Dated : 22.11.2011

NOTICE:

Sub: Comments invited on Draft Guidelines on Good Clinical Practices for Clinical trials On Ayurveda, Siddha, Unani (ASU) Medicines from various AYUSH Stakeholders and Experts (up to 22.12.2011)

Department of AYUSH has drafted guidelines on Good Clinical Practices for Clinical trials on Ayurveda, Siddha, Unani (ASU) Medicines. It is therefore requested to offer comments on the Draft Guidelines with in the period of 30 days (i.e. up to 22.12.2011) from the date of appearing on Department's Web site.

Good Clinical Practices For Clinical trials On Ayurveda, Siddha, Unani (ASU) Medicines

CONTENTS

3.1.2. Contract

3.1.3. SOP

3.1.4. Allocation of duties and responsibilities

3.1.5. Study management, data handling and record keeping

3.1.6. Compensation for Participation

3.1.7. Confirmation of review by the Ethics Committee

3.1.8. Information on Investigational Products

3.1.9. Supply, storage and handling of ASU Medicines

3.1.10 Safety Information

3.1.11 Adverse Drug Reaction Reporting

3.1.12 Study Reports

3.1.13 Monitoring

3.1.14 Audit

3.1.15 Multicentre Studies

3.1.16 Premature Termination or Suspension of a Study

3.1.17 Role of Foreign Sponsor

3.2. The Monitor

3.2.1. Qualifications

3.2.2. Responsibilities

3.3. Investigator

3.3.1. Qualifications

3.3.2. Medical Care of the Study Subjects

3.3.3. Monitoring and Auditing of records

3.3.4. Communication with Ethic Committee

3.3.5. Compliance with the Protocol

Appendices

Appendix I: Guidelines for Evaluation of Ayurveda, Siddha and Unani Medicines and other Traditional Medicines (*new notification to be appended*)

Appendix II: General Ethical Issues (*Ethical Guidelines for Biomedical Research Human Participants, Indian Council of Medical Research 2006*)

Appendix III: *Schedule Z (proposed)*.

Appendix IV: Patient Consent Forms (*Appendix V to Schedule Y*)

Appendix V: Investigator's Brochure

Appendix VI: Essential Documents

Appendix VII : Guidelines for conducting toxicity studies on ASU drugs.

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. Ayurveda has emphasized much on ethical guidelines while treating a patient through medical/ surgical interventions. Utmost priority has been accorded to ethical issues and prior consent of the patient was suggested in the Ayurvedic texts[1]. Further it has been enlisted the qualities of a physician, drug, supporting para-medical staff and role and responsibilities of the patient to achieve success in managing a patient[2].

As the guiding ethical code it is primarily known for its edict to do no harm to the patient. However, the complexities of ASU medicines research necessitate a more elaborate set of guidelines that address a Physician's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in ASU medicines research.

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

These guidelines are formulated based on CDSCO Document on GCP Guidelines (2001) for Clinical Trials on Pharmaceutical Products. They should be followed for carrying out all ASU medicines research in India at all stages of drug development, whether prior or subsequent to product registration in India.

[1] Susruta Samhita, Chikitsa Sthana – 15/2, Astanga Sangraha, Sareera Sthana – 4/37 and Astanga Hridaya, Sareera Sthana – 2/26

[2] Charak Samhita, Sutra Sthana – 9/5-9 & Astanga Sangraha, Sutra Sthana – 2/21&22

DEFINITIONS

1.1 Act

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

1.2 Adverse Event (AE)

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

1.3 Adverse Drug Reaction (ADR)

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

(b) In case of new unregistered ASU Medicines: A noxious and unintended response at any dose(s)

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

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

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

1.4 Audit of a Trial

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

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

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

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

1.5 Ayurveda Siddha Unani Drugs- (Added from D&C Act)

Ayurvedic, Siddha or Unani durg" includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of [disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani Tibb system of medicine, specified in the First Schedule;

1.6 Patent or Proprietary Medicine- (Added from D&C Act)

In relation to Ayurvedic, Siddha or Unani Tibb systems of medicine of all formulations containing only such ingredients mentioned in th formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb system of medicine specified in the first Schedule, but does not include a medicines which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a)

1.7 Other Traditional Medicine- (Definition of Traditional Medicine / Folk Medicines is given, however, for other TMs like Chinese, Japanese, Korean Medicines etc. parameters of Schedule Y have to be followed)

1.8 Blinding / Masking

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

1.9 *Case Record Form (CRF)*

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

1.10 Clinical Trial (Clinical Study)

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

1.11 Phases of clinical trial for ASU drugs

1.11.1. Human Pharmacology (Phase I).-

(i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an ASU Drugs / other T M new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with probable toxicity e.g. drugs with Schedule E-I ingredients are usually studied in patients. Phase I trials should preferably be carried out with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:-

(iii) 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.

(iv) 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.

1.11.2. Therapeutic exploratory trials (Phase II).-

(i) The primary objective of Phase II trials is to evaluate the effectiveness of an ASU 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(s) and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I. These studies should be intended to provide an adequate basis for marketing approval for ASU Drugs.

(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.

(iii) These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(iv) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

1.11.3. Therapeutic confirmatory trials (Phase III).-

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits(s). 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. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, 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 drug(s).

(ii) For drugs intended to be administered for long periods, trials 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 ASU drugs approved outside India, Phase III studies needs to be carried out 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 subjects, Licensing Authority may require detailed safety studies and if possible, pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

1.11.4. Post Marketing Trials (Phase IV).-

Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc.

1.12 Comparator Product

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

1.13 Confidentiality

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

1.11 Co-Investigator

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

1.12 Co-ordinating Investigator -See Principal Investigator

1.13 Clinical Research Organisation (CRO)

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

1.14 Contract

A written, dated and signed document describing the agreement between two or more parties involved in ASU Medicines, 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".

1.15 Documentation

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

1.15.1 Rescue Medicine

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

1.15.2 Essential Documents

The Documents that permit evaluation of the conduct of a study and the quality of the data generated.

1.15.3 Ethics Committee

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

1.15.4 Final Report

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

1.15.5 Good Clinical Practice (GCP)

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

1.15.6 Impartial Witness

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

1.15.7 Informed Consent

Voluntary written consent of a subject's willingness to participate in a particular study and in its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and of the subject's rights and responsibilities has been provided to the potential subject.

1.15.8 Inspection

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

1.15.9 Institution

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

1.15.10 Investigator

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

1.15.11 Investigational Labelling

Labelling developed specifically for products involved in the study.

1.15.12 Investigational Product

A ASU Medicines (including the Comparator Product) being tested or used as reference in a clinical study.

1.15.13 Investigator's Brochure

A collection of data (including justification for the proposed study) for the Investigator consisting of all the clinical as well as non-clinical information available on the Investigational Product(s) known prior to the onset of the trial. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new substantially relevant data is generated during the trial, the information in the Investigator's Brochure must be updated. *See Appendix IV.*

1.15.14 Monitor

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

1.15.15 Multi-Centric Study

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

1.15.16 Non-Clinical Study

Biomedical studies that are not performed on human subjects.

1.15.17 Non-Therapeutic Study

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

1.15.18 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.

1.16 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.

1.17 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.

1.17.1 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.

