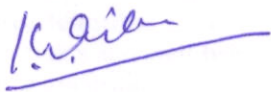


Standard Operating Procedures

◆ SOP Title:	Standard Operating Procedures of Institutional Ethics Committee at National Institute of Malaria Research
◆ SOP Author(s) :	IEC Committee Members
◆ SOP Status :	Final
◆ Version:	1 st - dated 06-04-2010, Effective date : 13-04-2011

Authored by: Dr. Neena Valecha, Member Secretary, IEC, NIMR, New Delhi.

Approved by:



Chairman, IEC, NIMR, New Delhi.

INSTITUTIONAL ETHIC COMMITTEE

NATIONAL INSTITUTE OF MALARIA RESEARCH

SOP NO: 1	SOP Title: Standard Operating Procedures to contribute towards	
Ver. No: 1	effective functioning of Institutional Ethics Committee of	
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1.0 OBJECTIVE:

The objective of this SOP is to contribute to the effective functioning of the Institutional Ethics Committee (IEC) at the National Institute of Malaria Research, New Delhi, India, so that a competent and consistent ethical review mechanism, in an objective manner, is put in place for all health and biomedical research proposals dealt by the committee in accordance with ICMR and DCGI guidelines for biomedical research in human subjects. (Ref. 1 page no 36)

2.0 SCOPE AND RESPONSIBILITIES:

- 2.1. The mandate of the IEC will be to review all research proposals involving human subjects to be conducted at the Institute, irrespective of the funding agency, with a view to safeguard the dignity, rights, safety and well being of all actual and potential research participants.
- 2.2. The goals of research however important should never be permitted to override the health and well being of the research subjects.
- 2.3. The IEC provides a multidisciplinary forum for the analysis and discussion of guidelines, regulatory laws and cardinal principles of research ethics (Reference I) viz. autonomy, beneficence, non-maleficence and Justice and ensures that these are adhered in planning, conducting and reporting of proposed research through the Committee's advisory, educational, policy development, and service functions.

Responsibilities of an IEC are defined as follows:-

- 2.4. To protect the dignity, rights and well being of the potential research participants, with particular care to protect all vulnerable subjects participating in the study, like members of a group with hierarchical structure (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.
- 2.5. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.
- 2.6. To assist in the development and education of a research community responsive to local health care needs.
- 2.7. To document its 'standard operating procedures' and should maintain a record of its proceedings.
- 2.8. To make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). 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.
- 2.9. 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.

3.0 PROCEDURES

3.1. Composition of IEC

1. Chairman
2. A Basic Scientist(2)
3. Two Clinicians(2) from various institutes
4. A Legal expert / retired judge
5. A Social Scientist/ representative of NGO voluntary organization.
6. A Philosopher/ Ethicist/ Theologian
7. A lay person
8. Member Secretary from NIMR

- 3.1.1. The **authority** under which IEC is constituted: DG, ICMR, New Delhi, to have at least 10-12 members.
- 3.1.2. The IEC appoints from among its members a **Chairman** who should be from outside the Institution and not head of the same Institution to maintain the independence of the Committee.
- 3.1.3. The **Member Secretary** is from this Institution and conducts the business of the Committee.
- 3.1.4. **Independent Consultants:** Based on the requirement of research area subject experts on ethical, legal, disease, methodology or representatives of patient groups, communities and special interest groups could be invited.

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3.1.5. If necessary, the applicant/investigator may be invited to present the protocol or offer clarifications in the meeting.

3.1.6. **Quorum** of Ethics committee: The minimum of 50% + 1 member are required to compose a quorum. All decisions should be taken in meetings and not by circulation of project proposals.

Note: Project proposals that approves drug trials should have at least **five** members and out of these one member has to be independent of institution / research site; balanced in gender; at least one representative of each following groups:

- a. One basic medical scientist (preferably one pharmacologist).
- b. One clinician
- c. One legal expert / retired judge
- d. One social scientist/NGO/philosopher/ethicist/theologian/similar person
- e. One lay person

3.1.7. Membership requirements and Terms of Reference :

- a. **Suitability criteria** include that they are to be **independent** of political, institutional, professional and market influences.
- b. The members are drawn from different Institutes, and specialties to give a multisectorial, multidimensional structure.
- c. **Qualities** of candidate include: interest and motivation, commitment and availability, experience and education, respect for divergent opinions, interest in committee work, integrity, diplomacy, trained in bioethics or conversant with ethical guidelines and laws of the country.
- d. **Conflict of Interest:** needs to be avoided, if unavoidable transparency should be there regarding interests.
- e. **Renewal of appointment:** duration of appointment is initially for a period of 3 years, extendable to another term.
- f. **Replacement:** At the end of 3 years, the committee is reconstituted, and 30% of the members will be replaced.
- g. **Removal:** A member can be replaced in the event of death or long-term assignments outside the country or for any misconduct deemed unfit for a member.
- h. **Resignation:** A member can tender resignation from the committee, which should be acceptable to the appointing authority.
- i. **Disqualification:** All members should maintain absolute confidentiality of all discussions during the meeting.
- j. **Substitute members:** may be nominated if **three or more** number of meetings are continuously missed by a member due to illness or other unforeseen circumstances.
- k. **Conditions of appointment: I:** a member should be willing to publicize his/her full name, profession and affiliation; **II:** all reimbursement for work and expenses, if any, within or related to an EC should be recorded and made available to the public upon request; **III:** a member should sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; in addition, all EC administrative staff should sign a similar confidentiality agreement.

3.2: APPLICATION PROCEDURE TO IEC:

3.2.1. the researcher must submit an application.

3.2.2. the name(s) and address(es) of the EC secretariat to whom application material is to be submitted:- **Member Secretary**

3.2.3. the language(s) in which (core) documents are to be submitted:- **English**

3.2.4. the means by which applications will be acknowledged:- **email/telephone;**

3.2.5. the application procedure for **amendments**. Revised document in required number of copies should be submitted within a stipulated period of time as specified in the communication or before the next meeting. Revisions can be in the protocol, the recruitment material, the potential research participant information, or the informed consent form

3.2.6. Notification to IEC by the Investigator and Sponsor are to be screened by Member Secretary and categorized depending on risk involved, communicated to Chairman, IEC and tabled in next IEC meeting.

