

**National Institute of Tuberculosis and Respiratory Diseases**



**ETHICAL GUIDELINES  
FOR  
BIOMEDICAL RESEARCH  
ON  
HUMAN SUBJECTS**

Based on

ICMR, CDSCO, GCP & International Ethical Guidelines

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# ABBREVIATIONS

<b>CDSO</b>	:	Central Drugs Standard Control Organization
<b>CECHR</b>	:	Central Ethics Committee on Human Research
<b>CIOMS</b>	:	Council for International Organization of Medical Sciences
<b>DTAB</b>	:	Drugs Technical Advisory Board
<b>FDA</b>	:	Food and Drug Administration
<b>FDC</b>	:	Food, Drug and Cosmetic Act
<b>GCP</b>	:	Good Clinical Practice
<b>ICH</b>	:	International Conference on Harmonization
<b>ICMR</b>	:	Indian Council of Medical Research
<b>ICH GCP 6.0</b>	:	Document E6 of the ICH guidelines, Conserving GCP
<b>IEC</b>	:	Institutional Ethics Committee
<b>SOP</b>	:	Standard Operating Procedure
<b>WHO</b>	:	World Health Organization
<b>QA</b>	:	Quality Assurance

## **INTRODUCTION**

Advances in the Biomedical Science and Technology and their application in the practice of medicine are provoking some anxiety among the public and society with new ethical problems. Society is expressing its concern about what it fears would be abuses in scientific investigation and biomedical technology. The new advances in science and medicine are a cause for celebration and jubilation, but at the same time, they need careful evaluation of risks against benefits and it raises some delicate and difficult issues of ethics. These need to be dealt with extreme sensitivity of human values with utmost care, and development of ethical guidelines for the clinical research. In view of the complexity of the subject, the guidelines can neither be exhaustive nor be static. They need to be updated, consistent with the change in the realms of science and technology.

## HISTORY

The first International Code of Ethics for Research involving human subjects '*The Nuremberg Code*' was a response to the cruelties committed by Nazi Research Physicians revealed at the Nuremberg war crimes trials. Thus, it was to prevent any repetitions by physician of such attacks on the rights and welfare of human beings that human research ethics came into being. The Nuremberg (1947) laid down standards for carrying out human experimentations, emphasizing the subject's voluntary consent. World Medical Association (1964) took a step further to reassure society by adopting the '*Declaration of Helsinki*', which laid down the ethical guidelines for research involving human subjects.

The Indian Council of Medical Research (ICMR), New Delhi had brought a document in February 1980, '*Policy Statement of Ethical Considerations involved in Research on Human Subject*' prepared by the Ethical Committee which is being used ,not only by ICMR, but also by Research Institutions, Government Agencies, Non-government Agencies. However, need to update this was required keeping in view the modern biology and recent developments in different medical fields. Therefore, the Central Ethics Committee on Human Research (CECHR) was constituted to consider various issues related to ethical, social and legal aspects. The Committee identified the following major areas and set up sub-Committees of experts for drawing up a set of guidelines related to clinical evaluation of drugs, epidemiological research, human genetic research, transplantation research, assisted reproductive technologies and many more. It was proposed that these guidelines be updated periodically, *paripasu*, with the development of the area of medical science. In view of the circumstances of developing countries in regard to the applicability of '*Nuremberg Code and Declaration of Helsinki*', the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) undertook and issued the proposed international guidelines for biomedical research involving human subjects (1982). The purpose of proposed guidelines was to indicate the ethical principles that should guide the conduct of biomedical research involving human subjects, as set in the '*Declaration of Helsinki*' which could be applied effectively and efficiently in developing countries.

*Good Clinical Practice* (GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well-being are protected, consistent with principles in the '*Declaration of Helsinki*'. A need was however felt to develop our own Indian guidelines to ensure uniform equality of clinical research throughout the country and to generate data for registration for new drugs before use in Indian population. An Expert Committee set by Central Drugs Standard Control Organization (CDSCO) in consultation with experts has formulated the GCP guidelines for clinical data generation on drugs. The Drug Technical Advisory Board (DTAB), the highest Technical Body under D&C Act, has endorsed adoption of GCP guidelines for streamlining the clinical studies in India which would be useful to Research Institutions, Investigators, Institutional Ethics Committee (IEC) in providing desired direction, protection of rights and welfare of human subjects of biomedical research.

