independentof the proposed research.

1.1.2 Principle of voluntariness whereby respect for the right of the participant/subjectto agree or not to agree to participate in research, or to withdraw from research at any time, is paramount. The informed consent process ensures that participants' rights are safeguarded.

1.1.3 Principle of non-exploitation whereby research participants are equitably selected so that the benefits and burdens of the research are distributed fairly and without arbitrariness or discrimination. Sufficient safeguards to protect vulnerable groups should be ensured.

1.1.4 Principle of social responsibility whereby the research is planned and conducted soas to avoid creation or deepening of social and historic divisions or in any way disturbsocial harmony in community relationships.

1.1.5 Principle of ensuring privacy and confidentiality whereby to maintain privacy of the potential participant, her/his identity and records are kept confidential and accessis limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.)privacy of the information can be breached in consultation with the EC for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant.

1.1.6 Principle of risk minimization whereby due care is taken by all stakeholders (including but not limited to researchers, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized, and appropriate care and compensation is given ifany harm occurs.

1.1.7 Principle of professional competence whereby the research is planned, conducted, evaluated and monitored throughout by persons who are competent and

have the appropriate and relevant qualification, experience and/or training.
1.1.8 Principle of maximization of benefit whereby due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits to the research participants and/or to the society.

1.1.9 Principle of institutional arrangements whereby institutions where the research is being conducted, have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.

1.1.10 Principle of transparency and accountability whereby the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants. Stakeholders involved in research should disclose any existing conflict of interest and manage it appropriately. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/ audit.

1.1.11 Principle of totality of responsibility whereby all stakeholders involved in research are responsible for their actions. The professional, social, and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.

1.1.12 Principle of environmental protection whereby researchers are accountable for ensuring protection of the environment and resources at all stages of the research, in compliance with existing guidelines and regulations.

2.0 General Ethical Considerations:

All research involving human participants should be conducted in accordance with the basic and general ethical principles as outlined in section 1. The researcher and the team are responsible for protecting the dignity, rights, safety and well-being of the participants enrolled in the study. They should have the appropriate qualifications and competence in research methodology and should be aware of and comply with the scientific, medical, ethical, legal and social requirements of the research proposal. The ECs are responsible for ensuring that the research is conducted in accordance with the afore mentioned principles.

2.1 Benefit-risk assessment
Benefits to the individual, community or society refer to any sort of favourable outcome of the research, whether direct or indirect. The social and scientific value of research should justify the risk, which is the probability of causing discomfort or harm anticipated as physical, psychological, social, economic or legal.

2.1.1 The researcher, sponsor and EC should attempt to maximize benefits and minimize risks to participants so that risks are balanced to lead to potential benefits at individual, societal and/or community levels.
2.1.2 The EC should assess the inherent benefits and risks, ensure a favourable balance of benefits and risks, evaluate plans for minimizing the risk and discomfort

and decide on the merit of the research before approving it.
2.1.3 The EC should also assess any altered risks in the study at the time of continuing review.
2.1.4 The type of EC review based on risk involved in the research, is categorized as given in Risk Table

2.2 Informed consent process

Informed consent protects the individual's autonomy to freely choose whether or not to participate in the research. The process involves three components – providing relevant information to potential participants, ensuring the information is comprehended by them and assuring voluntariness of participation. Informed consent should explain medical terminology in simple terms and be in a language that the participant/subjectunderstands.

Type of risk	Definition/description
Less than minimal risk	Probability of harm or discomfort anticipated in the research is nil or not expected. For example, research on anonymous or non-identified data/samples, data available in the public domain, meta-analysis, etc.
Minimal risk	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of an average healthy individual or general population or during the performance of routine tests where occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, physical examination, chest X-ray, obtaining body fluids without invasive intervention, such as hair, saliva or urine samples, etc.
Minor increase over minimal risk or Low risk	Increment in probability of harm or discomfort is only a little more than the minimal risk threshold. This may present in situations such as routine research on children and adolescents; research on persons incapable of giving consent; delaying or withholding a proven intervention or standard of care in a control or placebo group during randomized study/research; use of minimally invasive procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress, such as drawing a small sample of blood for testing; trying a new diagnostic technique in pregnant and breastfeeding women, etc. Such research should have a social value. Use of personal identifiable data in research also imposes indirect risks. Social risks, psychological harm and discomfort may also fall in this category.
More than minimal risk or High risk	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study using a drug, device or invasive procedure such as lumbar puncture, lung or liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

General Ethical Issues

2.2.1. The informed consent document (ICD), which includes patient/participant/subjectinformation sheet (PIS) and informed consent form (ICF) should have the required elements and should be reviewed and approved by the EC before enrolment of participants. For all biomedical and health research involving human participants, it is the primary responsibility of the researcher to obtain the written, informed consent of the prospective participant/subjector legally acceptable/authorized representative (LAR). In case of an individual who is not capable of giving informed consent, the consent of the LAR should be obtained. If a participant/subjector LAR is illiterate, a literate impartial witness should also be present during the informed consent process.

2.2.2. In certain circumstances audio/audio-visual recording of the informed consent process may be required, for example in certain clinical study/research as notified by CDSCO.

2.2.3. Verbal/oral consent/waiver of consent/re-consent may be obtained under certain conditions after due consideration and approval by the EC.

2.3 Privacy and confidentiality

Privacy is the right of an individual to control or influence the information that can be collected and stored and by whom and to whom that information may be disclosed or shared. Confidentiality is the obligation of the researcher/research team/organization to the participant/subjectto safeguard the entrusted information. It includes the obligation to protect information from unauthorized access, use, disclosure, modification, loss or theft.

2.3.1 The researcher should safeguard the confidentiality of research related data of participants and the community.

2.3.2 Potential limitations to ensure strict confidentiality must be explained to the participant. Researchers must inform prospective participants that although every effort will be made to protect privacy and ensure confidentiality, it may not be possible to do so under certain circumstances.

2.3.3 Any publication arising out of research should uphold the privacy of the individuals by ensuring that photographs or other information that may reveal the individual's identity are not published. A specific re-consent would be required for publication, if this was not previously obtained.

2.3.4 Some information may be sensitive and should be protected to avoid stigmatization and/or discrimination (for example, HIV status; sexual orientation such as lesbian, gay, bisexual, and transgender (LGBT); genetic information; or any other sensitive information).

2.3.5 While conducting research with stored biological samples or medical records/data, coding or anonymization of personal information is important and access to both samples and records should be limited.

2.3.6 Data of individual participants may be disclosed in certain circumstances with the permission of the EC such as specific orders of a court of law, threat to a person's or community's life, public health risk that would supersede personal rights to privacy, serious adverse events (SAEs) that are required to be communicated to an appropriate regulatory authority etc.

2.4 Distributive justice

2.4.1. Efforts must be made to ensure that individuals invited for research are

selected in such a way that the benefits and burdens of research are equitably distributed.
2.4.2. Vulnerable individuals/groups should not be included in research to solely benefit others who are better-off than themselves.

2.4.3 Research should not lead to social, racial or ethnic inequalities.
2.4.4 Plans for direct or indirect benefit sharing in all types of research with participants, donors of biological materials or data should be included in the study, especially if there is a potential for commercialization. This should be decided a priori in consultation with the stakeholders and reviewed by the EC.

2.5 Payment for participation
2.5.1 If applicable, participants may be reimbursed for expenses incurred relating to their participation in research, such as travel related expenses. Participants may also be paid for inconvenience incurred, time spent and other incidental expenses in either cash or kind or both as deemed necessary (for example, loss of wages and food supplies).
2.5.2 Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including investigations, patient work up, any interventions or associated treatment. This is applicable to all participants, including those in comparator/control groups.
2.5.3 If there are provisions, participants may also receive additional medical services at no cost.
2.5.4 When the LAR is giving consent on behalf of a participant, payment should not become an undue inducement and to be reviewed carefully by the EC. Reimbursement may be offered for travel and other incidental expenses incurred due to participation of the child/ward in the research.
2.5.5 ECs must review and approve the payments (in cash or kind or both) and free services and the processes involved, and also determine that this does not amount to undue inducement.

2.6 Compensation for research-related harm
Research participants who suffer direct physical, psychological, social, legal or economic harm as a result of their participation are entitled, after due assessment, to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, participant's dependents are entitled to financial compensation. The research proposal should have an in-built provision for mitigating research related harm.
2.6.1 The researcher is responsible for reporting all SAEs to the EC within 24 hours of knowledge. Reporting of SAE may be done through email or fax communication (including on non-working days). A report on how the SAE was related to the research must also be submitted within 14 days.
2.6.2 The EC is responsible for reviewing the relatedness of the SAE to the research, as reported by the researcher, and determining the quantum and type of assistance to be provided to the participants.
• For clinical study/research under the purview of CDSCO, the timeline and procedures as notified from time to time may be followed.
• All research participants who suffer harm, whether related or not, should be offered appropriate medical care, psycho-social support, referrals, clinical facilities, etc.
• Medical management should be free if the harm is related to the research.

• Compensation should be given to any participant/subjectwhen the injury is related to the research. This is applicable to participants in any of the arms of research, such as intervention, control and standard of care.
• While deliberating on the quantum of compensation to be awarded to participants who have suffered research-related injury, the EC should consider aspects including the type of research (interventional, observational, etc.), extent of injury (temporary/permanent, short/long term), loss of wages, etc.
• For other sponsored research, it is the responsibility of the sponsor (whether a pharmaceutical company, government or non-governmental organization (NGO), national or international/bilateral/multilateral donor agency/institution) to include insurance coverage or provision for possible compensation for research related injury or harm within the budget.
2.6.3 All AEs should be recorded and reported to the EC according to a pre-planned timetable, depending on the level of risk and as recommended by the EC.
2.6.4 In investigator initiated research/student research, the investigator/institution where the research is conducted becomes the sponsor.
• It is the responsibility of the host institution to provide compensation and/or cover for insurance for research related injury or harm to be paid as decided by the EC.
• The institution should create in-built mechanism to be able to provide for compensation, such as a corpus fund in the institution.
• In the applications for research grants to funding agencies – national or international, government or non-government agencies – the researcher should keep a budgetary provision for insurance coverage and/or compensation depending upon the type of research, anticipated risks and proposed number of participants.

2.7 Ancillary care
2.7.1 Participants may be offered free medical care for non-research-related conditions or incidental findings if these occur during the course of participation in the research, provided such compensation does not amount to undue inducement as determined by the EC.

2.8 Conflict of interest
Conflict of interest (COI) is a set of conditions where professional judgement concerning a primary interest such as participants welfare or the validity of research tends to be unduly influenced by a secondary interest, financial or non-financial (personal, academic, or political). COI can be at the level of researchers, EC members, institutions, or sponsors. If COI is inherent in the research, it is important to declare this at the outset and establish appropriate mechanisms to manage it.
2.8.1 Research institutions must develop and implement policies and procedures to identify, mitigate conflicts of interest and educate their staff about such conflicts.
2.8.2 Researchers must ensure that the documents submitted to the EC include a disclosure of interests that may affect the research.
2.8.3 ECs must evaluate each study considering any disclosed interests and ensure that appropriate means of mitigation are taken.
2.8.4 COI within the EC should be declared and managed in accordance with standard standard operating procedures (SOPs) of that EC.

2.9 Selection of vulnerable and special groups as research participants
Vulnerable groups and individuals may have an increased likelihood of incurring additional harm as they may be relatively (or absolutely) incapable of protecting

their own interests.

2.9.1 Characteristics that make individuals vulnerable are legal status – children; clinical conditions – cognitive impairment, unconsciousness; or situational conditions –including but not limited to being economically or socially disadvantaged, (for example, certain ethnic, individuals/communities which have hierarchical relationships, institutionalized persons, humanitarian emergencies, language barriers and cultural differences).

2.9.2 In general, such participants should be included in research only when the research is directly answering the health needs or requirements of the group. On the other hand, vulnerable populations also have an equal right to be included in research so that benefits accruing from the research apply to them as well. This needs careful consideration by researchers as well as the EC.

2.9.3 The EC should determine vulnerability and ensure that additional safeguards and monitoring mechanisms are established. It should also advise the researcher in this regard.

2.10 Community engagement

Community can be defined as a social group of people of any size sharing the same geographical location, beliefs, culture, age, gender, profession, lifestyle, disease, etc. The community should be meaningfully engaged before, during and after the research to mitigate culturally sensitive issues and ensure greater responsiveness to their health needs and requirements.

2.10.1 The community can be engaged in many ways and can provide valuable opinions. The degree of community engagement should depend on the type of research that is being conducted.

2.10.2 Community advisory board/group (CAB/CAG) can act as an interface between the community (from which participants are to be drawn), the researchers and the concerned EC. Members of the CAB should be such that they do not coerce the members of the community to participate in the research and also protect the rights and serve the requirements of the group.

2.10.3 Members of the community can also be represented in the EC either as members or special invitees.

2.10.4 Community engagement does not replace individual informed consent. It ensures that the community's health needs and expectations are addressed, informed consent is appropriate, and access to research benefits are provided through research that is designed and implemented in the best interests of science and the community.

2.10.5 After the study is completed, the researcher may communicate with the community representative, local institution or the government department from where the data was collected to help in dissemination of the results to the entire community.

2.11 Post research access and benefit sharing

The benefits accruing from research should be made accessible to individuals, communities and populations whenever relevant. Sometimes more than the benefit to the individual participant, the community may be given benefit in an indirect way by improving their living conditions, establishing counselling centres, clinics, or schools, and providing education on good health practices.

2.11.1 Efforts should be made to communicate the findings of the research study to the individuals/communities wherever relevant.

2.11.2 The research team should make plans wherever applicable for post-research

access and sharing of academic or intervention benefits with the participants, including those in the control group.

2.11.3 Post-research access arrangements or other care must be described in the study protocol so that the EC may consider such arrangements during its review.

2.11.4 If an investigational drug is to be given to a participant/subjectpost-study/research, appropriate regulatory approvals should be in place.

2.11.5 The EC should consider the need for an a priori agreement between the researchers and sponsors

2.11.6 In studies with restricted scope, such as student projects, post study benefit to the participants may not be feasible, but conscious efforts should be made by the institution to take steps to continue to support and give better care to the participants.

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 *Participants* and obtaining their *Informed Consent* including adequacy of the information being provided to the Participants. 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 programs 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 EC 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 ECs 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 EC 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

1. EC should be multidisciplinary and multi-sectorial in composition. Independence and competence are the two hallmarks of an EC.
2. Ethics Committee shall have a minimum of seven members from medical, non-medical, scientific and non-scientific areas with at least,
   (i) one lay person;
   (ii) one woman member;
   (iii) one legal expert;
   (iv) one independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or

philosopher or ethicist or theologian.

3. There should be adequate representation of age and gender.
4. The Ethics Committee referred to in sub-rule (1) shall consist of at least fifty percent of its members who are not affiliated with the institute or organization in which such committee is constituted.
5. One member of the Ethics Committee who is not affiliated with the institute or organization shall be the Chairperson and shall be appointed by such institute or organisation.
6. One member who is affiliated with the institute or organization shall be appointed as Member Secretary of the Ethics Committee by such Institute or organization.
7. The committee shall include at least one member whose primary area of interest or specialisation is nonscientific and at least one member who is independent of the institution.
8. The members of the Ethics Committee shall follow the provisions of these rules, Good Clinical Practices Guidelines, and other regulatory requirements to safeguard the rights, safety and well-being of study/research participants.
9. Every member of the Ethics Committee shall be required to undergo such training and development programmes as may be specified by the Central Licencing Authority from time to time; Provided that any member, who has not successfully completed such training and developmental programmes, shall be ineligible to hold the post of member of the Ethics Committee and shall cease to be a member of such committee.
10. The members representing medical scientists and clinicians shall possess at least post graduate qualification in their respective area of specialisation, adequate experience in the respective fields and requisite knowledge and clarity about their role and responsibility as committee members.
11. As far as possible, based on the requirement of research area such as Human Immunodeficiency Virus (HIV) or genetic disorder, specific patient group may also be represented in the Ethics Committee.
12. No member of an Ethics Committee, having a conflict of interest, shall be involved in the oversight of the clinical study/research or bioavailability or bioequivalence study protocol being reviewed by it and all members shall sign a declaration to the effect that there is no conflict of interest.
13. While considering an application which involves a conflict of interest of any member of the Ethics Committee, such member may voluntarily withdraw from the Ethics Committee review meeting, by expressing the same in writing, to the Chairperson.
14. The details in respect of the conflict of interest of the member shall be duly recorded in the minutes of the meetings of the Ethics Committee.

2.4.2.3 Terms of Reference

The EC 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 standard operating procedures available with

each member.

2.4.2.4 Review Procedures

The Ethics Committee should review every research proposal on human participants. 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 participants 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 proposal.

2.4.2.5 Submission of Application

The researcher should submit an appropriate application to the EC 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 participants in the light of existing knowledge.
2. Recent curriculum vitae of the Investigators indicating qualification and experience.
3. Participant/subject recruitment procedures.
4. Inclusion and exclusion criteria for entry of participants 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 study/research.
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 study/research.
17. Details of Funding agency / Sponsors and fund allocation for the proposed work.

18. Statement on conflict of interest, if any
19. Relevant administrative approvals (such as HMSC approval for International trials, if applicable)
20. Indemnity policy, clearly indicating the conditions of coverage, date of commencement and date of expiry of coverage of risk (if applicable)
21. Insurance policy (it is preferable to have the policy and not only the insurance certificate)for study participants indicating conditions of coverage, date of commencement and date of expiry of coverage of risk (if applicable)

2.4.2.6 Decision Making Process

The EC 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.

a. 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.
b. A member must voluntarily withdraw from the EC 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.
c. If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.
d. A negative decision should always be supported by clearly defined reasons.
e. An EC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit/risk ratio.
f. The discontinuation of a study/research should be ordered if the EC finds that the goals of the study/research have already been achieved midway or unequivocal results are obtained.
g. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
h. The following circumstances require the matter to be brought to the attention of EC :
    i. any amendment to the protocol form the originally approved protocol with proper justification;
    ii. serious and unexpected adverse events and remedial steps taken to tackle them;
    iii. any new information that may influence the conduct of the study.
i. 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.
j. Participant/subjectexperts may be invited to offer their views but should not take part in the decision-making process. However, her/his opinion must be recorded.
k. Meetings are to be minuted which should be approved and signed by the Chairperson.