1.17.2 Quality Assurance (QA)

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

1.17.3 Quality Control (QC)

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

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

1.18 Randomisation

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

1.19 *Raw Data*

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

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

Any untoward medical occurrence that any dose results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity or is a congenital anomaly /birth defect.

1.20 Schedule

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

1.20.1 Source Data

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

1.21.1 ***Sponsor***

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

1.21.2 ***Study Product***

Any ASU Medicines / therapies or *Comparator Product* used in a clinical study.

1.22 Sub-Investigator

See ***Co-Investigator***

1.22.1 Subject Files / Patient Files

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

1.22.2 ***Study Subject (Subject)***

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

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

1.22.3 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.

1.22.4 Subject Identification Code

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

1.22.5 Study Management

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

1.23 Traditional Medicine

'Traditional Medicine' / Folk medicine is the sum of total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, societies, communities, folklores in India, used for the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses, which do not find a mention in First Schedule of Drugs and Cosmetics Act 1940.

For clinical trial on Chinese Medicine/ Korean / Japanese/ Western Traditional Medicine and any other country TM, the Clinical Trail permission may be considered on the basis of data requirements of Schedule-Y.

Folk Medicine: Defined as above

1.24 **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.

NEW DEFINITIONS CREATED AS SUGESSTED FOR INCLUSION UNDER THIS CHAPTER:

Data Safety Management Board

The Data and Safety Monitoring Board (DSMB) is a board, charged with monitoring the accumulating data from a pharmacotherapeutic clinical trial to detect and report early evidence of prespecified or unanticipated benefit or harm to trial participants that may be attributable to one of the treatments under evaluation. The DSMB will conduct an independent, objective review of all accumulated data from both blinded and unblinded clinical trials in such a manner as to maximize benefit to the trial participants and to the research effort.

Interim Analysis

An interim analysis is any assessment of data done during the patient enrolment or follow-up stages of a trial for the purpose of assessing center performance, the quality of the data collected, or treatment effects.

Vulnerable Participant

A "vulnerable participant" is any individual who lacks the ability to fully consent to participate in a study.

Pre-requisites for the study

2.1. Investigational ASU Medicines***:***

Physical, chemical (wherever available), pharmaceutical properties and the formulation of the Investigational ASU Medicines 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.

2.2. Pre-clinical supporting data

The available pre-clinical data and clinical information on the Investigational ASU Medicines should be adequate and convincing to support the proposed study. As per guidelines.

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 designation 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)

g. Disease Review, which includes prevalence, economical burden, historical aspects, clinical features, existing diagnostics and treatment including the details of adverse drug reactions (ADRs) as described in respective ASU system along with related information(s) in modern system (if available).

h. Drug review, which includes of details of ingredients with supporting relevant scientific study and published papers (if available).

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 (if any) that potentially have clinical significance and from clinical studies that are relevant to the study and bibliographic references.

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

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

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 rationale 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 etc.), study design (parallel groups, cross-over technique etc.), blinding technique (double-blind, single-blind if used),

randomisation (method and procedure) and mention of controll. (e.g. placebo, standard etc if used) etc.

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

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

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

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

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

h. Proposed date of initiation of the study

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

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

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

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

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

n. Procedures for monitoring subjects' compliance

o. Information on Anupan, Desh, Kala, Pratyatmniyata, or Paynaya/pathya, samprpti vighaton etc. and /other relavant scientific considerations of respective system of medicine if appropriate and required.

2.3.1.5. Inclusion, Exclusion and Withdrawal of Subjects

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

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

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

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

e. Questionnaire for Prakriti evaluation if applicable.

2.3.1.6. Handling of the ASU Medicine

a. Measures to be implemented to ensure the safe handling and storage of the ASU Medicine.

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

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

2.3.1.7. Assessment of Efficacy

a. Specifications of the effect parameters to be used

b. Description of how effects are measured and recorded

c. Time and periodicity of effect recording

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

2.3.1.8. Assessment of Safety

a. Specifications of safety parameters

b. Methods and periodicity for assessing and recording safety parameters

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

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

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

2.3.1.9. Statistics

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

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

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

d. The level of statistical significance to be used

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

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

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

2.3.1.10. Data handling and management

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

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

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

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

2.3.1.11. Quality control and quality assurance

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

b. Specifications and instructions for anticipated deviations from the protocol

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

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

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

f. Considerations of confidentiality problems, if any arise

g. Quality control of methods and evaluation procedures

h. The laboratory tests methods to be predefined / specified.

2.3.1.12. Finance and insurance

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

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

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

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

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

2.3.1.13. Publication policy

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

2.3.1.14. Evaluation

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

b. Methods of computation and calculation of effects

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

2.3.2. Supplementaries and appendices:

The following documents should be appended with the protocol:

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

b. Instructions to staff

c. Descriptions of special procedures

2.4. Ethical & Safety Considerations

2.4.1. Ethical Principles

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

The following principles are to be followed:

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

b. **Principles of voluntariness, informed consent and community agreement** whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by them or by someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding.

c. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or

experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born.

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

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

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

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

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

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

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

k. **Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

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

2.4.2. Ethics Committee:

The sponsor and / or investigator should seek the opinion of an institutional *Ethics Committee* regarding suitability of the *Protocol*, methods and documents to be used in recruitment of *Subjects* and obtaining their *Informed Consent* including adequacy of the information being provided to the Subjects. The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the Ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the ICMR Guidelines 2006.

2.4.2.1 Basic Responsibilities

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

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

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

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

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

2.4.2.2. Composition

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

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

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

1. Chairperson

2. 1-2 basic medical scientists (preferably one pharmacologists).

3. 1-2 clinicians from various Institutes

4. One legal expert or retired judge

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

6. One philosopher / ethicist / theologian

7. One lay person from the community

8. Member Secretary

9. One expert member of ASU

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

2.4.2.3. Terms of Reference

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

2.4.2.4. Review Procedures

The Ethics Committee should review every research proposal on human subjects within reasonable period of time . It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. **The ethical review should be**

done through formal meetings and should not resort to decisions through circulation of proposals.

2.4.2.5. ***Submission of Application***

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

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

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

3. Subject recruitment procedures.

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

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

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

7. The plans for statistical analysis of the study.

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

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

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

11. Proposed compensation and reimbursement of incidental expenses.

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

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

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

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

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

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

18. Compensation for research related injury, risk benefit analysis and details of QC of investigational product should be included in application to EC. The EC should ensure that insurance is taken for care of patients.

2.4.2.6. Decision Making Process

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.4.2.7. Interim Review

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

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

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

iii) an urgent proposal of national interest.

2.4.2.8. Record Keeping

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

i. the Constitution and composition of the IEC;

ii. the curriculum vitae of all IEC members;

iii. standing operating procedures of the IEC;

iv. national and international guidelines;

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

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

vii. agenda of all IEC meetings;

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

ix. copies of decisions communicated to the applicants;

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

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

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

2.4.2.9. Special Considerations

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

2.4.3. Informed Consent Process

2.4.3.1. **Informed Consent of Subject :**

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

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

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

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

The Investigator(s), Sponsor or staff of the Institution should not coerce or unduly influence a potential Subject to participate or to continue to participate in the Study. Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure- such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. Persons with incurable diseases, in nursing homes, in detention, unemployed or impoverished, in emergency rooms, homeless persons, nomads, refugees and any ethnic or racial minority groups should be considered as vulnerable population whose mode of consent should be carefully considered and approved by the Ethics Committee.