## **INSTITUTIONAL ETHICS COMMITTEE (IEC)**

- “Institutional Ethics Committee (IEC) is an independent body constituted of medical / scientific professionals and non-medical / non-scientific members whose responsibility is to ensure the protection of the right, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection.
- All proposals on biomedical researches involving human subjects should be cleared by Institutional Ethics Committee (IEC), to safeguard the welfare of the rights of the subject involved.
- The sponsor and / or investigator should seek the opinion of *Institutional Ethics Committee* regarding suitability of the *protocol*, methods and documents to be used in recruitment of *subjects* and obtaining their *informed consent* including adequacy of the information being provided to the subjects. The Ethics Committee is entrusted not only with the initial view of the proposed research protocols prior to the initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approved programme till the same are completed. Such an ongoing review is in accordance with the '*Declaration of Helsinki*'.

## ETHICAL COMMITTEE OF NATIONAL INSTITUTE

Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases is actively involved in conducting the research of high standard on various aspects of tuberculosis and respiratory diseases. To accomplish the objective in most appropriate manner, Institution's Ethical Committee was constituted under the Chairmanship of Director on May, 10<sup>th</sup> 2001 and the guidelines were framed in accordance with international recommendations, which would be updated as and when required.

The Ethical Committee of National Institute is as per international guidelines and has the following as members: -

<b>Ms. Blessina Kumar</b> <b>TB/HIV Activist &amp; PH Consultant, India</b> <b>Chair-GCTA, Member-Globe TB CAB</b>	<b>Chairperson</b>
Dr. K.K.Chopra Director N.D.TB Centre	Member & Alternative Chairperson
Dr. Rajnish Gupta	Member-Convener
Dr.Lokender	Member
Dr.J.K.Saini	Member
Dr. Harmeet Singh Rehan, Prof & Head, Deptt of Pharmacology,LHMC, New Delhi	Member
Dr. Swati Subodh	Member
Shri Tejinder Singh Ahluwalia	Member
Dr. Pratibha Mishra	Member
Mrs. Madhu Sikri, Advocate, M/s Sikri & Co.	Member
Shri Santosh Srivastava, Advocate	Member

### BASIC RESPONSIBILITIES OF IEC

1. To protect the dignity, rights and` well-being of potential research participants.
2. To ensure that universal ethical values and International Scientific Standards are expressed in terms of local community values and customs.
3. To assist in the development and the education of a research community responsive to local health care requirements.

## SALIENT FEATURES OF IEC

1. Multidisciplinary and multi-sectorial in composition
2. Independent
3. Competent

## TERMS OF REFERENCE AND REVIEW PROCEDURES

1. The IEC should be aware of their role and responsibilities as Committee Members.
2. Each Committee should have its own operating procedures available with each member
3. Any change in the regulatory requirement should be brought to the notice of members, keeping in view the National and International developments.
4. The terms of references should include a statement on terms of appointment with reference to
  - a. the duration of the term of membership
  - b. the policy for removal / replacement
  - c. the resignation procedure etc.
5. The ethical review should be done through formal meetings and discussion should not be taken through circulation of proposals.
6. Every research proposal on human subjects should be reviewed scientifically, evaluated in terms of risks and benefits with proper justification
7. Scientific evaluation should be done completely prior to ethical review
8. The Committee should evaluate for the adequacy of documentation to ensure privacy confidentiality and legal aspects.
9. All proposals on biomedical researches involving human subjects should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), to safeguard the welfare of the rights of the subject involved.
10. The sponsor and / or investigator should seek the opinion of *Institutional Ethics Committee* regarding suitability of the *protocol*, methods and documents to be used in recruitment of *subjects* and obtaining their *informed consent* including adequacy of the information being provided to the subjects. The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to the initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approved programme till the same are completed. Such an ongoing review is in accordance with the '*Declaration of Helsinki*'.

11. **Interim review** : can be resorted to instead of waiting for the scheduled time of the meeting and decisions can be taken urgently and should be brought to the notice of the main committee for the following reasons :
- a. Re-examinations of a proposal already examined by the IEC
  - b. Research study of a minor nature such as examination of case records etc.
  - c. An urgent proposal of national interest.