2.4.2.8 Interim Review

The EC 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 EC;
ii) research study of a minor nature such as examination of case records etc.;
iii) an urgent proposal of national interest.

2.4.2.9 Record Keeping

All documentation and communication of an EC 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 EC;
ii. the curriculum vitae of all EC members;
iii. standing standard operating procedures of the EC;
iv. national and international guidelines;
v. copies of the Protocol, data collection formats, CRFs, investigational brochures etc. submitted for review;
vi. all correspondence with EC members and investigators regarding application, decision and follow up;
vii. agenda of all EC meetings;
viii. minutes of all EC 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.

2.4.2.10 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 EC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable participants and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of EC should be given in writing in unambiguous terms in such instances.

2.4.3 Informed Consent Process

2.4.3.1. Informed Consent of Participant

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 Participants 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 Participant(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 Participants and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the Participant(s) in both written and oral form, whenever possible.

Participants, 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 Participant/subjectto 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 Participant's participation in the Study the written Informed Consent form should be signed and personally dated by

1. (i) The Participant/subject*or* (ii) if the Participant/subjectis incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Participant's legal representative or guardian *or* (iii) if the Participant/subjectand 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 Participant/subjector the Participant's legal representative or the guardian, and that informed consent was freely given by the Participant/subjector

the Participant's legal representative or the guardian.

The Participant's legal representative or guardian (if the participant/subjectis 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 Participant. The agreement of a legal representative or the guardian that participation will promote the welfare and interest of the Participant/subjectshould 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 participants

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 participant/subjectparticipation;
iii. the benefits that might reasonably be expected as an outcome of research to the participant/subjector to others;
iv. any alternative procedures or courses of treatment that might be as advantageous to the participant/subjectas the procedure or treatment to which she/he is being participanted;
v. any foreseeable risk or discomfort to the participant/subjectresulting 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 participants 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 participant/subjectwould 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. Essential Information on Confidentiality for Prospective Research Participants

Safeguarding confidentiality **-** The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual participants. Data of individual participants 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.

P2.4.5 Reimbursement/payment for Participation

Participants 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 participants to consent to participate in research against their better judgement (inducement). All payments, reimbursement and medical services to be provided to research participants should be approved by the EC. 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 participant/subjectis withdrawn from research for medical reasons related to the study the participant/subjectshould get the benefit for full participation;
iii. when a participant/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.

2.4.5.1 Selection of Special Groups as Research Participant/subjectPregnant or nursing women

Pregnant or nursing women should in no circumstances be the participant/subjectof 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 participants of any clinical study/research except such study/research 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 participants.

a) The justification of participation of these women in clinical study/research 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 study/research are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, study/research 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 participants for such research as per as per The Medical Termination of Pregnancy Act, GOI, 1971. and Medical Termination of Pregnancy (Amendment) Act, 2021.
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 The Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition Of Sex Selection) Act (PCPNDT Act) 2003.

2.4.5.2 Children

Before undertaking study/research 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 study/research 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 participant/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 participant/subject as any available alternative interventions;
i. the risk presented by interventions not intended to benefit the individual child participant/subject is low when compared to the importance of the knowledge that is to be gained.

2.4.5.3 Vulnerable participants

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; persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them; rights and welfare of individual with intellectual disability, mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected.
b. Adequate justification is required for the involvement of participants such as prisoners, students, subordinates, employees, service personnel etc. who have reduced autonomy as research participants.

2.4.6 Clinical trials with marginalized community

Marginalization refers to individuals or groups who are kept at or pushed beyond the edges of society. In India, members of particular groups experience multiple socio-economic disadvantages which limits their access to health and healthcare. Some of the prominent factors on the basis of which individuals are discriminated in India are structural factors, age, disability, mobility and stigma that act as barriers to health and healthcare.

Besides this there are certain groups in Indian society that are subject to discriminatory treatment and feel marginalized. They need special attention to avoid exploitation as they belong to the vulnerable groups who are unable to acquire and use their rights.

2.4.7 Compensation in case of injury or death in clinical study/research or bioavailability or bioequivalence study of new drug or investigational new drug.

(1) Where any death of a study/research participant/subjectoccurs during a clinical study/research or bioavailability or bioequivalence study, the legal heir of the study/research participant/subjectshall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical study/research or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42 of NDCT rule.

(2) Where permanent disability or any other injury occurs to a study/research participant/subjectduring a clinical study/research or bioavailability or bioequivalence study, the study/research participant/subjectshall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical study/research or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42 NDCT rule.

(3) The financial compensation referred to in sub-rule (1) or sub-rule (2) shall be in addition to any expenses incurred on medical management of the study/research participant.

(4) In the event of an injury, not being permanent in nature, the quantum of compensation shall be commensurate with the loss of wages of the participant/subjectas provided in the Seventh Schedule of NDCT rules.

(5) The sponsor or its representative shall give an undertaking along with the application for clinical study/research permission to the Central Licensing Authority to provide compensation in the case of clinical study/research related injury or death for which participants are entitled to compensation.

(6) Where the sponsor or its representative, who has obtained permission to conduct clinical study/research or bioavailability or bioequivalence study, fails to provide financial compensation, as referred to in sub-rule (1) or sub-rule (2), the Central Licensing Authority shall, after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical study/research or bioavailability or bioequivalence study or restrict the sponsor including its representative, who has obtained permission to conduct clinical study/research or bioavailability or bioequivalence study, to conduct any further clinical study/research or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

2.4.7.1 Medical Management in clinical study/research or bioavailability and bioequivalence study of new drug or investigational new drug

(1) Where an injury occurs to any participant/subjectduring clinical study/research or bioavailability and bioequivalence study of a new drug or an investigational new drug, the sponsor, shall provide free medical management to such participant/subjectas long as required as per the opinion of investigator or till such time it is established that the injury is not related to the clinical study/research or bioavailability or bioequivalence study, as the case may be, whichever is earlier.

(2) The responsibility for medical management as referred to in sub-rule (1), shall be discharged by the sponsor or the person who has obtained permission from the Central Licensing Authority.

(3) Where the sponsor or its representative, who has obtained permission to conduct clinical study/research or bioavailability or bioequivalence study, fails to provide medical management, as referred to in sub-rule (1), the Central Licensing Authority shall after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical study/research or bioavailability or bioequivalence study or

restrict the sponsor including its representative, who has obtained permission to conduct clinical study/research or bioavailability or bioequivalence study, to conduct any further clinical study/research or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

2.4.7.2 Consideration of injury or death or permanent disability to be related to clinical study/research or bioavailability and bioequivalence study

Any injury or death or permanent disability of a study/research participant/subjectoccurring during clinical study/research or bioavailability or bioequivalence study due to any of the following reasons shall be considered as clinical study/research or bioavailability or bioequivalence study related injury or death or permanent disability, namely:-

(a) adverse effect of the investigational product;

(b) violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator leading to serious adverse event;

(c) failure of investigational product to provide intended therapeutic effect where, the required standard care or rescue medication, though available, was not provided to the participant/subjectas per clinical study/research protocol;

(d) not providing the required standard care, though available to the participant/subjectas per clinical study/research protocol in the placebo controlled study/research;

(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol;

(f) adverse effect on a child in-utero because of the participation of the parent in the clinical study/research;

(g) any clinical study/research procedures involved in the study leading to serious adverse event.

2.4.7.3 Procedure for compensation in case of injury or death during clinical study/research, bioavailability, and bioequivalence study

(1) The investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical study/research or bioavailability or bioequivalence study, as the case may be, and the Ethics Committee that accorded approval to the study protocol, within twenty-four hours of their occurrence; and if the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(2) A case of serious adverse event of death shall be examined in the following manner, namely:-

(i) the Central Licencing Authority shall constitute an independent expert committee to examine the cases and make its recommendations to the said authority for arriving at the cause of death and quantum of compensation in case of clinical study/research related death;

(ii) the sponsor or its representative and the investigator shall forward their reports on serious adverse event of death after due analysis to the Central Licencing

Authority and the head of the institution where the clinical study/research or bioavailability or bioequivalence study has been conducted within fourteen days of the knowledge of occurrence of serious adverse event of death;
(iii) the Ethics Committee for clinical study/research shall forward its report on serious adverse event of death after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the said sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical study/research or bioavailability or bioequivalence study, as the case may be, to the Central Licencing Authority within a period of thirty days of receiving the report of the serious adverse event of death from the investigator;
(iv) the Central Licencing Authority shall forward the report of the investigator, sponsor or its representative and the Ethics Committee to the Chairperson of the expert committee;
(v) the expert committee shall examine the report of serious adverse event of death and make its recommendations available to the Central Licencing Authority for the purpose of arriving at the cause of the serious adverse event of death within sixty days from the receipt of the report of the serious adverse event, and the expert committee while examining the event, may take into consideration, the reports of the investigator, sponsor or its representative and the Ethics Committee for clinical study/research;
(vi) in case of clinical study/research or the bioavailability or bioequivalence study related death, the expert committee shall also recommend the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule of NDCT rule 2019, to be paid by the sponsor or his representative who has obtained the permission to conduct the clinical study/research or the bioavailability or bioequivalence study, as the case may be;
(vii) the Central Licencing Authority shall consider the recommendations of the expert committee and shall determine the cause of death with regards to the relatedness of the death to the clinical study/research or the bioavailability or bioequivalence study, as the case may be;
(viii) in case of clinical study/research or the bioavailability or bioequivalence study related death, the Central Licencing Authority shall, after considering the recommendations of the expert committee, by order, decide the quantum of compensation, determined as per the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative and shall pass orders as deemed necessary within ninety days of the receipt of the report of the serious adverse event;
(ix) the sponsor or its representative shall pay the compensation in case the serious adverse event of death is related to clinical study/research or the bioavailability or bioequivalence study, as specified in the order referred to in clause (viii) of the Central Licencing Authority within thirty days of the receipt of such order.

(3) Cases of serious adverse events of permanent disability or any other injury other than deaths shall be examined in the following manner, namely:
(i) the sponsor or its representative, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Central Licencing Authority, chairperson of the Ethics Committee for clinical study/research and head of the institution where the study/research or bioavailability or bioequivalence study has been conducted within fourteen days of the reporting of serious adverse event;
(ii) the Ethics Committee for clinical study/research shall forward its report on

serious adverse event of permanent disability or any other injury other than deaths, as the case may be, after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative who has obtained permission to conduct clinical study/research or the bioavailability or bioequivalence study, as the case may be, within thirty days of receiving the report of the serious adverse event;

(iii) the Central Licencing Authority shall determine the cause of the injury and pass order as specified in clause (iv), or may constitute an independent expert committee, wherever it considers necessary, to examine such serious adverse events of injury, and such independent expert committee shall recommend to the Central Licencing Authority for the purpose to arrive at the cause of the serious adverse event and also the quantum of compensation, as determined in accordance with formula as specified in the Seventh Schedule in case of clinical study/research or bioavailability or bioequivalence study related injury, within a period of sixty days of receipt of the report of the serious adverse event;

(iv) in case of clinical study/research or the bioavailability or bioequivalence study related injury, the Central Licencing Authority shall, by order, decide the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his representative who has obtained the permission to conduct the clinical study/research or the bioavailability or bioequivalence study, as the case may be, within a period of ninety days of receipt of the report of the serious adverse event;

(v) the sponsor or its representative, who has obtained permission to conduct the clinical study/research or bioavailability or bioequivalence study, as the case may be, shall pay the compensation in case of clinical study/research or bioavailability or bioequivalence study related injury, as specified in the order of the Central Licencing Authority referred to in clause (iv) within thirty days of receipt of such order.

2.4.7.4 Medical management and compensation for injury or death relating to biomedical and health research overseen by an Ethics Committee for biomedical and health research

Notwithstanding anything contained in these rules, medical management and compensation for injury or death relating to biomedical and health research, overseen by an Ethics Committee for clinical study/research as referred to in Chapter IV of NDCT rules shall be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants specified by the Indian Council of Medical Research from time to time.

RESPONSIBILITIES

3.1 Sponsor:

3.1.1 Investigator and clinical study site 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 (including training and experience) 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, and their roles should be documented prior to their involvement in the study/research.

Before entering an agreement with an Investigator(s) and/or 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 or basic product information (e.g., prescribing information, package insert, summary of product characteristics etc.). Sponsor should provide sufficient time to Investigator(s) to review the Protocol and the information provided.

3.1.2 Agreement/ Contract:

The Sponsor should enter into a formal and legal agreement/ contract with the Investigator(s)/ Institution(s) and, where applicable, service provider 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 by sponsors, ECs, regulatory authorities (domestic and foreign) including providing direct access to source records and facilities, including to those of service providers
d) To retain the study related essential records for the required retention period in accordance with NDCT rules or until the Sponsor informs the Investigator(s) / Institution(s) in writing that these documents are no longer needed, whichever is longer

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

Agreements made by the sponsor with the investigator and/or institution, service providers and any other parties (e.g., independent data monitoring committee (IDMC), adjudication committee) involved with the clinical study/research should be documented prior to initiating the activities.

Agreements should be updated when necessary to reflect significant changes in the activities delegated.

In study/research with more than one sponsor, the sponsors should have a

documented agreement that sets out their respective responsibilities, in accordance with local regulatory requirements and/or practice. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors.

3.1.3 Sponsor Oversight

a) The sponsor should ensure that the study/research design and study/research conduct, the process undertaken, and the information and data generated are of sufficient quality to ensure reliable study/research results, study/research participant's safety and appropriate decision making.
b) The sponsor should ensure that study/research processes are conducted in compliance with the study/research protocol and related documents as well as with applicable regulatory requirements and ethical standards.
c) The sponsor should determine necessary study/research-specific criteria for classifying protocol deviations as important (i.e., those that impact the rights, safety and well-being of study/research participants and the reliability of results).
d) Decisions related to the study/research should be appropriately assessed for their impact on participant's rights, safety and well-being and the reliability of study/research results. Risks related to such decisions should be suitably managed throughout the planning, conduct and reporting of the study/research.
e) The range and extent of oversight measures should be fit for purpose and tailored to the complexity of, and risks associated with the study/research. The selection and oversight of investigators and service providers are fundamental features of the oversight process. Oversight by the sponsor includes quality assurance and quality control processes relating to the study/research-related activities of investigators and service providers.
f) The sponsor should ensure appropriate and timely escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner.
g) The sponsor may consider establishing an IDMC to assess the progress of a clinical study/research including the safety data and the efficacy endpoints at intervals and to recommend to the sponsor whether to continue, modify or stop a study/research.
h) Where appropriate, sponsors may also establish an endpoint assessment/adjudication committee in certain study/research to review important endpoints reported by investigators to determine whether the endpoints meet protocol-specified criteria. Such committees should typically be blinded to the assigned treatments when performing their assessments, regardless of whether the study/research itself is conducted in a blinded manner, to ensure that the data reviewed by committee are as free of bias as possible.
i) Committees established for purposes that could impact participant/subjectsafety or the reliability of study/research results should include members with relevant expertise and with managed conflicts of interest, have written standard operating procedures (e.g., charters) and document their decisions.
j) Standard Standard operating procedures : The Sponsor should ensure t h a t

detailed Standard Standard operating procedures are available for the conduct of study/research.

3.1.4. Allocation of activities

Prior to initiating a Study the Sponsor should define and allocate all Study related activities to the respective identified person(s) / organisation(s). The sponsor should utilise appropriately qualified individuals for the activities to which they are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors and monitors) throughout the study/research process.

3.1.4.1 Medical Expertise

The sponsor should have medical personnel readily available who will be able to advise on specific study/research-related medical questions or problems as applicable.

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 (as applicable):

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) Establishing, implementing and maintaining appropriate quality assurance and quality control processes and documented procedures to ensure that study/research are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).

The sponsor should ensure that all aspects of the study/research are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent, when applicable.

When using computerised systems in a clinical study/research, the sponsor should: (i) have a record of the computerised systems used in a clinical study/research. This should include the use, functionality, interfaces and validation status of each computerised system, and who is responsible for its management should be described. The record should also include a description of implemented access controls and internal and external security measures; (ii) ensure that the requirements for computerised systems deployed by the sponsor (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerised systems in clinical study/research. These requirements should be

proportionate to the importance of the computerised system and the data or activities they are expected to process;

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 five years after the completion of the study or after submission of the data to the regulatory authority(ies), whichever is later.

The sponsor should not make changes to data entered by the investigator or study/research participants unless justified and documented by the sponsor and agreed upon by the investigator.
The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records.
The sponsor should ensure that the investigator has access to data collected in accordance with the protocol during the course of the study/research including relevant data from external sources, for example, central laboratory data, centrally read imaging data and, if appropriate, ePRO data that are necessary to enable the investigators to make decisions (e.g., on eligibility, treatment, continuing participation in the study/research and care for the safety of the individual study/research participants). The sponsor should pay special attention to data that may unblind the investigator and include the appropriate provisions in the protocol.
The sponsor should ensure that the investigator receives instructions on how to navigate systems, data and relevant metadata for the study/research participants under their responsibility.
The sponsor should document the data management steps to be undertaken prior to data analysis. These steps may vary depending on the purpose of the analysis to be conducted (e.g., data for IDMC, for interim analysis or the final analysis).
Prior to provision of the data for analysis, edit access to the data acquisition tools should be restricted as appropriate to the purpose of the analysis; for example, for interim analysis, the restriction may only be temporary or managed differently compared to the final analysis.
The sponsor should use an unambiguous study/research participant/subjectidentification code (see glossary term) that allows identification of all the data reported for each participant.
The sponsor should ensure that study/research data are protected from unauthorised access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.

3.1.6 Reimbursement/payment for Participation

Participants may be paid compensation for participation in accordance with the guidelines listed in 2.4.5. The sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the study/research**,** except for claims that arise from malpractice and/or negligence. Payment should be such that it is not seen as undue inducement and approved by ethics committee.

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 Ethics Committee registration issued by CDSCO
b) EC should be registered by Department of Health Research (DHR) through Naitik portal for biomedical and health research
c) Documented approval/ favourable opinion of the Ethics Committee before the initiation of the Studyatio
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 or basic product information (e.g. prescribing information, package insert, summary of product characteristics etc.). 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) , Rescue medication(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. Manufacturing and labelling of Investigational product(s) should comply with NDCT rules.