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- 3.2.7 **Documentation** in prescribed format and number of copies:-- **Ten (10)**
 For a thorough and complete review, all research proposals to be submitted with the following documents:
- a. Name of the applicant with designation duly signed by Principal Investigator (PI) and Co-investigators or Collaborator
 - b. Name of the Institute/ Hospital / Field area where research will be conducted.
 - c. Approval of the Head of the Division.
 - d. **Protocol** of the proposed research (Appendix).
 - e. **Ethical issues** in the study and plans to address these issues like distribution of burden, benefits of research.
 - f. Case report format, patient dairy, questionnaires, follow up card etc.
 - g. Patient information sheet, **informed consent form** in local language and consent process.
 - h. For any drug / device trial, all relevant **pre-clinical data, clinical trial data** from other countries, if available.
 - i. Statement describing **compensation** for study subjects for participation and/or study related injuries.
 - j. Curriculum **vitae** of all the investigators with relevant publications in last five years.
 - k. Any **regulatory clearances** required.
 - l. Source of **funding** and financial requirements for the project..
 - m. An agreement to report any serious **side effects or adverse drug reactions** to IEC.
 - n. Statement of **conflicts of interest**, if any.
 - o. **Recruitment** material, procedure.
 - p. **Risk benefit ratio**
 - q. Description of arrangements for **indemnity** if applicable; **and insurance** for research participants.
 - r. All significant **previous decisions** of IEC with reasons and changes made to the protocol if any.
 - s. Any other **information** relevant to the study.

3.3 Screening of proposals for Ethical Review:

- 3.3.1. The IEC must review every research proposal on human participants before the research is initiated on approval by IEC.
 An investigator cannot decide that her/his protocol falls in the exempted category without approval from the IEC.
- 3.3.2. Prerequisite: EC must ensure that a scientific evaluation (SAC) has been completed before ethical review is taken up.
- 3.3.3. Member-secretary or secretariat are required to screen for their completeness and depending on the risk categorizes as :-

i) Exemption from review, ii) Expedited review iii) Full review (see Appendix III)

3.4 REVIEW PROCEDURES

3.4.1 Review Procedure Functions

- a. to review all new research proposals submitted and provide complete initial review of the research proposals by:
 - i: evaluating possible risks to the participants with proper justification;
 - ii evaluating the expected benefits;
 - iii: evaluating adequacy of documentation for ensuring privacy, confidentiality and the justice issues with overall objective of protecting the patient;
- b. to perform continuing responsibility of monitoring of approved programs for ethical compliance until completion;
- c. to evaluate progress/summary of ongoing research projects;
- d. to review serious adverse event (SAE) reports;
- e. to assess final reports/summary of all research activities involving human beings;
- f. to perform an independent advisory role within the institution by withholding approval or advising the institution for discontinuation of the trial, if necessary;
- g. to ensure adherence of research projects to regulatory laws, ethical considerations and guidelines.

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3.4.2 Frequency and Agenda of Ethic Review Meeting

Frequency

The meeting of the IEC will be held as and when the proposals are received for review. However, if need be, meetings can be held at scheduled intervals when large number of proposals are to be reviewed to ensure that a decision is not pending for more than **three (3) months**.

Agenda

The proposals will be sent to members at least **one (1) week** in advance along with:

- a. brief summary of the project with protocol
- b. informed consent and patient information sheet.

3.4.3 Review procedure methodology:

IEC should meet periodically at frequent intervals to review new proposals, evaluate annual progress/summary of ongoing ones, review serious adverse event (SAE) reports and assess final reports/summary of all research activities, involving human beings.

- a. The ethical review should be done in formal meetings and EC should not take decisions through circulation of proposals.
- b. If a member or conflict-of-interest (COI) involving a project then s/he should submit this in writing to the chairperson before the review meeting and withdraw, and it should also be recorded in the minutes
- c. One of the members has her/his own proposal for review then he/she should not vote for the approval.
- d. An IEC may decide to reverse its positive decision on a study if it receives information that may adversely affect the risk/ benefit ratio.
- e. 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.
- f. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
- g. The following circumstances require the matter to be brought to the attention of IEC for Followup review:
 - i. any amendment to the protocol from the originally approved protocol with proper justification;
 - ii. serious and unexpected adverse events and remedial steps taken to tackle them;
 - iii. any new information that may influence the conduct of the study.
- h. Meetings are to be minuted which must be approved and signed by the Chairperson/ alternate Chairperson/ designated member of the committee.
- i. All payments, reimbursement, medical services to be provided to research subjects should be approved by the IEC.
- j. 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 according to the insurance policy defined in the project.

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3.4.4 Element of Review

I: Scientific Design and Conduct of the Study

- a. the appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation), and the potential for reaching sound conclusions with the smallest number of research participants;
- b. the justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities;
- c. the justification for the use of control arms;
- d. criteria for prematurely withdrawing research participants;
- e. criteria for suspending or terminating the research as a whole;
- f. the adequacy of provisions made for monitoring and auditing the conduct of the research, including the constitution of a data safety monitoring board (DSMB);
- g. the adequacy of the site, including the supporting staff, available facilities, and emergency procedures;
- h. the manner in which the results of the research will be reported and published;

II Recruitment of Research Participants

- a. the characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity);
- b. the means by which initial contact and recruitment is to be conducted;
- c. the means by which full information is to be conveyed to potential research participants or their representatives;
- d. inclusion and exclusion criteria for research participants;

III Care and Protection of Research Participants

- a. the suitability of the investigator(s)'s qualifications and experience for the proposed study;
- b. any plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action;
- c. the medical care to be provided to research participants during and after the course of the research;
- d. the adequacy of medical supervision and psycho-social support for the research participants;
- e. steps to be taken if research participants voluntarily withdraw during the course of the research;
- f. the criteria for extended access to, the emergency use of, and/or the compassionate use of study products;
- g. the arrangements, if appropriate, for informing the research participant's general practitioner (family doctor), including procedures for seeking the participant's consent to do so;
- i. a description of any plans to make the study product available to the research participants following the research;
- j. a description of any financial costs to research participants;
- k. the rewards and compensations for research participants (including money, services, and/or gifts);
- l. the provisions for compensation/treatment in the case of the injury/disability/death of a research participant attributable to participation in the research;
- m. the insurance and indemnity arrangements;

IV Protection of Research Participant Confidentiality

- a. a description of the persons who will have access to personal data of the research participants, including medical records and biological samples;
- b. the measures taken to ensure the confidentiality and security of personal information concerning research participants;

V Informed Consent Process

- a. a full description of the process for obtaining informed consent, including the identification of those responsible for obtaining consent;
- b. the adequacy, completeness, and understandability of written and oral information to be given to the research participants and, when appropriate, their legally acceptable representative(s);
- c. clear justification for the intention to include in the research individuals who cannot consent, and a full account of the arrangements for obtaining consent or authorization for the participation of such individuals;
- d. assurances that research participants will receive information that becomes available during the course of the research relevant to their participation (including their rights, safety, and well-being);

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e. the provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project;

VI : Community Considerations

- a. the impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn;
- b. the steps taken to consult with the concerned communities during the course of designing the research;
- c. the influence of the community on the consent of individuals;
- d. proposed community consultation during the course of the research;
- e. the extent to which the research contributes to capacity building, such as the enhancement of local healthcare, research, and the ability to respond to public health needs;
- f. a description of the availability and affordability of any successful study product to the concerned communities following the research;
- g. the manner in which the results of the research will be made available to the research participants and the concerned communities.