## GENERAL STATEMENT

Medical and related research using human beings as subjects must necessarily ensure that:

1. The **PURPOSE** of research should be directed towards the increase of knowledge about human condition and for the betterment of all.
2. The research is **CONDUCTED** in a conducive manner. The dignity, well -being, transparency and fair professional treatment should be maintained.
3. **EVALUATION** must be done at all stages ensuring the safety of human life.

## GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely *respect for person, beneficence and justice*. The present guidelines are directed at the application of these principles to research involving human subjects.

(A) **RESPECT FOR PERSONS** includes at least two fundamental ethical considerations, namely

1. **Respect for autonomy**

It includes the idea that an individual is free to choose and to act. Both rational capacity and freedom from constraint are necessary elements. "Respect for persons" includes respecting the decisions of autonomous beings.

2. **Protection for those with impaired or diminished autonomy**

It means a recognition by the commission that these people are not capable of self determination at all times and in all circumstances.

(B) **BENEFICENCE** – includes the ethical obligation to maximize benefits and minimize harms and wrongs.

(C) **JUSTICE** – In the ethics of research involving human subjects the principle primarily refers to distributive justice, which means equitable distribution of both burden and the benefits of participation in research.

## TWELVE BASIC PRINCIPLES

(Common to all areas of biomedical research)

- 1 All biomedical researches on human subjects should be absolutely essential after a due consideration of all alternatives for the advancement of knowledge and human beings (**Principle of Essentiality**).
- 2 The concept of voluntariness and informed consent shall apply to the community as a whole and to each individual member who is subject of research (**Principle of voluntariness and Informed Consent**).
- 3 Irrespective of the socio-economic status and educational levels, research subject should be fully appraised of all risks arising as a result of research (**Principle of Non-exploitation**).
- 4 The identity of records of human subjects of research should be kept confidential and should not be disclosed without valid scientific and legal reasons (**Principle of Privacy and Confidentiality**).
- 5 Due care and caution is taken to ensure that research subjects are put to minimum risks / no irreversible risks (**Principle of Precautions and Risks Minimisation**).
- 6 The Research is conducted at all times by the competent and qualified persons (**Principle of Professional Competence**).
- 7 The research is committed in a fair, honest, impartial and transparent manner and records and data are maintained for a reasonable period (**Principle of Accountability and Transparency**).
- 8 The research is conducted to benefit all human kind and not just socially better off. (**Principle of Maximisation of Public Interest and of Distributive Justice**).
- 9 All institutional arrangements required to be made in respect of research are made in a bonafide and transparent manner and records are properly maintained and preserved. (**Principle of Institutional Arrangements**).
- 10 After due experimentation and due evaluation, results are brought into public domain through scientific and other publications under the law in force at that time (**Principle of Public Domain**).
- 11 It is the responsibility of all directly and indirectly involved with the research to monitor, review constantly and take remedial action at all stages of research (**Principle of Totality and Responsibility**).
- 12 All persons concerned directly and indirectly should scrupulously observe the laid down rules, guidelines, norms, directions (**Principle of Compliance**).

## SPECIFIC ETHICAL PRINCIPLES

1. For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative.
2. Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding :
  - That each individual is invited to participate as a subject in research, and the aims and methods of the research – the expected duration of the subject's participation – the benefits that might reasonably be expected to result to the subject or to others as an outcome of the research
  - Any foreseeable risks or discomfort to the subject, associated with participation in the research
  - Any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested
  - The extent of the investigator's responsibility, if any, to provide medical services to the subject
  - That therapy will be provided free of charge for specified types of research-related injury
  - Whether the subject or the subject's family or departments will be compensated for disability or death resulting from such injury and
  - That the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled.
3. The investigator has a duty to :
  - Communicate to the prospective subject all the information necessary for adequately informed consent
  - Give the prospective subject full opportunity and encouragement to ask questions
  - Exclude the possibility of unjustified deception, undue influence and intimidation
  - Seek consent only after the prospective subject has adequate knowledge of the relevant facts and of the consequences of participation, and has had sufficient opportunity to consider whether to participate
  - As a general rule, obtain from each prospective subject a signed form as evidence of informed consent and
  - Renew the informed consent of each subject if there are material changes in the conditions or procedures of the research
4. Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research ; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgement (“**undue inducement**”).
5. Pregnant or nursing women should in no circumstances be the subjects of non-clinical 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 pregnancy or lactation. As a general rule, pregnant or nursing women should not be subjects of any clinical trials except such trials as are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