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

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

write, an impartial witness who should be present during the entire informed consent discussion

2. The Investigator

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

The Subject's legal representative or guardian (if the subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability), the inclusion of such patients in the study may be acceptable if the ethics committee is in principle, in agreement, and if the investigator thinks that the participation will promote the welfare and interest of the Subject. The agreement of a legal representative or the guardian that participation will promote the welfare and interest of the Subject should also be recorded with dated signature. If, however, neither the signed Informed Consent nor the witnessed signed verbal consent are possible – this fact must be documented stating reasons by the Investigator and also brought to the knowledge of Ethics Committee without any delay.

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

i. the aims and methods of the research;

ii. the expected duration of the subject participation;

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

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

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

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

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

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

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

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

xi. 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;

xii. risk of discovery of biologically sensitive information;

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

xiii. information on standard of care (including modern medicines)

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

2.4.3.3. Informed Consent in Non-Therapeutic Study :

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

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

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

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

2.4.4. Essential Information on Confidentiality for Prospective Research Subjects

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

Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed.

2.4.5. Compensation for Participation

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

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

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

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

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

2.4.6. Selection of Special Groups As Research Subject

2.4.6.1. Pregnant or nursing women :

Pregnant or nursing women should in no circumstances be the subject of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be subjects of

any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

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

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

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

2.4.6.2. Children:

Before undertaking trial in children below the age of 18 years the investigator must ensure that –

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

b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

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

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

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

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

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

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

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

2.4.6.3. Vulnerable groups :

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

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

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

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

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

2.4.7. Compensation for Accidental Injury

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

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

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

RESPONSIBILITIES

3.1. Sponsor:

3.1.1. Investigator and Institution Selection:

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

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

3.1.2. Contract

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

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

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

c. To permit monitoring, auditing and inspection

d. To retain the study related essential documents until the Sponsor informs the Investigator(s) / Institution(s) in writing that these documents are no longer needed or minimum of five years period whichever is more

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

3.1.3. SOP

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

3.1.4. Allocation of duties and responsibilities:

Prior to initiating a Study the Sponsor should define and allocate all Study related duties and responsibilities to the respective identified person(s) / organisation(s), however, the overall responsibility lies with the sponsor.

3.1.5. Study management, data handling and record keeping:

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

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

b. Data processing

c. Breaking of the Code

d. Statistical analysis

e. Preparation of the Study Report

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

g. Reporting the ADRs, AEs to the Ethics Committee

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

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

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

3.1.6. Compensation for Participation

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

3.1.7. Confirmation of review by the Ethics Committee

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

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

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

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

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

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

3.1.8. Information on Investigational Products

As a prerequisite to planning of a Study, the Sponsor is responsible for providing the Investigator(s) with an Investigator's Brochure. The Brochure must contain the available information on product standardization and other data relevant to the study. This information should be accurate and adequate to justify the nature, scale and the duration of the Study. In addition, the Sponsor must bring any relevant new information arising during the period of Study to the attention of the Investigator(s) as well as the Ethics Committee.

3.1.9. Supply, storage and handling of Pharmaceutical Products

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

The Sponsor should determine the Investigational Product's acceptable storage conditions, and communicate them in writing to all involved parties, besides stating them on the Product labels where ever possible.

The Sponsor should document procedures and lay down responsibilities for

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

b. retrieval of unused Product from the Subjects and

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

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

Sponsor should also maintain records of the quantities of Investigational Product with proper batch numbers. The Sponsor should ensure that the Investigator is able to establish a system within his / her Institution for proper management of the Products as per the procedures.

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

3.1.10. Safety Information:

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

3.1.11. Adverse Drug Reaction Reporting:

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

3.1.12. Study Reports:

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

3.1.13. Monitoring

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

3.1.14. Audit:

Sponsor should perform an audit as a part of QA system. This audit should be conducted with the purpose of being independent and separate from routine monitoring or quality control functions. Audit should evaluate the study conduct and compliance with the protocol, SOPs, GCPs and applicable regulatory requirements. For the purpose of carrying out the audit – the

sponsor may appoint individuals qualified by training and experience to conduct audits. The Auditors should be independent of the parties involved in the study and their qualifications should be documented.

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

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

3.1.15. Multicentre Studies

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

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

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

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

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

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

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

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

b. role and responsibilities of the co-ordinating investigators

c. role and responsibilities of the CRO

d. randomisation procedure

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

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

3.1.16. Premature Termination or Suspension of a Study

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

3.2. The Monitor:

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

3.2.1. Qualifications

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

3.2.2. Responsibility

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

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

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

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

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

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

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

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

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

6. the investigator follows the protocol

7. the investigator maintains the essential documents

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

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

3.3. Investigator

3.3.1. Qualifications

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

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

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

3.3.2. Medical care of the study subjects

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

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

3.3.3. Monitoring and Auditing of Records

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

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

3.3.4. Communication with Ethics Committee

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

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

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

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

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

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

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

3.3.5. Compliance with the protocol

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

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

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

3.3.6. Investigational Product(s)

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

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

3.3.7. Selection and recruitment of study subjects:

The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects according to the protocol. It may be necessary to secure the co-operation of other physicians in order to obtain a sufficient number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or review retrospectively the availability of the subjects. Investigator should check whether the subject(s) so identified could be included in the study according to the protocol. The investigator should keep

a confidential list of names of all Study Subjects allocated to each study. This list facilitates the investigator / institution to reveal identity of the subject(s) in case of need and also serve as a proof of Subject's existence. The investigator / institution shall also maintain a Subjects' screening log to document identification of Subjects who enter pre-study screening. A Subject's enrolment log shall also be maintained to document chronological enrolment of Subjects in a particular Study.

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

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

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

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

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

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

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

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

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

3.3.8. Records/Reports

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

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

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

Progress Reports

The investigator should submit the written summaries of the study status at the periodicity specified in the protocol to the person(s) / organisation(s) to whom the investigator is reporting. to the concerned ethics committee and sponsor.

All reportings made by the investigator should identify the subjects by unique code numbers assigned to the study subjects rather than by the subjects' name(s), personal identification number(s) and / or addresses.

Termination and final report:

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

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

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

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

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

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

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

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

3.4 *Data safety management*

A data safety management board may be established to carefully monitor the data and side effects during the period of the study and put in a place where by prompt reporting of adverse event occur. The data should be reviewed at regular intervals. The research team should report immediately to the Investigator(s) and Data Monitoring Board regarding any life threatening condition, whether they are pursued to be study related or not. Protocols should be written and approved for the treatment of study related adverse event. The immediate transport facility should be provided to the study personnel to nearby hospital for medical referral.

RECORD KEEPING AND DATA HANDLING

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

4.1. Documentation

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

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

4.2. Corrections

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

4.3. Electronic Data Processing

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

4.4. Validation of Electronic Data Processing Systems

If trial data are entered directly into the computer there must always be an adequate safeguard to ensure validation including a signed and dated printout and backup records. Computerised systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.

4.5. Language

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

4.6. Responsibilities of the Investigator

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

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

by the investigator. Units of measurement must always be stated and transformation of units must always be indicated and documented.