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 (e.g., investigators, monitors, pharmacists, storage managers etc.), besides stating them on the Product labels wherever 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 respective Ethics Committee and study approval from 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 Participants and
c. return of unused Product to the Sponsor (or its alternative disposal procedure if authorised by the sponsor).

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. The samples do not need to be kept by the sponsor in study/research where an authorised medicinal product is used as an investigational product unmodified from its authorised state, since samples are kept by the manufacturer.

In blinded study/research, the sponsor should implement:

i. a process to blind the sponsor staff, study/research participant/subjectand/or investigator as appropriate to the investigational product identity and assignment to prevent and detect inappropriate unblinding;
ii. a procedure and mechanism that permits the investigator to rapidly identify the product(s) in case of a medical emergency where unblinding is considered necessary, while protecting the identity of the treatment assignment of the other study/research participants;
iii. a mechanism that protects the blinding of the study/research where a participant's treatment assignment is unblinded for the purpose of safety reporting to regulatory authorities and/or EC, where appropriate.

3.1.10 Safety assessment and reporting:

Sponsor is responsible for the ongoing safety evaluation of the Product. The Sponsor should notify all concerned (e.g.investigator, regulatory authority etc), in a timely manner, of findings that could adversely affect the safety of the Participants, 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 participants.

Safety Reporting

Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Central Licencing Authority, the Chairperson of the ethics committee and the head of the institution where the study/research has been conducted, within fourteen days of knowledge of occurrence of the serious adverse event as specified in Table 5 of Third Schedule NDCT Rules.

3.1.11 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 ICH E3 and/or NDCT rules 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.

3.1.12 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 (i.e. on-site or remote), 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.

3.1.13 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) and the regulatory authority(ies) accordingly. The EC should also be informed promptly by the investigator/institution. The notification should document the reason(s) for the termination or suspension by the sponsor or by the investigator / institution.

3.1.14 Transfer of activities to Service Provider(s)

If the sponsor is a foreign company, organisation or person(s) – it shall appoint a local representative or Service provider(s) 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 service provider 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 service provider should be specified in writing. Any Study related duties, functions or responsibilities not specifically transferred to and assumed by a service provider, or a local representative shall be deemed to have been retained by the Sponsor.

The sponsor is responsible for assessing the suitability of and selecting the service provider to ensure that they can adequately undertake the activities transferred to them. The sponsor should provide the service providers with the protocol where necessary as well as any other documents required for them to perform their activities.

The sponsor should have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers. The sponsor should ensure appropriate oversight of important study/research-related activities that are transferred to service providers and further subcontracted.

The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. However, the responsibility for such activities ultimately remains with the investigator. Study/research-related activities performed by service providers should be conducted in accordance with relevant GCP requirements, which may be fulfilled by a service provider's existing processes.

3.2 The Monitoring

The sponsor should determine the appropriate extent and nature of monitoring, based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of study/research participants, investigational product, current knowledge of the safety profile and endpoints of the study/research should be considered. The sponsor must appoint adequately trained monitors or service provider to supervise an ongoing study.

The monitor is the principal communication link between the sponsor and the investigator and other parties and individuals involved in the study/research conduct (e.g., centrally performed activities). In general, each site should have an assigned monitor as their contact point.
Monitoring activities may include site monitoring (performed on-site or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical study/research.

3.2.1 Qualifications

The monitor should have adequate pharmaceutical and / or scientific qualifications and clinical study/research experience. Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to participants, the sponsor's SOPs, GCP, and Indian regulatory requirements.

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.

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, and are used within their shelf-life
2. the investigational product(s) are supplied only to participants who are eligible to receive it and at the protocol-specified dose(s), time(s) and duration
3. the participants, investigator, investigator site staff and other relevant parties and individuals involved in the study/research conduct are provided with the necessary instructions on properly using, handling, storing, returning and destroying, or alternative disposition of the investigational product(s)
4. the receipt, use, return and destruction, or alternative disposition of the investigational 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, and confirming that informed consent was obtained before participation in the study/research for all enrolled participants at the site
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 documented procedures
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
11. Determining whether adverse events are appropriately reported within the time periods required by the protocol, GCP and the applicable regulatory requirement(s).
12. Verifying that the blinding is maintained, where applicable
13. Confirming the arrangement for the retention of the essential records and the final accountability of the investigational product (e.g., return and destruction or alternative disposition, if appropriate) during site close-out activity.

d) The monitor should promptly inform the sponsor and the investigator in case any unwarranted deviation from the protocol or any transgression of the principles embodied in GCP is noted. Important deviations should be highlighted and should be the focus of remediation efforts as appropriate.
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. The sponsor may develop a monitoring plan, if required, that is tailored to the identified potential safety risks,

the risks to data quality and/or other risks to the reliability of the study/research results. Particular attention should be given to procedures relevant to participant/subjectsafety and to study/research endpoints. The plan should describe the monitoring strategy, the monitoring activities of all the parties involved, the various monitoring methods and tools to be used, and the rationale for their use. The monitoring strategy should ensure appropriate oversight of study/research conduct and consider site capabilities and the potential burden. The plan should focus on aspects that are critical to quality. The monitoring plan should reference the sponsor's applicable policies and procedures.

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 participants is likely to be available during the study.

g) The monitor should observe and report the participant/subjectrecruitment 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 or monitoring plan

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

    i. the data required by the protocol and identified as critical are reported accurately on the CRFs and are consistent with the source documents
    ii. any dose and / or therapy modifications are well documented for each of the study participants
    iii. adverse events, concomitant medications and inter-current illnesses are promptly reported on the CRFs in accordance with the protocol and the SOPs
    iv. visits that the participants fail to make, tests that are not conducted and examinations that are not performed are clearly reported as such on the CRFs
    v. all withdrawals and drop-outs of enrolled participants 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.

3.2.3 Investigator Site Monitoring

(a) Monitoring may be performed in relation to the clinical study/research activities at the investigator sites (e.g., including their pharmacies and local laboratories, as appropriate). The frequency of monitoring activities should also be determined based on identified risks. Monitoring activities and their frequency should be modified as appropriate using knowledge gained.

(b) This monitoring activity may be performed on-site or remotely depending on the nature of the activity and its objectives.

(c) Monitoring may include secure, remote, direct read-only access to source records, other data acquisition tools and essential record retention systems.

3.2.4Centralised Monitoring

(a) Centralised monitoring is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician).

(b) Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Use of centralised data analytics can help identify systemic or site-specific issues, including protocol non-compliance and potentially unreliable data.

(c) Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring.

3.3 Investigator

3.3.1 Qualifications, resource, and responsibility

- **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 National Medical Commission (NMC)/Dental Council of India, in case of Dentist as investigator. The investigator should provide a copy of the curriculum vitae and / or other relevant documents requested by the sponsor, the ethics committee, service provider or the regulatory authorities. The investigator should also ensure that other studies do not divert essential participants 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 protocol, GCPs, relevant SOPs and the applicable regulatory requirements.

- **Resources**

  The investigator should be able to demonstrate (e.g., based on retrospective or

currently available data) a potential for recruiting the proposed number of eligible participants within the recruitment period as agreed with the sponsor.

The investigator should have sufficient time, an adequate number of available and qualified staff, and adequate facilities for the foreseen duration of the study/research to conduct the study/research properly and safely.

- **Responsibilities**

  The investigator may delegate study/research-specific activities to other persons or parties.

  The investigator may be supported by the sponsor to identify a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor.

  The investigator retains the ultimate responsibility and maintains appropriate supervision of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the study/research participants and data reliability.

  The investigator should ensure that persons or parties to whom the investigator has delegated study/research-specific activities are appropriately qualified and supervised and are adequately informed about the protocol, the investigational product(s) and their assigned study/research activities (including activities conducted by staff provided by other parties, for example, home nurses arranged by the sponsor). Study/research-related training to persons assisting in the study/research should correspond to what is necessary to enable them to fulfil their delegated study/research activities that go beyond their usual training and experience.

  Agreements made by the investigator/institution with service providers for study/research-related activities should be documented.

3.3.2 Medical care of the study participants

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

Adverse events and/or laboratory abnormalities required for safety evaluations (as outlined in the protocol) should be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

Although a participant/subjectis 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 participant'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, participant/subjectrecruitment procedures (e.g. advertisements) and any written/ verbal information to be provided to the participants.

As part of the investigator's/institution's written application to the EC, the investigator/institution should provide the EC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the study/research, the investigator/institution should supply a copy of the updated Investigator's Brochure to the EC.

During the study/research the investigator/institution should provide to the EC all documents participant/subjectto review.

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 participants
2. changes that increase the risk to participant(s) and / or affecting significantly the conduct of the study
3. all serious adverse events (in addition to regulatory authority)
4. new information that may adversely affect safety of the participants 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 should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study/research participants, or when the change(s) involves only logistical or administrative aspects of the study/research (e.g., change in monitor(s), change of telephone number(s)).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.

3.3.6 Investigational Product(s) management

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 participant, 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 participants. Investigator should maintain records that describe that the participants 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 or other document (i.e. investigational product manual).

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 participant/subjectand should check at intervals appropriate for the study that each participant/subjectis following the instructions properly. The person who carries them out should document such periodic checks.

3.3.7 Selection and recruitment of study participants

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

The Investigator is responsible for giving adequate information to participants about the study/research 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 -

a) Communicate to prospective participants all the information necessary for informed consent. There should not be any restriction on participant's right to ask

any questions related to the study as any restriction on this undermines the validity of informed consent.

b) Exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the participant/subjectis not permissible However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.
c) Seek consent only after the prospective participant/subjectis adequately informed. Investigator should not give any unjustifiable participant's decision to participate in the study.
d) As a general rule obtain from each prospective participant/subjecta signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the study/research, and in case of incompetence to do so, a legal guardian or other duly authorised representative.
e) Renew the informed consent of each participant, if there are material changes in the conditions or procedures of the research or new information becomes available during the ongoing study/research.
f) Not use intimidation in any form which invalidates informed consent. The investigator must assure prospective participants 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 Participant, the Investigator should supply participants with, and encourage them to carry with them, information about their participation in the study/research and information about contact persons who can assist in an emergency situation.

3.3.8 Randomisation Procedures and Unblinding

The investigator should follow the study/research's randomisation procedures, if any, and, in the case of an investigator-blinded study/research, should ensure that the identification code is broken only in accordance with the protocol. In the case of an emergency, to protect patient safety, the investigator should be prepared and capable from the start of the study/research to perform unblinding without undue delay and hinderance. The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect study/research participant, unblinding due to an SAE) of the investigational product(s).

3.3.9 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.

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

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.

The investigator should have timely access to and be responsible for the timely review of data, including relevant data from external sources (e.g., central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data) which can have an impact on, for example, participant/subjecteligibility, treatment or safety. The protocol may provide exceptions for access, for instance, to protect blinding.

Upon request of the monitor, auditor, EC or regulatory authority, the investigator/institution should make available for direct access all requested study/research-related records.

The investigator should ensure that data acquisition tools and other systems deployed by the sponsor for clinical study/research purposes are used as specified in the protocol or study/research related instructions.

When using computerised systems in a clinical study/research, the investigator/institution should do the following:

(a) for systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access;

(b) for systems deployed by the investigator/institution specifically for the purposes of clinical study/research, ensure that the requirements for computerised systems are addressed;

(c) where equipment for data acquisition is provided to study/research participants by the investigator, ensure that traceability is maintained and participants are provided with appropriate training;

(d) ensure that incidents in the use and operation of computerised systems, which in their judgement may have a significant and/or persistent impact on the study/research data, are reported to the sponsor and, where applicable, to the EC.

Progress Reports

The investigator should submit the written summaries of the study status at the periodicity as specified by EC, the person(s)/ organisation(s) to whom the investigator is reporting. All reportings made by the investigator should identify the participants by unique code numbers assigned to the study participants rather than by the participants' 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 Participants, the Ethics Committee as well as the Regulatory Authorities. The investigators should also ensure appropriate therapy and follow-up for the participants.

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 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. 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 study/research participant(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.

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

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. 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 study/research 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.

4.4.1 Computerised Systems

As described in sections for the responsibilities of the sponsor, investigator and the activities of other parties with respect to a computerised system used in clinical study/research should be clear and documented. In summary, the sponsor is responsible for ensuring that for computerised systems which they put in place, the expectations for computerised systems as described in this section are addressed in a risk proportionate manner. The sponsor should review whether the systems used by the investigator/institution (e.g., electronic health records and other record keeping

systems for source data collection) are fit for purpose in the context of the study/research. In the event that the investigator/institution deploys systems specifically for the purposes of conducting clinical study/research, the investigator/institution should ensure that the expectations are proportionately addressed and implemented.

The responsible party should ensure that those developing computerised systems for clinical study/research are aware of the intended purpose and the regulatory requirements that apply to them.

It is recommended that representatives of intended participant/subjectpopulations and healthcare professionals are involved in the design of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population.

4.4.1.1 Procedures for the Use of Computerised Systems

Documented procedures should be in place to ensure the appropriate use of computerised systems in clinical study/research for essential activities related to data collection, handling and management.

4.4.1.2 Training

The responsible party should ensure that those using computerised systems are appropriately trained in their use.

4.4.1.3 Security of Computerised Systems

The security of the study/research data and records should be managed throughout the data life cycle. The responsible party should ensure that security controls are maintained for computerised systems. These controls should include user management and ongoing measures to prevent, detect and/or mitigate security breaches. Aspects such as user authentication requirements and password management, firewall settings, antivirus software, security patching, system monitoring and penetration testing should be considered. The responsible party should maintain adequate backup of the data. Procedures should cover the following: system security measures, data backup and disaster recovery.

4.4.2 Validation of Computerised Systems

The responsible party is responsible for the validation status of the system throughout its life cycle. The approach to validation of computerised systems should be based on a risk assessment that considers the intended use of the system; the purpose and importance of the data/record that is collected/generated, maintained and retained in the system; and the potential of the system to affect the well-being, rights and safety of study/research participants and the reliability of study/research results.

Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy, and reliability and is consistent with intended performance. Systems should be appropriately validated prior to use with adequate change control procedures implemented. Validation of changes should be based on risk and consider both previously collected and new data.

Both basic system functionality and protocol specific configurations and

customisations, including automated data entry checks and calculations, should be validated. Interfaces between systems should also be defined and validated. Different degrees of qualification/validation may be needed for bespoke systems, systems designed to be configured or systems where no alterations are needed. Where relevant, procedures should cover the following: system design, validation, and functionality testing; release; setup; installation and change control until decommissioning. The responsible party should ensure that the computerised systems used in clinical study/research processes are qualified and validated, including those developed by other parties. They should ensure that qualification and validation documentation is maintained and retained.

Validation should generally include defining the requirements and specifications for the system and their testing, along with the associated documentation, to ensure the system is fit for purpose, especially for critical functionality, such as randomisation, dosing and dose titrations and reductions, and collection of endpoint data. Unresolved issues, if any, should be justified and, where relevant, addressed by mitigations prior to and/or during the continued use of the system. The study/research-specific systems (including updates resulting from protocol amendments) should only be implemented to enable the conduct of the study/research by the investigator after all necessary approvals for the clinical study/research have been received.

4.4.3 System Failure

Contingency procedures should be in place to prevent loss or lack of accessibility to data essential to participant/subjectsafety, study/research decisions or study/research outcomes.

4.4.4 Technical Support

Where appropriate, there should be mechanisms (e.g., help desk support) in place to document, evaluate and manage issues with the computerised systems (e.g., raised , and there should be periodic review of these cumulative issues to identify those that are repeated and/or systemic. Defects and issues should be resolved according to their criticality. Issues with high criticality should be resolved in a timely manner.

4.4.5. User Management

Access controls are integral to computerised systems used in clinical study/research to limit system access to authorised users and to ensure attributability to an individual. The security measures should be selected in such a way that they achieve the intended security and do not unduly impact user-friendliness. Procedures should be in place to ensure that user access rights are appropriately assigned based on a user's duties and functions, blinding arrangements and the organisation to which users belong. Access rights should be revoked when they are no longer needed. Authorised users and access privileges should be clearly documented, maintained and retained. These records should include any updates to a user's roles, access rights and permissions, and time of access privileges given (e.g., time stamp).

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 Participants,

paramedical staff, Monitors etc.)

QUALITY ASSURANCE

Quality Assurance and Quality Control

The Sponsor is responsible for the implementation of a system of quality control and quality assurance in order to ensure that a study is conducted, and data is generated, recorded and reported in compliance with the approved Protocol, GCP and other applicable requirements. Documented Standard Standard operating procedures are a prerequisite for quality assurance.

All observations and data 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 conducted according to written down procedures.

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

Audit must be commissioned by the sponsor and should be conducted by person or auditors independent of those responsible for the Study. Investigational sites, facilities, all data and documentation should be available for audit and inspection by the Sponsor's auditor as well as by the Regulatory Authority(ies).

The sponsor should adopt a proportionate and risk-based approach to quality management, which involves incorporating quality into the design of the clinical study/research (i.e., quality by design) and identifying factors that are likely to have a meaningful impact on participant's rights, safety and well-being and the reliability of the results (i.e., critical to quality factors as described in ICH E8(R1)). The sponsor should describe the quality management approach implemented in the study/research in the clinical study/research report (see ICH E3).

Quality assurance should be applied throughout the clinical study/research and includes implementing strategies to identify potential or actual causes of serious non-compliance with the protocol, GCP and/or applicable regulatory requirements, and to enable their corrective and preventive actions.

Audit

When performed, audits should be conducted in a manner that is commensurate with the risks associated with the conduct of the study/research. The purpose of a sponsor's audit is independent assessment of and separate from routine monitoring or quality control functions.

Selection and Qualification of Auditors

The sponsor should appoint individuals as auditors who are independent of the clinical study/research being conducted. The sponsor should ensure that the auditors are qualified, trained and experienced to conduct audits.

Auditing Procedures

The sponsor should ensure that the audit of clinical study/research/processes is conducted in accordance with the sponsor's documented procedures on what to audit, how to audit (i.e., on-site or remote), the frequency of audits and the form and content of audit reports. The sponsor's audit plan, content and procedures for a study/research audit should be guided by the importance of the study/research in submissions to regulatory authorities, the number of participants in the study/research, the type and complexity of the study/research, the level of risks to the study/research participants and any identified problem(s).

The observations and findings of the auditor(s) should be documented. To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis when evidence of serious GCP non-compliance exists or in the course of legal proceedings. When required by applicable regulatory requirements, the sponsor should provide an audit certificate.