6. Before undertaking research involving children, the investigator must ensure that :
  - Children will not be involved in research that might equally well be carried out with adults
  - The purpose of the research is to obtain knowledge relevant to the health needs of children
  - A parent or legal guardian of each child has given proxy consent
  - The consent of each child has been obtained to the extent of the child's capabilities
  - The child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically – acceptable alternative
7. Prisoners with serious illness or at risk of serious illness should not arbitrarily be denied access to investigational drugs, vaccines or other agents that show promise of therapeutic or preventive benefit.
8. For several types of epidemiological research individual informed consent is either impracticable or inadvisable. In such cases, the ethical review committee should determine whether it is ethically acceptable to proceed without individual informed consent and whether the investigator's plans to protect the safety and respect the privacy of research subjects and to maintain the confidentiality of the data are adequate
9. Individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied.
10. The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigator's ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality.
11. Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependants are entitled to material compensation. The right to compensate may not be waived.
12. All proposals to conduct research involving human subjects must be submitted for review and approval to IEC. The investigator must obtain such approval of the proposal to conduct research before the research is begun.
13. An external sponsoring agency should submit the research protocol for ethical and scientific review as per the guidelines for the IEC.
14. After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements.

15. In the treatment of the sick person, the physician must be free to sue to a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering
16. The potential benefits, hazards and discomfort of a new method should be weighted against the advantages of the best current diagnostic and therapeutic methods.
17. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.
18. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
19. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to IEC.
20. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.
21. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health that person on whom biomedical research is being carried out.
22. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
23. The investigator or the investigating team should discontinue the research if in his / her or their judgment it may, if continued, be harmful to the individual.
24. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.
25. **Safeguarding confidentiality** – The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual subjects. Data of individual subjects can be disclosed only in the court of law under the orders of the presiding judge or in some cases may be required to communicate to drug registration authority or to health authority.
26. **Obligation of the sponsor to pay** – The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any physical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible.
27. **Research and Publication** – The results of the experimental research may be reported in such a way that it would seem that human application is of main concern. Premature reports and publicity stunts should be avoided. Researchers should take care to avoid talking to journalists or reporters about preliminary feelings of seemingly promising research.

## **SUBMISSION OF APPLICATION**

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

1. Clear research objectives and rationale for undertaking the investigation in human subjects in the light of existing knowledge.
2. Recent curriculum vitae of the Investigators indicating qualification and experience.
3. Subject recruitment procedures
4. Inclusion and exclusion criteria for entry of subjects in the study
5. Precise description of methodology of the proposed research, including intended dosages of drugs, planned duration of treatment and details of invasive procedures if any.
6. A description of plans to withdraw or withhold standard therapies in the course of research
7. The plans for statistical analysis of the study
8. Procedure for seeking and obtaining informed consent in English and / or vernacular language.
9. Safety of proposed intervention and any drug or vaccine to be tested including results of relevant laboratory and animal research.
10. An account of plans to provide medical therapy for research carrying more than minimal injury, toxicity due to over dosages
11. Proposed compensation and reimbursement of incidental expenses
12. Details of storage and maintenance of data collected during the trial
13. Plan for publication of results – positive or negative – while maintaining the privacy and confidentiality of the study participants.
14. A statement on probable ethical issues and steps taken to tackle the same
15. All other relevant documents related to the study protocol including regulatory clearances.
16. Agreement to comply with institutional ethical guidelines for clinical trials.
17. Details of Funding agency / Sponsors and fund allocation for the proposed work.
18. New proposals will be received every quarter as per following schedule. Emergency meeting can be called by the Chairman anytime.

**S.No. Application Review  
Submission Dates  
Dates**

1	2 <sup>nd</sup> Week March	1 <sup>st</sup> Week April
2	2 <sup>nd</sup> Week June	1 <sup>st</sup> Week July
3	2 <sup>nd</sup> Week September	1 <sup>st</sup> Week October
4.	2 <sup>nd</sup> Week December	1 <sup>st</sup> Week January