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

4.8. Responsibilities of the Sponsor and the Monitor

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

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

QUALITY ASSURANCE

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

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

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

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

STATISTICS

6.1. Role of a Biostatistician

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

6.2. Study Design:

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

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

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

3. in case of observational studies proper care should be taken for unbiased reporting.

6.2.1. Randomisation and blinding:

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

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

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

6.3. Statistical Analysis

The type(s) of Statistical Analyses to be used must be clearly identified and should form basis of the statistical model for the Study. Any subsequent deviation(s) should be described and justified in the Final Report. The need and extent of an interim analysis must be specified in the Protocol. The results of the statistical analyses should be presented in a manner that is likely to facilitate the interpretation of their

clinical importance, e.g. by estimates of the magnitude of the treatment effect / difference and confidence intervals rather than sole reliance on significance testing.

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

SPECIAL CONCERNS

7.1. Clinical Trials of Contraceptives

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

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

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

7.2 Clinical trials with Panchakarma / para-surgical procedures/ medical devices in ASU medicine / other Traditional Medicine.

Panchakarma including Snehana Swedana, Dhara, Pizhichil and para-surgical procedures like Ksharasutra, Leach therapy, Agni karma, Hajamat, Hammam, Nutul Dalk, Riazat, Prachanna, Rakta mokshana, Tarpana, Vidalaka, Verm etc are special strength areas of ASU systems of medicine especially of Ayurveda, Proper documentation of end point, procedure, standardization of drugs used in the procedures, parameters of evaluation, statistical consideration should be given special attention while conducting clinical trials on them.

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

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

APPENDICES

Appendix I:

Guidelines for Evaluation of Ayurveda, Siddha and Unani Medicines and other Traditional Medicines

(Revised Gazette Notification to be inserted here)

Appendix II:

GENERAL ETHICAL ISSUES

(Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research 2006)

All the research involving human participants should be conducted in accordance with the four basic ethical principles, namely autonomy (respect for person /participant) beneficence, non-maleficence (do no harm) and justice. The guidelines laid down are directed at application of these basic principles to research involving human participants. The Principal Investigator is the person responsible for not only undertaking research but also for observance of the rights, health and welfare of the participants recruited for the study. S/he should have qualification and competence in biomedical research methodology for proper conduct of the study and should be aware of and comply with the scientific, legal and ethical requirements of the study protocol.

I. INFORMED CONSENT PROCESS

1. **Informed Consent of Participants:** For all biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed consent protects the individual's freedom of choice and respect for individual's autonomy and is given voluntarily to participate in research or not. Adequate information about the research is given in a simple and easily understandable unambiguous language in a document known as the **Informed Consent Form with Participant/ Patient Information Sheet**. The latter should have following components as may be applicable:

    1. Nature and purpose of study stating it as research
    2. Duration of participation with number of participants
    3. Procedures to be followed
    4. Investigations, if any, to be performed
    5. Foreseeable risks and discomforts adequately described and whether project involves more than minimal risk
    6. Benefits to participant, community or medical profession as may be applicable
    7. Policy on compensation
    8. Availability of medical treatment for such injuries or risk management
    9. Alternative treatments if available
    10. Steps taken for ensuring confidentiality
    11. No loss of benefits on withdrawal
    12. Benefit sharing in the event of commercialization
    13. Contact details of PI or local PI/Co-PI in multi-centric studies for asking more information related to the research or in case of injury
    14. Contact details of Chairman of the IEC for appeal against violation of rights

15. Voluntary participation
16. If test for genetics and HIV is to be done, counseling for consent for testing must be given as per national guidelines
17. Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipt of its results

A copy of the participant/patient information sheet should be given to the participant for her/ his record. The informed consent should be brief in content highlighting that it is given of free will or voluntarily after understanding the implications of risks and benefits and s/he could withdraw without loss of routine care benefits. Assurance is given that confidentiality would be maintained and all the investigations/ interventions would be carried out only after consent is obtained.

When the written consent as signature or thumb impression is not possible due to sensitive nature of the project or the participant is unable to write, then verbal consent can be taken after ensuring its documentation by an unrelated witness. In some cases ombudsman, a third party, can ensure total accountability for the process of obtaining the consent. Audio-visual methods could be adopted with prior consent and adequate precaution to ensure confidentiality, but approval of EC is required for such procedures. For drug trials, if the volunteer can give only thumb impression then another thumb impression by the relative or legal custodian cannot be accepted and an unrelated witness to the project should then sign.

Fresh or re-consent is taken in following conditions:

1. Availability of new information which would necessitate deviation of protocol.
2. When a research participant regains consciousness from unconscious state or is mentally competent to understand the study. If such an event is expected then procedures to address it should be spelt out in the informed consent form.
3. When long term follow-up or study extension is planned later.
4. When there is change in treatment modality, procedures, site visits.
5. Before publication if there is possibility of disclosure of identity through data presentation or photographs (which should be camouflaged adequately).

Waiver of consent

Voluntary informed consent is always a requirement for every research proposal. However, this can be waived if it is justified that the research involves not more than minimal risk or when the participant and the researcher do not come into contact or when it is necessitated in emergency situations elaborated in the previous Chapter. If such studies have protections in place for both privacy and confidentiality, and do not violate the rights of the participants then IECs may waive off the requirement for informed consent in following instances:

i. When it is impractical to conduct research since confidentiality of personally identifiable information has to be maintained throughout research as may be required by the sensitivity of the research objective, *e.g.*, study on disease burden of HIV/AIDS.

ii. Research on publicly available information, documents, records, works, performances, reviews, quality assurance studies, archival materials or thirdparty interviews, service

programs for benefit of public having a bearing on public health programs, and consumer acceptance studies.

iii. Research on anonymised biological samples from deceased individuals, left over samples after clinical investigation, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognized institutions or qualified investigators, samples or data from repositories or registries etc.

iv. In emergency situations when no surrogate consent can be taken.

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

i. communicate to prospective participants all the information necessary for informed consent.

Any restriction on participant's right to ask any questions related to the study will undermine the validity of informed consent;

ii. exclude the possibility of unjustified deception, undue influence and intimidation. Although deception is not permissible, if sometimes such information would jeopardize the validity of research it can be withheld till the completion of the project, for instance, study on abortion practices;

iii. seek consent only after the prospective participant is adequately informed. The investigator should not give any unjustifiable assurances to prospective participant, which may influence the her/his decision to participate;

iv. obtain from each prospective participant a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial, and in case the participant is not competent to do so, a legal guardian or other duly authorized representative;

v. take verbal consent when the participant refuses to sign or give thumb impression or cannot do so. This can then be documented through audio or video means;

vi. take surrogate consent from the authorized relative or legal custodian or the institutional head in the case of abandoned institutionalized individuals or wards under judicial custody;

vii. renew or take fresh informed consent of each participant under circumstances described earlier in this chapter;

viii. if participant loses consciousness or competence to consent during the research period as in Alzheimer or psychiatric conditions, surrogate consent may be taken from the authorized person or legal custodian.

ix. 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.