VII Plans for data analysis and reporting

VIII Adherence to all regulatory requirements

3.4.5 Expedited / Interim Review

- a. All **revised** proposals, unless specifically required to go to the main committee, will be examined in a meeting of identified members convened by the Chairman to expedite decision making.
- b. This can be done for the following reasons:
 - i. re-examination of a proposal already examined by the IEC;
 - ii. research study of minor nature such as examination of case records etc;
 - iii. an urgent proposal of national interest;
- c. Decisions are taken subject to confirmation and brought to the notice of the next main ethic committee meeting.
- d. Responsibility:
 - i. The Member- Secretary and the Chairperson of the IEC or
 - ii. Designated member of the Committee or
 - iii. Subcommittee of the IEC

3.4.6 Periodic Review of Ongoing Research Project

The ongoing research may be reviewed at regular intervals.

3.4.7 Continuing Review of Ongoing Projects

The IEC has the responsibility to continue reviewing approved projects for continuation, new information, adverse event monitoring, follow-up and later after completion if need be.

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3.4.8 Decision making and communicating the decision

- a. The decision must be taken by a broad consensus; when a consensus appears unlikely, then decision may be taken by majority vote;
- b. Decisions should only be made at meetings where a quorum is fulfilled; documents required for a full review of the application are complete and the relevant review elements have been considered.
- c. A decision may only be taken when sufficient time has been allowed for review and discussion of an application in the absence of non-members (e.g., the investigator, representatives of the sponsor, independent consultants) from the meeting, with the exception of EC staff;
- d. Decision may be to approve, reject or modify the proposals or advise appropriate steps.
- e. In conditional decisions, specific suggestions should be given for modifications and the procedure for having the application of re-reviewed should be specified (repeat / interim review). Advice that is non-binding may be appended to the decision;
- f. A negative decision should always be supported by clearly defined reason.
- g. An IEC may decide to reverse its positive decision on a study if it receives information that may adversely affect the risk/ benefit ratio.
- h. Member Secretary should communicate the decision in writing to the PI.
- i. Decision is taken preferably within 1 week;
- j. Decisions taken by interim review meeting have to be tabled in the next main ethic committee.
- k. Name of the specific expert or member who made the review is not communicated.

The communication of the decision should include, but is not limited to, the following:

- a. the exact title of the research proposal reviewed;
- b. the clear identification of the protocol of the proposed research or amendment, date and version number (if applicable) on which the decision is based;
- c. the names and (where possible) specific identification numbers (version numbers/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;
- d. the name and title of the applicant;
- e. the date and place of the decision;
- f. the name of the EC taking the decision;
- g. A clear statement of the decision reached;
- h. Any advice by the EC;
- i. In the case of a conditional decision, any requirements by the EC, including suggestions for revision and the procedure for having the application re-reviewed;
- j. In the case of a positive decision, a statement of the responsibilities of the applicant; for example, confirmation of the acceptance of any requirements imposed by the EC; submission of progress report(s); the need to notify the EC in cases of protocol amendments (other than amendments involving only logistical or administrative aspects of the study); the need to notify the EC in the case of amendments to the recruitment material, the potential research participant information, or the informed consent form; the need to report serious and unexpected adverse events related to the conduct of the study; the need to report unforeseen circumstances, the termination of the study, or significant decisions by other ECs; the information the EC expects to receive in order to perform ongoing review; the final summary or final report;
- k. in the case of a negative decision, clearly stated reason(s) for the negative decision;
- l. signature (dated) of the chairperson/Member Secretary (or other authorized person) of the EC.

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3.5 Archiving/Record keeping

- a. All documentation and communication of an IEC are to be dated, filed and preserved after the completion/ termination of the study for a minimum period of 3 years.
- b. Strict confidentiality is to be maintained during access and retrieval procedures;
- c. The documents are to be accessible to Member Secretary and secretariat
- d. Documents, files and archives include, but are not limited to:
 - i. Standing operating procedures of the IEC;
 - ii. Constitution and composition of IEC;
 - iii. Copy of all existing national and international guidelines on research ethics;
 - iv. Curriculum Vitae (CV) of all members of IEC.
 - v. Training records of members, if any;
 - vi. Copy of all submissions by applicant , study protocols, enclosed documents, annual reports, event reports.
 - vii. Agenda of all IEC meetings and minutes of all meetings with due signature of Chairperson;
 - viii. Copy of all correspondence with members, researchers, regulatory bodies like application, follow up;
 - ix. Copies of decisions, advise communicated to the applicants;
 - x. Record of all notification of completion or premature suspension / termination of a study with reasons.
 - xi. Final summary / report of the approved projects.

3.6 Training and Updating IEC members

- 3.6.1. All relevant new guidelines or changes are to be brought to the attention of the members.
- 3.6.2. Members should be encouraged and supported to attend national and international training programs in research ethics for maintaining quality in ethical review and to be aware of the latest developments in this area.
- 3.6.3. They should be aware of local, social and cultural norms.
- 3.6.4. For drug trial review it is preferable to train the IEC members in Good Clinical Practice.

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4.0 ADMINISTRATION AND MANAGEMENT

- a. A full time secretariat and space for keeping records is required for a well functioning IEC.
- b. The members could be given a reasonable compensation for the time spared for reviewing the proposals.
- c. A reasonable fees can be charged to cover the expenses related to review and administrative processes.
- d. Institution may allocate funds for smooth functioning of the IEC.
- e. SOP of IEC is not a confidential document and is required to be made publicly available (internet/website)
- f. SOP will be drafted, amended by EC Secretariat and approved by IEC.