## **CHECK-LIST FOR PROTOCOL**

- ❑ Title of study
- ❑ Summary of proposed research
- ❑ Statement of justification of study
- ❑ Summary of previous studies on the topic including the nature, extent and relevance of animal studies and other pre-clinical studies
- ❑ An account of the previous submissions of the protocol for ethical review, if any, and its outcome.
- ❑ Brief description of the site where the research is to be conducted
- ❑ Relevant demographic and epidemiological information
- ❑ Name and address of the sponsor
- ❑ Name, address and qualification of the Principal Investigator
- ❑ The objectives of the trial
- ❑ The design of the trial
- ❑ The number of the research subjects with justification
- ❑ Inclusion and exclusion criteria
- ❑ Description and explanation of all interventions including the method of treatment, route of administration, dose, dose interval treatment period, and other details of the investigational product in case of drug trials
- ❑ Any other treatment that may be given / permitted / contraindicated during the study
- ❑ Clinical and laboratory tests to be carried out during the study
- ❑ Samples of case report forms to be used
- ❑ Methods to determine the compliance with the treatment and its recording
- ❑ Definitive criteria for removing the subjects from the study or trial.
- ❑ Methods of recording and reporting adverse events / reactions
- ❑ Methods of dealing with complications
- ❑ The known side effects of trial drug / vaccine / product used, if relevant
- ❑ The potential benefit of the research to the subjects and to others.
- ❑ The informed consent form formatted in English and Hindi.
- ❑ An account of any economic or incentives to prospective subjects such as cash payment / gifts /

free medical services etc.

- ❑ Description of plans for statistical analysis of the study including plans for interim analysis, if any, and criteria for pre-maturely terminating the study as a whole, if necessary
- ❑ A list of references in the protocol.
- ❑ The source and amount of funding of the research : the organization that is sponsoring .
- ❑ A detailed account of the sponsor's financial commitments to the research institution, the investigators, the research subjects, and, when relevant, the community.
- ❑ The time schedule for completion of the study.

Date: \_\_\_\_\_

**Name** \_\_\_\_\_

**Signature** \_\_\_\_\_

## DECISION MAKING

The IEC provides complete and adequate review of the research proposals submitted to them. It meets periodically at frequent intervals to review new proposals, evaluate annual progress of ongoing ones and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate. The following guidelines are followed for decision making.

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice appropriate steps.
2. A member must voluntarily withdraw from the IEC while making a decision on an application, which evokes a conflict of interest, which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.
3. A negative decision should always be supported by clearly defined reasons.
4. An IEC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit / risk ratio.
5. The discontinuation of a trial should be ordered if the IEC finds that the goals of the trials have already been achieved midway or unequivocal results are obtained
6. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
7. If necessary, the applicant / investigator may be invited to present the protocol or offer clarifications in the meeting.
8. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her / his opinion must be recorded.
9. The following circumstances required the matter to be brought to the attention of IEC :
  - a) Any amendment to the protocol from the originally approved protocol with proper justification
  - b) Serious and unexpected adverse events and remedial steps taken to tackle them
  - c) Any new information that may influence the conduct of the study.
10. Minutes of the Meeting should be approved and signed by the Chairperson.

## **RECORD KEEPING**

All documentation and communication of the IEC are dated, filed and preserved according to written procedure. Strict confidentiality is to be maintained during access and retrieval procedures.

The following records are maintained :

- i. The Constitution and composition of the IEC
- ii. The curriculum vitae of all IEC members
- iii. Standing operating procedures of the IEC
- iv. National and International guidelines
- v. Copies of protocols submitted for review
- vi. All correspondence, with IEC members and investigators regarding application, decision and follow up
- vii. Agenda of all IEC meetings
- viii. Minutes of all IEC meetings with signature of the Chairperson
- ix. Copies of decisions communicated to the applicants
- x. Record of all notification issued for premature termination of a study with a summary of the reasons
- xi. Final report of the study including microfilms, CDs and Video-recordings etc.

**\* It is recommended that all records must be safely maintained after the completion / termination of the study for at least a period of 15 years, it is not possible to maintain the same permanently.**

## **QUALITY ASSURANCE**

1. The sponsor is responsible for the implementation of a system of quality assurance in order to ensure that the study is performed and data is generated, recorded and reported in compliance with the protocol, GCP and other requirements. Documented standard operating procedures are a prerequisite for quality assurance.
2. All observations & findings should be verified for credibility of the data.
3. Statistically controlled sampling may be an acceptable method of data verification in each study.
4. Quality control must be applied to each step of data handling
5. Audit should be conducted by persons independent of those responsible for study.
6. All data and documentation should be available for inspection of audit.