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

i. the aims and methods of the research;
ii. the expected duration of the participation;
iii. the benefits that might reasonably be expected as an outcome of research to the participant or community or to others;
iv. any alternative procedures or courses of treatment that might be as advantageous to the participant as the procedure or treatment to which s/he is being subjected;
v. any foreseeable risk or discomfort to the participant resulting from participation in the study;
vi. right to prevent use of her/ his 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 maintained ie., the limits to which the investigator would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality;
viii. responsibility of investigators;
ix. free treatment for research related injury by the investigator and/ institution and sponsor(s);
x. compensation of participants for disability or death resulting from such injury;
xi. insurance coverage if any, for research related or other AEs;
xii. freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to;
xiii. the identity of the research teams and contact persons with address and phone numbers;
xiv. 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;
xv. risk of discovery of biologically sensitive information and provision to safeguard confidentiality;
xvi. publication, if any, including photographs and pedigree charts.

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

II. COMPENSATION FOR PARTICIPATION

Participants may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. When this is reasonable then it cannot be termed as benefit. During the period of research if the participant requires treatment for complaints other than the one being studied necessary **free ancillary care** or appropriate referrals may be provided. However, payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement. All payments, reimbursement and medical services to be provided to research participants should be approved by the IEC. Care should be taken:

i. when a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;
ii. when a participant is withdrawn from research for medical reasons related to the study the participant should get the benefit for full participation;

iii. when a participant withdraws for any other reasons s/he should be paid an amount proportionate to the amount of participation.

III. CONFLICT OF INTEREST

A set of conditions in which professional judgment concerning a primary interest like patient's welfare or the validity of research tends to be or appears to be unduly influenced by a secondary interest like non-financial (personal, academic or political) or financial gain is termed as Conflict of Interest (COI).

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 interest*e*s. (***.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/ committee should advise accordingly. Significant financial interest means anything of monetary

value that would reasonably appear to be a significant consequence of such research including salary or other payments for services like consulting fees or honorarium per participant; equity interests in stocks, stock options or other ownership interests; and intellectual property rights from patents, copyrights and royalties from such rights. The investigators should declare such conflicts of interest in the application submitted to IEC for review. Institutions and IECs need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. The IEC can determine the conditions for management of such conflicts in its SOP manual. 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. Those who have also to be informed of the secondary interest in financial terms should include the institution, IEC, audience when presenting papers and should be mentioned when publishing in popular media or scientific journals.

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. Undue compensation would include

assistance to related person(s) for transport of body for cremation or burial, provision for insurance for unrelated conditions, free transportation to and fro for examination not included in the routine, free trip to town if the participants are from rural areas, free hot meals, freedom for prisoners, free medication which is generally not available, academic credits and disproportionate compensation to researcher / team/institution. However, in remote and inaccessible areas some of the features mentioned above may be a necessity and culture specific. Therefore, the IEC should examine this on a case-by-case basis, as some of these elements may be justifiable for collecting vital data for national use or necessary to find if some interventions may significantly have direct impact on health policies.

IV. SELECTION OF SPECIAL GROUPS AS RESEARCH PARTICIPANTS

i. ***Pregnant or nursing women:*** Pregnant or nursing women should in no circumstances be the participant of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus,

pregnancy and lactation. As a general rule, pregnant or nursing women should not be participants of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable participants.

a. The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting foetal 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. Compensation in terms of supplying supplementary food such as milk formula should be considered in such instances.

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 The Medical Termination of Pregnancy Act, GOI, 1971.

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

ii. *Children:* Before undertaking trial in children the investigator must ensurethat –

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

b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

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

d. the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors from the age of seven years up to the age of 18 years.;

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 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 as any available alternative interventions;

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

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

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

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

c. rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected. Appropriate proxy consent from the legal guardian should be taken after the person is well informed about the study, need for participation, risks and benefits involved and the privacy and confidentiality procedures. The entire consent process should be properly documented;

d. 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, since the consent provide may be under duress or various other compelling reasons.

V. 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 under the following circumstances:

a. only in a court of law under the orders of the presiding judge or

b. there is threat to a person's life or

c. in cases of severe adverse reaction may be required to communicate to drug registration authority or

d. if there is risk to public health it takes precedence over personal right to privacy and may have to be communicated to health authority.

Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed and communicated to appropriate individuals or authorities as the case may be.

VI. COMPENSATION FOR ACCIDENTAL INJURY

Research participants who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, their dependents are entitled to material compensation.

Obligation of the sponsor to pay :- The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, in the *a priori* agreement to provide compensation for any physical or psychological injury for which participants are entitled or agree to provide insurance coverage for an unforeseen injury whenever possible.

An Arbitration committee or appellate authority could be set up by the institution to decide on the issue of compensation on a case-by-case basis for larger trials where such a step is feasible.

Alternately an institution can also establish such a committee to oversee such claims, which would be common for projects being undertaken by it.

Compensation for **ancillary care** for unrelated illness as free treatment or appropriate referrals may also be included in the *a priori* agreement with the sponsors whenever possible.

VII. POST - TRIAL ACCESS

The Helsinki Declaration of the World Medical Assembly (WMA), 2000 states that at the end of the trial every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. This led to a lot of debate globally on account of lack of even basic drugs in most of the developing countries. The Declaration of the WMA in 2004 reaffirmed "its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review." Therefore, whenever possible I\EC should consider such an arrangement in the *a priori* agreement. Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices. For smaller scale or student projects post trial benefit to the participants may not be feasible but keeping in mind the post trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants.

VIII. INTERNATIONAL COLLABORATION / ASSISTANCE IN BIO-MEDICAL / HEALTH RESEARCH

Research in biomedical and health areas has gained greater momentum only by the second half of the 20th Century, especially since the 1960s, the scope of international co-operation and collaboration assumed such proportions as to have exploitative connotations with commercial and human dimensions. On the one hand, collaboration in medical research suggests an interest in a humane and civil society, while on the other it could give the impression of experimentation on the population of one country by another. Different levels of development in terms of infrastructure, expertise, social and cultural perceptions, laws relating to intellectual property rights etc., necessitate an ethical framework to guide such collaboration. The same concerns are applicable even when there is no formal collaboration between countries, but the research is undertaken with assistance from international organizations as sponsors (Governmental like National Institutes of Health, USA, non-Governmental like Bill & Melinda Gates Foundation, Ford Foundation or others like WHO, UNICEF, UNAIDS etc.).

Special Concerns

1. Given the magnitude and severity of the health problems in different countries, capacity building to address ethical issues that arise out of collaborative research must be promoted on a priority basis. Strategies should be implemented so that various countries and communities can practise meaningful self-determination in health development and can ensure the scientific and ethical conduct of research.

2. The collaborating investigators, institutions and countries can function as equal partners with sponsors even when in a vulnerable position by building appropriate safeguards. Community representatives should be involved early enough while designing the protocol and in a sustained manner during the development, implementation, monitoring and dissemination of results of research.

3. Careful consideration should be given to protect the dignity, safety and welfare of the participants when the social contexts of the proposed research can create foreseeable conditions for exploitation of the participants or increase their vulnerability to harm. The steps to be taken to overcome these should be described and approval taken from concerned IEC/IndEC.

4. Every adult participant in the research should voluntarily give informed consent and child her/his assent as may be applicable.

5. As different kinds of research (epidemiological studies, clinical trials, product development, behavioural and social science oriented research *etc*.) have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each type of study should be justified in advance in scientific and ethical terms regardless of the place from where the study population is selected. Generally, early clinical phases of research, particularly of drugs, vaccines and devices, should be conducted in communities that are less vulnerable to harm or exploitation. However, for valid scientific and public health reasons, if sufficient scientific and ethical safeguards are ensured it may be conducted in any phase after obtaining relevant regulatory clearances.