Authored by :	Dr. Neena Valecha, Member Secretary	Date: 06-04-2010
Approved by :	Dr. K.D.Tripathi,Chariman	Date: 13-04-2011

This is not a confidential document and has to be publicly available.

DEFINITIONS

Act

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

Adverse Event (AE)

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

Adverse Drug Reaction (ADR)

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

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

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

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

Audit of a Trial

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

- (a) (a) Study related activities to determine consistency with the *Protocol*
- (b) (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) (c) Compliance with the adopted Standard Operating Procedures (*SOPs*)

Blinding / Masking

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

Case Record Form (CRF)

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

Clinical Trial (Clinical Study)

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

Human/Clinical Pharmacology trials (Phase I)

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

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

Exploratory trials (Phase II)

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

Confirmatory trials (Phase III)

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

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

Phase IV

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

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

Comparator Product

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

Confidentiality

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

Co-Investigator

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

Co-ordinating Investigator

See Principal Investigator

Clinical Research Organisation (CRO)

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

Contract

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

Documentation

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

Escape Treatment

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

Essential Documents

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

Ethics Committee

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

Final Report

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

Good Clinical Practice (GCP)

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

Impartial Witness

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

Informed Consent

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

Inspection

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

Institution

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

Investigator

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

Investigational Labelling

Labelling developed specifically for products involved in the study.

Investigational Product

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

Investigator’s Brochure

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

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.

Minimal risk would be defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of general population or during the performance of routine physical or psychological examinations or tests.

However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current every day life.

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.

Non-Clinical Study

Biomedical studies that are not performed on human subjects.

Non-Therapeutic Study

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

Pharmaceutical Product(s)

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

Principal Investigator

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

Protocol

A document that states the background, objectives, rationale, design, methodology (including the methods for dealing with AEs, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed. The content and format of the protocol should take into consideration the adopted SOPs, the regulatory requirements and the guiding principles of GCP. The term Protocol, unless otherwise specified, relates to the latest amended version of the document, read in conjunction with all its appendices and enclosures.

Protocol Amendment(s)

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

Quality Assurance (QA)

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

Quality Control (QC)

The operational techniques and activities undertaken within the system of QA to verify that the requirements for quality of the trial related activities have been fulfilled. QC activities concern everybody involved with planning, conducting, monitoring, evaluating, data handling and reporting. The objective of QC is to avoid exposure of study subjects to unnecessary risks and to avoid false conclusions being drawn from unreliable data.

Randomisation

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

Regulatory Authority

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

Raw Data

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

Schedule

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

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

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

Source Data

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

Sponsor

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

Study Product

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

Sub-Investigator: See *Co-Investigator*

Subject Files / Patient Files

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

Study Subject (Subject)

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

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

Standard Operating Procedures (SOP)

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

Subject Identification Code

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

Study Management

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

Validation 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.

CONSTITUTION OF ETHICS COMMITTEE

1. Chairman
2. Basic Scientists (2)
3. Two Clinicians (2) from various institutes
4. A Legal expert / retired judge
5. A Social Scientist/ representative of NGO voluntary organization.
6. A Philosopher/ Ethicist/ Theologian
7. A lay person
8. Member Secretary from NIMR

ICMR Guideline: www.icmr.nic.in/human_ethics.htm**1. Exemption from review**

Proposals which present less than minimal risk fall under this category as may be seen in following situations: Research on educational practices such as: (a) instructional strategies or (b) effectiveness of instructional techniques or (c) the comparison among instructional techniques, curricula, or classroom management methods.

Exceptions:

- I. When research on use of educational tests, survey or interview procedures, or observation of public behavior can identify the human participant directly or through identifiers, and the disclosure of information outside research could subject the participant to the risk of civil or criminal or financial liability or psychosocial harm.
- II. When interviews involve direct approach or access to private papers.

2. Expedited Review

Qualifying Criterion: The proposals presenting no more than minimal risk to research participants may be subjected to expedited review, only if the protocols involve -

1. Minor deviations from originally approved research during the period of approval (usually of one year duration).
2. Revised proposal previously approved through full review by the IEC or continuing review of approved proposals where there is no additional risk or activity is limited to data analysis.
3. Research activities that involve only procedures listed in one or more of the following categories:
 - a. Clinical studies of drugs and medical devices only when -
 - i. research is on already approved drugs except when studying drug interaction or conducting trial on vulnerable population or
 - ii. adverse Event (AE) or unexpected Adverse Drug Reaction (ADR) of minor nature is reported.
4. Research involving clinical materials (data, documents, records, or specimens) that have been collected for non-research (clinical) purposes.
5. When in emergency situations like serious outbreaks or disasters a full review of the research is not possible, prior written permission of IEC may be taken before use of the test intervention. Such research can only be approved for pilot study or preliminary work to study the safety and efficacy of the intervention and **the same participants should not be included** in the clinical trial that may be initiated later based on the findings of the pilot study.
 - a. **Research on interventions in emergency situation:** When proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, physicians may use new intervention as investigational drug (IND) / devices/ vaccine to provide emergency medical care to their patients in life threatening conditions. Research in such instance of medical care could be allowed in patients –
 - i. when consent of person/ patient/ responsible relative or custodian/ team of designated doctors for such an event is not possible. However, information about the intervention has to be given to the relative/ legal guardian when available later;
 - ii. when the intervention has undergone testing for safety prior to its use in emergency situations and sponsor has obtained prior approval of DCGI;
 - iii. only if the local IEC reviews the protocol since institutional responsibility is of paramount importance in such instances.
 - iv. if Data Safety Monitoring Board (DSMB) is constituted to review the data;

b. Research on disaster management: A disaster is the sudden occurrence of a calamitous event at any time resulting in substantial material damage, affecting persons, society, community or state(s). It may be periodic, caused by both nature and humans and creates an imbalance between the capacity and resources of the society and the needs of the survivors or the people whose lives are threatened, over a given period of time. It may also be unethical sometimes not to do research in such circumstances. Disasters create vulnerable persons and groups in society, particularly so in disadvantaged communities, and therefore, the following points need to be considered when reviewing such research:

- i. Research planned to be conducted after a disaster should be essential culturally sensitive and specific in nature with possible application in future disaster situations.
- ii. Disaster-affected community participation before and during the research is essential and its representative or advocate must be identified.
- iii. Extra care must be taken to protect the privacy and confidentiality of participants and communities.
- iv. Protection must be ensured so that only minimal additional risk is imposed.
- v. The research undertaken has to provide direct or indirect benefits to the participants, the disaster-affected community or future disaster- affected population and *a priori* agreement has to be reached on this, whenever possible, between the community and the researcher.

