Ethical Guidelines for Biomedical Research on Human Subjects

INDIAN COUNCIL OF MEDICAL RESEARCH NEW DELHI

2000

TABLE OF CONTENTS

Justice M.N. Venkatachaliah
(Former Chief Justice of India)
Chairperson

S

NATIONAL COMMISSION TO REVIEW THE WORKING OF THE CONSTITUTION
VIGAN BHAWAN ANNEXE,
MAULANA AZAD ROAD,
NEW DELHI-110011

FOREWORD

The Central Ethics Committee on Human Research (CECHR) of the Indian Council of Medical Research has now put together a set of "Ethical Guidelines for Biomedical Research on Human Subjects".

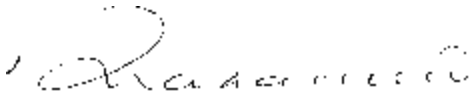
One of the breath-taking breakthrough in science in the recent years is its spectacular intrusion into the nature's hitherto closely guarded secrets of life. Genome-mapping, Genetic Recombinant Engineering, Assisted Reproductive technology, Stem-Cell Research, Human cloning etc. have opened up hitherto unimagined vistas in the practical application of Biomedical Technologies for the benefit of the mankind. Biomedical Research is perched on the threshold of a bold and brave new world. Crucial to its management is the ability of the scientitists and the society to handle these forces of change.

Correspondingly, as in all frontier-line researches, our ignorance of the areas of the yet unknown might, paradoxically, expand with the expansion of our knowledge. Biomedical Research has acquired dimensions which are at once exciting and awesome. It raises some delicate and difficult issues of ethics which need to be dealt with sensitivity to human values and with great circumspection. While research which promises to mankind the great blessings of Science should not be stifled by too restrictive an approach, however, great care should be taken to ensure that something does not go out of hand. Therefore, any system of ethical guidelines on research needs to be cognizant of, and informed by, a sensitive balance of the risks and benefits.

Indeed in this area of research the only constancy is the constancy of change. At no stage can the last word be said. This phenomenon is amply illustrated by the vacillating responses of the scientific community to the extremely difficult area of human asexual replication. The issues concern Stem Cells, the unspecialised cells which have not yet differentiated into a specific tissue. While the present ethical guidelines of the CECHR entertain reservations on Human Cloning, there has, in the very recent past, some drastic rethinking on the subject in Britain. The British Government is contemplating a legislation to lift the ban on human cloning to allow scientific research on embryo cells. Britain might, perhaps, be the first country to authorise cloning from humans. England's Chief Medical Officer Professor Lam Donaldson has advised the proposed changes on the basis of a report of an expert group chaired by him. It was felt by the expert group that, in the long term, there could be considerable potential for the use of tissues derived from stem cells in the treatment of a wide range of disorders by replacing cells that have become damaged or diseased, such as the insulin secreting cells or liver cells etc. Views on the other side of the Atlantic seem to be sharply divided. All these indicate that the ethical issues involved need an on-going open-minded evaluation or re-evaluation.

The CECHR Guidelines contain, apart from the Statement of General Principles on Ethical Considerations, separate chapters on 'Ethical Review Procedures'; 'General Ethical Issues'; Statements on 'Specific Principles for Clinical Evaluation of Drugs/Devices/Diagnostics/Vaccines/Herbal Remedies'; Statement on 'Specific Principles for Epidemiological Studies'; on 'Specific Principles on Human Genetic Research; on 'Specific Principles for Research in Transplantation including Foetal Tissue Transplantation' and on 'Assisted Reproductive Technologies'.

As Chairman of the CECHR, I take this opportunity to express my gratitude to the Members of the Committee and the expert-groups for their valuable contribution. Interaction with them was, in itself, a rewarding and exciting experience. I particularly acknowledge the help from Dr. G.V. Satyavati and Dr. N.K. Ganguly, the former and the present Directors-General, respectively, of the ICMR; and the great patience and courtesy of Dr. Vasantha Muthuswamy.



New Delhi
Dated 06 September, 2000

Justice M.N. Venkatachaliah

PREFACE

The need for uniform ethical guidelines for research on human subjects is universally recognised. Indeed, it has acquired a new sense of urgency as the critical issues in the areas of biogenetic research involving human subjects have become acute. Apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and preventive measures including the use of vaccines are being introduced which involve human subjects. Further, the advent of new medical devices and radio-active materials, and therapeutic benefits of recombinant DNA products have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

With the ushering-in of the era of biotechnology (including genetic engineering) medical procedures and therapeutics have undergone tremendous changes and many techniques based on these advances are no longer in the realms of science fiction, but have become a reality today. Recent advances in the field of Assisted Reproductive Technologies, Organ Transplantation, Human Genome Analysis and Gene Therapy promise unquestionable and hitherto undreamed of benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern. On the one hand, there is a need to requite legitimate public concern, and on the other, there is need to appreciate and encourage and not unduly deter new scientific innovations for the benefits of mankind. The new advances in Science and Medicine are a cause for celebration, at the same time they need careful evaluation of risk-benefit. It is imperative that specific guidelines for such research are provided from time to time, taking into consideration all these new and ever changing dimensions. It is, however, to be emphasized that in their very nature and in view of the innate complexity of the subject the Guidelines can be neither exhaustive nor static. They need to be updated, consistent with the speed of change in Science and Technology.

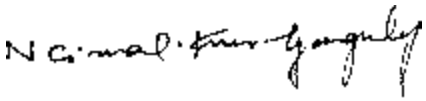
The Indian Council of Medical Research (ICMR) had brought out in February 1980, a document entitled '*Policy statement on ethical considerations involved in research on human subjects*' prepared by the ethical committee under the chairmanship of Honorable Justice Shri H.R. Khanna. This document is being widely used by not only ICMR but also by other Government agencies, research institutions and scientists. The document, however, needed to be updated in view of the recent developments in modern biology as also in different branches of medical science so as to add to its contemporary relevance.

Therefore, a Central Ethics Committee on Human Research (CECHR) was constituted under the chairmanship of Honourable Justice Shri M.N. Venkatachaliah by the then Director General, Dr. G.V. Satyavati to consider various issues related to the Ethical, Legal and Social dimensions of research involving human subjects. The committee first met on 10th September, 1996 and identified following major areas and set up sub-committees of experts for drawing up a set of guidelines:

1. **Clinical evaluation of Drugs/Devices/Diagnostics/Vaccines/ Herbal remedies**
2. **Epidemiological research**
3. **Human Genetics research**
4. **Transplantation research, including Fetal tissue transplantation**
5. **Assisted Reproductive Technologies**

The CECHR met on 10th August 1997 to consider the draft guidelines prepared by all the five groups and a Draft Consultative Document was prepared for wide circulation and subsequent regional/national debates before finalisation. A series of four regional public debates at Calcutta, Mumbai, Hyderabad and New Delhi on the Draft Consultative Document were conducted in the years 1998-99. The process of public debates highlighted the regional and cultureal differences in our country. The reports and recommendations of all the four debates along with the comments that were received from various scientists and scientific institutions both, medical and non-medical, voluntary groups, and media were examined by the concerned drafting Sub-Committees before finalising the specific guidelines in the respective areas. A separate chapter on 'Ethical Review Procedures is also added. It is proposed that these guidelines will be updated periodically *pari passu* with the developments in the area of Biomedical Sciences. It is expected that all institutions in the country which carry out any form of biomedical research involving human beings should follow these guidelines in letter and spirit to protect the safety and well being of all individuals who participate in such research for the progress of science through acquisition of new knowledge.

The Council acknowledges with gratitude the contribution of all the professionals, public and the media involved in bringing out these guidelines over a period of 4 years without which this would not have been possible.



New Delhi
September, 2000

N.K.Ganguly
Director General

ACKNOWLEDGEMENTS

The Council gratefully acknowleges the valuable contribution of all the members of the Central Ethics Committee on Human Research and the Sub-committees for providing continued guidance in drafting and finalizing the Guidelines.

Special thanks go to the following scientists for conducting the regional public debates on the 'Consultative Document on Ethical Guidelines' :

- Prof. M.G.K. Menon, former Minister of Science & Technology and former Member of Parliament, New Delhi.
- Dr. D. Balasubramaniam, Research Director, L.V. Prasad Eye Institute, Hyderabad.
- Dr. Sunil Pandya, Consultant, Jaslok Hospital, Mumbai.
- Prof. Partha Majumdhar, Professor, Indian Statistical Institute, Calcutta.

Our deep gratitude is extended to Prof. V. Ramalingaswami, National Professor, All India Institute of Medical Sciences and former Director General, Indian Council of Medical Research, New Delhi for chairing the special Sub-committee to finalize the document.

Sincere thanks are due to various individuals, Institutions, government and non-governmental organizations, media personnel etc. for their constructive suggestions.

Efforts made by Dr. Nandini K. Kumar, Assistant Director General, ICMR in assisting during the entire process of documentation and compilation of the Guidelines is thankfully appreciated.

Secretarial assistance provided by Shri B.K. Gulati and Ms. Poonam Dhawan is also placed on record.

STATEMENT OF GENERAL PRINCIPLES IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

This statement of **Ethical Guidelines for Biomedical Research on Human Subjects** shall be known as the **ICMR Code** and shall consist of the following : -

(a) Statement of General Principles on Research using Human Subjects in Biomedical Research

(b) Statement of Specific Principles on Research using Human Subjects in specific areas of Biomedical Research

These Statements of General and Specific Principles may be varied, amended, substituted and added from time to time.