6. The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research programme should be specified in the research protocol and explained to the participants as fully as can be reasonably done. Moreover, the modalities by which to address these, including **provision for the best possible nationally available care** to participants who experience adverse reactions to drug under study, compensation for injury related to the research, and referral for psychosocial and legal support if necessary, need to be described.

7. The research protocol should outline the benefits that persons / communities /countries participating in such research should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation. The burden and the benefit should be equally borne by the collaborating countries.

8. Guidelines, rules, regulations and cultural sensitivities of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country. These could be with reference to intellectual property rights, exchange of biological materials (human, animal, plant or microbial), data transfer, security issues, and issues of socially or politically sensitive nature. In this context, it is essential for researchers to follow the GOI notification on “Exchange of Human Biological Material for Biomedical Research” issued on 19.11.97 and obtain appropriate regulatory clearances as prevalent in the country for international collaboration and EC approval from all trial sites before the initiation of research.

IX. RESEARCHER’S RELATIONS WITH THE MEDIA AND PUBLICATION PRACTICES

Researchers have a responsibility to make sure that the public is accurately informed about results without raising false hopes or expectations. It should also not unnecessarily scare the people. Researchers should take care to avoid talking with journalists or reporters about preliminary findings as seemingly promising research that subsequently cannot be validated or could lead to misconcepts if reported prematurely. Or, the results of research may be reported in such a way that it would seem that the human application is round the corner, only to be told later by the researchers that considerable time has to pass before these findings can be translated into tools for human use. In such circumstances, retractions most often do not appear in the media. Therefore, it is important to avoid premature reports and publicity stunts. The best safeguard against inaccurate reporting is for the researcher to talk to media on condition that the reporter submit a full written, rather than oral version, of what will be reported, so that it enables the researcher to make necessary corrections, if needed, prior to publication.

Investigator's publication plans should not threaten the privacy or confidentiality of participants, for example publication of pedigrees in the report on research in genetics can result in identification of study participants. It is recommended that a clear consent for publication be obtained besides the consent for participation in research or treatment and such a consent should preferably be obtained on two different occasions and not as a blanket one at the commencement of the study. Maintenance of confidentiality while publishing data should be taken care of. In case there is need for publication / presentation of photographs/ slides / videos of participant (s), prior consent to do so should be obtained. Identification features should be appropriately camouflaged. The same safeguard should be observed for video coverage.

With regard to authorship, the International Committee of Medical Journal Editors (ICJME) has laid down criteria based on credit and accountability. Only those who make substantial contribution to the article and take responsibility for the published matter can be co-authors. Plagiarism or falsification of data and authorship are important ethical issues in publications. The term 'misconduct in research' means fabrication, falsification, plagiarism, selective omission of data and claiming that some data are missing, ignoring outliers without declaring it, not reporting data on side effects/ adverse reactions in a clinical trial, publication of post-hoc analysis without declaring it, gift authorship, not citing others' work, not disclosing conflict of interest, redundant publication, and failure to adequately review existing research. The Commission on Research Integrity in US created by US Congress addresses the scientific, ethical, social and legal issues involving scientific misconduct in research. Consolidated standards of reporting trials (CONSORT) guidelines have been prescribed for publishing results of clinical research especially RCTs (Randomized Controlled Trials) and are available at http://www.consort-statement.org .

APPENDIX III

"(Proposed) SCHEDULE- Z"

[See rules 153,158 (B)]

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO MANUFACTURE OF ASU DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS [although the schedule is for permission to manufacture of ASU Drugs for sale or to undertake clinical trials,thereis no information on the former point ie manufacture for sale in (proposed) schedule Z-------View of Department the care may be taken at the time of framing of the rules at the time of amendment of the rule.]

I. Application for permission.- (1) Application for permission to manufacture ASU drugs for sale or to undertake clinical trials shall be made in Form 24D accompanied with data in accordance with the Appendix-I and for renewal with data in accordance with the appendix-II.

II. CLINICAL TRIAL

(1) Approval for clinical trial

(i) Clinical trial on an ASU drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 152, and the approval obtained from the respective ethics committee(s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics comittee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committees (constituted as per Appendix VIII), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified ASU physician, who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions in mutual consultation with investigator or a sub-investigator or a co-investigator of modern system of medicines, if associated with the clinical trial. If services of a laboratory or a facilities are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies) /facilities to be used for the

trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from the charges to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) Responsibilities of Sponsor.-

(i) The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice(GCP) Guidelines for ASU drugs issued by the Department of AYUSH, Ministry of Health and Family Welfare, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing 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 (Appendix XI), if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

(iv) Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study (see Appendix XI).

(3) Responsibilities of the Investigator(s).- The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the Investigators for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure

that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within 7 working days of their occurrence.

(4) Informed Consent.-

(i) In all trials, a freely given, informed written consent is required to be obtained from each study subject. 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 subject. The Subject'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 Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) Where a subject is 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 (a legally acceptable representatives a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write - an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the informed Consent Form for study Subjects is given in Appendix V.

(5) Responsibilities of the Ethics Committee.-

(i) It is the responsibility of the ethics committees that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects. The ethics committee should exercise particular care to protect the rights, safety and well being of all vulnerable subjects 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 others incapable of personally giving consent. Ethics committee(s) should get document 'standard operating procedures' and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

(ii) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Licensing Authority.

(6) Human Pharmacology (Phase I).-

(i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an ASU Drugs / other T M new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with probable toxicity e.g. drugs with Schedule E-I ingredients are usually studied in patients. Phase I trials should preferably be carried out with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) 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.

(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.

7. Therapeutic exploratory trials (Phase II).-

(i) The primary objective of Phase II trials is to evaluate the effectiveness of an ASU 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(s) and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I. These studies should be intended to provide an adequate basis for marketing approval for ASU Drugs.

(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 trials.

(ii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

8. Therapeutic confirmatory trials (Phase III).-

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits(s). 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. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, 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 drug(s).

(ii) For drugs intended to be administered for long periods, trials 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 ASU drugs approved outside India, Phase III studies needs to be carried out 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 subjects, Licensing Authority may require detailed safety studies and if possible, pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

(iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application.

9. Post Marketing Trials (Phase IV).- Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of ASU drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. exploration of new indications of classical ASU drugs, mortality/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. Any claim sought to be made for the drug product that is not based on data submitted under preceding items of this Schedule should be supported by studies included under this item of the Schedule (Appendix I item 8.3).

(1) Geriatrics.-Geriatric patients should be included in Phase III clinical trials (and in Phase Initials, 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.

(2) Paediatrics.-

(i) The timing of paediatric studies in the ASU 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 trial to younger children and then infants.

(ii) If the ASU drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial 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.

(iii) If the ASU 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 trials 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.

(iv) If the ASU 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.

(vi) If the ASU 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 ASU drug application.

(vii) Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/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. Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date separately designed written assent form. 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(s)/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/legal guardian consent should be sufficient to allow participation in the study.

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

(3) Pregnant or nursing women.-

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

(ii) For new ASU drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that ASU 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.