- vi. All international collaborative research in the disaster-affected area has to be done with a local partner on equal partnership basis.
- vii. Transfer of biological material, if any, has to be done as per Government rules taking care of intellectual property rights issues.

3. Full Review

Full review by all the members has to be done for all research presenting with:

- a) more than minimal risk,
- b) proposals/ protocols which do not qualify for exempted or expedited review and
- c) projects that involve vulnerable population and special groups

Following situations are to be carefully assessed against the existing facilities at the research site for risk/benefit analysis:

a. Collection of blood samples by finger prick, heel prick, ear prick, or veni puncture:

- i. from healthy adults and non-pregnant women who weigh normal for their age and not more than 500 ml blood is drawn in an 8 week period and frequency of collection is not more than 2 times per week;
- ii. from other adults and children, where the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected has been considered and not more than 50 ml or 3 ml per kg, whichever is lesser is drawn in an 8 week period and not more than 2 times per week;
- iii. from neonates depending on the haemodynamics, body weight of the baby and other purposes not more than 10% of blood is drawn within 48 – 72 hours. If more than this amount is to be drawn it becomes a risky condition requiring infusion/blood transfusion;
- iv. prospective collection of biological specimens for research purposes by noninvasive means for instance:
 1. skin appendages like hair and nail clippings in a non-disfiguring manner;
 2. dental procedures - deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction of permanent teeth; supra and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth;
 3. excreta and external secretions (including sweat);
 4. uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum or by applying a dilute citric solution to the tongue;
 5. placenta removed at delivery;
 6. amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
 7. mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 8. sputum collected after saline mist nebulization and bronchial lavages.

b. Collection of data through noninvasive procedures routinely employed in clinical practice. Where medical devices are employed, they must be cleared/ approved for marketing, for instance -

- i. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy;
- ii. weighing or testing sensory acuity;
- iii. magnetic resonance imaging;
- iv. electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow,
- v. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

c. Research involving clinical materials (data, documents, records, or specimens) that will be collected solely for non-research (clinical) purposes.

d. Collection of data from voice, video, digital, or image recordings made for research purposes.

e. Research on individual or group characteristics or behavior not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

PROTOCOL ELEMENTS FOR SUBMISSION OF APPLICATION (SCH Y AND ICMR GUIDELINE CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS)

1. Title Page

- a. Full title of the clinical study,
- b. Protocol / Study number, and protocol version number with date
- c. The IND name/number of the investigational drug
- d. Complete name and address of the Sponsor and contract research organization if any
- e. List of the Investigators who are conducting the study, their respective institutional affiliations and site locations
- f. Name(s) of clinical laboratories and other departments and/or facilities participating in the study.

2. Table of Contents

A complete Table of Contents including a list of all Appendices.

1. Background and Introduction

- a. Preclinical experience
- b. Clinical experience

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

2. Study Rationale

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

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

4. Study Design

- a. Overview of the Study Design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Subjects in each group and investigative site, Subject number assignment, and the type, sequence and duration of study periods.
- b. Flow chart of the study
- c. A brief description of the methods and procedures to be used during the study.
- d. Discussion of Study Design: This discussion details the rationale for the design chosen for this study.

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

6. Subject Eligibility

- a. Inclusion Criteria
- b. Exclusion Criteria

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

8. Study Conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc. Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued Subjects: Describes the circumstances for Subject withdrawal, dropouts, or other reasons for discontinuation of Subjects. State how drop outs would be managed and if they would be replaced

Describe the method of handling of protocol waivers, if any. The person(s) who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

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

9. Study Treatment

- a. Dosing schedule (dose, frequency, and duration of the experimental treatment) Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.
 - b. Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations Details of the product stability, storage requirements and dispensing requirements should be provided.
 - c. Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.
 - d. Possible drug interactions
 - e. Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Subject is not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrollment, these should be described here.
 - f. Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Subject
 - g. Unblinding procedures: If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used for unblinding should be given.
- 10. Adverse Events** (See Appendix XI): Description of expected adverse events should be given. Procedures used to evaluate an adverse event should be described.
- 11. Ethical Considerations:** Give the summary of:
- a. Risk/benefit assessment:
 - b. Ethics Committee review and communications
 - c. Informed consent process
 - d. Statement of Subject confidentiality including ownership of data and coding procedures
- 12. Study Monitoring and Supervision:** A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring. Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specifics required in filling out the forms CRF correction requirements, including who is authorized to make corrections on the CRF and how queries about study data are handled and how errors, if any, are to be corrected should be stated. Investigator study files, including what needs to be stored following study completion should be described.
- 13. Investigational Product Management**
- a. Give Investigational product description and packaging (stating all Ingredients and the formulation of the investigational drug and any placebos used in the study)
 - b. The precise dosing required during the study
 - c. Method of packaging, labeling, and blinding of study substances
 - d. Method of assigning treatments to Subjects and the Subject identification code numbering system
 - e. Storage conditions for study substances
 - f. Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned/destroyed.
 - g. Describe policy and procedure for handling unused investigational products.
- 14. Data Analysis:**
- Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.
- Statistical analysis:** Give complete details of how the results will be analyzed and reported along with the description of statistical tests to be used to analyze the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and Subject withdrawals; rationale and conditions for any interim analysis if planned.
- Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable
- 15. Undertaking by the Investigator** (see Appendix VII)
- 16. Appendices:** Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.
- 17. Registration** of Clinical Trial.
- 18.** Recent curriculum vitae of the Investigators indicating qualification and experience.
- 19.** Participant recruitment procedures and brochures, if any.
- 20.** Plan to withdraw or withhold standard therapies in the course of research.
- 21.** An account of storage and maintenance of all data collected during the trial.
- 22.** Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.

23. Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.
24. Details of Funding agency/ Sponsors and fund allocation.
25. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee(HMSC) or appropriate Committees under other agencies/authority like Drug Controller General of India (DCGI).
26. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners.
27. A statement on conflict-of-interest (COI), if any.

Compensation for Participation (Sch Y)

All payments, reimbursement and medical services to be provided to research subjects should be approved by the IEC. 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). Care should be taken:

- i. when a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;
- ii. when a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation;
- iii. when a subject withdraws for any other reasons he/she should be paid in proportion to the amount of participation.