BACKGROUND

The Second World War (1939-45) in its aftermath, gave rise to an intense concern about the use of human subjects for medical research as revealed by the shocking details of the trial of German medical practitioners accused of conducting experiments on human subjects without their consent and exposing them to grave risk of death or permanent impairment of their faculties. Thus, the first International Statement on the ethics of medical research using human subjects namely, the **Nuremberg Code** was formulated in 1947, which emphasised consent and voluntariness. In 1948, **Universal Declaration of Human Rights** (adopted by the General Assembly of the United Nations) expressed concern about human beings being subjected to involuntary maltreatment. In 1966, the **International Covenant on Civil and Political Rights** specifically stated, ***'No one shall be subjected to torture or to cruel,inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.'***

Based on the preliminary efforts of the Council for International Organisations of Medical Sciences (CIOMS) in 1964 at Helsinki, the World Medical Association formulated general principles on use of human subjects in medical research in addition to specific guidelines for biomedical research, known as the **Helsinki Declaration** which was revised from time to time. In February 1980, the Indian Council of Medical Research released a **'Policy Statement on Ethical Considerations involved in Research on Human Subjects'** for the benefit of all those involved in clinical research in India. In 1982, the World Health Organisation (WHO) and the CIOMS issued the **'Proposed International Guidelines for Biomedical Research involving Human Subjects.'**

Subsequently the CIOMS brought out the **'International Guidelines for Ethical Review in Epidemiological studies'** in 1991 and **'International Ethical Guidelines for Biomedical Research involving Human subjects'** in 1993. Over the years, various bodies in national jurisdictions have also laid down general and specific principles in specific areas of scientific research entailing the use of human beings as subjects in medical research. These 'national' Codes (drawn from the international codes and the universal principles underlying them) outline 'guidelines' to be followed in their respective jurisdictions.

GENERAL STATEMENT

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

(i) The **PURPOSE,** of such research is that it should be directed towards the increase of knowledge about the human condition in relation to its social and natural environment, mindful that the human species is one of the many species in a planet in which the well being of all species is under threat, no less from the human species as any other, and that such research is for the betterment of all, especially the least advantaged.

(ii) Such research is **CONDUCTED** under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subject to any medical research or scientific experimentation are dealt with in a manner conducive to and consistent with their dignity and well being, under conditions of professional fair treatment and transparency; and after ensuring that the subject is placed at no greater risk other than such risk commensurate with the well being of the subject in question in the light of the object to the achieved.

(iii) Such research must be subjected to a regime of **EVALUATION** at all stages of the proposal i.e., research design and experimentation, declaration of results and use of the results thereof, and that each such evaluation shall bear in mind the objects to be achieved, the means by which they are sought to be achieved, the anticipated benefits and dangers, the potential uses and abuses of the experiment and its results, and above all, the premium that civilised society places on saving and ensuring the safety of each human life as an end in itself.

STATEMENT OF GENERAL PRINCIPLES

Any research using the human beings as subjects of medical or scientific research or experimentation shall bear in mind the following principles –

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

II. **Principles of voluntariness, informed consent and community agreement** whereby, research subjects are fully apprised of the research and the impact and risk of such research on the research subject and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human subjects 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 subject, 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 subject of the research or experiment. Where the human subject 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 subjects 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 subjects 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 subject 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 subject's person and privacy, health and life generally, and, the overall purpose and the importance of the research.

III. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born. Such human subjects 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 subjects either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive after-care, 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 subject 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 subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorised on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

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 subject and those affected by it are put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research or experiment; 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 or 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, 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 subject themselves.

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.

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 subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

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.

ETHICAL REVIEW PROCEDURES

The need for evaluation of research proposals has been emphasized under the Statement of General Principles at item no. 5 pertaining to **precaution and risk minimisation.** It is mandatory that all proposals on biomedical research involving human subjects should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB) in many countries, to

safeguard the welfare and the rights of the participants. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research.

BASIC RESPONSIBILITIES

The basic responsibility of an IEC is to ensure a competent review of all ethical aspects of the project proposals received and execute the same free from any bias and influence that could affect their objectivity. IECs should provide advice to the researchers on all aspects of the welfare and safety of the research participants after ensuring the scientific soundness of the proposed research through appropriate Scientific Review Committees. In smaller institutions the Ethics Committee may take up the dual responsibility of Scientific and Ethical Review. It is advisable to have separate Committees for each taking care that the scientific review preceeds the ethical scrutiny. The scientific evaluation should ensure technical excellence of the proposed study.

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

1. To protect the dignity, rights and well being of the 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

COMPOSITION

IECs should be multidisciplinary and multisectorial in composition. Independence and competence are the two hallmarks of an IEC.

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

The Chairperson of the Committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary who generally belongs to the same Institution should conduct the business of the Committee. Other members should be a mix of medical /

non-medical, scientific and non-scientific persons including lay public to reflect the differed viewpoints. The composition may be as follows:-

1. Chairperson
2. 1-2 basic medical scientists.
3. 1-2 clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist / representative of non-governmental voluntary agency
6. One philosopher / ethicist / theologian
7. One lay person from the community
8. Member Secretary

The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. There should be adequate representation of age, gender, community, etc. in the Committee to safeguard the interests and welfare of all sections of the community / society. Members should be aware of local, social and cultural norms, as this is the most important social control mechanism. If required subject experts could be invited to offer their views, for example for drug trials a pharmacologist, preferably a clinical pharmacologist, should be included. Similarly, based on the requirement of research area, for example HIV, genetic disorders etc., specific patient groups may also be represented in the Committee.

TERMS OF REFERENCE

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

REVIEW PROCEDURES

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

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 with sample of patient information sheet and informed consent forms in English and vernacular languages.
9. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research.
10. For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to overdosage should be included.
11. Proposed compensation and reimbursement of incidental expenses.
12. Storage and maintenance of all data collected during the trial.
13. Plans for publication of results – positive or negative – while maintaining the privacy and confidentiality of the study participants.
14. A statement on probable ethical issues and steps taken to tackle the same.
15. All other relevant documents related to the study protocol including regulatory clearances.
16. Agreement to comply with national and international GCP protocols for clinical trials.
17. Details of Funding agency / Sponsors and fund allocation for the proposed work.

DECISION MAKING PROCESS

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

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice

appropriate steps. The Member Secretary should communicate the decision in writing.

2. A member must voluntarily withdraw from the IEC while making a decision on an application which evokes a conflict of interest, which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.
3. If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.
4. A negative decision should always be supported by clearly defined reasons.
5. An IEC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit / risk ratio.
6. The discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.
7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.
8. The following circumstances require the matter to be brought to the attention of IEC:

    a. any amendment to the protocol from the originally approved protocol with proper justification;
    b. serious and unexpected adverse events and remedial steps taken to tackle them;
    c. any new information that may influence the conduct of the study.

9. If necessary, the applicant/investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.
10. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her / his opinion must be recorded.
11. Meetings are to be minuted which should be approved and signed by the Chairperson.

INTERIM REVIEW

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

i) re-examination of a proposal already examined by the IEC;
ii) research study of a minor nature such as examination of case records etc.;
iii) an urgent proposal of national interest.

RECORD KEEPING

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

i. the Constitution and composition of the IEC;
ii. the curriculum vitae of all IEC members;
iii. standing operating procedures of the IEC;
iv. national and International guidelines;
v. copies of 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.

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 if it is not possible to maintain the same permanently.

SPECIAL CONSIDERATIONS

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

GENERAL ETHICAL ISSUES

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

I. INFORMED CONSENT PROCESS

1. **Informed Consent of Subject :** 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 consent of a legal guardian. Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not. Informed consent protects the individual's freedom of choice and respect for individual's autonomy.

When research design involves not more than minimal risk (for example, where the research involves only collecting data from subject's records) the Institutional Ethics Committee may waive off some of the elements of informed consent.

Waiver of informed consent could also be considered during conditions of emergency. However, this would be permissible only if Ethical Committee has already approved the study or use of drug. However, the patient or the legal guardian should be informed after she/he regains consciousness or is able to understand the study.

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

i. Communicate to prospective subjects all the information necessary for informed consent. There should not be any restriction on subject's right to ask any questions related to the study as any restriction on this undermines the validity of informed consent.
ii. Exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the subject is not permissible. However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.
iii. Seek consent only after the prospective subject is adequately informed. Investigator should not give any unjustifiable assurances to prospective subject, which may influence the subject's decision to participate in the study.
iv. As a general rule obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by

a person not related to the trial, and in case of incompetence to do so, a legal guardian or other duly authorised representative.

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

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

3. **Essential information for prospective research 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 maintained ie., the limits to which the investigator would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality;
viii. responsibility of investigators;
ix. free treatment for research related injury by the investigator / institution;
x. compensation of subjects for disability or death resulting from such injury;
xi. 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;
xii. the identity of the research teams and contact persons with address and phone numbers;
xiii. 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;
xiv. risk of discovery of biologically sensitive information;
xv. 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.

II. COMPENSATION FOR PARTICIPATION

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

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

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

III. *SELECTION OF SPECIAL GROUPS AS RESEARCH SUBJECTS*

i. ***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 tech-niques : In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, GOI, 1994 and not for sex determination of the foetus.

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

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

a. research on genetics should not lead to **racial inequalities**;
b. persons who are **economically or socially disadvantaged** should not be used to benefit those who are better off than them;
c. rights and welfare of **mentally challenged and mentally differently able persons** who are incapable of giving informed consent or those with behavioral disorders must be protected;
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.

IV. *ESSENTIAL INFORMATION ON CONFIDENTIALITY FOR PROSPECTIVE RESEARCH SUBJECTS*

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

V. *COMPENSATION FOR ACCIDENTAL INJURY*

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

Obligation of the sponsor to pay :- The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, 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.

VI. *INTERNATIONAL COLLABORATION/ ASSISTANCE IN BIO-MEDICAL / HEALTH RESEARCH*

Research in biomedical and health areas have been subjects of international interaction over the centuries. However, it was only in the second half of the 20th Century, especially since 1960s, that the scope of co-operation and collaboration assumed such proportions as to have exploitative connotations with commercial and human dimensions. On the one hand, collaboration in medical research suggests an interest in humane and civil society, while on the other it could give the impression of experimentation on the population of one country by another. Different levels of development in terms of infrastructure, expertise, social and cultural perceptions, laws relating to intellectual property rights etc., necessitate an ethical framework to guide such collaboration. The same concerns are applicable even if and when there is no formal collaboration between countries, but the research is undertaken with assistance from sponsors in the form of international organisations (Governmental, non-Governmental or others for example, WHO, UNICEF, UNAIDS etc.).

SPECIAL CONCERNS

1. Given the magnitude and severity of the health problems in different countries, capacity building to address ethical issues that arise out of collaborative research must be promoted on a priority basis.

2. Strategies should be implemented to build capacity in various countries and communities so that they can practise meaningful self-determination in health development, can ensure the scientific and ethical conduct of research, and can function as equal partners with sponsors and others in a collaborative process. Community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of research.

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

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

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

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

7. Guidelines, rules, regulations and laws of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country. These could be with reference to intellectual property rights, exchange of biological materials (human, animal, plant or microbial), data transfer, security issues, and issues of socially or politically sensitive nature. In this context, it is essential for researchers to follow the GOI notification on " Exchange of Human Biological Material for Biomedical Research" issued on 19.11.97.