Quality Control

Quality control should be applied to conduct and each stage of the data handling to ensure that data are reliable and have been processed correctly. Within clinical study/research, monitoring and data management processes are the main quality control activities.

The quality control of study activities/procedure and study sites (other than investigator sites, such as centralised imaging reading facilities), including on site and/or centralised activities, may be undertaken and reported using a risk-based approach.

Risk Management

A standardized approach to the identification and management of risk is described below:

Risk Identification

The sponsor should identify risks that may have a meaningful impact on critical steps of study and quality aspects of conduct and recording. Risks should be considered across the processes used in the clinical study/research (e.g., patient selection, informed consent process, randomisation and investigational product administration, data handling, and service provider activities).

Risk Evaluation

The sponsor should evaluate potential risks by considering:

a) the likelihood of harm/hazard occurring;
b) the extent to which such harm/hazard would be detectable;
c) the impact of such harm/hazard on study/research participant/subjectprotection and the reliability of study/research results.

Risk control

Risk control should be proportionate to the risk to participants' rights, safety and well-being and the reliability of study/research results. Risk mitigation activities may be incorporated in protocol design and implementation,

monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs, and training in processes and procedures.

The sponsor should set acceptable ranges to support this process within which variation can be accepted. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action should be initiated.

Risk Communication

The sponsor should communicate the identified risks and mitigating activities, if applicable, to those who are involved in taking action or are affected by such activities. Communication also facilitates risk review and continual improvement during clinical study/research conduct.

Risk Review

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

Risk Reporting

The sponsor should summarise and report the risks and the remedial actions taken in relation to important deviations from the acceptable ranges and document them in the clinical study/research report.

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 Participants 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 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 study/research 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 participants 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 participants, 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 Participant'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 Study/research of Vaccines

7.1.1 Phases of Vaccine Study/research

The guidelines to conduct the clinical study/research on investigational vaccines are similar to those governing a clinical study/research. The phase of these study/research differ from drug study/research 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 participants**. For example, immunogenicity to hepatitis vaccine should not be determined in high-risk participants.

Phase II: This refers to the initial study/research examining effectiveness (immunogenicity) in a limited number of volunteers. Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal participants, 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

a) The sponsor and investigator should be aware of the approval process(es) involved in conduct of clinical study/research of vaccines. They should familiarize themselves with the guidelines provided by CDSCO, Department of Biotechnology (DBT) and Ministry of Environment and Genetic Engineering Approval Committee (GEAC) in the case of vaccines produced by recombinant DNA technology.
b) Some vaccines that contain active or live-attenuated microorganisms possess a small risk of producing that particular infection. The participants to be vaccinated should be informed of the same.
c) The participants in control groups or when participanted to ineffective vaccines run a risk of contracting the disease.
d) 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 followed.
e) Study/research should be conducted by qualified investigator with the requisite training and experience and having necessary infrastructure for the laboratory evaluation of seroconversion.
f) Protocols for such study/research should include appropriate criteria for selection of participants, plan of frequency of administration of the test vaccine in comparison to the reference vaccine. It should accompany detailed validation of testing method to detect the antibody levels.

g) It should specify methodology to be adopted for the purpose of testing.
h) The investigator should be provided with Quality Control data of the experimental batch of the vaccine made for the purpose of clinical study/research.
i) The sponsor should provide the Ethics committee approval of the nodal body (ies) to carry out clinical study/research with the vaccine.
j) The generic version of new vaccines already introduced in the other markets after step up clinical study/research including extensive Phase III study/research should be compared to the reference vaccine with regard to seroconversion in a comparative manner in a significant sample size.
k) Post Marketing Surveillance (PMS) should be conducted following completion of seroconversion studies. PMS data should be generated in a significant sample size sensitive to detect side effects and address other safety issues.
l) 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 Study/research of Contraceptives

All procedures for clinical study/research are applicable. Participants should be clearly informed about the alternative available.

In women where implant has been used as a contraceptive for study/research, a proper follow up for removal of the implant should be done, whether the study/research is over, or the participant/subjecthas withdrawn from the study/research.

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 study/research with surgical procedures/ medical devices

Clinical investigations should be conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki. These principles protect the rights, safety and well-being of human participants, which are the most important considerations and should prevail over interests of science and society. These principles should be understood, observed, and applied at every step in the clinical investigation.

a) No person, sponsor, clinical research organization, any other organisation or investigator, shall conduct any clinical investigation in respect of any investigational medical device, in human participants except under, and in accordance with, the permission granted by the Central Licensing Authority participant/subjectto such conditions in such form and manner as may be prescribed.
b) Clinical investigation shall be carried out in respect of such investigational medical devices in such manner as may be prescribed
c) The Central Licensing Authority may, in public interest, abbreviate, defer, or waive the requirement of conducting clinical investigation for reasons to be

recorded in writing.

d) Medical device requiring clinical investigation but claiming substantial equivalence to a predicate device shall not be marketed unless the Central Licensing Authority approves equivalence in such manner as may be prescribed.
e) A device shall be deemed to be substantially equivalent if, in comparison to a predicate device, it has the same intended use and same technological characteristics or has the same intended use and different technological characteristics and also demonstrates that the device is at least as safe and effective as the predicate device
f) The Ethics committee shall also be the Ethics Committee for the purposes of clinical investigation and may supervise the conduct of clinical investigation.
g) Where any participant/subjectis injured on account of his participation in the clinical investigation, the person, sponsor, clinical research organisation, any other organisation or investigator who has obtained permission for conduct of investigation shall provide medical management to that participant/subject
h) Where an injury is caused to the participant/subjectin the clinical investigation of any investigational medical device and such injury is attributable to the use of investigational medical device, the person, sponsor, clinical research organisation, any other organisation or investigator who has obtained permission for conduct of investigation shall provide to that participant/subjectsuch compensation in such manner as may be prescribed
i) Where death of a participant/subjectis related to clinical investigation and is attributable to the use of an investigational medical device, the person, sponsor, clinical research organisation, any other organisation or investigator who has obtained permission for conduct of investigation shall provide to the legal heir of that participant, such compensation in such manner as may be prescribed.
j) Every person, sponsor, clinical research organization, any other organization or investigator conducting a clinical investigation or his agent holding a permission to conduct clinical investigation shall keep and maintain such data, record, registers and other documents as may be prescribed and shall furnish such information as may be required by the Central Licensing Authority or any other officer authorized by it in this behalf.
k) Every person, sponsor, clinical research organization, any other organization or investigator conducting a clinical investigation or his agent, as the case may be, shall, if so required, disclose to the Medical Devices Officer or any other officer authorized by the Central Licensing Authority the names, addresses and other particulars of the persons involved in conducting clinical investigation and participants in such clinical investigation.
l) Whoever himself, or by any other person on his behalf, conducts clinical investigation of any investigational medical device, without obtaining permission under Medical Device rules, shall be liable to penal provision as prescribed time to time by central licensing authority.

7.4 Clinical study/research 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 participants 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 participants 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 participant/subjectabout 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 study/research of Herbal Remedies and Medicinal Plants

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic/modern medicine System and which may later be used in allopathic hospitals, the procedures laid down by the CDSCO 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 study/research described earlier pertain also to herbal remedies. However, when clinical study/research of herbal drugs used in recognized Indian systems of Medicine and Homoeopathy are to be undertaken in Allopathic Hospitals, physicians from the concerned system as co-investigators/ collaborators/ members of the expert group is desirable for designing and evaluating a study.

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 Central Council of Indian Medicine (CCIM). While all the other GCP requirements are applicable to ASU Medicine research irrespective of the specialty of research, there are certain specific concerns pertaining to specialised areas of research which require additional safeguards / protection and specific considerations for the EC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable participants, and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of EC should be given in writing in unambiguous terms in such instances.

Panchakarma including Snehana, Swedana, Dhara, Pizhichil and para-surgical

procedures like Ksharasutra, Leech therapy, Agni karma, Hajamat, Hammam, Nutul Dalk, Riazat, Prachhanna, Rakta mokshana, Tarpana, Vidalaka, Varmam etc. are special strength areas of ASU systems of medicine. Proper documentation of end point, procedure, standardization of ASU drug / Patent or Proprietary Medicines used in the procedures, parameters of evaluation, statistical consideration should be given special attention while conducting clinical study/research on them.

Informed consent procedures should be followed as in drug study/research. The patient information sheet should contain information on the procedure to be adopted in case patient wishes to opt out of the study/research.

ASU Medical Devices: Such ASU devices having proven quality and safety and intended for internal or external use or for the diagnosis, treatment, mitigation or prevention of disease or disorders in human beings or animals, as may be specified from time to time by Central Government through Gazette notification.

7.5.1 Categories of Herbal Products

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

a) Traditional knowledge exists about the use of a plant or its extract in the ancient Ayurveda, Siddha or Unani literature or a plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years. The same substance may be clinically evaluated for same indication for which it is being used or as has been described in the tradional 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 traditional 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 cGMP 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 study/research 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 study/research is subsequently planned based on results of phase II study.

Clinical study/research 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, participant, inducements for participation, information to be provided to the participant, withdrawal from study and research involving children or persons with diminished autonomy, all apply to study/research on plant drugs also. These study/research have also got to be approved by the appropriate scientific and ethics committees of the concerned Institutes. However, it is essential that such clinical study/research be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator in such a clinical study/research. 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 commercialization 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.

7.6 Clinical study/research of Stem Cell

In recent years, stem cell research has emerged as an important area of biomedical science. It has potential applications in varied areas of biomedicine including developmental biology, disease modelling, tissue engineering, drug development, toxicity testing. Use of stem cells in regenerative medicine holds promise for improving human health by restoring the function of cells and tissues that are damaged due to degeneration and/or injury. Like all other medical innovations, basic and translational research in the field not only requires a sound scientific rationale, but also needs to take into consideration ethical, legal and social norms. Apart from challenges of selecting the appropriate stem cells for a particular condition, there are important concerns related to the use of embryos for creating human embryonic stem cell (hESC) lines as these may lead to commoditization of human cells and tissues. Further, there are challenges related to gene editing/modification, human germ-line engineering and reproductive cloning. Besides, the robust technologies are being developed for deriving pluripotent stem cells from a variety of sources which may be easily accessible for clinical applications, often without rationale. The potential danger of tumorigenicity of stem cells, considering their capacity for unlimited proliferation, possible risk of contamination and genomic changes arising due to *in vitro* manipulations, and limitations related to
immunological tissue incompatibility between individuals are all areas of serious concern. All of these pose an inherent risk of exploitation of individuals particularly those belonging to the underprivileged groups. Hence the guidance for stem cell research, development and its possible application in the frame of clinical study/research is critical.

Stem cells and their derivatives fall under definition of ‘Drug’ as per the Drugs and Cosmetics Act 1940, and are categorized as ‘Investigational New Drug (IND)’ or

'Investigational New Entity (INE)' when used for clinical application. Hence the principles of bioethics and regulation must be followed accordingly before initiating clinical study/research. Adequate safeguards must be in place so that recipients of these cells in clinical study/research are fully protected. Societal concerns regarding compensation for research related injuries and unforeseen adverse effects are additional concerns that need to be adequately addressed.

Based on the cell type/tissue of origin, stem cells are classified as 'Somatic Stem Cells' (SSCs), and 'Embryonic Stem Cells' (ESCs). SSCs may have a limited capacity of differentiation and may be multipotent or unipotent, whereas ESCs are pluripotent. The pluripotent stem cells can also be generated in the laboratory by reprogramming somatic cells, and the products thus generated are referred to as 'Induced Pluripotent Stem Cells (iPSCs)'. The regulatory requirements for research on each of these stem cells depend on their origin and potency.

Stem cells, whether autologous or allogeneic, require variable degree of *in vitro* or *ex vivo* processing before their use for clinical application/transplantation/translational research. This carries the risk of contamination and may also lead to alteration in their properties which may vary according to the degree and type of manipulation. The investigators should follow the requirements as given in all applicable regulations including D&C Act and rules, DBT and GEAC. All laboratory procedures should be carried out under aseptic conditions in a CDSCO certified cGMP (schedule M) and GLP (schedule L 1) facility for human applications. For preclinical studies on animals, the laboratory should have GLP certification from the Department of Science and Technology (DST).

Research involving stem cells can be conducted only after approval both from the ICSCR (Institutional Committee for Stem Cell Research). Additional approvals as spelt in may also be necessary depending on the research category. The proposal should be reviewed ethics committee and EC should invite 2 additional experts in cell and gene therapy.

Clinical study/research with Gene therapy products:

Gene therapy refers to the technique of using normal functioning gene to treat a genetic disease either by repairing or replacing or regulating the defective gene. Gene therapy is classified into somatic cell gene therapy and germline gene therapy.

Somatic cell gene therapy cannot be transferred to the next generation and the two approaches followed here are *ex vivo* and *in vivo*. In germline gene therapy, the genetically modified cells are transplanted into gametes and vertical transmission occurs here. Due to ethical and social reasons, germline gene therapy is banned in India.

GTP is defined as "a biological substance or therapeutic molecule which could modify the genome, or the extra-genomic DNA or RNA segments (mitochondrial and episomal)." It also encompasses gene modified or edited cells, tissues, organs.

Scientific and Ethical Considerations in Gene Therapy:

Mutations, insertions, deletions and similar alterations in these genes or its regulatory elements may result in reduced or absent production of the encoded proteins, or expression of structurally or functionally abnormal proteins, thereby

leading to genetic disorders. GTPs work by repairing, replacing or deactivating dysfunctional disease-causing genes aiming to restore normal function. The biological and technical complexities of GTPs, their design and production pose challenges for their translation into clinic.

The scientific considerations for GTPs include selection of appropriate gene delivery vector/modality for the disease/tissue target, design of the expression cassette to ensure clinically relevant expression levels, specificity of gene expression to prevent unwanted side effects or off-target effects and minimising immune reactions of the host.

The design of preclinical and clinical studies for GTP differ significantly from the other chemical and biological drugs, because of the complexity of the vector interaction with the host cells wherein the effects of vector uptake into host cells, response of the host immune system, the outcome of integration of genetic material into host chromosomes (in case of lentivirus or gamma-retrovirus) and levels of transgene expression from the host cells determine the final therapeutic efficiency of the GTP.

The precautions which should be followed at the various levels of preclinical and clinical studies of GTP include appropriate selection of vector for gene delivery depending on the target tissue. The expression cassette should be designed in a such a way so that only clinically relevant levels must be expressed and gene expression should be very specific to avoid unwanted adverse effects and off-target effects in the host. There may be risk of teratogenicity, excessive immune activation and unwanted mutations (e.g., off-target gene editing) or unwanted host-immune response to GTP which should be informed to patient in advance.

The scientific and ethical concerns for gene therapy primarily stem from the profound effect that genes exert on living cells by conferring novel properties and functions. The GTP ideally should not cause harm such as teratogenicity (e.g. integration of transgene cassette into tumour suppressor genes), excessive immune activation (e.g. aberrant CAR-T activity), introduction of unwanted mutations (e.g. off-target gene editing) or unwanted host immune response to GTP (e.g. neutralising antibodies to AAV). In addition, such gene augmentation techniques have the potential for misuse to gain unnatural advantages (e.g. in sports or defence sectors to enhance physical function) or to select for specific traits in new-borns (designer babies by gene editing).

All such applications are prohibited unless scientific or ethical justification can be provided which is acceptable under socio-ethical norms and the laws of the land.

Clinical study/research with Nanoparticles:

Nanoscience is the study of materials which are in nanoscale range. Conversion of any material in nanoscale results in alteration of its physicochemical, biological, mechanical, optical, electronic, etc. properties. These newly acquired (novel) properties of the materials due to conversion into nanoscale can be utilized for different useful activities.

Nanopharmaceutical is an emerging field that combines nanotechnology with pharmaceutical and biomedical science with the goal of targeted drug delivery which may improve efficacy and safety profile. Alteration of the substance into nanoscale associated with drug delivery may also significantly alter the pharmacokinetic, biodistribution and toxicokinetic parameters of the conventional/traditional drugs raising various concerns related to quality, safety and efficacy of the nanopharmaceutical products as nanopharmaceuticals have a higher tendency of tissue sequestration.

Nanopharmaceuticals should be demonstrated clinically through appropriate design, patient selection hypothesis and biomarkers to exploit the increased permeability and retention of drug. Clinical development of a nanopharmaceutical using a well characterized drug delivery system will be successful if the development plan is designed based on clear understanding of parameters driving the efficacy of the free drug and the *in vivo* behavior of the delivery system. Majority of approved nanopharmaceuticals, especially oncology products, have been designed clinically to exploit the increased permeability and retention effect. Such effect may minimize the peak concentration of free drug while increasing the overall bioavailability of the drug, providing prolong exposure of the drug at the site of action. At times, the development of a nanopharmaceutical may fail to achieve the clinical end point in terms of lack of adequate level of efficacy or increased toxicity due to multiple reasons. Appropriate design of clinical trials based on proper understanding of accumulation, retention, toxicity and efficacy profile of the agent and correlation between the *in vivo* behavior and the delivery system is of paramount importance for successful assessment of clinical profile of the drug. In general, clinical trials should be conducted in stages. However, depending on the status of the Active Pharmaceutical Ingredient (API), whether it is an New Chemical Entity (NCE) or an approved drug molecule and the nano carrier, clinical trial of appropriate phase may be conducted on a 'case by case approach' basis.

Clinical study/research with food supplements

Different types of clinical trials are designed by manufacturing companies and others to explore specific product features impacting human health. Food trials are often designed to evaluate specific marketing claims needing scientific substantiation while drug trials document the safety and efficacy of a specific drug for a specific intended use (e.g., to treat, mitigate or cure a human disease). Food trials tend to be more pragmatic and exploratory as they document human experiences with specific foods in the context of the human diet while drug trials tend to be more explanatory as they document specific drug doses and schedules and specific disease responses. Food trials typically enroll healthy individuals while drug trials enroll patients with a specific disease type potentially needing the research treatment. Foods are complex mixtures of ingredients (e.g., plant parts, meats, eggs, chemicals, beverages, whole meals, etc.) designed to be palatable and which may have the general health effect under investigation while drugs are highly purified and designed to have a specific effect on a disease.