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

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

Informed Consent Process (Sch Y)

Informed Consent of Subject:

1. Prior to the beginning of the Study the Investigator(s) should obtain the Ethics Committee's approval for the written informed consent form and all information being provided to the Subjects and / or their legal representatives or guardians as well as an impartial witness. **2.** 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. **3.** 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. **4.** 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. **5.** 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. **6.** 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. **7.** Persons with incurable diseases, in nursing homes, in detention, unemployed or impoverished, in emergency rooms, homeless persons, nomads, refugees and any ethnic or racial minority groups should be considered as vulnerable population **whose mode of consent should be carefully considered and approved by the Ethics Committee.**

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

1. (i) The Subject *or* (ii) if the Subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Subject's legal representative or guardian *or* (iii) if the Subject and his legal representative or guardian is unable to read / write,
2. An impartial witness who should be present during the entire informed consent discussion
3. The Investigator

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

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

Essential information for prospective research on subjects:

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

- i. the aims and methods of the research;
- ii. the expected duration of the subject participation;
- iii. the benefits that might reasonably be expected as an outcome of research to the subject or to others;
- iv. any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected;

- v. any foreseeable risk or discomfort to the subject resulting from participation in the study;
- vi. right to prevent use of his/her biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;
- vii. the extent to which confidentiality of records could be able to safeguard, confidentiality and the anticipated consequences of breach of confidentiality;
- viii. free treatment for research related injury by the investigator / institution;
- ix. compensation of subjects for disability or death resulting from such injury;
- x. freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to;
- xi. the identity of the research teams and contact persons with address and phone numbers;
- xii. foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;
- xiii. risk of discovery of biologically sensitive information;
- xiv. publication, if any, including photographs and pedigree charts.

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

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)

Waiver Of Informed Consent

The IEC may waive the requirements for obtaining informed consent or approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent listed above, provided that :-

1. The research involves no more than minimal risk to the subjects
2. The waiver or alteration will not adversely effect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Consent Process by using a consent form that has been reviewed and approved by the IEC. The following are the acceptable methods for documentation of informed consent of human research subjects:-

1. **The IEC must be made aware of the person (s) who will be conducting the consent interviews.** These faculty/staff members should be the only personnel allowed to obtain consent unless indicated otherwise. The IEC requires that the person obtaining consent is medically trained.
2. Each subject (or their legally authorized representative) must be provided adequate time to read and review the consent form, in addition to being advised of the procedures, risks, potential benefit, alternatives to participation, etc. This is frequently accomplished using the consent form as an outline for the interview process.
3. After completing the consent interview and assuring that the subject (or their representative) has no further questions and agrees to participate in the research activity, the interviewer should instruct the subject to sign and date the consent form in the appropriate spaces.
4. A witness must sign and date in the appropriate spaces. The witness cannot be the person conducting the consent interview, but is not further restricted.
5. The person conducting the consent interview must then sign and date the consent form in the appropriate spaces (PI or designee). It is assumed that in most cases, all persons signing the consent form will do so at the conclusion of the consent interview.
6. Each subject (or their representative) must be given a copy of the signed consent form. The original consent form should be filed in such a manner as to insure immediate retrieval when required by auditing entities, IEC, or sponsor monitors.
7. The regulations are clear that written documentation informed consent is required. Therefore, obtaining consent from an authorized third party via the telephone is not acceptable.
8. The regulations also include provisions for approval of a waiver or alteration of part or all of the consent process. The IEC will consider written requests for waiver or alteration of the process when accompanied by sufficient justification.
9. Obtaining informed consent from subjects must be accomplished prior to performing the research activity and using only an IEC approved consent form. Written requests for amendments to an existing consent form must be approved by the IEC prior to implementation.
10. Upon receipt of an IEC approved consent form, all old versions should be discarded to prevent inadvertent use of an outdated consent form. Copies of the most recently approved consent form may be made and should be used until superseded by an amended consent form. The consent form must be reviewed at least annually as part of the continuing review process.

Selection of Special Groups As Research Subject (Sch Y)

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.

Children:

Before undertaking trial in children the investigator must ensure that -

- a. children will not be involved in research that could be carried out equally well with adults;
- b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;
- c. a parent or legal guardian of each child has given proxy consent;
- d. the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc;
- e. research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;
- f. interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;
- g. the child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian;
- h. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child subject as any available alternative interventions;
- i. the risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained.

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.

Communication / Role of Investigator and Sponsor with Ethic Committee

Investigator's communication with Ethics Committee (Sch Y 3.3.4.)

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.
6. 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).

Sponsor's Role in confirmation of review by the Ethics Committee (Sch Y 3.1.7.)

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

1. The particulars about the members of the Investigator's / Institution's Ethics Committee including their names, addresses, qualifications and experience
2. An undertaking that the Ethics Committee is organised and operates according to the GCP and the applicable laws and regulations.
3. Documented approval / favourable opinion of the Ethics Committee before the initiation of the Study
4. 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
5. Ethics Committee's documents relating to re-evaluations / re-approvals with favourable opinion, and of any withdrawals or suspensions of approval / favourable opinion

FORMAT I

NATIONAL INSTITUTE OF MALARIA RESEARCH, DWARKA, NEW DELHI

INTIMATION OF START OF STUDY

1. Project/Trial Code Number:
2. Title of the drug/multicentric trial:
3. Principal Investigator (Name & Department):
4. Sponsor:
5. Contract Research Organization (CRO) if any:
6. Date of sanction by IEC:
7. Date of start:

Date:

(Signature of Principal Investigator)

NATIONAL INSTITUTE OF MALARIA RESEARCH, DWARKA, NEW DELHI

PROGRESS REPORT / FINAL REPORT

1. Project/Trial Code Number
2. Title of the drug/multicentric trial
3. Principal Investigator (Name & Department)
4. Sponsor
5. Contract Research Organization (CRO) if any
6. Date of sanction by IEC
7. Date of start
8. Objectives of the study
9. Progress report as per objectives (attach separate sheet)
10. Serious Adverse Events if any with details (in summary form)
11. Protocol deviation if any with reasons/justifications
12. Report/publications/conference presentation
13. Awards/recognition

Date:

(Signature of Principal Investigator)

(Signature of Head of the Department)

NATIONAL INSTITUTE OF MALARIA RESEARCH

APPLICATION TO ETHICS COMMITTEE

(Form to be filled by the Principal Investigator (PI) for submission to Institutional Ethics Committee (IEC) for attachment to each copy of the proposal)

Code No. of IEC:

* To be filled by IEC Member Secretary

Proposal Title:

Name, Designation & Qualifications:

Departmental Tel. Nos.:

Email ID:

Signature:

Principle Investigator: _____

Co- Principle Investigator / Collaborators: 1. _____

2. _____ **3.** _____

Please attach Curriculum Vitae of all Investigators (with subject specific publications limited to previous 5 years) not working at NIMR. The investigators should sign their CV.