VII. *RESEARCHER'S RELATIONS WITH THE MEDIA AND PUBLICATION PRACTICES*

Researchers have a responsibility to make sure that the public is accurately informed about results without raising false hopes or expectations. It should also not unnecessarily scare the people. Researchers should take care to avoid talking with journalists or reporters about preliminary findings as seemingly promising research that subsequently cannot be validated could lead to misconcepts if reported prematurely. Or, the results of experimental research may be reported in such a way that it would seem that the human application is round the corner only to be told by the researchers later that considerable time has to pass before these findings can be translated into human use. In

such circumstances, retractions most often do not appear in the media. Therefore, it is important to avoid premature reports and publicity stunts.

The best safeguard against inaccurate reporting is for the researcher to talk to media on condition that the reporter submit a full written, rather than oral version, of what will be reported, so that it enables the researcher to make necessary corrections, if needed, prior to publication.

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

STATEMENT OF SPECIFIC PRINCIPLES FOR CLINICAL EVALUATION OF DRUGS /VACCINES / DEVICES / DIAGNOSTICS/HERBAL REMEDIES ETC.

Human studies designed to evaluate the safety, effectiveness, or usefulness of an intervention include research on therapeutics, diagnostic procedures and preventive measures including vaccines. The type of experimental procedures that a patient is submitted to has become more complex and varied as the complexities of medical research have increased. It is clearly accepted that it is essential to carry out research on human subjects to discover better medical and therapeutic modalities for the benefit of mankind. It is equally clear that such research on normal subjects and patients is associated with some degree of risk to the individual concerned. These guidelines have been framed to carry out the evaluation of drugs, vaccines, devices and other diagnostic materials on human subjects including herbal remedies, in accordance with the basic ethical principles. These guidelines are important for the protection of research subjects against any avoidable risk and to guide the researchers in the preparation of research proposals/protocols.

For the clinical evaluation of proposed research intervention, the framework of guidelines is provided for the following areas:

1. Drug trials
2. Vaccine trials
3. Surgical procedures / medical devices
4. Diagnostic agents - with special reference to use of radioactive materials and X-rays
5. Trials with herbal remedies

GENERAL PRINCIPLES

All the research involving human subjects should be conducted in accordance with the four basic ethical principles, namely Autonomy or respect for person / subject, Beneficence, Non-maleficence and Justice. The guidelines laid down are directed at application of these basic principles to research involving human subjects. An investigator is the person responsible for the research trial and for protection of the rights, health and welfare of the subjects recruited for the study. He / she should have qualification and competence in clinical trial research methods for proper conduct of the trial and should be aware of and comply with all requirements of the study protocol as enumerated under the General Principles and General Issues.

SPECIFIC PRINCIPLES

1. DRUG TRIALS

Clinical trial of drugs is a randomised single or double blind controlled study in human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs / new formulations. The new drug as defined under the Drugs and Cosmetic Rules 1945 (DCR), and subsequent amendments include:

(a) a new chemical entity (NCE);
(b) 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;
(c) 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).

The proposed trial 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.

PHASES OF CLINICAL TRIALS

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

Phase I :- The objective of phase 1 of clinical trial is to determine the safety of the maximum tolerated dose in healthy adults of both sexes. Healthy female volunteers could be included provided they have completed their family or do not intend to have a child in the future. At least two subjects should be administered each dose to establish the safe dose range, pharmacokinetic, pharmacodynamic effects, and adverse reactions, 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 :- 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 when necessary. Normally 20 – 25 patients should be studied for assessment of each dosage. These studies are usually limited to 3 – 4 centres.

Phase III :- The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of both sexes in multiple centres usually in

comparison with a standard drug and / or a placebo if a standard drug does not exist for the disease under study. On successful completion of phase III trials permission is granted for marketing of the drug.

Phase IV :- After approval of the drug for marketing, phase IV study or post marketing surveillance is undertaken to obtain additional information about the drug's risks, benefits and optimal use. Although this is outside the purview of the ethical committee, it is an important aspect of drug trial on the long-term effects of the drugs and the adverse reactions induced by drugs, if any, should be brought to the **notice of the Ethics Committee.**

Throughout the drug trials, the distinction between therapy and research should be maintained. A physician /investigator who participates in research by administering the new drug to consenting patients should ensure that the patients understand and remember that the drug is experimental and that its benefits for the condition under study are yet unproven. Use of a placebo in drug trials and sham surgery has come under severe scrutiny at the present age and requires careful consideration before approval. Denial of the available treatment to control (placebo) group of patients is unethical.

- 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 clinical 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 a priori 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 drug. The trial can be discontinued thereafter and better drug should be given to patient receiving less effective drug.
- Issues of partner notification and discordant couples should be taken care of before initiating any HIV / AIDS related trial.

Good Clinical Practices (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 Standard Operating Procedures (SOP) for Indian GCP are formulated, the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) should be followed.

SPECIAL CONCERNS

1. Multicentric Trials

A multicentric trial is conducted simultaneously by several investigators at different centres following the same protocol and proformae. Ideally, these trials should be initiated at the same time at all the centres.

- All the Investigators should give a written acceptance of the protocol to be followed for the trial duly approved by the ethics committee of the host institutes.
- Meetings should be organised at the initial and intermediary stages of the trial to ensure uniform procedures at all centres.
- Training should be imparted to research staff at the participating centres to familiarise them with the uniform procedures.
- Standardisation of methods for recruitment and evaluation/monitoring of laboratory procedures and conduct of trial should be carried out.
- There should be monitoring of adherence to protocol including measures to terminate the participation of some centres, if necessary.
- Specific role of coordinators and monitors should be defined.
- Centralised data management and analysis should be planned.
- Drafting of a common final report and publication procedure should be decided at the outset. No individual centre should publish any data till appropriate authorities accept the combined report.
- The code of the administered drug could be broken in the event of a severe adverse reaction occurring during the conduct of a double blind trial necessitating such a step.

2. Contraceptives

- All procedures for clinical trials are applicable. Subjects should be clearly informed about the alternatives available.
- In women where implant has been used as a contraceptive for trial, a proper follow up for removal of the implant should be done, whether the trial is over or the subject has withdrawn from the trial.
- Children born due to failure of contraceptives under study should be followed up for any abnormalities if the woman does not opt for medical termination of pregnancy.

MONITORING AND REPORTING ADVERSE REACTIONS OR EVENTS

Any serious adverse events occurring during the course of the trial should be immediately brought to the attention of ethics committee, sponsors and Drug Controller General of India. At the end of the trial, all adverse events whether related to trial or not are to be listed, evaluated and discussed in detail in the final report.

II. VACCINE TRIALS

The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a drug trial. 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 trials examining effectiveness (immunogenicity) in a limited number of volunteers. Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal subjects, therapeutic or curative vaccines may be given to patients suffering from particular disease.

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

SPECIAL CONCERNS

- Some 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.

III. CLINICAL TRIALS WITH SURGICAL PROCEDURES / MEDICAL DEVICES

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

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

DEFINITIONS

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

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

a) Non critical devices - An investigational device that does not present significant risk to the patients eg. Thermometer, BP apparatus.

b) Critical devices - An investigational medical device that presents a potential serious risk to the health, safety or welfare of the subject - for example, pace markers, implants, internal catheters.

All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. As for the drugs, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained before pre-market certification. The duration of the trial and extent of use may be decided in case to case basis by the appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects :

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.
- Clinical trial of medical devices is different from drug trials, as former cannot be done in healthy volunteers. Hence Phase I of drug trials is not necessary for trial on devices.
- Medical devices used within the body may have greater risk potential than those used on or outside the body, for example, orthopaedic pins vs crutches.
- Medical devices not used regularly have less risk potential than those used regularly, for example, contact lens vs intraocular lenses.

- Safety procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.
- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information on following procedures to be adopted if the patient decides to withdraw from the trial.

IV. DIAGNOSTIC AGENTS - USE OF RADIO- ACTIVE MATERIALS AND X-RAYS

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

SPECIAL CONCERNS

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

V. CLINICAL EVALUATION OF HERBAL REMEDIES AND MEDICINAL PLANTS

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Drugs Controller General of India for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of Ayurveda, Siddha or Unani drugs by experts in those systems of medicine which may be used later in their own hospitals and clinics. All the general principles of clinical trials described earlier pertain also to herbal remedies. However, when clinical trials of herbal drugs used in recognised Indian Systems of Medicine and Homeopathy

are to be undertaken in Allopathic Hospitals, association of physicians from the concerned system as co-investigators / collaborators / members of the expert group is desirable for designing and evaluating the study.

SPECIAL CONCERNS

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

1. A lot is known about the use of a plant or its extract in the ancient Ayurveda, Siddha or Unani literature or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years. The substance is being clinically evaluated for same indication for which it is being used or as has been described in the texts.

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

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

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

Clinical trials with herbal preparations should be carried out only after these have been standardised and markers identified to ensure that the substances being evaluated are always the same. The recommendations made earlier regarding informed consent, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons with diminished autonomy, all

apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. However, it is essential that such clinical trials be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator in such a clinical trial. It would neither ethically acceptable nor morally justifiable, if an allopathic physician, based on references in ancient literature of above-mentioned traditional systems of Medicine, carries out clinical evaluation of the plant without any concept or training in these systems of medicine. Hence, it is necessary to associate a specialist from these systems and the clinical evaluation should be carried out jointly.

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

STATEMENT OF SPECIFIC PRINCIPLES FOR EPIDEMIOLOGICAL STUDIES

INTRODUCTION

Epidemiology is defined as the study of the distribution and determinants of health related states or events in specified populations and the application of this study to control health problems. Epidemiological studies are of primary importance in a large developing country like ours where the natural history, incidence, prevalence and impact on morbidity and mortality of a variety of diseases are not known. It has usually been considered that epidemiology of infectious diseases is of prime importance in our country. However, the evolving pattern of change in the society with upward economic mobility and increasing number of middle classes would mean that a significant number of life style related diseases such as Ischaemic Heart Disease are increasing. There is very little information about this and it would be useful to undertake long term cohort studies in different population groups.

Epidemiological studies are generally considered in two categories - observational and experimental. Designs of these studies are based on cross-sectional, case-control or cohort approaches. Epidemiological studies cover research, programme evaluation and surveillance. Scope of ethical guidelines for epidemiological studies are concerned with epidemiological research. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health and the social milieu.