## **GUIDELINES FOR DRUG TRIALS**

The Ethical Committee while reviewing proposals on Drug Trials will ensure that following guidelines in this regard are strictly followed.

- ❑ Clinical trial of drugs is a randomized single or double blind controlled study in human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs.
- ❑ The proposed drug trials should be carried out, only after approval of the Drugs Controller General of India (DCGI), as is necessary under The Schedule Y of Drugs and Cosmetics Act, 1940.
- ❑ The investigator should also get the approval of Ethical Committee of the Institution before submitting the proposal to DCGI.
- ❑ All the guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside India or not.
- ❑ The new drug as defined under the Drugs and cosmetic Rules 1945 (DCR), and subsequent amendments include.
  - A new chemical entity (NCE)
  - A drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed to be used for another indication, by another route, or in another dosage regimen
  - A combination of two or more drugs which, although approved individually, are proposed to be combined for the first time in a Fixed Dose Combination (FDC).

## PHASES OF CLINICAL TRIALS

The first three of the following four phases require ethical clearance :-

### Phase I (Human / Clinical Pharmacology trial) :

- The objective of phase 1 of clinical trial is to determine the *safety* of the maximum tolerated dose in healthy adults of both sexes.
- At least two subjects should be administered each dose to establish the safe dose range, *pharmacokinetic*, *pharmacodynamic* effect, and *adverse* reaction, if any, with their intensity and nature.
- Investigator trained in clinical pharmacology should preferably carry out these studies.
- The duration of time lapsing between two trials in the same volunteer should be a minimum of 3 months.
- The volunteers should preferably be covered under some insurance scheme.

### Phase II (Exploratory trial) :

- These are controlled studies conducted in a limited number of patients of both sexes to determine therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics.
- Usually, 20 –25 patients should be studied for each dose.
- Studies are limited to 3 – 4 centres

### Phase III (Confirmatory trial) :

- The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients from both sexes at multiple centers.
- Only after successful completion of phase III trials, permission is granted for marketing the drug.

### Phase IV (Post Marketing Surveillance) :

- It is undertaken to obtain additional information about the drug's risks, benefits and optimal use
- Long term effects and adverse drug reaction if any should be brought to the notice of Ethics Committee.

\*\* Trials of drugs without the approval of the appropriate authority should be dealt according to the law of the land and the Guidelines formulated by the country's regulatory agencies.

\*\*\* After the trial is over, if need be, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country.

\*\*\*\* The criteria for termination of a trial must be defined as a priority in the proposal of the trial and plan of interim analysis must be clearly presented. This is important when on interim analysis the test drug is found to be clearly more effective or less effective than the standard drugs. The trial can be discontinued thereafter and better drug should be given to patient receiving less effective drug.

**\*\*\*\*\* GCP provide operative guidelines for ethical and scientific standards for the designing of a trial protocol including conduct, recording and reporting procedures and should be strictly adhered to while carrying out a trial. Till such time that the SOP for Indian GCP are formulated, the international guidelines issued by WHO and ICH should be followed.**

## **GUIDELINES FOR VACCINE TRIALS**

The Ethical Committee while reviewing proposals on vaccine trials will ensure that the guidelines in this regard are strictly followed. The phases of these trials differ from drug trials as given below :

### **Phase I :**

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

### **Phase II :**

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

### **Phase III :**

- ❑ This focuses on assessment of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of volunteers (in thousands) in multi-centres.
  - Vaccines that contain active or live – attenuated micro-organisms can possibly possess a small risk of producing that particular infection. The subject to be vaccinated should be informed of the same.
  - The subjects in control groups or when subjected to ineffective vaccines run a risk of contracting the disease
  - The risks associated with vaccines produced by recombinant DNA techniques are not completely known. However, for all the recombinant vaccines / products the Guidelines issued by the Department of Biotechnology should be strictly followed.

## **PRINCIPLES FOR HUMAN GENETICS RESEARCH**

In the area of biomedical research, there has been concern for ethical issues in the field of human genetics. In recent years this concern has grown even further because of the possibility of commercial eugenics. The advent of recombinant DNA technology has provided one of the most powerful tools in the hands of mankind to unravel the mysteries of the human genome.