All clinical trials should be conducted using Good Clinical Practices (GCP) with appropriate Human Subject Protections (HSPs) and all products used in human testing should be produced under Good Manufacturing Practices (GMP) using a

well-established Quality Management System (QMS). All clinical trial protocols should clearly define the study objective/s, inclusion/exclusion criteria, treatments (including stopping rules for high risk products), study measurements and statistical analyses to be used for data analysis. The study investigator must ensure the study staff are trained and experienced, treat only appropriate study subject's and collect clinical trial data in a manner allowing appropriate evaluation of product effects on the human subject.

Principles of good clinical trial practices followed are similar between food and drug clinical trials, including the use of: 1. Safe products for human testing (food grade products food trials and drug products passing preclinical safety testing for drug products). Production lines should not introduce unsafe contaminants. Formulations should be well characterized considering the intended use, appropriate dose, batch variability and control products (if any). Cellular and animal testing may be required prior to first in man studies. Properly labeled test products (e.g., placebo should not be distinguishable from the test product, if the study is blinded) should be used. Clearly documented shelf life stability during the timeframe of the trial is important. Appropriate trial designs, including comprehensive reviews of past clinical trials, Clear study objectives and test methods, Well-defined eligibility criteria (inclusion and exclusion criteria), Precise dosing schedules (e.g., the minimal effective dose to avoid side effects), Effective randomization methods (if any), Accurate/validated performance criteria (e.g., to measure clinical endpoints and to enable specific statistical plans), Covering outcomes, compliance and adverse events are critical point to consider. Enrolling study subjects should represent the population of interest and allowing trial results to be generalizable to entire population of interest. Well-designed Informed Consent Form is must for any food trial. Trial registration (Listing prior to trial start) is desired.

Best practices for food clinical trials Effective food clinical trials are highly variable and often start with the desired claim in mind during the trial design. The food trial is built around the claim as the rationale for the study. Using thoughtful objectives and hypotheses based on a thorough review of the scientific literature, the benefits and risks of the food clinical trials are carefully considered as both safety and efficacy endpoints are defined in the study protocol.

Best practices for food clinical trials include:

1. Ensuring the claim is relevant for human health and the precise meaning of the claim has been fully supported by the food clinical trial data
2. Ensuring the quantity/pattern of food consumption is possible as part of a balanced diet in the target population for the claim
3. Linking the claimed effect to the consumption of the food (e.g., strength, consistency, specificity, dose-response, biological plausibility, etc. should be fully considered)
4. Defining effects and outcomes measures clearly –although subjective measures like cognition, pain, or hunger are more difficult to measure than objective measures like hemoglobin levels or weight, food trials often use measures involving the senses: food taste, texture, and feelings of satiety, bloating, GI discomfort, etc.
5. Special considerations and measurements of specific food related items (like the food matrix for the test material, the background diet, food-related confounding issues)
6. Considering the totality of the evidence for each specific condition of use

Compliance is monitored by careful diet analyses and sometimes includes validated biomarkers of exposure.

DISCLOSURE OF SITE SPECIFIC SAFETY/EFFICACY DATA

8.1 Disclosure of site specific safety/efficacy data:

As per ICH GCP, Indian GCP and WHO GCP requirement on reporting of site-specific safety and efficacy data is to report individual case safety report (ICSR) to Ethics Committee, Sponsor and Regulatory Agency in specified time period and submit follow up data in the form of follow up safety reports and CIOMS report. Also, as per CT approval condition, site specific safety data by way of individual case safety report and adverse event as per Adverse event reporting requirement of NDCT rules. The same has been communicated to EC and sponsor in the timeline define in the NDCT rules.

Efficacy data is not being reported by individual site. The efficacy data at the end of the study has been analyzed at the end of study by statistical plan given in the protocol and compiled clinical study report comprising of safety and efficacy assessment is being submitted to the regulatory agencies to the sites and site submit the copy of report to EC. During the comparative clinical study, if investigator need to know the patient is in which arm active/comparator then Investigator can break the blind in benefit of the patient health and well being keeping the ethical principles for Medical Research Involving Human Subjects as per Declaration of Helsinki consideration.

However, that cannot be constituted as efficacy assessment because efficacy data can not be analyzed on single patient reporting. This need to be validated against the agreed plan/statistical model given in the study protocol."

APPENDICES

Appendix I

World Medical Association - Declaration of Helsinki

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, SomersetWest, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly,Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human participants, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human participants to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are Involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human participants.
6. The primary purpose of medical research involving human participants is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is participant/subjectto ethical standards that promote and ensure respect for all human participants and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research participants.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research participants. The responsibility for the protection of research participants must always rest with the physician or other health care professionals and never with the research participants, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human participants in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research participants set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human participants must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research participants.
15. Appropriate compensation and treatment for participants who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human participants may only be conducted if the importance of the objective outweighs the risk and burdens to the research participants.
17. All medical research involving human participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human participants unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be

carried out in a nonvulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human participants must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human participants must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for participants and information regarding provisions for treating and/or compensating participants who are harmed as a consequence of participation in the research study. In clinical study/research, the protocol must also describe appropriate arrangements for post-study/research provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research participants set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research participants and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as participants in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human participants capable of giving informed consent, each potential participant/subjectmust 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, post-study provisions and any other relevant aspects of the study. The potential participant/subjectmust be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs

of individual potential participants as well as to the methods used to deliver the information. After ensuring that the potential participant/subjecthas understood the information, the physician or another appropriately qualified individual must then seek the potential participant's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research participants should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential participant/subjectis in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research participant/subjectwho is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit form unless it is intended to promote the health of the group represented by the potential participant, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research participant/subjectwho is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential participant's dissent should be respected.
30. Research involving participants who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving participants with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the participant/subjector a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no

intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be participant/subjectto additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Study/research Provisions

34. In advance of a clinical study/research, sponsors, researchers and host country governments should make provisions for post-study/research access for all participants who still need an intervention identified as beneficial in the study/research. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human participants must be registered in a publicly accessible database before recruitment of the first participant.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human participants and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing heath or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix II

New Drugs and Clinical Trials Rules, 2019 - GENERAL PRINCIPLES AND PRACTICES FOR CLINICAL STUDY/RESEARCH

GENERAL PRINCIPLES AND PRACTICES FOR CLINICAL STUDY/RESEARCH

1. General Principles

(1) The principles and guidelines for protection of study/research participants as described in Third Schedule as well as Good Clinical Practices guidelines shall be followed in conduct of any clinical study/research.

(2) The sponsor and investigator share the responsibilities for the protection of study/research participant/subjecttogether with ethics committee. The responsibilities of sponsor, investigator and ethics committee are described in the Third Schedule.

(3) The results of non-clinical studies or previous clinical study/research should be sufficient to ensure that the new drugs or investigational new drug is safe for the proposed clinical study/research.

(4) Throughout the clinical study/research and drug development process, the animal toxicological data and clinical data generated should be evaluated to ensure their impact for the safety of the study/research participant.

2. Approach in design and analysis

Clinical study/research should be planned, designed, conducted, analysed and reported according to sound scientific and ethical principles. Following important principles should be followed:

a. The primary objective of any clinical study/research should be clearly and explicitly stated which may include exploratory or confirmatory characterisation of safety, efficacy, assessment of pharmacokinetic and pharmacodynamic parameters;

b. The clinical study/research should be designed appropriately so that it provides the desired information;

c. Appropriate comparator may be utilised to achieve the objective with respect to primary and secondary end points. Comparison may be made with placebo, no treatment, active controls or of different doses of the new drug or investigational new drug;

d. The number of participants to be included in the clinical study/research should be adequate depending on the nature and objective of the clinical study/research.

3. Development Methodology

(1) Non clinical studies, -

(a) The nature of non-clinical studies and their timing in respect of conduct of clinical study/research should be determined taking following aspects in to consideration:

(i) characteristics of the new drug or investigational new drug;

(ii) disease of conditions for which the new drug or investigational new drug is intended to be indicated;

(iii) duration and exposure in clinical study/research participant;

(iv) route of administration.

(b) The detailed requirements of non-clinical studies have been specified in the Second Schedule.

(c) For first in human studies the dose should be calculated carefully based on the non-clinical pharmacological, toxicological data generated.

(2) Phases in Clinical Study/research: Clinical drug development generally consists of four phases (Phase I-IV). The details of these phases are described as under.

(a) Phase I

The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy participants or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I study/research should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the participants. Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives: -

- Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.
- Pharmacokinetics, i.e., characterisation of a drug's absorption, distribution, metabolism and excretion: Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.
- Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic or pharmacodynamic studies) may be conducted in healthy volunteer participants or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.
- Early measurement of drug activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(b) Phase II

(i) The primary objective of Phase II study/research is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose

and regimen for Phase III study/research. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in study/research.

(c) Phase III

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drugs.

(ii) For drugs intended to be administered for long periods, study/research involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies may need to be carried out if scientifically and ethically justified, primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian participants, Central Licencing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad. In case of an application of a new drug already approved and marketed in other country, where local clinical study/research in India is waived off or not found scientifically justified for its approval for manufacturing first time in the country, the bioequivalence studies of such drug, as appropriate, is required to be carried out and the test batches manufactured for the purpose shall be inspected before its approval.

(d) Phase IV

Phase IV or post marketing study/research of new drugs are performed after the approval of the drug and

related to the approved indication. Such study/research go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Such study/research might not have been considered essential at the time of new drug approval due to various reasons such as limitation in terms of patient exposure, duration of treatment during clinical development of the drug, need for early introduction of the new drug in the interest of patients etc.

Phase IV study/research include additional drug-drug interaction, dose

response or safety studies and study/research design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies, etc.

(3) Studies in special populations: Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern.

(A) *Geriatrics*

Geriatric patients should be included in Phase III clinical study/research (and in Phase II study/research, at the Sponsor's option) in meaningful numbers, if_

(a) the disease intended to be treated is characteristically a disease of aging; or

(b) the population to be treated is known to include substantial numbers of geriatric patients; or

(c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or

(d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(B) *Paediatrics*

(i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the study/research to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical study/research data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical study/research early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iii) If the new drug has a potential for use in paediatric patients – paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application, more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

(iv) The paediatric studies should include,

(a) clinical study/research,

(b) relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

(v) If the new drug is a major therapeutic advance for the paediatric population the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vi) For clinical study/research conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about paediatric, ethical, clinical and psychosocial issues.

(C) *Pregnant or nursing women*

(i) Pregnant or nursing women should be included in clinical study/research only when the drug is intended for use by pregnant or nursing women or fetuses or nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

4. Conduct of Clinical Study/research

Clinical study/research should be conducted in accordance with the principles as specified in Third Schedule of NDCT rules. Adherence to the clinical study/research protocol is essential and if amendment of the protocol becomes necessary the rationale for the amendment shall be provided in the form of a protocol amendment. Serious adverse events shall be reported during clinical study/research in accordance with NDCT Rules.

5. Analysis

The results of a clinical study/research shall be analysed according to the plan specified in the clinical study/research protocol. Safety data should be appropriately tabulated and all adverse events should be classified according to their seriousness and causal relationship with the study drug.

6. Reporting

Report of clinical study/research shall be documented in accordance with the approaches specified in Table 6 of
the Third Schedule. The report shall be certified by the principal investigator or if no principal investigator is designate then by each of the participating investigators of the study.

Appendix III. Animal toxicology (Non-clinical toxicity studies)

(1) General principles. -

Toxicity studies should comply with the norms of Good Laboratory Practices (GLP). Briefly, these studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard standard operating procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Test substances and test systems (in-vitro or in-vivo) should be properly characterised and standardized. All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of five years after marketing of the drug.

Toxicokinetic studies (generation of pharmacokinetic data either as an integral component of the conduct of non-clinical toxicity studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include obtaining data to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in nonclinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

(1.1) Systemic toxicity studies, -

(1.1.1) Single-dose toxicity studies These studies (see Table 1) should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans. In addition, unless the intended route of administration in humans is only intravenous, at least one more route should be used in one of the species to ensure systemic absorption of the drug. This route should depend on the nature of the drug. A limit of 2g/kg (or 10 times the normal dose that is intended in humans, whichever is higher) is recommended for oral dosing. Animals should be observed for 14 days after the drug administration, and Minimum Lethal Dose (MLD) and Maximum Tolerated Dose (MTD) should be established. If possible, the target organ of toxicity should also be determined. Mortality should be observed for up to seven days after parenteral administration and up to 14 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD10 and LD50 should be reported preferably with 95 percent confidence limits. If LD50 cannot be determined, reasons for the same should be stated.

The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be up to 14 days. Mice should first be used for determination of MTD. Findings should then be confirmed in rat for establishing linear relationship between toxicity and body surface area. In case of nonlinearity, data of the more sensitive species should be used to determine the Phase I starting dose. Where rodents are known to be poor predictors of human toxicity (e.g., antifolates), or where the cytotoxic drug acts by a novel mechanism of action, Maximum Tolerated Dose (MTD) should be established in non-rodent species.

(1.1.2) Repeated-dose systemic toxicity studies These studies (see Table 1) should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose

ranging studies should precede the 14-, 28-, 90- or 180- day toxicity studies. Duration of the final systematic toxicity study will depend on the duration, therapeutic indication and scale of the proposed clinical study/research. If a species is known to metabolise the drug in the same way as humans, it should be preferred for toxicity studies. In repeated-dose toxicity studies the drug should be administered seven days a week by the route intended for clinical use. The number of animals required for these studies, i.e., the minimum number of animals on which data should be available.

Wherever applicable, a control group of animals given the vehicle alone should 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. To make allowance for the sensitivity of the species the intermediate dose should cause some symptoms, but not gross toxicity or death, and should be placed logarithmically between the other two doses.

The parameters to be monitored and recorded in long-term toxicity studies should include PK, PD, behavioural, physiological, biochemical and microscopic observations. In case of parenteral drug administration, the sites of injection should be participated to gross and microscopic examination. Initial and final electrocardiogram and fundus examination should be carried out in the non-rodent species. In the case of cytotoxic anticancer agents dosing and study design should be in accordance with the proposed clinical schedule in terms of days of exposure and number of cycles. Two rodent species may be tested for initiating Phase I study/research. A non-rodent species should be added if the drug has a novel mechanism of action, or if permission for Phase II, III or marketing is being sought.

For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half-life, incomplete elimination or unanticipated organ toxicity.

Notes:

(i) Single dose toxicity study. - Each group should contain at least five animals of either sex. At least four graded doses should be given. Animals should be exposed to the test substance in a single bolus or by continuous infusion or several doses within 24 hours. Animals should be observed for 14 days. Signs of intoxication, effect on body weight, gross pathological changes should be reported. It is desirable to include histo-pathology of grossly affected organs, if any.

(i i) Dose- ranging study. - Object ives of this study include the identification of target organ of toxicity and establishment of Maximum Tolerated Dose (MTD) for subsequent studies.

a.Rodents. - Study should be performed in one rodent species (preferably rat) by the proposed clinical route of administration. At least four graded doses including control

should be given, and each dose group as well as the vehicle control should consist of a minimum of five animals of each sex. Animals should be exposed to the test substance daily for 10 consecutive days. Highest dose should be the maximum tolerated dose of single-dose study. Animals should be observed daily for signs of intoxication (general appearance, activity and behavior etc), and periodically for the body weight and laboratory parameters. Gross examination of viscera and microscopic examination of affected organs should be done.

b. Non-rodents. - One male and one female are to be taken for ascending Phase Maximum Tolerated Dose (MTD) study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be three to five times the extrapolated effective dose or Maximum Tolerated Dose (MTD) (whichever is less), and dose escalation in suitable steps should be done every third day after drawing the samples for laboratory parameters. Dose should be lowered appropriately when clinical or laboratory evidence of toxicity are observed. Administration of test substance should then continue for 10 days at the well-tolerated dose level following which, samples for laboratory parameters should be taken. Sacrifice, autopsy and microscopic examination of affected tissues should be performed as in the case of rodents.

(iii) 14-28 Day repeated-dose toxicity studies. - One rodent (6-10/sex/group) and one non-rodent (2-3/sex/group) species are needed. Daily dosing by proposed clinical route at three dose levels should be done with highest dose having observable toxicity, mid dose between high and low dose, and low dose. The doses should preferably be multiples of the effective dose and free from toxicity. Observation parameters should include cage side observations, body weight changes, food or water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv) 90 Days repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. Daily dosing by proposed clinical route at three graded dose levels should be done. In addition to the control a “high-dose-reversal” group and its control group should be
also included. Parameters should include signs of intoxication (general appearance, activity and behavior etc), body weight, food intake, blood biochemical parameters, haematological values, urine analysis, organ weights, gross and microscopic study of viscera and tissues. Half the animals in “reversal” groups (treated and control) should be sacrificed after 14 days of stopping the treatment. The remaining animals should be sacrificed after 28 days of stopping the treatment or after the recovery of signs or clinical pathological changes – whichever comes later, and evaluated for the parameters used for the main study.

(v) 180-Day repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. At least four groups, including control, should be taken. Daily dosing by proposed clinical route at three graded dose levels should be done. Parameters should include signs of intoxication, body weight, food intake, blood biochemistry, hematology, urine analysis, organ weights, gross and microscopic examination of organs and tissues.

(1.2) Male fertility study: One rodent species (preferably rat) should be used. Dose selection should be done from the results of the previous 14 days or 28 days toxicity study in rat. Three dose groups, the highest one showing minimal toxicity in systemic studies, and a control group should be taken. Each group should consist of six adult male animals. Animals should be treated with the test substance by the intended route of clinical use for

minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in a ratio of 1:2 for mating. Drug treatment of the male animals should continue during pairing. Pairing should be continued till the detection of vaginal plug or 10 days, whichever is earlier. Females getting thus pregnant should be examined for their fertility index after day 13 of gestation. All the male animals should be sacrificed at the end of the study. Weights of each testis and epididymis should be separately recorded. Sperms from one epididymis should be examined for their motility and morphology. The other epididymis and both testes should be examined for their histology.

(1.3) Female reproduction and developmental toxicity studies: These studies need to be carried out for all drugs proposed to be studied or used in women of child bearing age. Segment I, II and III studies (see below) are to be performed in albino mice or rats, and segment II study should include albino rabbits also as a second test species. On the occasion, when the test article is not compatible with the rabbit (e.g. antibiotics which are effective against gram positive, anaerobic organisms and protozoas) the Segment II data in the mouse may be substituted.