Perhaps the code of ethics is much better understood for clinical research, where the interaction between a patient and a clinical researcher is of supreme importance. In epidemiological research the researcher is dealing with a group of individuals and the questions faced by an epidemiologist are more of a professional nature. These questions would pertain to interactions with individual subjects, sources of funding or employer, fellow epidemiologist and the society at large. Need for a code of ethics for epidemiologists is being recognised globally and the issues for such a code in the context of epidemiological research in India deserve attention.

Epidemiological research differs from clinical research in the context of the large number of study subjects and generally a long time frame. If some mistakes or aberrations get detected during the course of conduct of such studies, repeating the whole exercise will be expensive, time consuming and may not even be feasible. Hence utmost care needs to be taken for various aspects - technical, practical and ethical.

DEFINITIONS

Observational Epidemiology : This includes the following types :-

a. **Cross Sectional Studies (Surveys)** : This is primarily population based and involves selecting random samples of the population to be representative based on

census data and then applying questionnaires to understand the prevalence of various diseases. Its aim is to assess aspects of the health of a population or to test hypotheses about possible cause of disease or suspected risk factors.

b. **Case Control Studies:** This usually compares the past history of exposure to risks among patients who have a specified condition/disease (cases) with the past history of exposure to this among persons who resemble the cases in such respects as age, sex socioeconomic status, geographic location, but who do not have the disease. (controls) Case control studies can be done by following up available records, usually records in a hospital, but in the context of a country like ours it may require direct contact between research workers and study subjects and informed consent to participation in the study is necessary. However, if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

c. **Cohort Studies:** These are longitudinal or prospective studies of a group of individuals with differing exposure levels to suspected risk factors. They are observed over a long period usually several years. The rate of occurrence of the condition of interest is measured and compared in relation to identified risk factors. It requires a study of large number of subjects for a long time and involves asking questions, usually routine medical examination and sometimes laboratory investigations. Individuals are being followed up as the cohort and it is essential to identify precisely every individual to be studied.

Experimental Epidemiology:

In experimental epidemiology the investigators alter one or more parameters under controlled conditions to study the effects of the intervention. These are usually randomised controlled trials done to test a preventive or therapeutic regimen or the efficacy of a diagnostic procedure. Although these are strictly speaking epidemiological studies they come under the purview of clinical evaluation of drugs /devices / products / vaccines etc. The possibility of use of placebo as one of the arm of the trial should be explained and informed consent taken in such studies.

GENERAL PRINCIPLES

General ethical principles of respect for persons, duty to maximise possible benefits and minimise possible harm are important considerations in ethical guidelines. At the same time it is essential that all individuals in an epidemiological research are treated alike keeping in mind the rules of distributive justice. The welfare of the individual has to be balanced against the welfare of the community and society at large.

The C.I.O.M.S / W.H.O Guidelines for Epidemiological Research assumes that the individuals or population being studied are capable of giving informed consent understanding the implications of the study. With large segments of our population, given their level of education, the full understanding in the sense of industrialised countries may not be achievable. How the principle of "do no harm" is ensured under such circumstances without being paternalistic is a major issue that has to be taken into consideration in ethical guidelines.

In cohort or survey techniques for incidence and prevalence of various diseases, a major issue that has to be considered is how much of intervention is justified and whether one is justified in withholding interventions. For example, if you are looking at longitudinal morbidity in a population group, should you give them health education that is well established with regard to preventive aspects, or should you leave them alone so that the natural evolution of the disease can be studied? Health education or other interventions including non-health interventions can be quite expensive. An alternate strategy that may be followed is to make curative therapy available to the population at their own request. This usually involves running a clinic, which is readily accessible to the population without any other intervention. However, it is generally considered unethical to withhold intervention or services.

SPECIFIC PRINCIPLES

1. **Informed Consent** : When individuals are to be the subject of any epidemiological studies, the purpose and general objectives of the study has to be explained to them keeping in mind their level of understanding. It needs to be ensured that privacy will be maintained.

   In the context of developing countries, obtaining informed consent has been considered many times as difficult/ impractical / not meeting the purpose on various grounds such as incompetence to comprehend the meaning or relevance of the consent and culturally being dependent on the decision of the head of the family or village / community head. However, **there is no alternative to obtaining individual's informed consent** but what should be the content of the informed consent is also a crucial issue.

   In spite of obtaining informed individual consent, it is quite likely that the subjects / patients may not be fully aware of their rights. In this context, the role of investigator is crucial and he / she should remain vigilant and conscious of his/ her obligations towards the subjects / patients, all through the course of the studies.

2. In most epidemiological research it would be necessary to have the **consent of the community** which can be done through the Village Leaders, the Panchayat head, the tribal leaders etc.

3. In obtaining the consent of individuals or communities it is important to keep in mind that working through peer groups or through Panchayat etc. may mean that the individuals or community would feel reluctant to disagree and refuse to give consent because of **societal pressures**. This is something that has **to be carefully avoided**.

4. Particularly in a country like India, with the level of poverty that is prevalent it is easy to use inducements, especially financial inducements, to get individuals and communities to consent. **Such inducements are not permissible**. However, it is necessary to provide for adequate compensation for loss of wages and travel / other expenses incurred for participating in the study.

5. **All risks involved** including the risk of loss of privacy must be explained to the participants in an epidemiological study.

6. The design of the study should ensure that the **benefits of the study are maximised** for the individuals and communities taking part in the study.This means that at the onset itself the investigators should design the way in which the results of the study are going to be communicated and also decide whether individuals identified at particular risk during the course of the studies would be informed. It may also be necessary in some instances to inform the concerned family members about the results. For example, as in AIDS, STD etc. It may not always be possible to communicate study results to individuals but research findings and advise should be publicized by appropriate available means. It is also important that the beneficial results of epidemiological studies are fed into the health system and necessary training modules should be developed as part of the epidemiological project.

7. All attempts should be made to **minimise harm** to the individuals and society at large. Special consideration for the cultural characteristics of the communities that are being studied is essential to prevent any disturbance to cultural sensitivities because of the investigation.

8. **Maintaining confidentiality** of epidemiological data is absolutely essential. A particular concern is the fact that some population based data may also have implications to issues like national security and these need to be carefully evaluated at the beginning.

9. In all situations where there is likely to be **conflicts of interest** it must be ensured that the interest of the individuals involved in the study are protected at all cost.

10. **Scientific objectivity** should be maintained with honesty and impartiality, both in the design and conduct of the study and in presenting and interpreting findings. Selective withholding of data and similar practices are unethical.

11. **Ethical Review Procedures:** In all Ethical Committees at least one or two individuals with an understanding of the principles of epidemiological ethics

have to be included. These Committees should be independent and comprise of epidemiologists, clinicians, statisticians, social scientists, philosophers, legal experts and representatives from community / voluntary groups who should be aware of local, social and cultural norms, as this is the most important social control mechanism.

12. **Distinction between research and programme evaluation:** It is difficult to make a distinction between epidemiological research and programme evaluation. Whenever a programme evaluation and surveillance is launched, the monitoring and evaluating mechanisms should clearly be planned and ethically cleared before initiation as is done in all epidemiological studies.

STATEMENT OF SPECIFIC PRINCIPLES FOR HUMAN GENETICS RESEARCH

INTRODUCTION

In no other area of biomedical research there has been a greater concern for ethical issues than in the field of human genetics. It has largely stemmed from the movements of eugenics and nazism in nineteen twenties and thirties. In recent years this concern has grown even further because of the possibility of commercial eugenics. While 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, it has also led to a great deal of concern about our ability to handle the information so derived. With the successful completion of Human Genome sequencing in June 2000 there is an urgent need for clear-cut guidelines and dissemination of information to all stakeholders through media and public debates as there is a great need for improving awareness and understanding of human genetic disorders amongst public, the majority of whom have little knowledge of genetics.

The knowledge about human genes and genetic diseases prior to fifties was so poor that there was hardly any human genetic experimentation. Since then, and especially in the past two decades, there has been a veritable explosion in knowledge in the field of human genetics which has culminated in gene therapy (the ultimate in therapy for genetic diseases) and various other therapies based on genetic engineering including the glib talk of 'Designer babies'. 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 the Human Rights issues of dignity, autonomy, and justice, the Human Genome Project (HGP) has also precipitated an unprecedented concern for Intellectual Property Rights. Recent experiments on cloning sheep and mice have brought human cloning into the realm of possibility, raising additional set of Ethical, Legal and Social Issues (ELSI). This calls for laying down of special guidelines to contain the potential harm without clamping a moratorium on research and service in this field. Also, there should be no restrictions in availing the gains of latest technology, which are beneficial to the mankind. In fact ensuring access to genetic services to all irrespective of their ability to pay, particularly to those who need it the most, is an equally important moral concern.

In this rapidly evolving field there is a need for a watchdog body to continuously monitor such developments and respond to emerging ethical issues promptly and judiciously.

GENERAL GUIDELINES

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 : -

(i) 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. Appropriate communication skills are necessary for genetic counselling. There is a likelihood of social stigmatisation and discrimination in schooling, employment, health and general insurance, which requires much greater care in recruiting subjects in research study, obtaining informed consent and maintaining confidentiality of research findings, than in any other area of research.

(ii) There is great importance of spoken word in medical genetics, since genetic counselling is akin to therapy in other fields. In that sense in medical genetics, the 'word' is equivalent to drug/intervention in other fields of medicine. Written explanation understandable to layman about presentation and natural course of the disease, interventions available and their outcome, as also implication of the information for progeny and family, has special place in clinical research in this field.

(iii) Genetic counselling deals with discussion on personal matters such as reproductive options, and the couple may have to make a choice with far reaching social implications. Therefore, it calls for special care that should be documented in research proposals and carefully considered by the Institutional Ethics Committee.

(iv) Genetic manipulations have consequences for the future, some of which are unknown. Hence, greater care towards potential dangers is necessary.

(v) There is greater likelihood of situations cropping up where there is conflict of interest between an individual, and that of family and society at large. Careful guidelines need to be evolved by peers in the profession to tackle such situations. The professional societies should actively participate in these activities.

(vi) 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.

(vii) 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 (DBT) to organize national debates on such issues to evolve consensus on them.