(2) Post Marketing Surveillance.-

(i) Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

(a) report all the relevant new information from appropriate sources;

(b) relate these data to patient exposure;

(c) summarize the market authorization status in different countries and any significant variations related to safety; and

(d) indicate whether changes should be made to product information in order to optimize the use of the product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years- the PSURs need to be submitted annually. Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

(v) A PSUR should be structured as follows:

(a) A title page stating: Periodic safety update report for the product, applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;

(b) Introduction,

(c) Current worldwide market authorization status,

(d) Update of actions taken for safety reason,

(e) Changes to reference safety information,

(f) Estimated patient exposure,

(g) Presentation of individual case histories,

(h) Studies,

(i) Other information,

(j) Overall safety evaluation,

(k) Conclusion,

(l) Appendix providing material relating to indications, dosing, pharmacology and other related information.

Appendix-I (Of Proposed Schedule 'Z')

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS /IMPORT / MANUFACTURE OF ASU DRUGS FOR MARKETING IN THE COUNTRY.

1. Introduction

A brief description of the drug and the disease condition where the use is intended

2. Available pharmaceutical information on ingredient(s) from classical literature and from modern literature (wherever available)

2.1 Information on ingredients
Drug information (Official Name, Scientific Name)

2.2. Physicochemical Data of GLP compliant laboratory
a. Phyto-chemical / chemical constituents
b. Physical properties (organoleptic as per texts)
Description

2.3. Analytical Data of GLP compliant laboratory

2.4. Complete monograph specification including
Identification
Identity/quantification of impurities
Assay

2.5. Validations
Assay method
Impurity estimation method

2.6. Stability Studies
Final release specification
Reference standard characterization
Material safety data sheet

2.7. Data on Formulation
Dosage form

Composition
Master manufacturing formula
Details of the formulation (including inactive ingredients)
In process quality control check
Finished product specification
Excipient compatibility study / Excipient added
Analytical methods adopted with SoP
Comparative evaluation with other approved Indian brands fro same indication, if applicable
Pack presentation
Finished Product Specifications
Stability evaluation in market intended pack at proposed storage conditions
Packing specifications
Process validation
When the application is for clinical trials only, the generic name, drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in item nos.2.1, 2.3, 2.6, 2.7) are required.

3. Animal Pharmacology, if applicable.
3.1. Summary with specific pharmacological findings

4. Animal Toxicology (for details refer Appendix III)
4.1. General Aspects
4.2. Systemic Toxicity Studies
4.3. Male Fertility Study, if applicable (For other than hydro-alcoholic extracts)
4.4. Female Reproduction and Developmental Toxicity Studies, if applicable (For other than hydro-alcoholic extracts)
4.5. Local toxicity, if applicable (For other than hydro-alcoholic extracts)
4.6. Allergen city/Hypersensitivity, if applicable (For other than hydro-alcoholic extracts)
4.7. Genotoxicity, if applicable (For other than hydro-alcoholic extracts)
4.8. Carcinogenicity, if applicable (For other than hydro-alcoholic extracts)

5. Human / Clinical pharmacology (Phase I)
5.1. Summary

6. Therapeutic exploratory trials (Phase II)
6.1. Summary
6.2. Study report(s) as given in Appendix II

7. Therapeutic confirmatory trials (Phase III)
7.1. Summary
7.2. Individual study reports with listing of sites and Investigators.

8. Special studies, if applicable
8.1. Summary
8.3. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

9. Prescribing information

9.1. Proposed full prescribing information
9.2. Drafts of labels and cartons
10. Samples and Testing Protocol/s
10.1. Samples of crude drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

NOTES:

(1) All items may not be applicable to all drugs.
(2) For requirements of data to be submitted with application for clinical trials refer text of this proposed Schedule.

APPENDIX I-A (Of Proposed Schedule 'Z')

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR RENEWAL OF LICENSE TO MANUFACTURE AND SALE OF AN ASU DRUG.

1. Introduction
A brief description of the drug and the therapeutic class
2. Chemical and pharmaceutical information
2.1. Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; phyto-chemical properties
2.2. Dosage form and its composition
2.3. Test specifications
(a) active ingredients
(b) inactive ingredients
2.4. Tests for identification of the active ingredients and method of its assay
2.5. Outline of the method of manufacture of active ingredients
2.6. Stability data
3. Marketing information
3.1. Proposed package insert / promotional literature
3.2. Draft specimen of the label and carton
4. Post Marketing Surveillance studies conducted with approval of Licensing Authority
4.1. Summary
4.2. Sub-acute animal toxicity studies for intravenous infusions and injectables

Appendix II (Of Propose Schedule 'Z')

STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS

As per Schedule-Y with minor changes relevant to ASU drugs.

As per schedule

Appendix-III (Of Proposed Schedule 'Z') Animal Toxicology (non-clinical toxicity study)

Guidelines for Toxicity Studies:

1. ACUTE TOXICITY TEST

2. SUB- CHRONIC TOXICITY TESTS

3. GENOTOXICITY STUDIES (AMES TEST), IF APPLICABLE.

Required Toxicity studies shall be conducted in accordance to the guidelines describe in scheduled Y of Drug and Cosmetics Act of 1940.

Administration period

The period of administration of the test substance to animals will depend on the expected period of clinical use. The period of administration of the toxicity study may vary from country to country, according to its individual regulations.

The following table reflects commonly used ranges of administration periods:

Expected period of clinical use	Administration period for the toxicity study
Single administration or repeated administration for less than one week	2 weeks to 1 month
Repeated administration, between one week to four weeks	4 weeks to 3 months
Repeated administration, between one to six months	3 to 6 months
Long-term repeated administration for more than six months	9 to 12 months

As a rule, the test substance should be administered seven days a week. Administration periods for the toxicity study must be recorded in each result.

Herbal medicines are by nature considered as safer and non-toxic in comparison to synthetic chemicals and compounds. Therefore, in many cases, full battery of toxicity studies may not be applicable. In such cases, limited toxicity studies, which include acute oral toxicity and repeated dose oral toxicity of specified period as prescribed in the above table shall be applicable.

Animal toxicity requirements for clinical trials and marketing of a new ASU drug in term of number of animals, species, methodology of conducting study etc.:

As per Schedule-Y

Appendix-IV (Of Proposed Schedule 'Z') Animal Pharmacology

In the conduct of non-clinical research on ASU medicines, standard methods should usually be employed. However, the use of novel technologies and methods resulting from scientific progress should be encouraged.

Pharmacodynamic and general pharmacological methods should utilize animal models or bioassays that closely relate to human disease as described by either traditional or modern medicine.

Appendix-V (Of Proposed Schedule 'Z') Informed Consent

As per Schedule-Y

Appendix VI (Of Proposed Schedule 'Z')

UNDERTAKING BY THE INVESTIGATOR

As per Schedule-Y

Appendix VII (Of Proposed Schedule 'Z')

ETHICS COMMITTEE

As per Schedule-Y with inclusion of Clinician of respective field /speciality /system in place of clinician.

Appendix VIII (Of Proposed Schedule 'Z')

STABILITY TESTING OF ASU DRUGS

As per Schedule-Y with following modifications / specification in relation to the duration of the study-

(i) Study conditions for drug substances and formulations intended to be stored under general conditions.