(1.3.1) Female fertility study (Segment I). - The study should be done in one rodent species (rat preferred). The drug should be administered to both males and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period. Three graded doses should be used, the highest dose (usually the Maximum Tolerated Dose (MTD) obtained from previous systemic toxicity studies) should not affect general health of the parent animals. At least 15 males and 15 females should be used per dose group. Control and the treated groups should be of similar size. The route of administration should be the same as intended for therapeutic use. Dams should be allowed to litter and their medication should be continued till the weaning of pups. Observations on body weight, food intake, clinical signs of intoxication, mating behaviour, progress of gestation or parturition periods, length of gestation, parturition, postpartum health and gross pathology (and histopathology of affected organs) of dams should be recorded. The pups from both treated and control groups should be observed for general signs of intoxication, sex-wise distribution in different treatment groups, body weight, growth parameters, survival, gross examination, and autopsy. Histopathology of affected organs should be done.

(1.3.2) Teratogenicity study (Segment II). - One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. The drug should be administered throughout the period of organogenesis, using three dose levels as described for segment I. The highest dose should cause minimum maternal toxicity and the lowest one should be proportional to the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as intended for human therapeutic use. The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level. All foetuses should be participanted to gross examination, one of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities. Observation parameters should include: (Dams) signs of intoxication, effect on body weight, effect on food intake, examination of uterus, ovaries and uterine contents, number of corpora lutea, implantation sites, resorptions (if any); and for the foetuses, the total number, gender, body length, weight and gross or visceral or skeletal abnormalities, if any.

(1.3.3) Perinatal study (Segment III). - This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications

of possible adverse effects on foetal development. One rodent species (preferably rat) is needed. Dosing at levels comparable to multiples of human dose should be done by the intended clinical route. At least four groups (including control), each consisting of 15 dams should be used. The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams should then be sacrificed and examined as described below. One male and one female from each litter of F1 generation (total 15 males and 15 females in each group) should be selected at weaning and treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation. Mating performance and fertility of F1 generation should thus be evaluated to obtain the F2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier. Animals should be sacrificed at the end of the study and the observation parameters should include (Dams) body weight, food intake, general signs of intoxication, progress of gestation or parturition periods and gross pathology (if any); and for pups, the clinical signs, sex-wise distribution in dose groups, body weight, growth parameters, gross examination, survival and autopsy (if needed) and where necessary, histopathology.

(1.4) Local toxicity- These studies are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g., skin or vaginal mucous membrane) to determine local effects in a suitable species. Typical study designs for these studies should include three dose levels and untreated or vehicle control, preferably use of two species, and increasing group size with increase in duration of treatment. Where dosing is restricted due to anatomical or humane reasons, or the drug concentration cannot be increased beyond a certain level due to the problems of solubility, pH or tonicity, a clear statement to this effect should be given. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required.

Notes:

(i) ***Dermal toxicity study*** - The study may be done in rabbit and Guinea pig . The initial toxicity study shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. In rabbit and Guinea pig studies, daily topical (dermal) application of test substance in its clinical dosage form should be done.; Test material should be applied on shaved skin covering not less than 10% of the total body surface area. Porous gauze dressing should be used to hold liquid material in place. Formulations with different concentrations (at least 3) of test substance, several fold higher than the clinical dosage form should be used. Period of application may vary from seven to 90 days depending on the clinical duration of use. Where skin irritation is grossly visible in the initial studies, a recovery group should be included in the subsequent repeated-dose study. Local signs (erythema, oedema and eschar formation) as well as histological examination of sites of application should be used for evaluation of results.

(ii) ***Photoallergy or dermal photo-toxicity*** - It should be tested by Armstrong or Harber test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential (e.g., drugs to be used in treatment of leucoderma). Pretest in eight animals should screen four concentrations (patch application for two hours ±15 min.) with and without UV exposure (10J/cm2). Observations recorded at 24 and 48 hours should be used to ascertain highest

non-irritant dose. Main test should be performed with 10 test animals and five controls. Induction with the dose selected from pretest should use 0.3 ml/patch for 2 hour ±15 min. followed by 10 J/cm2 of UV exposure. This should be repeated on day 0, 2,4,7,9 and 11 of the test. Animals should be challenged with the same concentration of test substance between day 20 to 24 of the test with a similar 2-hour application followed by exposure to 10 J/cm2 of UV light. Examination and grading of erythema and oedema formation at the challenge sites should be done 24 and 48 hours after the challenge. A positive control like musk ambrett or psoralin should be used.

(iii) ***Vaginal toxicity test*** **-** Study is to be done in rabbit or dog. Test substance should be applied topically (vaginal mucosa) in the form of pessary, cream or ointment. Six to ten animals per dose group should be taken. Higher concentrations or several daily applications of test substance should be done to achieve multiples of daily human dose. The minimum duration of drug treatment is seven days (more according to clinical use), participant/subjectto a maximum of 30 days. Observation parameters should include swelling, closure of in troit us and histopathology of vaginal wall.

(iv) ***Rectal tolerance test*** - For all preparations meant for rectal administration this test may be performed in rabbits or dogs. Six to ten animals per dose group should be taken. Formulation in volume comparable to human dose (or the maximum possible volume) should be applied once or several times daily, per rectally, to achieve administration of multiples of daily human dose. The minimum duration of application is seven days (more according to clinical use), participant/subjectto a maximum of 30 days. Size of suppositories may be smaller, but the drug content should be several folds higher than the proposed human dose. Observation parameters should include clinical signs (sliding on backside), signs of pain, blood or mucus in faeces, condition of anal region or sphincter, gross and (if required) histological examination of rectal mucosa.

(v) ***Parenteral drug s-*** For products meant for intravenous or intramuscular or subcutaneous or intradermal injection the sites of injection in systemic toxicity studies should be specially examined grossly and microscopically. If needed, reversibility of adverse effects may be determined on a case-to-case basis.

(vi) ***Ocular toxicity studies (for products meant for ocular instillation)*** **-** These studies should be carried
out in two species, one of which should be the albino rabbit which has a sufficiently large conjunctival sac. Direct delivery of drug onto the cornea in case of animals having small conjunctival sacs should be ensured. Liquids, ointments, gels or soft contact lenses (saturated with drug) should be used. Initial single dose application should be done to decide the exposure concentrations for repeated-dose studies and the need to include a recovery group. Such initial toxicity studies shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. Duration of the final study will depend on the proposed length of human exposure participant/subjectto a maximum of 90 days. At least two different concentrations exceeding the human dose should be used for demonstrating the margin of safety. In acute studies, one eye should be used for drug administration and the other kept as control. A separate control group should be included in repeated-dose studies. Slit-lamp examination should be done to detect the changes in cornea, iris and aqueous humor. Fluorescent dyes (sodium fluorescein, 0.25 to 1.0%) should be used for detecting the defects in surface epithelium of cornea and conjunctiva. Changes in intra-ocular tension should be monitored

by a tonometer. Histological examination of eyes should be done at the end of the study after fixation in Davidson's or Zenker's fluid.

(vii) ***Inhalation toxicity studies*** **-** The studies are to be undertaken in one rodent and one non-rodent species using the formulation that is to be eventually proposed to be marketed. Acute, subacute, and chronic toxicity studies should be performed according to the intended duration of human exposure. Standard systemic toxicity study designs (described above) should be used. Gases and vapours should be given in whole body exposure chambers; aerosols are to be given by nose-only method. Exposure time and concentrations of test substance (limit dose of 5mg/l) should be adjusted to ensure exposure at levels comparable to multiples of intended human exposure. Three dose groups and a control (plus vehicle control, if needed) are required. Duration of exposure may vary participant/subjectto a maximum of 6 hours per day and five days a week. Food and water should be withdrawn during the period of exposure to test substance. Temperature, humidity and flow rate of exposure chamber should be recorded and reported. Evidence of exposure with test substance of particle size of 4 micron (especially for aerosols) with not less than 25% being 1 micron should be provided. Effects on respiratory rate, findings of bronchial lavage fluid examination, histological examination of respiratory passages and lung tissue should be included along with the regular parameters of systemic toxicity studies or assessment of margin of safety.

(1.5) Allergenicity or Hypersensitivity - Standard tests include guinea pig maximization test (GPMT) and local lymph node assay (LLNA) in mouse. Any one of the two may be done. Notes: (i) Guinea pig maximization test. - The test is to be performed in two steps: first, determination of maximum non-irritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, four dose levels should be tested by the same route in a batch of four male and four female animals (2 of each sex should be given Freund's adjuvant). The minimum irritant dose should be used for induction. Similarly, a topical minimum irritant dose should be determined for challenge. This should be established in two males and two females. A minimum of six male and six female animals per group should be used in the main study. One test and one control group should be used. It is preferable to have one more positive control group. Intradermal induction (day 1) coupled with topical challenge (day21) should be done. If there is no response, re-challenge should be done 7 to 30days after the primary challenge. Erythema and oedema (individual animal scores as well as maximization grading) should be used as evaluation criteria.
(ii) Local lymph node assay. - Mice used in this test should be of the same sex, either only males or only females. Drug treatment is to be given on ear skin. Three graded doses, the highest being maximum non-irritant dose plus vehicle control should be used. A minimum of 6 mice per group should be used. Test material should be applied on ear skin on three consecutive days and on day 5, the draining auricular lymph nodes should be dissected out 5 hours after i.v. H-thymidine or bromo-deoxy-uridine (BrdU). Increase in H-thymidine or BrdU incorporation should be used as the criterion for evaluation of results.

(1.6) Genotoxicity: Genotoxic compounds, in the absence of other data, shall be presumed to be transspecies carcinogens, implying a hazard to humans. Such compounds need not be participanted to long term carcinogenicity studies. However, if such a drug is intended to be administered for chronic illnesses or otherwise over a long period of time - a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects. Genotoxicity tests are in vitro and in vivo tests conducted to detect compounds which

induce genetic damage directly or indirectly. These tests should enable a hazard identification with respect to damage to De-oxy Ribonucleic Acid (DNA) and its fixation.

The following standard test battery is generally expected to be conducted:
(i) A test for gene mutation in bacteria.
(ii) An in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphomatic assay.
(iii) An in vivo test for chromosomal damage using rodent haematopoietic cells. Other genotoxicity tests e.g. tests for measurement of De-oxy Ribonucleic Acid (DNA) adducts, De-oxy Ribonucleic Acid (DNA) strand breaks, De-oxy Ribonucleic Acid (DNA) repair or recombination serve as options in addition to the standard battery for further investigation of genotoxicity test results obtained in the standard battery. Only under extreme conditions in which one or more tests comprising the standard battery cannot be employed for technical reasons, alternative validated tests can serve as substitutes provided sufficient scientific justification should be provided to support the argument that a given standard battery test is not appropriate.
(iv) Both in-vitro and in-vivo studies should be done. In-vitro studies should include Ames Salmonella assay and chromosomal aberrations (CA) in cultured cells. In-vivo studies should include micronucleus assay (MNA) or chromosomal aberrations (CA) in rodent bone marrow. Data analysis of chromosomal aberrations (CA) should include analysis of "gaps".
(v) Cytotoxic anticancer agents. - Genotoxicity data are not required before Phase I and II study/research. But these studies should be completed before applying for Phase III study/research.
Notes: *Ames' Test (Reverse mutation assay in Salmonella):* S. typhimurium tester strains such as TA98, TA100, TA102, TA1535, TA97 or Escherichia coli WP2 uvrA or Escherichia coli WP2 uvrA (pKM101) should be used.
(vi) In-vitro exposure (with and without metabolic activation, S9 mix) should be done at a minimum of 5 log dose levels. "Solvent" and "positive" control should be used. Positive control may include 9-amino-acridine, 2-nitrofluorine, sodium azide and mitomycin C, respectively, in the tester strains mentioned above. Each set should consist of at least three replicates. A 2.5 fold (or more) increase in number of revertants in comparison to spontaneous revertants would be considered positive.
(vii) In-vitro cytogenetic assay. - The desired level of toxicity for in vitro cytogenetic tests using cell lines should be greater than 50% reduction in cell number or culture confluency. For lymphocyte cultures, an inhibition of mitotic index by greater than 50% is considered sufficient. It should be performed in Chinese Hamster Ovary (CHO) cells or on human lymphocyte in culture. In-vitro exposure (with and without metabolic activation, S9 mix) should be done using a minimum of 3 log doses. "Solvent" and "positive" control should be included. A positive control like Cyclophosphamide with metabolic activation and Mitomycin C for without metabolic activation should be used to give a reproducible and detectable increase clastogenic effect over the background which demonstrates the sensitivity of the test system. Each set should consist of at least three replicates. Increased number of aberrations in metaphase chromosomes should be used as the criteria for evaluation.
(viii) In-vivo micronucleus assay. - One rodent species (preferably mouse) is needed. Route of administration of test substance should be the same as intended for humans. Five animals per sex per dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. A positive control like mitomycin C or cyclophosphamide should be used. Dosing should be done on day one and two of study

followed by sacrifice of animals six hours after the last injection. Bone marrow from both the femora should be taken out, flushed with fetal bovine serum (20 min.), pelletted and smeared on glass slides. Giemsa-May Gruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(ix) In-vivo cytogenetic assay. - One rodent species (preferably rat) is to be used. Route of administration of test substance should be the same as intended for humans. Five animals/sex/dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. Positive control may include cyclophosphamide. Dosing should be done on day one followed by intraperitoneal colchicine administration at 22 hours. Animals should be sacrificed two hours after colchicine administration. Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 minutes), pelletted and resuspended in Carnoy's fluid. Once again, the cells should be pelletted and dropped on clean glass slides with a Pasteur pipette. Giemsa staining should be done and increased number of aberrations in metaphase chromosomes (minimum 100) should be used as the evaluation criteria.

(1.7) Carcinogenicity- Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than six months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. Carcinogenicity studies are also to be performed for drugs if there is concern about their carcinogenic potential emanating from previous demonstration of carcinogenic potential in the product class that is considered relevant to humans or where structure-activity relationship suggests carcinogenic risk or when there is evidence of preneoplastic lesions in repeated dose toxicity studies or when long-term tissue retention of parent compound or metabolites results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Central Licencing Authority may allow carcinogenicity testing to be conducted after marketing permission has been granted. In instances where the life-expectancy in the indicated population is short (i.e., less than 2 - 3 years) no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such drugs are intended for adjuvant therapy in tumour free patients or for prolonged use in non-cancer indications, carcinogenicity studies may be needed. Completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical study/research, unless there is special concern for the patient population.

Carcinogenicity studies should be done in a rodent species (preferably rat). Mouse may be employed only with proper scientific justification. The selected strain of animals should not have a very high or very low incidence of spontaneous tumors. At least three dose levels should be used. The highest dose should be sub-lethal, and it should not reduce the life span of animals by more than 10% of expected normal. The lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 2.5x; to make allowance for the sensitivity of the species. The intermediate dose to be placed logarithmically between the other two doses. An untreated control and (if indicated) a vehicle control group should be included. The drug should be administered seven days a week for a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Generally, the period of dosing should be 24 months for rats and 18 months for mice.

Observations should include macroscopic changes observed at autopsy and detailed histopathology of organs and tissues. Additional tests for carcinogenicity (short-term

bioassays, neonatal mouse assay or tests employing transgenic animals) may also be done depending on their applicability on a case to case basis.

Note: Each dose group and concurrent control group not intended to be sacrificed early should contain at least 50 animals of each sex. A high dose satellite group for evaluation of pathology other than neoplasia should contain 20 animals of each sex while the satellite control group should contain10animals of each sex. Observation parameters should include signs of intoxication, effect on body weight, food intake, clinical chemistry parameters, hematology parameters, urine analysis, organ weights, gross pathology and detailed histopathology. Comprehensive descriptions of benign and malignant tumour development, time of their detection, site, dimensions, histological typing etc. should be given.

(1.8) Animal toxicity requirements for clinical study/research and marketing of a new drug:

Systemic Toxicity Studies			
Route of administration	**Duration of proposed human administration**	**Human Phase(s) for which study is proposed to be conducted**	**Long term toxicity requirements**
Oral or Parenteral or Transdermal	Single dose or several doses in one day, up to 1 week	I, II, III	2 species; 2 weeks
	>1 week but upto 2 weeks	I, II, III	2 species; 2weeks
	Upto 2 weeks	Marketing permission	2 species; 4weeks
	>2 weeks but upto 4 weeks	I, II, III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 12 weeks
	> 4 weeks but upto 12 weeks	I, II, III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 24 weeks
	> 12 weeks but upto 24 weeks	I, II, III	2 species; equal to duration of human exposure
		Marketing permission	2 species; Rodent 24 weeks, non- rodent 36 weeks
	> 24 weeks	I, II, III	2 species; Rodent 24 weeks, non- rodent 36weeks
		Marketing permission	2 species; Rodent 24 weeks, non-rodent 36 weeks

Inhalation (general Anaesthetics, aerosols)	Up to 2 weeks	I, II, III	2 species; I month (Exposure time 3h/d, 5d/week)
	Up to 4 weeks	I, II, III	2 species; 12 weeks (Exposure time 6h/d, 5d/week)
	>14 weeks	I, II, III	2 sp; 24 weeks (Exposure time 6h/d, 5d/week)
Local Toxicity Studies			
Dermal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Ocular or Optic or Nasal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Vaginal or Rectal	Up to 2 weeks	I, II	1 species; 4weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks

Special Toxicity Studies
Male Fertility Study: Phase III in male volunteers or patients
Female Reproduction and Development Toxicity Studies:
Segment II studies in 2 species; Phase II, III involving female patients of childbearing age.
Segment I study; Phase III involving female patients of child-bearing age.
Segment III study; Phase III for drugs to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.
Allergenicity or Hypersensitivity:
Phase I, II, III - when there is a cause of concern or for parenteral drugs (including dermal application)
Photo-allergy or dermal photo-toxicity:
Phase I, II, III - if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential.
Genotoxicity:
In-vitro studies – Phase I
Both in-vitro and in-vivo – Phase II, III
Carcinogenicity:
Phase III – when there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: d -day; **h**-hour; **I**, **II**, **III** - Phase of clinical study/research.

Note:

(1) Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated or duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory where such data has been generated.

(2) Requirements for fixed dose combinations are given in clause 4 of this Schedule.