(viii) Concerned with the misuse of genetic tests, particularly for the pre-selection of sex, the Government of India has enacted a law known as "The Prenatal Diagnostic Techniques (Regulation & 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).

I. PEDIGREE STUDIES

These involve obtaining history of other members of the family of the proband under investigation. It may reveal information about the likelihood of individual members of the family being either carriers of genetic defects or being affected by the disease.

Special privacy and confidentiality concerns arise in genetic family studies because of relationship between the participants. It should be kept in mind that within families each person is an individual who has the right to keep the information about himself or herself confidential. **Family members are not entitled to know each other's diagnosis.** Before revealing medical or personal information about individuals to other family members, investigator must obtain consent of the individual to do so. In view of the cultural background of our country where woman is still a vulnerable and exploited subject, revealing information to the husband that his wife is the carrier of balanced chromosomal translocation (leading to recurrent abortions or a genetic syndrome in her child) or that she is a carrier of a single gene causing 'X' linked or recessive disease, may lead to grounds for a divorce despite the fact that the husband himself is a carrier of the autosomal recessive disorder. While general principles of counseling require presence of both the spouses, necessary care must be taken not to end up in breaking the families.

Subject recruitment

The familial nature of research cohorts involved in pedigree studies can pose a challenge for ensuring that recruitment procedures are free of elements that unduly influence decision to participate. The very nature of research exerts pressure on family members to take part, because more complete the pedigree, the more reliable the resulting information. Problems of the following kind could arise:

(i) Revealing who else in the family has agreed to participate may lead to breach of confidentiality.
(ii) If a proband is used for revealing his personal interest he/she may put undue pressure on relatives to enroll in the study.
(iii) Direct recruitment by telephone calls etc. may be seen as an invasion of privacy by family members.
(iv) Contact through personal physicians may imply that their health care may get compromised if they do not agree to participate.

There is no satisfactory alternative, which can be recommended. The likely problems are listed, so that appropriate caution may be exercised.

Informed consent

For biogenetic research involving human subjects certain special considerations have to be kept in mind while obtaining informed consent of the prospective subjects enrolled in the study. These are in addition to general principles that are applicable to all medical research.

Confidentiality of data

This includes codification of the biological samples, where necessary. The investigator must establish secure safeguards for the confidentiality of the research data. Subjects should be told of the limits of the investigator's ability to safeguard confidentiality and of the anticipated consequences of breach of confidentiality. When commercial companies, are involved in research, it is necessary to protect researchers and subjects from possible coercion/inducement to participate in the study.

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 the investigator in the company developing a new product). In cases where the Ethics Committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, it 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 or of information infrastructure, reimbursement costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

Defining risks and benefits

Potential risks and benefits should be discussed thoroughly with prospective subjects. In genetic research, the primary the risks are psychosocial rather than physical.

Adequate counseling should be given to subjects on the meaning of genetic information they receive. **Only those persons who are qualified and experienced in communicating the meaning of genetic information should undertake genetic counseling.**

II. GENETIC SCREENING

Genetic screening implies search in population of individuals who have, or are susceptible to have a serious genetic disease; or who, though not at risk themselves, are carriers and thus at risk of having children with the particular genetic disease.

It is essential that screening must be purposive. Also, besides validation of screening tests, it shall also be ensured that a suitable intervention is possible. Rarely, screening may be permissible to allay anxiety, but it should not be forgotten that response of different individuals may vary. It should not entirely be a matter of individual's choice, but should be determined after careful evaluation by the health care provider. Depending on nature of the genetic defect that is identified and its pattern of inheritance, siblings and other blood relations as well as existing and future offsprings may be affected. This raises ethical questions that differ significantly, from the normal rules and standards applied to handling of personal medical records.

- A well informed consent is, therefore, essential. Those being screened are entitled to receive sufficient information in a way that :-
  - i. they can understand what is proposed to be done.
  - ii. they must be made aware of any substantial risk.
  - iii. they must be given time to decide whether or not they would like to participate or withdraw from screening.
- Details about the disorder to be screened and its inheritance pattern, reliability of the screening test and what will be done with the samples should be explained. Information about the implications of a positive screening test (abnormal) should also be explained.
- Confidentiality should be maintained in handling of results with emphasis on responsibility of individuals with a positive (abnormal) result to inform partners and family members. It needs to be emphasized that consent for screening or a subsequent confirmatory test does not imply consent to any specific treatment or termination of the pregnancy.
- General guidelines have to be followed for a vulnerable individual i.e. minors, mentally ill, prisoners, students, subordinates and people who do not speak the language of the investigator etc.
- Genetic counseling should be readily available for those who are being screened. Law protects confidentiality of medical information, but this is not absolute.

Information may be disclosed where it is in the public interest to do so, or if required by the court of law. However, great care is needed in this regard as well.

Screening new borns : Screening of new borns is permissible to detect those genetic diseases like phenylketonuria where serious effects of the disease could be prevented by a suitable intervention such as special diet or treatment. It should not be done when there is no immediate cure / intervention for diseases manifesting later in life. The same applies to investigations to detect genetic, chromosomal, metabolic abnormalities, etc. The diseases can be screened as and when intervention/therapy becomes available in future.

Prenatal testing: It is aimed at detecting presence of abnormalities in the foetus. The foetal sample for examination may be obtained through amniocentesis, chorionic villi sampling, placentocentesis, cordocentesis (blood sampling from the umbilical cord) and skin or other biopsies. Foetal cells in maternal circulation can also be used for prenatal testing. Non-invasive methods should be preferred whenever available.

Anonymous testing: Researchers may conduct anonymous testing on general population in order to establish prevalence of genetic traits / diseases. Blood spots collected for screening newborns for treatable disorders could also be used for this purpose. In case information derived from stored specimens might be useful to an individual, the code of anonymity may be broken with the approval of the Institutional Ethics Committee (IEC).

III. THERAPEUTIC TRIALS INCLUDING GENE THERAPY

Recombinant protein products

Genetic disorders, which require replacement therapy like ADA deficiency, do not pose any ethical problem. Replacement with animal products should follow the rules as stipulated for other diseases.

Gene Therapy

The goal of human genetic research is to alleviate human suffering. Gene therapy is a proper and logical part of this effort. Gene therapy should be subject to all the ethical codes that apply to research involving patients.

i) **Somatic cell gene therapy** is the only method that may be permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option. It should be restricted to alleviation of life threatening or seriously disabling genetic disease in individual patients and should not be permitted to change normal human traits. However, rapid advance in science necessitates periodic review of guidelines in this area. This includes evaluation of safety and efficacy of DNA vaccines and transgenic foods as well.

Gene Therapy trial consists of two parts. The first part is preparation of the 'gene construct' to be administered, and the second part is evaluation of the efficacy and safety of the administered 'gene (construct)'. As far as the first part is concerned, the guidelines and clearance for it is to be regulated by the National Bioethics Committee under Department of Biotechnology (DBT) and for the second part clearance from the local IEC and Central Ethical Committee (CEC) of the ICMR shall be obtained.

Safety should be ensured especially because of the possibility of unpredicted consequences of gene insertion. All gene therapy trials should have the provision for long term surveillance. Informed consent must be taken especially regarding uncertainties about outcome. Children could be candidates for therapy, if the therapy is meant for a childhood disorder.

ii) **Germ Line Therapy** is prohibited under the present state of knowledge in these areas.

iii) **Gene Therapy for enhancement** of genetic characteristics (so called designer babies) should not be attempted, as we possess insufficient information at present to understand the effects of attempts to alter/enhance the genetic machinery of humans. Also, the influence of environmental interaction on the expression of genetic characters is poorly understood.

It is not safe or ethical for parents to give, for example, growth hormone to their normal offspring in order to produce very large football or basketball players. Similarly it would be unethical to use genetic engineering for improvement of intelligence, memory etc. even if specific gene/genes are identified in future.

iv) **Eugenic Genetic Engineering** for selection against personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics is prohibited.

IV. HUMAN GENOME PROJECT (HGP)

The human genome project (HGP) is an international research effort, the goal of which was to determine the location of estimated 40 - 1,00,000 genes and to sequence the entire human DNA. Another component of the programme is to analyze the DNA of a set of non-human model organisms, which may contribute to understanding of the human genome. The project began formally in 1990 and has been completed by June 2000. This project has resulted in exploring the potential for profoundly altering our approach to medical care from treatment of advanced disease to prevention, based on the identification of individuals at risk, and designing it specific to targets / individuals.

Implications of using this genetic knowledge pose a number of questions for:

i. individuals and families – whether to participate in testing, with whom to share the results, and how to act on them;

ii. health professionals – when to offer testing, how to ensure its quality, how to interpret the results and to whom to disclose information;

iii. employers, insurers, the courts and other social institutions – the relative value of genetic information to the decision they must make about individuals;

iv. governments – about how to regulate the production, and use of genetic tests and the information they provide and how to provide access to testing and counselling services for society; and

v. the society – how to improve public understanding of science and its social implications and increase participation of the public in science policy making.

The above questions should be addressed to by the scientific community before application of this knowledge could be considered as ethically valid.

V. DNA BANKING

Primary use:

Primary use is the use for original intent for which consent and approval of Local IEC has been obtained. It is recommended that normally the use of the samples shall be reserved for this purpose only.

Secondary Use:

Every request for secondary use shall be examined by the Institutional Ethical Committee:

i. to ensure that the proposed use does not transgress the original consent given for the earlier study;
ii. the validity of the objectives of the new study; and
iii. provisions for ensuring anonymity of the samples for secondary use.

VI. DNA DIAGNOSIS

The general principles of informed consent, confidentiality and other criteria used for any investigation in genetics should be followed. Since the knowledge in this field is new, and relatively complicated, a DNA test must be preceeded and followed by appropriate genetic counselling.

Pre-implantation DNA diagnosis : It is a type of prenatal diagnosis. Same precautions and safeguards should be adopted for this purpose also.

Pre-morbid diagnosis in children : Parents are advised not to get the diagnosis done especially in cases like Huntington's disease etc. for which there is no available intervention till the child reaches the age of proper "consent".

Pre-morbid diagnosis in adults: It may be carried out with informed consent. However, appropriate genetic counseling must be provided and documented before offering such services,

DNA diagnosis in forensics : The laboratories carrying out DNA diagnosis in forensics should follow the guidelines evolved by National Accreditation Board for Laboratories functioning under the Department of Science and Technology.