Serious issues related to participation of human subjects in genetic research are raised particularly when the intervention involves rights of human embryo and subjects who are not competent to give informed consent. Besides Human Rights, issues of dignity, autonomy and justice, the Human Genome Project (HGP) has also precipitated an unprecedented concern for Intellectual Property Rights.

Clinical research in fields of human genetics and human genome, including gene therapy, besides being subject to general ethical considerations of protection from harm and voluntariness of participation has following additional considerations :-

- The harm may not only be physical, but also psychosocial. Psychologically, the genetic information may produce anxiety and depression or damage familial relationship, which should be safeguarded.
- Written explanation understandable to layman about presentation and natural course of the diseases, interventions available and their outcome, as also implication of the information for progeny and family, has special place in clinical research in this field.
- Genetic manipulations have consequences for the future, some of which are unknown. Hence, greater care towards potential dangers is necessary.
- Careful guidelines need to be evolved by peers in the profession to tackle such situation. The professional societies should actively participate in these activities.
- The science of Medical Genetics is progressing very rapidly. Therefore, there is a need for frequent updating of any guidelines for research in this field. To meet this challenge not only the guidelines should be flexible, but there should also be a built-in mechanism to review the guidelines from time to time.
- The Institutional Ethical Committees reviewing research proposals related to research on human genetics should have necessary expertise, which includes knowledge of latest developments in the field of human genetics. In areas of doubt, open discussion should be encouraged. This has to be the responsibility of National agencies e.g. Central Ethical Committee (ICMR) and / or National Bioethics Committee to organize national debates on such issues to evolve consensus on them.
- Concerned with the misuse of genetic tests, particularly for the pre-selection of sex, the Government India has enacted a law known as “The Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act 1994”. All researchers in this area shall follow the provisions of this act (and such other acts which may be passed in future).

## APPENDIX – I

### THE NUREMBERG CODE – 1949

Beginning with the outbreak of World War – II, Criminal Medical experiments on non-German Nationals, both prisoners of war civilians were carried out on large scale by the Nazi Physicians. Evidence given during these trials revealed unprecedented suffering, pain and disfigurement. In response to these findings, the judges proposed 10 principles “moral, ethical and legal” human experimentation, which collectively came to be known as The Nuremberg Code. Today, it is the basis of GCP in scientific research and is the fundamental document in the history of bioethics.

1. *The voluntary consent of the human subject is absolutely essential.*
2. *The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.*
3. *The experiment should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.*
4. *The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.*
5. *No experiment should be conducted where there is an a priority reason to believe that death or disabling injury will occur except, perhaps, in those experiments where the experimental physicians also service as subjects.*
6. *The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.*
7. *Proper preparations should be made and adequate facilities provide to protect the experimental subject against even remote possibilities of injury, disability, or death.*
8. *The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.*
9. *During the course for the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.*
10. *During the course of the experiment the scientific in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.*

## APPENDIX – II

### THE DECLARATION OF HELSINKI – 1964

Unlike the Nuremberg Code the declaration of Helsinki focused on the integrity and the experience of scientific investigators, in the protection of human subjects. According to the declaration of Helsinki issued by World Medical Assembly each potential subject involved in a clinical investigation must be adequately informed of the aims, methods, anticipated benefits and the potential hazards of the study and the discomfort it may entail. The declaration of Helsinki forms the basis of ICH GCP 6.0. Therefore it is a more universally used document than the Nuremberg code. It has the following principals.

- 1. The World Medical Association has developed the declaration of Helsinki as a statement of ethical principle to provide guidance to physicians and other participants in medical research involving human subjects. Medical Research involving human subjects includes research on identifiable human material or identifiable data.*
- 2. It is the duty of physician to promote and safeguard the health of the people. The physicians knowledge and conscience are dedicated to the fulfillment of this duty.*
- 3. The Declaration of Geneva of World Medical Association binds the physician with the words, “The health of my patient will be my first consideration”, and the International code of medical ethics declares that, “A physician shall at only in the patients interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient”.*
- 4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.*
- 5. In medical research on humn subjects, considerations related to the well-being of the human subject should take precedence over the interest of science and society.*
- 6. The Primary purpose of medical research involving human subject is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.*
- 7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involved risks and burdens.*
- 8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give a refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those whom the research is combined with care.*
- 9. Research investigators should be aware of ethical, legal, and regulatory requirements for research on human subject in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set-forth in this Declaration.*

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