Sponsor Information:

1. Indian a) Government () Central () State () Institutional ()
b) Private ()

2. International a) Government () Private () UN Agencies()

3. Industry b) National () Multinational()

4. Contact address of sponsor: _____

5. Budget: _____

1. Type of study: Epidemiological () Basic Sciences() Behavioral()
Clinical () Single Centre() Multicentric()

2. Status of review: New () Revised ()

3. Clinical trial of: Drug / Vaccines / Device / Herbal Remedies / Insecticide

i. Does the study involve use of Drugs () Devices () Vaccines () Indian Systems () Any Other() None() of Medicines/
Alternate systems of Medicine.

ii. Is it approved and marketed In India () UK & Europe() USA()
Other Countries, Specify _____

iii. Does it involve a change in use, dosage, route of administration? Yes () No ()
If yes, whether DCGI's/Any other Regulatory Authority's Permission is obtained? Yes() No()

If yes, copy of permission attached Yes () No ()

iv. Is it an Investigational New Drug? Yes () No ()
If yes

- a. Investigator's Brochure enclosed: Yes () No ()
 b. Preclinical studies data available (If yes, provide summary): Yes () No ()
 c. Clinical studies data available (If yes, provide summary) : Yes () No ()
 d. Clinical study is Phase I () Phase II () Phase III () Phase IV () NA ()
 e. DCGI's permission obtained Yes () No () **If yes**, copy of letter enclosed Yes () No ()

4. Brief description of the proposal-aim(s) and objectives, justification for study, methodology describing the potential risks and benefits, outcome measures, statistical analysis and whether it is of national significance with rationale (Attach sheet with maximum 500 words)

5. Subject selection

- i. Number of subjects _____
 ii. Duration of (a) Study _____ (b) Subject participation: _____
 iii. Will subjects from both sexes be recruited Yes () No ()
 iv. Inclusion/exclusion criteria given Yes () No ()
 v. Type of subjects: Volunteers () Patients ()
 vi. Vulnerable subjects: Yes () No ()
 If yes (Tick the appropriate boxes)
 Pregnant Women () Children () Elderly () Fetus () Illiterate () Handicapped ()
 Terminally ill () Seriously ill () Mentally () Challenged Economically & () Any other ()
 vii. Special group subjects Yes () No ()
 (Tick the appropriate boxes)
 Captives () Institutionalized () Employees ()
 Students () Nurses/Dependent () Armed () Forces Any Other () Staff ()

6. Privacy and confidentiality

- i. Study Involves Direct Identifiers () Indirect Identifiers/Coded () Completely Anonymised /Delinked ()
 ii. Confidential handling of data by staff Yes () No ()

7. Use of biological/hazardous materials

- i. Use of fetal tissue or abortus. **If yes** provide details Yes () No ()
 ii. Use of organs or body fluids. **If yes** provide details Yes () No ()
 iii. Use of recombinant/gene therapy products Yes () No ()
If yes, has Department of Biotechnology (DBT) approval for rDNA products been obtained? Yes () No ()
 iv. Use of pre-existing/stored/left over samples Yes () No ()
 v. Collection for banking/future research Yes () No ()
 vi. Use of ionizing radiation/radioisotopes Yes () No ()
If yes, has Bhabha Atomic Research Centre (BARC) approval for
 Radioactive Isotopes been obtained? Yes () No ()
 vii. Use of Infectious/biohazardous specimens Yes () No ()
 viii. Proper disposal of material Yes () No ()
 ix. Will any sample collected from the patients be sent abroad? Yes () No ()
If yes, give details and address of collaborators
 a. Sample will be sent abroad because (Tick appropriate box)
 Facility not available in India () Facility in India inaccessible () Facility available but not being accessed ()
 If so, reasons _____
 b. Has necessary clearance been obtained Yes () No ()

8. Consent * Written () Oral () Audio-Visual ()

- i. **Patient Information Sheet attached:** (Tick the included elements) Yes () No ()
 Understandable language () Alternatives to participation ()
 Statement that study involves research () Confidentiality of records ()
 Sponsor of study () Contact information ()
 Purpose and procedures () Statement that consent is voluntary ()
 Risks & discomforts () Right to withdraw ()
 Benefits () Consent for future use of material biological ()
 Compensation for participation ()
 Benefits if any on future commercialization e.g. Genetic basis for drug development ()
 Compensation for study related injury ()
 Translation of information sheet in local language ()
 ii. If healthy volunteers will be included, information sheet for them attached Yes () No ()
 iii. Consent form in English () Local Languages ()

iv. Who will obtain consent? PI-Co-PI () Nurse/Counsellor () Research Staff () Any Other ()
*If written consent is not obtained, give reasons

9. Will any advertising be done for recruitment of Subjects? Yes() No()
(Posters, flyers, brochure, websites – if so attach a copy)

10. Risks & benefits

i. Is the risk reasonable compared to the anticipated benefits to subjects/community/country? Yes () No()
ii. Is there physical/social/psychological risk/discomfort? Yes() No()
If yes, Minimal or no risk () More than minimum risk() High risk()
iii. Is there benefit a) to the subject? Yes() No() Direct () Indirect ()
b) to the society Yes() No()

11. Data monitoring

i. Is there a data & safety monitoring committee/Board (DSMB)? Yes () No ()
ii. Is there a plan for reporting of adverse events? Yes () No ()
If yes, reporting will be done to Sponsor () IEC() DSMB()
iii. Is there a plan for interim analysis of data? Yes () No ()

12. Is there compensation for injury? Yes() No()

If yes, by Sponsor() Investigator() Insurance Company() Any Other ()

13. Do you have conflict of interest? No()Yes() If yes, specify _____

(Financial/Non financial)

Check list for attached documents:

- Project proposal-11 copies ()
- Curriculum Vitae of non SGPGI Investigators ()
- Brief description of proposal/summary ()
- Copy of the Protocol/Project and questionnaire (if any) ()
- Investigator’s Brochure, if applicable ()
- Copy of Patient information sheet & Consent form in local language ()
- Copy of Advertisements/Information brochures ()
- DCGI/DBT/BARC clearance if obtained ()
- Copy of Insurance Policy ()
- Copy of Clinical trial agreement ()
- Copy of IEC proforma ()
- Copy of PI undertaking, if applicable ()
- Copy of Case Report Form ()

Signature of PI

Date

Signature of HOD

**NATIONAL INSTITUTE OF MALARIA INSTITUTE
UNDERTAKING BY THE PRINCIPAL INVESTIGATOR**

1. NAME AND CODE NUMBER OF THE PROJECT:
2. NAME, DESIGNATION AND DEPARTMENT OF THE PRINCIPAL INVESTIGATOR:
3. OTHER MEMBERS OF THE RESEARCH TEAM:
4. NAME AND ADDRESS OF ANY OTHER MEDICAL COLLEGE, HOSPITAL OR INSTITUTION WHERE PARTS OF THE STUDY WILL BE DONE:
5. NUMBER OF ONGOING PROJECTS/CLINICAL TRIALS IN WHICH YOU ARE PI:
 - a. I confirm that I will initiate the study only after obtaining all regulatory clearances.
 - b. I will not implement any deviation from the approved protocol without prior consent of the sponsor nature and it will be intimated to the IEC at the earliest.
 - c. I confirm that the CO PI and other members of the study team have been informed about their obligations and are qualified to meet them
 - d. I will personally supervise the study and ensure that requirements of obtaining informed consent and other ethical requirements under ICMR and National Regulatory Guidelines are adhered to.
 - e. I will maintain accurate and complete record of all cases in accordance with GCP provisions and make them available for audit/inspection by IEC, Regulatory authorities, Sponsors or their authorized representatives.
 - f. I will inform the IEC and the Sponsors of any unexpected or serious adverse event at the earliest and definitely within seven days of its occurrence.
 - g. I will maintain confidentiality of the identity of all participating subjects and assure security and confidentiality of study data.
 - h. I and my colleagues will comply with statutory obligations, requirements and guidelines applicable to such clinical studies.
 - i. I will inform IEC of the date of starting the study within 2 weeks of initiation of the trial and submit progress reports and final report to Member Secretary, IEC within 4 weeks of the due date.

Signature of Principal Investigator Date

STATEMENT OF GENERAL PRINCIPLES

Any research using the human beings as participants shall follow the principles given below –

I. Principles of essentiality whereby the research entailing the use of human participants 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.

II. Principles of voluntariness, informed consent and community agreement whereby research participants are fully apprised of the research and the impact and risk of such research on the research participant and others; and whereby the research participants 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 such human participants or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research participant, these principles of voluntariness and informed consent shall apply, *mutatis mutandis*, to the community as a whole and to each individual member who is the participant of the research or experiment. Where the human participant is incapable of giving consent and it is considered essential that research or experimentation be conducted on such a person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research participants by someone who is empowered and under a duty to act on their behalf. The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applied use so that research participants are continually kept informed of any and all developments in so far as they affect them and others. However, without in any way undermining the cardinal importance of obtaining informed consent from any human participant involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall depend upon the degree and seriousness of the invasiveness into the concerned human participant's person and privacy, health and life generally, and, the overall purpose and the importance of the research. Ethics committee shall decide on the form of consent to be taken or its waiver based on the degree of risk that may be involved.

III. Principles of non-exploitation whereby as a general rule, research participants 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 participants 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. Such human participants should be selected so that the burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice. Each research shall include an in-built mechanism for compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.

IV. Principles of privacy and confidentiality whereby the identity and records of the human participants of the research or experiment are as far as possible kept confidential; and that no details about identity of said human participants, 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 participant concerned, or someone authorised on their behalf; and after ensuring that the said human participant does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

Principles in Biomedical Research Involving Human Participants

V. 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 participant and those affected by it including community are put to the minimum risk, suffer from no known irreversible adverse effects, and generally, benefit from and by the

research or experiment; and that requisite steps are taken to ensure that both professional and ethical reviews of the research are undertaken at appropriate stages so that further and specific guidelines are laid down, and necessary directions given, in respect of the conduct of the research / experiment.

VI. 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 are mindful of, preferably through training, the ethical considerations to be borne in mind in respect of such research or experiment.

VII. 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 research or experiment of each aspect of their interest in the research, 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.

VIII. 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 participants themselves and or the community from which they are drawn.

IX. 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.

X. 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.

Statement of General Principles in Biomedical Research Involving Human Participants

XI. 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.

XII. 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 participant 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.

These 12 principles laid down under Statement on General Principles are common to all areas of biomedical research. The specific issues are mentioned under relevant topics.

Applying the Ethical Principles

Respect for Persons. Required by the moral principle of respect for persons, **informed consent** contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether or not to participate, including the research procedure(s), their purposes, risks and anticipated benefits,

alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Responding to the question of what constitutes adequate information, the Report suggests that a "reasonable volunteer" standard be used: "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate to the extent they are able to do so, and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (*e.g.*, minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. ECs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence. Closely related to the principle of beneficence, **risk/benefit assessments** "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the EC and the investigator and EC insistence upon precise answers to direct questions. The EC should: (1) determine the "validity of the presuppositions of the research;" (2) distinguish the "nature, probability and magnitude of risk with as much clarity as possible;" and (3) "determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies."

Five basic principles or rules apply when making the risk/benefit assessment: (1) "brutal or inhumane treatment of human subjects is never morally justified;" (2) risks should be minimized, including the avoidance of using human subjects if at all possible; (3) ECs must be scrupulous in insisting upon sufficient justification for research involving "significant risk of serious impairment" (*e.g.*, direct benefit to the subject or "manifest voluntariness of the participation" (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice. The principle of justice mandates that the **selection of research subjects** must be the result of fair selection procedures and must also result in fair selection outcomes. The "justness" of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because the researcher favors them or because they are held in disdain (*e.g.*, involving "undesirable" persons in risky research). Further, "social justice" indicates an "order of preference in the selection of classes of subjects (*e.g.*, adults before children) and that some classes of potential subjects (*e.g.*, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Investigators, institutions, or ECs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that "arises from social, racial, sexual, and cultural biases institutionalized in society."

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are "easy to manipulate as a result of their illness or socioeconomic condition." Care should be taken to avoid overburdening institutionalized persons who "are already burdened in many ways by their infirmities and environments." Nontherapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate[s] to the specific conditions of the class involved."