The consequences of DNA testing for conditions for which no treatment is available or for conditions manifesting late in life e.g. breast cancer, Alzheimer's disease etc. should be seriously considered before embarking on such studies. Information so derived should not disclose the identity of the individuals.

VII. ASSISTED REPRODUCTIVE TECHNIQUES

This includes any fertilization involving manipulation of gametes outside the human body and the transfer of gametes or embryos into the body.

- Informed consent should include information regarding use of spare embryos. It should be made clear whether embryos that are not used for transfer could or could not be used for research purposes or implanted in another woman's womb, or "preserved " for use at a later date or destroyed. Investigators should ensure that participants are informed and consent is taken in writing on the above issues.
- Investigators should clarify the ownership of the embryos that they belong to the biological mother or the laboratory. Abortions should never be encouraged for research purposes.
- There is no ethical objection at the moment for IVF or any other related procedure for research or for clinical application.

Respect for embryo can be shown by **(1)** accepting limits on what can be done in embryo research, **(2)** committing to an inter-disciplinary process of peer group review of planned research, and **(3)** carrying out an informed consent process for gamete and embryo donors. Further, respect for the embryo's moral status can be shown by careful regulation of conditions of research, safeguards against commercial exploitation of embryo research, and limiting the time within which research can be done to **14 days** i.e. when the **primitive streak** appears. This restriction is in keeping with the policy in several nations that permit research with embryos. At this time, the development of nervous system begins and the embryo begins to become a distinct individual.

Women have a special position as care givers for children with disabilities. Since the bulk of care falls upon the women, she should make the final decision among reproductive options, without coercion from her partner, her doctor, or the law. Choice is more than the absence of legal prohibition or coercion. Choice should include the economic and social ability to act upon a decision, including disability. There should be a positive right to affordable genetic services, safe abortion and medically indicated care for children with disabilities.

Cloning (through nuclear transplantation or embryo splitting) : The possibility of human cloning cannot be rejected since sheep and mice have already been cloned. However, since its safety, success, utility and ethical acceptability is not yet established, r**esearch on cloning** with intent to produce an identical human being, as of today, is prohibited.

VIII. PRENATAL DIAGNOSIS

This should be performed only for reasons relevant to the health of the foetus or the mother. Prenatal diagnosis should not be performed solely to select the sex of the child (in the absence of an X-linked disorder). Sex selection, whether for male or female, denigrates the fundamental personhood of those yet to be born, and has the power to harm societies by unbalancing sex ratios. The potential harm to large groups of people outweighs any immediate benefits to individuals or families. The Government of India has already passed legislation banning diagnosis of sex for non-medical reasons.

Prenatal diagnosis can be used to prepare parents for the birth of a child with a disability. Therefore, prenatal diagnosis should be available to such parents who request it but oppose abortion, provided that they understand and are willing to accept the risks to the foetus.

In some cases, prenatal diagnosis may be performed to protect the health of the mother. These include clinically confirmed cases of morbid anxiety or situations where prenatal paternity testing would benefit the mother's mental health (e.g. if rape occurred while a couple was trying to conceive).

Professionals should recognize the human and economic costs involved in prenatal diagnosis and should limit its use to situations where there is a clear benefit.

ANNEXURE

DEFINITIONS

Genetic material / genome : Genetic material refers to DNA or any other material carrying hereditary information in each cell of an organism. It consists of unique, single copies of genes, which make up approximately 10% of the DNA. The total informational content of an individual is known as 'genome'.

Chromosome: The thread-like DNA in a cell is divided into several separate lengths. Each length forms a structure called a chromosome. There are two copies of each chromosome in every cell. Human cells contain 23 pairs of chromosomes.

Gene: A gene is a length of DNA that contains the information needed to make one polypeptide. For example, the beta globin gene contains the information needed to make the beta globin polypeptide found in hemoglobin of red blood cells. More than one gene may be involved in making one protein, and more than one polypeptide may be formed from one gene as a result of alternate splicing.

Genetic Engineering : It is the process of creating new DNA such as by cutting and patching (recombinant DNA technology). Several other technologies such as site directed mutagenesis, vector mediated integration or deletion of DNA etc. have evolved and are continuing to evolve.

Heterozygote : Each cell of an organism contains two copies of each gene. In a heterozygote, the two genes of a pair are different from each other (allelic).

Homozygote : Each cell of an organism contains two copies of each gene. In a homozygote, both copies of the gene are identical to each other.

Mutation : A process by which the DNA of an organism changes or mutates. In humans this can lead to disease such as thalassemia in which the mutation results in decreased production of beta or alpha globin. The mutant gene is passed on from parent to the offspring, so the condition is inherited. In viruses and other infectious organisms, mutations can lead to emergence of organisms with new characteristics. It can make them more virulent or resistant to antibiotics thus increasing their infectivity.

Recombination : A cross-over between two members of a homologous pair of chromosomes results in the formation of a recombined chromosome wherein a new set of gene (allele) arrangement is created.

Transgenesis : This refers to the introduction of a foreign gene into an animal or other organism. The transferred gene is called a transgene.

HUMAN GENOME DIVERSITY

Department of Biotechnology, Government of India has brought out a document on genomic diversity which envisages the following:-

i) There is worldwide interest in the study of genomic diversity of anthropologically well-defined populations for understanding the origin of people which has evolutionary implications.

ii) This may require establishment of national repository of biological samples (DNA, cell lines etc.) but it should be done with appropriate safeguards and regulations to ensure anonymity of the sample (the identity of the sample should not be no traceable) and protection of the rights of the people.

iii) It shall be ensured that participation in these studies is entirely voluntary, and no coercion or inducement is employed for the purpose. The intent for collection of these samples and possible impact of the information desired shall be explained to the participants.

iv) The analysis of DNA samples shall be carried out by Indian scientists / laboratories. No sample shall be sent out without following the guidelines of the Government of India (GOI) in this regard. In the event of failure of agreement the guidelines of the country (India) shall prevail. International collaboration, if any, shall be carried out with well-documented MOU, which is approved by the Institutional Ethical Committee. This should include the scope of utilization of exchanged material and related IPR issues, as well as concerns for human rights.

Scientists involved in these studies shall ensure that rights and sensitivities of the participating individuals and populations are protected. Relevant issues like **(a)** consent for collection of samples, **(b)** access to these samples and for what purposes, **(c)** Property rights of the DNA; and **(d)** quality control of the laboratories shall be appropriately documented in the research proposal for scrutiny by the Institutional Ethical Committees.

A major concern regarding these studies is the possibility that generated information may produce ethnic disharmony. Therefore, great care is necessary for handling of this data, particularly, in reference to release of news to media and publication of research results.

STATEMENT OF SPECIFIC PRINCIPLES FOR RESEARCH IN TRANSPLANTATION INCLUDING FETAL TISSUE TRANSPLANTATION

INTRODUCTION

The practice of transplantation is in its infancy in India. The exceedingly high cost restricts its application, and also reduces the interest in research into this field. The same reason makes it imperative that Indian scientists should devise means of reducing the cost and improving the success rate, to make it feasible to increase the number of Indians who can benefit by this treatment.

At present the protocols devised in the West are followed which are not necessarily ideal. The ethical principles of research in human subjects have been well enunciated in the Declaration of Helsinki adopted by the World Medical Association in 1964, and amended in 1975, 1983, 1989 and 1996. Transplantation, however, raises some peculiar aspects, and these will have to be weighed in that light. The problem has been considered with special reference to the following points:-

I. Transplants from live or cadaver donors
II. Embryonic and foetal tissue and organ transplantation
III. Xeno-transplantation
IV. Transplantation for cosmetic purposes.

I. TRANSPLANTS FROM LIVE OR CADAVER DONORS

DEFINITIONS

Cadaver: A dead body. For purposes of this document, the term refers to a dead human body.

Death: This was originally defined as entire and continuous cessation of respiration and circulation. It has since been recognised that the heart could continue beating for a time, even for days, though the brain lacked the ability to maintain respiration and sustain life. Death of the brain stem, also called brain death, has since been recognised internationally, and in the 'Indian Transplantation of Human Organs Act', 1994.

Brain death: This is as specified in 'Transplantation of Human Organs Act, 1994' with ' Transplantation of Human Organs Rules, 1995'. Salient features are described below:-

- Entire, permanent, and irreversible cessation of functions of the brain stem –this is synonymous with brain-stem death, since the centres for the control of essential body functions such as consciousness, respiration, and blood pressure are situated within the brain stem. In many countries strict criteria for diagnosis of brain death have been established. These include the presence of deep coma, the absence of any brain-stem functions such as spontaneous respiration, pupillary reactions, eye

movements, gag and cough reflexes, and the exclusion of low body temperature and drugs as relevant to the comatose state. The EEG is a useful (but not essential) confirmatory test. Brain death is when 'Damage is judged irremediable' based on its context, the passage of time, and the failure of all attempts to remedy it. Secondly, all possible causes of reversible brain-stem dysfunction, such as hypothermia, drug intoxication, or severe metabolic upset, must be excluded. Finally, the absence of all brain-stem reflexes must be demonstrated, and the fact that the patient cannot breathe, however strong the stimulus, must be confirmed.

- When testing the brain-stem reflexes, the following normal responses must be looked for: (1) constriction of the pupils in response to light, (2) blinking in response to stimulation of the cornea, (3) grimacing in response to firm pressure applied just above the eye socket, (4) movements of the eyes in response to the ears being flushed with ice water, and (5) coughing or gagging in response to a suction catheter being passed down the airway. All responses have to be absent on at least two occasions with an interval of six hours between them. Apnoea, which also must be confirmed twice, is assessed by disconnecting the patient from the ventilator, (prior to this test, the patient is fully oxygenated by administering 100% oxygen for several minutes to ensure that the patient will not suffer serious oxygen deprivation while being disconnected from the ventilator). The purpose of this test is to establish the total absence of any inspiratory effort as the carbon dioxide concentration in the blood (the normal stimulus to breathing) reaches more than sufficient levels to stimulate any respiratory centre cells that may still be alive.

GUIDELINES ON LIVE DONOR TRANSPLANTS

1. Donation from a live donor should be restricted to renewable tissues like bone marrow, or to a paired organ whose removal will not greatly alter physiological functions, like the kidney. Since the removal of an eye will compromise binocular vision and produce disfigurement, it should not be permitted in a live donor.