(1.9) Number of animals required for repeated-dose toxicity studies:

14 to 28 days					84 to 182 days			
Group	**Rodent (Rat)**		**Non-rodent (Dog or Monkey)**		**Rodent (Rat)**		**Non-rodent (Dog or Monkey)**	
	Male	Female	Male	Female	Male	Female	Male	Female
Control	6 to 10	6 to 10	2 to 3	2 to 3	15 to 30	15 to 30	4 to 6	4 to 6
Low dose	6 to 10	6 to 10	2 to 3	2 to 3	15 to 30	15 to 30	4 to 6	4 to 6
Intermediate dose	6 to 10	6 to 10	2 to 3	2 to 3	15 to 30	15 to 30	4 to 6	4 to 6
High dose	6 to 10	6 to 10	2 to 3	2 to 3	15 to 30	15 to 30	4 to 6	4 to 6

(1.10) Laboratory parameters to be included in toxicity studies:

Haematological parameters			
Haemoglobin	**Total Red Blood Cell count**	**Haematocrit**	**Reticulocyte**
Total White Blood Cell count	Differential White Blood Cell Count	Platelet count	Terminal Bone Marrow Examination
Erythrocyte sedimentation rate (ESR) (Non-rodents only)	General Blood Picture: A Special mention of abnormal and immature cells should be made		
Coagulation parameters (Non-rodents only): Bleeding Time, coagulation Time, prothrombin time, Activated partial Thromboplastin Time			
Urinalysis Parameters			
Colour	**Appearance**	**Specific Gravity**	**24 hours urinary output**
Reaction(pH)	Albumin	Sugar	Acetone
Bile pigments	Urobilinogen	Occult Blood	
Microscopic examination of urinary sediment			
Blood Biochemical parameters			
Glucose	Cholesterol	Triglycerides	High density lipoproteins (HDL) cholesterol (Non-rodents only)
Low density lipoproteins (LDL)	Bilirubin	Serum glutamic pyruvic transaminase (SGPT) (Alanine aminotransferase (ALT)	Serum glutamic oxaloacetic transaminase (SGOT)

Cholesterol (Non-rodents only) Aspartate aminotransferase (AST)			
Alkaline Phosphatase (ALP)	GGT (Non-rodents only)	Blood urea Nitrogen	Creatinine
Total proteins	Albumin	Globulin (Calculated values)	Sodium
Potassium	Phosphorus	Calcium	
Gross and Microscopic Pathology			
Brain*: Cerebrum, Cerebellum, Midbrain	(Spinal cord)	Eye	(Middle Ear)
Thyroid	(Parathyroid)	Spleen	Thymus
Adrenal*	(Pancreas)	(Trachea)	Lung*
Heart*	Aorta	Oesophagus	Stomach
Duodenum	Jejunum	Terminal ileum	Colon
(Rectum)	Liver*	Kidney*	Urinary bladder
Epididymis	Testis*	Ovary	Uterus*
Skin	Mammary gland	Mesenteric lymph node	Skeletal muscle

* Organs marked with an asterisk should be weighed.
( ) Organs listed in parenthesis should be examined if indicated by the nature of the drug or observed effects.

Non-clinical toxicity testing and safety evaluation data of an Investigational New Drug (IND) needed for the conduct of different phases of clinical study/research.

Note: Refer clause 2 of Second Schedule for essential features of study designs of the nonclinical toxicity studies listed below

For Phase I Clinical Study/research:

Systemic Toxicity studies: -

a. Single dose toxicity studies
b. Dose Ranging Studies
c. Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

- In-vitro genotoxicity tests, –Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure).
- Allergenicity or Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application).
- Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential).

For Phase II Clinical Study/research:

Provide a summary of all the non-clinical safety data (listed above) already submitted

while obtaining the permissions for Phase I study/research, with appropriate references. In case of an application for directly starting a Phase II study/research - complete details of then on clinical safety data needed for obtaining the permission for Phase I study/research, as per the list provided above must be submitted.
Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.
In-vivo genotoxicity tests.
Segment II reproductive or developmental toxicity study (if female patients of childbearing age are going to be involved).

For Phase III Clinical Study/research:
Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II study/research, with appropriate references. In case of an application for directly initiating a Phase III study/research - complete details of the non-clinical safety data needed from obtaining the permissions for Phase I and II study/research, as per the list provided above must be provided. Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Reproductive or developmental toxicity studies
Segment I (if female patients of childbearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development). Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

For Phase IV Clinical Study/research: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III study/research, with appropriate references. In case an application is made for initiating the Phase IV study/research, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III study/research, as per the list provided above must be submitted.

Application of Good Laboratory Practices (GLP) –
The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.
The animal toxicology requirements as referred above should be viewed as general guidance for drug developments. Animal toxicology studies may be planned, designed and conducted as per the International Council of Harmonization (ICH) guidelines to promote safe, ethical development and availability of new drugs with reduced use of animals in accordance with the 3R (reduce/refine/replace) principles.

3. Animal Pharmacology

(1) General Principles.- Specific and general pharmacological studies should be conducted to support use of therapeutics in humans. In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied. Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation

to exposure within the therapeutic range or above.

1.1 Specific pharmacological actions,- Specific pharmacological actions are those which demonstrate the therapeutic
potential for humans. The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug. Scientifically validated methods should be used. The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

1.2 General pharmacological actions,-
1.2.1 Essential safety pharmacology.- Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above. These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic or pathophysiological effects observed in toxicology or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed or suspected. The aim of the essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain tests or exploration(s) of certain organs, systems or functions should be scientifically justified.
1.2.1.1 Cardiovascular system: Effects of the investigational drug should be studied on blood pressure, heart rate, and the electrocardiogram. If possible in vitro, in vivo and/or ex vivo methods including electrophysiology should also be considered.
1.2.1.2 Central nervous system: Effects of the investigational drug should be studied on motor activity, behavioural changes, coordination, sensory and motor reflex responses and body temperature.
1.2.1.3 Respiratory system: Effects of the investigational drug on respiratory rate and other functions such as tidal volume and haemoglobin oxygen saturation should be studied.

1.3 Follow-up and supplemental safety pharmacology studies.- In addition to the essential safety pharmacological
studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical study/research, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports.
1.3.1 Follow-up studies for essential safety pharmacology: Follow-up studies provide additional information or a better und er s tand ing than tha t pr o vid ed b y the e s s ent ia l sa f e ty pharmacology.
1.3.1.1 Cardiovascular system: These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.
1.3.1.2 Central nervous system: These include behaviour al s tudies , learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.
1.3.1.3 Respiratory system: These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.
1.3.2 Supplemental safety pharmacology studies: These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety

pharmacological studies and are a cause for concern.

1.3.2.1 Urinary system: These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.

1.3.2.2 Autonomic nervous system: These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses in vivo or in vitro, and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

1.3.2.3 Gastrointestinal system: These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time in vivo and ileocaecal contraction in vitro.

1.3.2.4 Other organ systems: Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example, dependency potential, skeletal muscle, immune and endocrine functions may be investigated.

1.4 Conditions under which safety pharmacology studies are not necessary: Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low. Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

1.5 Timing of safety pharmacology studies in relation to clinical development :

1.5.1 Prior to first administration in humans: The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans. Any follow-up or supplemental studies identified, should be conducted if necessary, based on a cause for concern.

1.5.2 During clinical development: Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

1.5.3 Before applying for marketing approval: Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified. Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

1.6 Application of Good Laboratory Practices (GLP): The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

Appendix IV - Conduct of Clinical Study/Research

1. **Conduct of clinical study/research**-

(i) Clinical study/research shall be conducted in accordance with the provisions of the Act and these Rules and principles of Good Clinical Practice Guidelines.

(ii) Clinical study/research on a new drug shall be initiated only after the permission has been granted by the Central Licencing Authority and the approval obtained from the respective ethics committee.

(iii) The Central Licencing Authority shall be informed of the approval of the respective ethics committee in accordance with these rules.

(iv) All study/research investigator should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed study/research protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the study/research, should be responsible for all study/research-related medical (or dental) decisions. Laboratories used for generating data for clinical study/research should be compliant with good laboratory practices.

(v) Protocol amendments, if become necessary before initiation or during the course of a clinical study/research, all such amendments should be submitted to the Central Licencing Authority in writing along with the approval by the ethics committee, if available, which has granted the approval for the study.

(vi) No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and Central Licencing Authority except when it is necessary to eliminate immediate hazards to the study/research participant/subjector when change involves only logistic or administrative or minor aspects of the study/research. All such exceptions must be immediately notified to the ethics committee as well as to the Central Licencing Authority. Administrative or logistic changes or minor amendments in the protocol should be notified to the Central Licencing Authority within thirty days.

2. **Informed Consent** –

(a) In all study/research, a freely given, informed, written consent is required to be obtained from each study participant. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is nontechnical and understandable by the study participant.

(b) The participant's consent must be obtained in writing using an "Informed Consent Form". Both the patient information sheet as well as the informed consent form should have been approved by the ethics committee and furnished to the Central Licencing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Central Licencing Authority before such changes are implemented.

(c) Where a participant/subjectis not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental

illness or disability), the same may be obtained from a legally acceptable representative

Legally acceptable representative is a person who is able to give consent for or authorise and intervention in the patient as provided by the law of India).

(d) If the study/research participant, his or her legally acceptable representative is unable to read or write an impartial witness should be present during the entire informed consent process who must append his or her signature to the consent form.

(e) In case of clinical study/research on paediatrics, the participants are legally unable to provide written informed consent and are dependent on their parent or legal guardian to assume responsibility for their participation in clinical studies. In such case, -

(i) Written informed consent should be obtained from the parent or legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand.

(ii) Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form.

(iii) Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent or legal guardian, the welfare of a paediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental or legal guardian consent should be sufficient to allow participation in the study.

(f) A checklist of essential elements to be included in the study participant's informed consent document as well as a format for the informed consent form for study/research participant/subjectis given in Table 3of this Schedule.

(g) An audio-video recording of the informed consent process in case of vulnerable participants in clinical study/research of New Chemical Entity or New Molecular Entity including procedure of providing information to the participant/subjectand his understanding on such consent, shall be maintained by the investigator for record:

Provided that in case of clinical study/research of anti-HIV and anti-leprosy drugs, only audio recording of the informed consent process of individual participant/subjectincluding the procedure of providing information to the participant/subjectand his understanding on such consent shall be maintained by the investigator for record.

3. Responsibilities -

(1) Sponsor- (i) The clinical study/research sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the

clinical study/research is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practices Guidelines as well as with all applicable statutory provisions. Standard standard operating procedures should be documented to ensure compliance with Good Clinical Practices Guidelines and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical study/research to the Central Licencing Authority at the prescribed periodicity.

(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Central Licencing Authority, the Chairperson of the ethics committee and the head of the institution where the study/research has been conducted, within fourteen days of knowledge of occurrence of the serious adverse event as specified in Table 5 of this Schedule;

(v) In case of injury or death occurring to the study/research participant, the sponsor (whether a pharmaceutical company or an institution) or his representative or the investigator or the institution or centre where the study was conducted, as the case may be, shall make payment for medical management of the participant/subjectand also provide financial compensation for the clinical study/research related injury or death in accordance with the procedure as prescribed in Chapter VI of these rules

(vi) The sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical study/research, shall submit details of compensation provided or paid for clinical study/research related injury or death, to the Central Licencing Authority thirty days of the receipt of the order of the Central Licencing Authority.

(vii) The sponsor shall provide post-study/research access of the investigational drug by giving the drug free of cost to the study/research participant/subjectas per directions of the Central Licencing Authority in special circumstances on the recommendations of the investigator and the ethics committee and written consent of the patient in accordance with rule 27.

(2) Investigator- (i) The investigator shall be responsible for the conduct of the study/research according to the protocol and the Good Clinical Practices Guidelines and also for compliance as per the undertaking given in Table 4. Standard standard operating procedures are required to be documented by the investigators for the tasks performed by them.

(i) During and following a participant's participation in study/research, the investigator should ensure that adequate medical care is provided to the participant/subjectfor any adverse events.

(ii) Investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical study/research, and the ethics committee that accorded approval to the study protocol, within twenty-four hours of their occurrence.

(iv) In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the investigator to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the study/research has been conducted within fourteen days of the occurrence of the serious adverse event.

(v) The investigator shall provide information to the study/research participant/subjectthrough informed consent process as provided in Table 3about the essential elements of the clinical study/research and the participant's right to claim compensation in case of study/research related injury or death. He shall also inform the participant/subjecthis or her nominee of their rights to contact the sponsor or his representative whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical study/research for the purpose of making claims in the case of study/research related injury or death.

(3) Ethics committee-

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a study/research protocol to safeguard the rights, safety and well-being of all study/research participants.

(ii) The ethics committee should exercise particular care to protect the rights, safety and well-being of all vulnerable participants participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or other incapable of personally giving consent.

(iii) Ethics committee should get documented "standard standard operating procedures ' and should maintain a record of its proceedings.

(iv) Ethics committee should make, at appropriate intervals, an ongoing review of the study/research for which they have reviewed the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or visiting the study sites.

(v) In case an ethics committee revokes its approval accorded to a study/research protocol, it must record the reasons for doing so and at once

communicate such a decision to the Investigator as well as to the Central Licencing Authority.

(vi) In case of serious adverse event occurring to the study/research participant, the ethics committee shall forward its report or order on the event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the sponsor or his representative or institution or centre, as the case may be, in accordance with Chapter VI of these rules.

Appendix V Information To Be Submitted By An Applicant And Format

TABLE 1: INFORMATION TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF REGISTRATION OF ETHICS COMMITTEE AND FORMAT FOR ACCORDING TO APPROVAL

(A) Information required to be submitted by the applicant for registration of ethics committee:

(a) Name of the ethics committee.

(b) Authority under which the ethics committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.

(c) The procedure for resignation, replacement or removal of members.

(d) Address of the office of the ethics committee.

(e) Name, address, qualification, organisational title, telephone number, fax number, email, mailing address and brief profile of the Chairperson.

(f) Names, qualifications, organisational title, telephone number, fax number, e-mail and mailing address of the members of the ethics committee. The information shall also include member's specialty (primary, scientific or non-scientific), member's affiliation with institutions and patient group representation, if any.

(g) Details of the supporting staff.

(h) The standard standard operating procedures to be followed by the committee in general.

(i) Standard standard operating procedures to be followed by the committee for vulnerable population Policy regarding training for new and existing committee members along with standard standard operating procedures .

(j) Policy to monitor or prevent the conflict of interest along with standard standard operating procedures .

(k) If the committee has been audited or inspected before, give details.

(B) Format for according to approval to clinical study/research protocol by the ethics committee

TO Dr.

Dear Dr._____

The Ethics committee or independent ethics committee (state name of the committee, as appropriate) reviewed and discussed your application to conduct the

clinical study/research entitled "……..."on…….(date).

The following documents were reviewed:

(a) Study/research protocol (including protocol amendments), dated…….version No.(s) ……

(b) Patient information sheet and informed consent form (including updates, if any) in English or vernacular language.

(c) Investigator's brochure, dated..... , Version no…… Proposed methods for patient accrual including advertisements etc. proposed to be used for the purpose.

(d) Principal investigator's current Curriculum Vitae.

(e) Insurance policy or compensation for participation and for serious adverse events occurring during the study participation.

(f) Investigator's agreement with the sponsor.

(g) Investigator's undertaking (Table 4).

The following members of the ethics committee were present at the meeting held on (date, time, place).

….....Chairperson of the ethics committee;

….....Member-Secretary of the ethics committee;

….....Name of each member with designation;

We approve the study/research to be conducted in its presented form.

The ethics committee to be informed about the progress of the study, any Serious Adverse Events (SAE) occurring in the course of the study, any changes in the protocol and patient information or informed consent and to be provided with a copy of the final report.

Yours sincerely,

Member Secretary, Ethics Committee

TABLE 2: CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL STUDY/RESEARCH

Title Page

(a) Full title of the clinical study,

(b) Protocol, Study number, and protocol version number with date.

(c) The Investigational New Drug (IND) name/number of the investigational drug.

(d) Complete name and address of the Sponsor and contract research

organization if any.

(e) List of the investigators who are conducting the study, their respective institutional affiliations and site locations

(f) Name of clinical laboratories and other departments and/or facilities participating in the study. Table of Contents

1. Background and introduction:

   (a) Preclinical experience

   (b) Clinical experience

   Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/biologic/medical device, and previous efficacy and safety experience should be described.

2. Study rationale: This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study objective (primary as well as secondary) and their logical relation to the study design.

4. Study design–

   (a) Overview of the study design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Participants in each group and investigative site, Participant/subjectnumber assignment, and the type, sequence and duration of study periods.

   (b) Flow chart of the study

   (c) A brief description of the methods and procedures to be used during the study.

   (d) Discussion of study design: This discussion details the rationale for the design chosen for this study.

5. Study population: the number of participants required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the participant/subjectpopulation required is also mentioned.

6. Participant/subjecteligibility

   (a) Inclusion criteria

   (b) Exclusion criteria

7. Study assessments – plan, procedures and methods to be described in detail.

8. Study conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function

tests, symptom measurement, dispensation and retrieval of medication, Participant/subjectcohort assignment, adverse event review, etc.

Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued participants: Describes the circumstances for Participant/subjectwithdrawal, dropouts, or other reasons for discontinuation of Participants. State how drop outs would be managed and if they would be replaced describe the method of handling of protocol waivers, if any. The person who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for noncompliance with the protocol.

9. Study treatment-

   (a) Dosing schedule (dose, frequency, and duration of the experimental treatment) Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.

   (b) Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations Details of the product stability, storage requirements and dispensing requirements should be provided.

   (c) Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.

   (d) Possible drug interactions

   (e) Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Participant/subjectis not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrolment, these should be described here.

   (f) Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Participant

   (g) Un-blinding procedures: If the study is blinded, the circumstances in which un-blinding may be done and the mechanism to be used for un-blinding should be given

10. Adverse Events:

    Description of expected adverse events should be given. Procedures used to evaluate an adverse event should be described.

11. Ethical considerations: Give the summary of:

    (a) Risk/benefit assessment:

    (b) Ethics committee review and communications

    (c) Informed consent process

    (d) Statement of participant/subjectconfidentiality including ownership of data

and coding procedures.

12. Study monitoring and supervision:

    A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

    Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specific required in filling out the forms Case Record Form correction requirements, including who is authorized to make corrections on the Case Record Form and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

    Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management:

    (a) Give investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study)

    (b) The precise dosing required during the study

    (c) Method of packaging, labelling, and blinding of study substances

    (d) Method of assigning treatments to participants and the participant/subjectidentification code numbering system

    (e) Storage conditions for study substances

    (f) Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned or destroyed.