Study	Study conditions	Duration of study
Long term	30°C± 2°C/65% RH ± 5%RH	6 months
Accelerated	40°C± 2°C/75% RH ± 5% RH	3 months

Appendix IX (Of Proposed Schedule 'Z')

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

As per Schedule-Y with following changes-

Under Title Page

c. The official name / number of the investigational drug (and other minor changes relevant to ASU drugs).

Appendix X (Of Proposed Schedule 'Z')

Data Elements for reporting serious adverse events occurring in a clinical trial

As per Schedule-Y

APPENDIX IV

INVESTIGATOR'S BROCHURE (IB)

Introduction

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

Contents of the Investigator's Brochure

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

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

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

1 Table of Contents

2 Introduction: This section includes information relevant to the stage of clinical development including the significant physical properties , chemical properties (wherever applicable), pharmaceutical, pharmacological (pharmacological class, advantages over other substances in that class and rationale for performing the proposed study), toxicological, , and

clinical information (anticipated prophylactic/ therapeutic or diagnostic indication(s)) of all ingredients. The introductory statement should necessarily provide the general approach to be followed in evaluating the Investigational Product.

3 Physical, Chemical, and Pharmaceutical Properties and Formulation parameters (standardization data on ASU formulation): A description should be provided of the Investigational Product substance(s), including the composition of the product and details procedures followed for standardizing the procedures . Information should also be provided on the excipients, if used.

Appropriate storage and dosage handling instructions should also be given.

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

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

· Species used

· Number and sex of animals in each group

· Unit dose (mg/kg)

· Dose interval

· Route of administration

· Duration of dosing

· 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

If relevant the following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to

be studied in humans. If applicable, the effective and non-toxic dose findings in the same animal species should be compared (i.e. The therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed.

(c) Toxicology as per guideline for evaluation of Ayurveda, Siddha and Unani Medicines and other Traditional Medicines

5 Effects in Humans:

A thorough discussion of the known effects of the investigational product(s) in humans or traditional use should be provided, including dose response, safety, efficacy, and other pharmacological activities. Brief summaries of other clinical studies conducted on the same product should be provided if available. Alternatively traditional use data with documentation should be provided.

(a) Safety and Efficacy

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

(b) Regulatory & Post-marketing Experiences

Any significant information arising from the marketed use should be summarised (eg. formulations, dosages, routes of administration, and adverse product reactions).

6 Summary of Data and Guidance for the Investigator

7 Bibliography

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

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

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

APPENDIX V

ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

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

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

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

1. before the clinical phase of the study commences,

2. during the clinical conduct of the study, and

3. after completion or termination of the study.

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

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

Legend :

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

E - IEC, • - Yes, ° - Not applicable

Title of the document	Purpose	**Located in files of**			
		I	**S**	**C**	**E**
Before the Clinical Phase of the Trial Commences					

During this planning stage the following documents should be generated and should be on file before the trial formally starts.						
1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	●	●	●	●
2	Signed protocol and amendments, if any, and sample case report form(CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	●	●	●	●
3	Information given to trial subject - informed consent form (including all applicable translations)	To document the informed consent	●	○	○	○
4	- Any other written information	To document that subjects will be given appropriate information (content and wording) to support their ability to give fully informed consent	●	○	○	○
5	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	●	●	●	●
6	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	●	●	●	●
7	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	●	●	●	●
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**

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

	and/or other relevant documents evidencing qualifications of Investigator(s) and Co-Investigator / Sub-Investigator(s)	qualifications and eligibility to conduct trial and/or provide medical supervision of subjects				
12	Normal value(s) / range(s) for medical / laboratory / technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	•	•	•	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	•	•	•	°
14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	•	•	•	°
15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	•	•	•	°
16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	•	•	°
	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded	•	•	•	°

		investigational product can be revealed without breaking the blind for the remaining subject's treatment				
17	Master randomisation list	To document method for randomisation of trial population	°	•	•	°
18	Pre-trial monitoring report	To document that the site is suitable for trial (may be combined with Trial initiation monitoring report)	°	•	•	°
19	Trial initiation monitoring report	To document that the trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with Pre-trial monitoring report)	•	•	•	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available						
20	Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	•	•	•	•
21	Any revision to: - protocol amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject	To document revisions of these trial related documents that take effect during trial	•	•	•	•

	recruitment(if used)					
22	Dated, documented approval / favourable opinion of Independent ethics committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information provided to subject - advertisement for subject recruitment(if used) - any other documents given approval / favourable opinion - continuing review of trial (where required)	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s).	•	•	•	•
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
23	Regulatory authority(ies) authorisations /	To document compliance with applicable regulatory requirements	•	•	•	•

	approvals / notifications where required for: - protocol amendment(s) and other documents					
24	Curriculum vitae for new investigator(s) and / or sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	•	•	•	•
25	Updates to normal value(s) / range(s) for medical / laboratory / technical procedure(s) / test(s) included in the protocol	To document normal values and ranges that are revised during the trial	•	•	•	°
26	Medical / laboratory / technical procedures / tests - certification or - accreditation or - established quality control and / or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period	•	•	•	°
27	Documentation of investigational product(s) and trial-related material shipment	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	•	•	•	°
28	Certificate(s) of analysis for new batches of investigational products	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	•	•	°
29	Monitoring visit	To document site visits	°	•	•	°

	reports	by, and findings of, the monitor				
30	Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	•	•	•	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
31	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	• (Original)	° (Copy)	• (Copy)	°
32	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trials, to medical treatment, and history of subject	• (Original)	• (Copy)	• (Copy)	°
33	Signed, dated and completed case report forms (CRF)	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	• (Copy)	• (Copy)	• (Copy)	°
34	Documentation of CRF corrections	To document all changes / additions or corrections made to CRF after initial data were recorded	• (Original)	• (Copy)	• (Copy)	°

35	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports	•	•	•	•
36	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IEC(s) of unexpected serious adverse drug reactions and of other safety information	•	•	•	•
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
37	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	•	•	•	•
38	Interim or annual reports to IEC and authority(ies)	Interim or annual reports provided to IEC and to authority(ies)	•	•	•	•
39	Subject screening log	To document identification of subjects who entered pre-trial screening	•	• (Where required)	• (Where required)	°
40	Subject identification code list	To document that investigator / Institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ Institution to reveal	•	°	•	°

		identity of any subject				
41	Subject enrolment log	To document chronological enrolment of subjects by trial number	•	• (Copy)	• (Copy)	°
42	Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol	•	•	•	°
43	Signature sheet	To document signatures and initials of all persons authorised to make entries and / or corrections on CRFs	•	•	•	°
44	Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	•	•	•	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	E
After Completion or Termination of the Trial After completion or termination of the trial, all of the documents identified should be in the file together with the following						
45	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, return by the subjects, and returned to sponsors	•	•	•	°
46	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site	• (if destroyed at site)	•	•	°
47	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up	•	°	•	°

		is required. List should be kept in a confidential manner and for agreed upon time				
48	Audit certificate (if available)	To document that audit was performed	°	•	•	°
49	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	°	•	•	°
50	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	°	•	•	°
Title of the document		Purpose	**Located in files of**			
			I	**S**	**C**	**E**
51	Final report by investigator to IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	•	•	•	•
52	Clinical study report	To document results and interpretation of trial	•	•	•	•