2. Surgery on the donor inflicts bodily harm on him or her, the extenuating circumstances being the saving of another human life. It is imperative that no risk be imposed on the donor beyond that inherent in surgery and the loss of a vital organ. Any manner of experimentation, though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest extra risk to the donor. Examples are pre-treatment of the donor with immuno-suppressives or anticoagulants.

3. Every such research project should be preceded by careful assessment of predictable risks and compared to foreseeable benefits and improvement in the success rate of transplantation.

4. The interests of the donor should always take priority over those of the recipient of the transplant.

5. In view of the risk involved, the voluntary consent of the donor is absolutely essential. Further, the donor should be informed of all possible risks in a manner easily understood by the subject before the consent is taken.

6. It follows that the donor should have the legal capacity to give consent and be in a position to exercise free power of choice without the slightest element of force, duress, or coercion, and should have sufficient knowledge and comprehension of the subject to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults as also individuals with restricted autonomy should not be used as organ donors or as subjects for such experiments.

7. Since the experiment would have consequences for the recipient too, the donor must be fully informed of the nature of the procedures and the possible effects on the recipient before consent is taken.

8. The responsibility of providing the above information to the donor, and of making sure that he / she understands fully the implications of what is to be done and what he or she consents to, rests entirely on the individual who directs the research project.

9. The experiment should be such as to yield fruitful results for the overall good of the donee without any risk to the life of the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised.

10. The experiment should be so planned and conducted as to avoid all unnecessary risks to the donor, to the organ to be transplanted, and to the recipient of the organ. Proper precautions should be taken and adequate facilities should be available to protect the donor from the most remote possibility of harm.

11. The donor should be at liberty to withdraw from the experiment and to abrogate the consent given earlier, with no requirement to offer any explanation of the reasons for his or her doing so.

12. If at any time during the course of the experiment the investigator comes to know that there is risk to the donor or to the recipient as a result of the procedure, it is his or her responsibility to terminate the experiment forthwith.

13. This does not preclude any treatment or procedure done on the organ or tissue after removal from the donor's body, aimed at reducing its antigenicity and improving graft survival.

Creation of human beings for transplantation purposes should be banned.

GUIDELINES ON CADAVER DONOR TRANSPLANTS

1. Every one should give a thought to the need for organ donation after death. In such an event one should make a decision and inform the next of kin, and register oneself with an appropriately constituted authority. Where one is opposed to donating his or her organs, this too, should be made known to the next of kin, so that this wish of the deceased may be respected after death. Such a **"Living Will"** is in vogue in a number of countries in the world.

2. In the absence of such prior directions from the deceased, the person in lawful possession of the body will make the decision to use the organs or not, as he may think fit, after consultation with the family.

3. It is important that the medical team uses the body only for the purpose for which consent has been given.

4. Remaining tissue and organs should be treated with the respect due to a human body, and will not be used for any purpose to which explicit consent had not been given.

5. Under no circumstances should financial gain be made from any such procedure.

6. There shall be no coercion and no monetary inducements offered to the family of the prospective cadaver donor.

7. Confidentiality of the donation must be maintained on both sides: the recipient and his or her family will not be informed of the identity of the donor, and the family of the donor will equally be kept unaware of who receives the donated organ. This is essential to avoid any form of exploitation by the donor's family.

GUIDELINES ON RECIPIENTS OF TRANSPLANTS

1. The patient with failure of a vital organ is at a particular disadvantage in developing countries due to the enormous cost involved for the available interventions. If the organs involved are the kidneys, most Indians cannot afford to maintain themselves on dialysis. Similarly ventilators are available at very few centres. There are no artificial supports for other organs like the heart, the lungs and the liver, so death is imminent and no means is available to keep the individual alive short of replacing the organ concerned. Thus a measure of urgency is introduced into the search for a donor organ.

2. A desperate patient may consent to procedures which put him or her at risk. It is all the more important that every research protocol for transplantation should be carefully reviewed by an appropriate committee of suitably qualified scientists,

jurists and other eminent members of society, so that its scientific and ethical basis may be impartially evaluated.

3. The transplant research team should have high technical expertise.

4. Adequate data management, tissue storage facilities, and surveillance procedures should be available in a centre before it is authorised to conduct research into transplantation.

5. If, at any time, a patient should refuse to take part as a subject for a research project, it should in no way interfere with his or her right to receive treatment of the best quality, which the team is capable of providing.

6. Under no circumstances should there be a conflict between scientific content of a study and the best interests of the patient. Should there be need to choose, the experiment should be abandoned and the patient should receive the best treatment possible.

II. EMBRYONIC AND FOETAL TISSUE AND ORGAN TRANSPLANTATION

INTRODUCTION

Human foetal tissue has been used in research for a wide range of purposes over decades. The thought of using foetal cells as transplants was first occasioned when scientists attempted to find ways of treating patients with loss of nerve cells in the brain and spinal cord. Since damaged nerve cells do not regenerate, repair to damage in the brain and spinal cord is severely limited. Attempts to trick the neurones into repair and re-growth have yet to bear fruit. That was when the attempts to transplant healthy neural tissue into damaged areas of the brain were started in an effort to allow the re-establishment of damaged neural circuits. The immunological complications that result, whenever any foreign tissue is transplanted into a human, proved a barrier.

The use of foetal tissue is one of the means to minimise the chances of rejection. In the early weeks after conception, foetal cells multiply rapidly and show very little antigenicity because many surface antigens would not yet have developed. These cells are not fully differentiated and adapt easily to the signals received from surrounding tissue in a host. They grow and differentiate in such a manner that they are integrated to form part of the host organ. Foetal cells can also be successfully preserved by cooling and be reanimated. As the technology for developing immortal foetal cell lines for study of gene regulation, pattern formation in embryogenesis, as models of cell interaction and function, for vaccine development and study on cell growth and regulation, cancer and immune response was perfected, hopes for the use of these cells as transplants strengthened.

Non-neural foetal tissue transplantation has included injection of immune cells from the thymus and liver of aborted foetuses into the umbilicus of a 30 week old foetus with bare lymphocyte syndrome, a rare and always fatal immuno-deficiency disorder. Success has also been reported on the use of foetal thymus in the reconstitution of a severe combined immuno-deficient (SCID) child in Italy who survived 17 years exhibiting normal immune responses even though his T cells were of foetal donor origin. Other potential uses of foetal tissue include treatment of diabetes, genetic retinal abnormalities, optic nerve and spinal cord injury, Alzheimer's disease, aplastic anaemia, acute leukaemia / lymphoma and liver failure.

DEFINITIONS

Embryonic state: Between 15 days and 8 weeks post-conception of a pregnancy. In the absence of more precise information (i.e. menstrual cycle length), conception is presumed to have taken place two weeks after the beginning of the woman's last menstrual period. The distinction of the 15-day stage as the beginning of the embryonic stage is not arbitrary: the pre-embryo is not isomorphic with the later developmental stages, since cells cannot yet be defined as contributing to the embryo or to the extra-embryonic tissue, and complete implantation has not yet been accomplished. At 8 weeks, the rudiments of nearly all the main structures have been laid down giving a general appearance of a mammal-to-be with four limbs and a head.

Foetal stage: Subsequent period between 8 weeks and the time the baby is born, at approximately 38 weeks post-conception (40 weeks post-last menstrual period).

(a) **Live aborted foetus** : If an aborted foetus is alive, it is a person, no matter how short the period of gestation, and using it for an experiment would, in law, be considered an assault upon it.

(b) **Dead foetus** : An expelled or delivered foetus that exhibits no heart beat or spontaneous breathing. Some organs, tissue and cells remain alive for varying periods after the moment of death of the foetus.

Neonate stage : Newly born live individual of any gestation period.

GUIDELINES FOR RESEARCH ON FOETAL TISSUE OR ORGANS FOR TRANSPLANTATION

1. Every transplantation or research project involving the use of embryonic or foetal tissue must be approved by the local scientific and ethics committees and referred to National or Central Ethical Committee for final approval.

2. All members of the hospital or research staff - medical and paramedical - directly involved in any of the procedures will be fully informed of the purpose and implications of the research project.

3. The researcher shall not be a party to deliberate conception and / or subsequent abortion for the sake of obtaining tissue or organ for research or saving the life of a family member or for the purpose of commercialisation.

4. No research is permitted on the live aborted foetus.

5. Tissue for transplantation or research may be obtained from dead embryos or foetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or foetus is defined as absence of respiration and heart beat.

6. Voluntary, informed, written consent will be obtained from the mother in two stages - first for the abortion, next for the donation of tissue from the foetus. The mother's decision to donate foetal tissue is sufficient for the use of the tissue unless the father objects in writing. In cases of incest or rape, the father's objection carries no significance.

7. The mother will not dictate who shall receive the foetal tissue taken for transplantation.

8. Anonymity of donor and recipient will be maintained so that neither party is aware of the identity of the other.

9. The procedure of abortion, or its timing, will not be influenced by the requirements of the transplantation activity. These should solely be based on concern for the safety of the mother.

10. Those participating in termination of pregnancy will not, in any way, be party to the subsequent usage of embryonic or foetal tissue for commercial purposes.

11. The procurement of embryos, foetuses or their tissue for commercial purposes will not involve profit or remuneration.

12. **Intact embryos or foetuses** will **not be kept alive** artificially for the purpose of removing usable material.

13. **Tissues from aborted foetus can be cultured and banked** for use in research on transplantation. If such stored tissue is to be subsequently used for any purpose other than the original objective, a fresh sanction will be obtained from the scientific and ethical committees.

14. Cells obtained from foetuses will not be patented for commercial considerations for their subsequent usage.

15. Use of **umbilical cord blood from a live foetus or neonate** for transplantation: The fundamental principle in any operation on a live foetus or neonate will be to

ensure that no harm will occur to the foetus or neonate. Since the exact timing of the clamping of the umbilical cord has a significant impact on the neonate and early clamping may cause an abrupt surge in arterial pressure resulting in cerebral intra-ventricular haemorrhage, particularly in premature neonates, normal clamping protocol will be followed when collecting foetal blood for transplantation. There is a risk that the neonate donor may need his or her own cord blood later in life. If the blood has been used for another, he or she might be without blood when it is needed. Parents will be fully informed of the risks of the donation and written consent obtained from them on behalf of the foetus.