    (g) Describe policy and procedure for handling unused investigational products.

14. Data Analysis: Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

    Statistical analysis: Give complete details of how the results will be analysed and reported along with the description of statistical tests to be used to analyse the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and Participant/subjectwithdrawals; rationale and conditions for any interim analysis if planned.

    Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator (see Table 4)

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); Case Record Form (CRF) and other data collection forms; a summary of relevant pre- clinical safety information and any other documents referenced in the clinical protocol.

TABLE 3 INFORMED CONSENT

1. Checklist of informed consent documents for clinical study/research participant, –

1.1 Essential elements:

(i) Statement that the study involves research and explanation of the purpose of the research.

(ii) Expected duration of the participation of participant.

(iii) Description of the procedures to be followed, including all invasive procedures.

(iv) Description of any reasonably foreseeable risks or discomforts to the Participant.

(v) Description of any benefits to the Participant/subjector others reasonably expected from research. If no benefit is expected Participant/subjectshould be made aware of this.

(vi) Disclosure of specific appropriate alternative procedures or therapies available to the Participant.

(vii) Statement describing the extent to which confidentiality of records identifying the Participant/subjectwill be maintained and who will have access to Participant's medical records.

(viii) Study/research treatment schedule and the probability for random assignment to each treatment (for randomized study/research).

(ix) Statement describing the financial compensation and the medical management as under:

(a) In case of an injury occurring to the participant/subjectduring the clinical study/research, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical study/research, whichever is earlier.

(b) In the event of a study/research related injury or death, the sponsor or his representative or the investigator or centre, as the case may be, in accordance with the rule 39, as the case may be, shall provide financial compensation for the injury or death.

(x) An explanation about whom to contact for study/research related queries, rights of Participants and in the event of any injury.

(xi) The anticipated prorated payment, if any, to the participant/subjectfor participating in the study/research.

(xii) Responsibilities of participant/subjecton participation in the study/research.

(xiii) Statement that participation is voluntary, that the participant/subjectcan withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the participant/subjectis otherwise entitled.

(xiv) Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

(xv) Statement that in the case of placebo-controlled study/research, the placebo

administered to the participants shall not have any therapeutic effect.

(xvi) Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the participation of the participant/subjectmay be terminated by the Investigator without his or her consent.

(b) Additional costs to the participant/subjectthat may result from participation in the study.

(c) The consequences of a Participant's decision to withdraw from the research and procedures for orderly termination of participation by Participant.

(d) (d) Statement that the Participant/subjector Participant's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Participant's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Participant/subject(or to the embryo or foetus, if the Participant/subjectis or may become pregnant), which are currently unforeseeable.

(f) Approximate number of Participants enrolled in the study.

2. Format of informed consent form for Participants participating in a clinical study/research – Informed Consent form to participate in a clinical study/research

Study Title:

Study Number:

Participant's Initials: _____ Participant's Name: _____
Date of Birth/Age: _____
Address of the Participant/subject__ Qualification _____
Occupation: Student or Self-Employed or Service or Housewife or Others (Please click as appropriate) . Annual Income of the participant:
Name and address of the nominees and his relation to the participant/subject(for the purpose of compensation in case of study/research related death).

Place Initial box (Participant)

(i) I confirm that I have read and understood the information [ ]
Sheet dated _____for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and [ ]
that I am free to withdraw at any time, without giving any reason,

without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical study/research, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study/research.
I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Participant/Legally Acceptable Representative:

Date: _____/ _____/

Signatory's Name: _____

Signature of the Investigator: ____ Date: ____/ ____/

Study Investigator's Name: _____ _____

Signature of the Witness_____ Date: ____/ ____/

Name of the Witness:_____

Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the participant/subjecthis or her attendant.

TABLE 3 UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigators when there is no Principal Investigator).
2. Name and address of the medical college, hospital or other facility where the clinical study/research will be conducted: Education, training & experience that qualify the Investigator for the clinical study/research (Attach details including Medical Council registration number, or any other statements of qualifications)
3. Name and address of all clinical laboratory facilities to be used in the study.
4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.
5. Names of the other members of the research team (Co-or sub-Investigators) who will be assisting the Investigator in the conduct of the

investigations.

6. Protocol Title and Study number (if any) of the clinical study/research to be conducted by the Investigator.

7. Commitments:

   (i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary ethics committee and regulatory approvals have been obtained.

   (ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favourable opinion from the ethics committee of the amendment, except where necessary to eliminate an immediate hazard to the study/research participant/subjector when the changes involved are only logistical or administrative in nature.

   (iii) I agree to personally conduct or supervise the clinical study/research at my site.

   (iv) I agree to inform all study/research participant, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the New Drugs and Clinical Trials Rules, 2019 and Good Clinical Practices guidelines are met.

   (v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory requirements and Good Clinical Practices guidelines.

   (vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

   (vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the study/research.

   (viii) I agree to maintain adequate and accurate records and to make those records available for audit or inspection by the Sponsor, ethics committee, Central Licencing Authority or their authorised representatives, in accordance with regulatory provisions and the Good Clinical Practices guidelines. I will fully cooperate with any study related audit conducted by regulatory officials or authorised representatives of the Sponsor.

   (ix) I agree to promptly report to the ethics committee all changes in the clinical study/research activities and all unanticipated problems involving risks to human participants or others.

   (x) I agree to inform all serious adverse events to the Central Licencing Authority, sponsor as well as the ethics committee within twenty-four hours of their occurrence. In case, of failure to do so, I shall furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(xi) The report of the serious adverse event, after due analysis, shall also be forwarded by me to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the study/research has been conducted within fourteen days in accordance with the regulatory requirements.

(xii) I will maintain confidentiality of the identification of all participating participants and assure security and confidentiality of study data.

(xiii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical study/research.

8. Signature of Investigator with date.

TABLE 4: DATA ELEMENTS FOR REPORTING SERIOUS ADVERSE EVENTS OCCURRING IN A CLINICAL STUDY/RESEARCH OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

1. Patient Details:

Initials and other relevant identifier (hospital or out-patient department (OPD) record number etc)* Gender
Age or date of birth
Weight
Height
Suspected Drug(s): Generic name of the drug*
Indication(s) for which suspect drug was prescribed or tested.
Dosage form and strength.
Daily dose and regimen (specify units - e.g., mg, ml, mg/kg). Route of administration.
Starting date and time of day.

Stopping date and time, or duration of treatment

2. Other Treatment(s):

Provide the same information for concomitant drugs (including non-prescription or Over the Counter OTC drugs) and non-drug therapies, as for the suspected drug(s).

3. Details of Serious Adverse Event :
Full description of the event including body site and severity, as well as the criterion (or criteria) for considering the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the event*

Start date (and time) of onset of event. Stop date (and time) or duration of event. Dechallenge and rechallenge information.
Setting (e.g., hospital, out-patient clinic, home, nursing home).

4. Outcome

Information on recovery and any sequelae; results of specific tests or treatment that may have been conducted.
For a fatal outcome, cause of death and a comment on its possible relationship to the suspected event; Any post-mortem findings.
Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.
Details about the Investigator* Name and Address
Telephone number Profession (specialty)
Date of reporting the event to Central Licencing Authority:
Date of reporting the event to ethics committee overseeing the site:
Signature of the Investigator or Sponsor
Note: Information marked * must be provided.

TABLE 5: STRUCTURE, CONTENT AND FORMAT FOR CLINICAL STUDY/RESEARCH REPORT

1. Title Page: This page should contain information about the title of the study, the protocol code, name of the investigational product tested, development Phase, indication studied, a brief description of the study/research design, the start and end date of patient accrual and the names of the Sponsor and the participating Institutes (Investigators).
2. Study Synopsis (1 to 2 pages): A brief overview of the study from the protocol development to the study/research closure should be given here. This section will only summarise the important conclusions derived from the study.
3. Statement of compliance with the Good Clinical Practices Guidelines.
4. List of abbreviations and definitions
5. Table of contents
6. Ethics Committee: This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and dates of approvals of study/research documents for each of the participating sites should be provided. A declaration should state that Ethics Committee (EC) notifications as per Good Clinical Practice Guidelines and Ethical Guidelines for Biomedical Research on Human Participants, issued by Indian Council of Medical Research have been followed.
7. Study Team: Briefly describe the administrative structure of the study (Investigators, site staff, Sponsor or designates, Central laboratory etc.).
8. Introduction: A brief description of the product development rationale should be given here.

9. Study Objective: A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.

10. Investigational Plan: This section should describe the overall study/research design, the Participant/subjectselection criteria, the treatment procedures, blinding or randomisation techniques if any, allowed or disallowed concomitant treatment, the efficacy and safety criteria assessed, the data quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

11. Study/research Participants: A clear accounting of all study/research Participants who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. Efficacy evaluation: The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the study/research patients should also be provided along with a listing of patients and observations excluded from efficacy analysis.

13. Safety Evaluation: This section should include the complete list

    13.1 all serious adverse events, whether expected or unexpected and

    13.2 unexpected adverse events whether serious or not (compiled from data received as per Table 5 of this Schedule).

    The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14 Discussion and overall Conclusion: Discussion of the important conclusions derived from the study/research and scope for further development.

15. List of References:

16. Appendices: List of Appendices to the Clinical Study Report

    (a) Protocol and amendments

    (b) Specimen of Case Record Form

    (c) Investigators' names with contact addresses, phone, e-mail etc.

    (d) Patient data listings

    (e) List of study/research participants treated with investigational product

    (f) Discontinued participants

    (g) Protocol deviations

    (h) Case Record Forms of cases involving death and life threatening adverse event cases

    (i) Publications from the study/research

(j) Important publications referenced in the study

(k) Audit certificate, if available

(l) Investigator' certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

TABLE 6 INVESTIGATOR'S BROCHURE

The Investigator's Brochure should contain the version number, release date along with the following sections, each with literature references where appropriate:

1 Table of Contents

2 Summary: A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3 Introduction: A brief introductory statement should be provided that contains the chemical name (and generic and trade name when approved) of the investigational product, all active ingredients, the investigational product pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product, and the anticipated prophylactic, therapeutic, or diagnostic indication. Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

4 Physical, Chemical, and Pharmaceutical Properties and Formulation: A description should be provided of the investigational product substance (including the chemical or structural formula), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the study/research, a description of the formulation to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form should also be given. Any structural similarities to other known compounds should be mentioned.

5 Nonclinical Studies

5.1 Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in human. The information provided may include the following, as appropriate, if known or available:

- Species tested

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

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

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

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

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

  - Single dose
  - Repeated dose

- Carcinogenicity
- Special studies (e.g. irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

6 Effects in Humans:

(a) A thorough discussion of the known effects of the investigational products in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical study/research should be provided. Information should also be provided regarding results of any use of the investigational products other than from in clinical study/research, such as from experience during marketing.

(b) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational products 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, or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical study/research(s).

(c) Safety and Efficacy: A summary of information should be provided about the investigational product's or products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding study/research in humans (healthy volunteers or patients). The implications of this information should be discussed. In cases where a number of clinical study/research have been completed, the use of summaries of safety and efficacy across multiple study/research by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical study/research (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 Investigators Brochure 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 products.

(d) Marketing Experience: The Investigator's Brochure should identify

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

7 Summary of Data and Guidance for the Investigator: This section should provide an overall discussion of the nonclinical and clinical data and should summarise the information from various sources on different aspects of the investigational products, wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical study/research. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical study/research. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical study/research. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational products. Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug a reaction that is based on previous human experience and on the pharmacology of the investigational product.

TABLE 7 PRESCRIBING INFORMATION

1. Generic Name
2. Qualitative and quantitative composition
3. Dosage form and strength
4. Clinical particulars
   - 4.1 Therapeutic indication
   - 4.2 Posology and method of administration
   - 4.3 Contraindications
   - 4.4 Special warnings and precautions for use
   - 4.5 Drugs interactions
   - 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
   - 4.7 Effects on ability to drive and use machines
   - 4.8 Undesirable effects
   - 4.9 Overdose
5. Pharmacological properties
   - 5.1 Mechanism of Action
   - 5.2 Pharmacodynamic properties
   - 5.3 Pharmacokinetic properties
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

7. Description

8. Pharmaceutical particulars

8.1 Incompatibilities

8.2 Shelf-life

8.3 Packaging information

8.4 Storage and handing instructions

9. Patient Counselling Information

10. Details of manufacturer

11. Details of permission or licence number with date

12. Date of revision

APPENDIX VI: 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 STUDY/RESEARCH

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

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

   (b) Details on cytokine profiles in healthy participants.

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

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

   (e) Details on haematological and clinical chemistry.

2. **Phase II: Exploratory Clinical Study/research- Preventive/Therapeutic Efficacy (Data to be generated in participants 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 Study/research**

   (a) Preventive / therapeutic effects.

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

APPENDIX V: Essential documents for the conduct of a clinical study/research

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a study/research and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

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

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

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

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

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the study/research and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the study/research should be supplemented or may be reduced where justified (in advance of study/research initiation) based on the importance and relevance of the specific documents to the study/research.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the study/research.

1.1 Before the study/research commences

During this planning stage the following documents should be generated and should be on file before the study/research formally start

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO STUDY/RESEARCH PARTICIPANT INFORMED CONSENT FORM (Including all applicable translations)**	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that participants will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR PARTICIPANT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE STUDY/RESEARCH**	To document the financial agreement between the investigator/institution and the sponsor for the study/research	X	X
	Title of Document	**Purpose**	**Located in Files of**	
			Investigator /Institution	**Sponsor**
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to participant(s) for study/research- related injury will be available	X	X

8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:** - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document agreements	X X X	X X (where required) X X
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (EC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the participant(s) - advertisement for participant/subjectrecruitment (if used) - participant/subjectcompensation (if any) - any other documents given approval/ favourable opinion	To document that the study/research has been participant/subjectto EC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the EC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the study/research in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct study/research and/or provide medical supervision of participants	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the participants		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND STUDY/RESEARCH -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 study/research-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND STUDY/RESEARCH -RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and study/research-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the study/research		X
8.2.17	**DECODING PROCEDURES FOR BLINDED STUDY/RESEARCH**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participants' treatment	X	X (third party if applicable)
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of study/research population		X (third party if applicable)
8.2.19	**PRE-STUDY/RESEARCH MONITORING REPORT**	To document that the site is suitable for the study/research (may be combined with 8.2.20)		X
8.2.20	**STUDY/RESEARCH INITIATION MONITORING REPORT**	To document that study/research procedures were reviewed with the investigator and the investigator's study/research staff (may be combined with 8.2.19)	X	X

1.2 During the Clinical Conduct of the Study/research

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

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to participants - advertisement for participant/subjectrecruitment (if used)	To document revisions of these study/research related documents that take effect during study/research	X	X
8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (EC) OF THE FOLLOWING:** - protocol amendment(s) - revision(s) of: informed consent form any other written information to be provided to the participant advertisement for participant/subjectrecruitment (if used) - any other documents given approval/favourable opinion - continuing review of study/research (where required)	To document that the amendment(s) and/or revision(s) have been participant/subjectto EC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
			Located in Files of	

	Title of Document	Purpose	Investigator /Institution	Sponsor
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**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 study/research (see 8.2.11)	X	X
8.3.7	**UPDATES OF 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 study/research period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND STUDY/RESEARCH-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding study/research administration, protocol violations, study/research conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each participant/subjectin study/research. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the participant/subjectand substantiate integrity of study/research data collected. To include original documents related to the study/research, to medical treatment, and history of participant	X	
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/EC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/EC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO EC AND AUTHORITY(IES)**	Interim or annual reports provided to EC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	**PARTICIPANT/SUBJECTS CREENING LOG**	To document identification of participants who entered pre-study/research screening	X	X (where required)
8.3.21	**PARTICIPANT/SUBJECTI DENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all participants allocated to study/research numbers on enrolling in the study/research. Allows investigator/institution to reveal identity of any participant	X	
8.3.22	**PARTICIPANT/SUBJECTE NROLMENT LOG**	To document chronological enrolment of participants by study/research number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X

8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

1.3 After Completion or Termination of the Study/research

After completion or termination of the study/research, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator /Institution	Sponsor
8.4.1	**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 participants, returned by the participants, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED PARTICIPANT/SUBJECTIDENTIFICATION CODE LIST**	To permit identification of all participants enrolled in the study/research in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL STUDY/RESEARCH CLOSE-OUT MONITORING REPORT**	To document that all activities required for study/research close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X

8.4.7	**FINAL REPORT BY INVESTIGATOR TO EC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the study/research	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of study/research	X (if applicable)	X

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- Ethical guidelines for biomedical research on human subjects : Indian Council of Medical Research; 2017.
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- Drugs and Cosmetic Act and Rules, 1945
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- National guidelines for stem cell research: Indian Council of Medical Research and Department of Biotechnology; 2017.
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- Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, US FDA
- Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods, TGA
- Guidelines for Bioavailability and Bioequivalence studies, CDSCO

- ICMR guideline on The Ethical Conduct of Controlled Human infection studies In India
- Medical Devices Rules 2017, CDSCO
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- Guidance for Industry, Investigators, and Other Stakeholders, USFDA
- Handbook for good clinical research practice WHO
- Good Clinical Practice Guidelines for Clinical Trials in Ayurveda, Siddha and Unani Medicine (GCP-ASU), Department of Ayush, Ministry of Health and Family welfare
- Guidelines on Similar Biologics, Department of Biotechnology and CDSCO
- Guidance for Industry Electronic Source Data in Clinical Investigations, USFDA Sept 2013
- Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees, USFDA
- The Evolving Role of Decentralized Clinical Trials and Digital Health Technologies, USFDA
- Applications of Radiation in Health Care, BARC, Department of Atomic Energy, Government of India
- Key Information and Facilitating Understanding in Informed Consent - Guidance for Sponsors, Investigators, and Institutional Review Boards, March 2024, USFDA
- Guidance on clinical trial Inspection, CDSCO Dec 2022
- Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants, USFDA
- Use of Data Monitoring Committees in Clinical Trials -Guidance for Industry, Feb 2024, USFDA
- ICMR GCP guidelines for tribals
- ICMR guideline for left over biological samples
- ICMR guideline on palliative care
- ICMR guideline on euthanasia
- ICMR guideline on publication policy
- ICMR guideline on systemic review and meta- analysis
- OECD guidelines on clinical toxicity studies