16. **Use of tissue or organs from dead anencephalic foetus or neonate** (foetus or neonate lacking brain development above the level of the brainstem) is permitted. Physicians may provide anencephalic neonates with ventilator assistance and other medical therapies that are necessary to sustain organs till such time as the diagnosis of death is made on the basis of cessation of cardiac function. Retrieval and transplantation of organs of anencephalic foetus are ethically permissible only after such diagnosis of death is made.

17. No transplantation of foetal tissue into man will be permitted unless the following criteria have been met:

i. there will be a detailed scientific basis for such transplantation;
ii. animal experiments must show successful results - eradication of disease, elimination or amelioration of symptoms and signs or successful substitution of deficient chemicals and restoration of normal physiological function by the transplant. These must be documented in one or more indexed journals with good peer review mechanisms;
iii. all records pertaining to animal experiments must be complete and submitted to specialist and general scientific scrutiny. These records must be preserved for a minimum period of five years after the completion of the study preferably on a permanent basis as far as possible;
iv. Success in animal experimentation must be shown on a long-term basis. The studies must include investigations on animals receiving the transplants at periodic intervals after the procedure specially with reference to unequivocal demonstration of absence of any transmission of disease through the transplant.
v. Trials in human patients will commence only on those patients where no other form of treatment is available and where, in the absence of the transplant, the patient is likely to suffer relentless deterioration in his health with fatal termination.
vi. After obtaining her consent, the mother must be screened for transmissible disease. If possible, the material to be transplanted must also be similarly screened.
vi. Trials in human patients will be carried out only at the institutions having clinical and research facilities needed for such trials, including those that may be required to treat complications that may follow such research.

vii. The research group and the institution(s) in which they work will undertake to conduct free of charge the research on their human subjects and also treat completely any complication that may follow their study even if it appears several years after the conclusion of the study.

ix. The research group will provide the human subjects a printed document explaining in simple, non-technical language, the purpose of the study, details of the procedures the human subject is to undergo, complications that may follow these procedures, financial implications, interests of the researchers in the conduct of the study, and a commitment to treat completely and free of cost any complication that may ensue. The human subject must certify in writing that he has studied and understood the contents of this document and that he / she is willing to participate in the study.

x. Any adverse effects noted will be immediately discussed with members of the ethics committee and the project grounded if these cannot be explained or reasonably corrected in the course of the study.

18. The local ethics committee must ensure report-back measures at every stage of research and confirm that a detailed report on the procedures, findings and conclusions is submitted to an indexed journal for publication even when the results are of a negative nature. The National/Central Ethics Committee should be kept informed.

19. As with therapeutic transplantation, constantly updated local (metropolitan), regional or national lists of available tissues and organs should be maintained to ensure that optimal use is made of all available donations. These lists should be made freely available to all authorised research workers.

III. XENO-TRANSPLANTATION

INTRODUCTION

Paucity of organs from humans for transplantation into other humans has led to the search for other sources such as animals. Initially the focus was on the great apes, as they appear to be nearest to man in the evolutionary scale. It was soon realised that unbridled use of simians would lead to possible extinction of their species. Attention has thus turned to other animals.

DEFINITIONS

Primates: The most highly evolved of animals. Includes simians and homo-sapiens.

Simians: The monkey species, including the great apes.

Species: Group of individuals sharing similar biological characteristics and who can breed within the group to produce fertile offspring.

Source animal: Animal from whom tissues or organs are removed for transplantation in humans. The term 'donor animal' has been discarded as the animals cannot give consent.
Tissue: A collection of similar cells, all of which perform the same function. An example is neural tissue within the brain.

Transgenesis: The introduction of a foreign gene into an animal or organism. The transferred gene is called transgene.

Xeno-transplant: Transplant of cells, tissue or organ from one species to another. This principally concerns transplant from animal to man.

Zoonoses: Diseases peculiar to animals in the normal course of events that can, under special circumstances - as after xeno-transplant - be transferred to man.

ETHICAL CONSIDERATIONS

Transmission of disease from animal to man:

There has been considerable apprehension that tissues or organs transplanted from animal to man may convey infection or unwanted genetic abnormalities. This anxiety has prompted most countries, to ban all research on transplanting animal organs to human beings till this issue has been satisfactorily addressed. Measures proposed include the breeding of successive generations of animals and studying them for all known and possible unknown organisms that can cause disease. Only those animals certified free from disease could be considered for transplantation.

Our immune responses are likely to reject all foreign tissue and organs transplanted into us. The chances of rejection are minimised if the source animal is genetically similar to man. This is the reason for considering the great apes as likely source animal.

Once the apes were ruled out in order to preserve their species, attention turned to cattle, sheep and pigs. In each of these species, transplant of unaltered tissue or organ will certainly lead to rejection.

Pigs are currently the animals of choice as the size of their organs and the anatomical and physiological loads they must carry are similar to those in man. Besides, pigs breed easily and are maintained without much difficulty. Experimental studies have been carried out on kidneys, liver, heart, heart valves and bone marrow, islet cells of the pancreas and nerve cells obtained from pigs with encouraging results.

Attempts are on so that pigs be engineered to possess genetic material similar to that in man. This can be achieved by replacing porcine genes by human genes into the cell that will form the pig embryo. Tissues and organs from such transgenic pigs will, it is hoped, stand the scrutiny by the immune systems of the patients into whom they are transplanted and will be left unmolested. However, there are possible problems in using porcine tissue or organs in human transplantation. The average pig

survives for only twenty years. Will transplanted tissues function efficiently in man with a life span of three score years and ten, or will they fail after two decades, necessitating further transplants?

Equally worrying is the possibility of transferring germs and viruses peculiar to pigs into man through transplanted tissues. We are aware of species-specific infective diseases that limit themselves to that species. Under special circumstances - as after transplantation - such organisms may make the leap from one species to another and cause untold havoc in the new species, which has no immunity against them. Some of the most deadly viruses currently devastating individuals and groups in some African countries - that causing Lassa Fever, the Marburg virus and the Ebola virus are such examples. They appear to have spread from bats or other animals to man. The human immunodeficiency virus (HIV) also appears to fall into this category. These questions are still unresolved.

Apart from the known bacteria, fungi and viruses, there is concern for those hitherto unknown and undetected, especially so with slow viruses, that produce manifestation of the disease years - often decades - after they gain entry into our systems. Equally disquieting is the fact that once an infective organism makes a jump across species, it may spread like wildfire in the new species - in this case, man.

It is also proposed that extensive research, with long-term follow-up studies be carried out on animal-animal transplants so that we may learn of possible pitfalls and develop measures to avoid them before undertaking the first experiment involving man.

GUIDELINES ON XENO-TRANSPLANTATION

1. Experimental xeno-transplantation must only be permitted between different animal species. Animal - to - man transplants must not be permitted at the present level of knowledge which may be referred to the Central/National Ethical Committee on Human Research.

2. Institutional scientific and ethics committees must approve of such research studies, with special attention being paid to their relevance, availability of facilities for extensive, sophisticated and long-term studies for transmission of disease through transplantation.

3. An advisory committee consisting of reputed scientists in the field, medical professionals, veterinary experts and microbiologists must oversee all such transplants.

4. Records on all research studies must be detailed, scrupulously maintained and kept available for a long period of time, perhaps decades.

5. Safeguarding the interest of the pioneer human recipients when such transplants are permitted in future, it is proposed that each and every animal - to - man transplant be very carefully vetted and sanctioned on a case-by-case basis. In each instance, extensive studies on the animals to ensure freedom from infection must be made mandatory. The human recipients of tissues or organs must be carefully followed up over a long term.

IV. TRANSPLANTATION FOR COSMETIC PURPOSES

1. Research on transplantation for cosmetic purposes (such as the creation of a new ear after transferring tissue from the patient on to a mould which is later implanted into the subcutaneous tissue of a transgenic mouse) will be governed by the same principles as those in using donation of tissue or organ from a live donor.

2. Donation of tissue should be restricted to renewable tissues like skin to an extent where such removal will not greatly alter the normal functions of such tissue.

3. It is imperative that no risk be imposed whilst removing tissue beyond that inherent in surgery. Any manner of experimentation, though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest extra risk to the donor. Examples are pre-treatment of the donor with immuno-suppressives or anticoagulants.

4. Every such research project should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits and improvement in the success rate of transplantation.

5. The patient must be informed of all possible risks, including those of failure of the transplant in a manner easily understood by him, before his consent is taken.
6. It follows that the donor should be competent to give consent; should be in a position to exercise free power of choice without the slightest element of force, duress, or coercion; and should have sufficient knowledge and comprehension of the subject to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults so also persons with limited autonomy should not be subjected to such surgery.

7. The experiment should be such as to yield fruitful results for the good of patients who need transplantation without having the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised.

8. The experiment should be so planned and conducted as to avoid all unnecessary risks to the donor, to the tissue to be transplanted, and to the recipient site.

9. Where tissue is to be temporarily transferred to an animal, all necessary precautions should be taken, and adequate facilities should be available, to protect the patient from the most remote possibility of harm.

10. The subjects should be at liberty to withdraw from the experiment and to abrogate the consent given earlier, with no requirement to offer any explanation of the reasons for his or her doing so.

STATEMENT OF SPECIFIC PRINCIPLES FOR ASSISTED REPRODUCTIVE TECHNOLOGIES

INTRODUCTION

The special programme by WHO on human reproduction has estimated that there are 60 to 80 million infertile couples worldwide. It has also been variously estimated that between 6-10% of the couple are infertile. The advent of Assisted Reproductive Technologies (ART) have not only enhanced the possibility of pregnancy but have also made women conceive in situations which would not have been possible decade ago. However many of these technologies require enormous technical expertise and infrastructure, carry a success rate below 30% even in the best of hands, are expensive, and tax the couple's endurance physically, emotionally and economically. There is an urgent need to draw up necessary guidelines, so that optimum benefit of these newer technologies are made available to appropriate persons by skilled team of experts, at affordable health and economic cost, at identified facilities for Assisted Reproductive Technology in our country. In order to ensure quality of care it is imperative that a proper accreditation procedure is followed in establishment of ART Centres, which should follow standardised protocols and guidelines. A national registry pertaining to all centres that are accredited by the licensing authority should be maintained and should contain records of treatment cycles and outcome.

DEFINITION

Assisted Reproduction is defined as 'manipulating the gametes outside the body and the transfer of gametes or embryos into the body'.

All protocols used in the laboratory for Assisted Reproduction (AR) procedures must be documented and available as manuals. These manuals should be revised periodically. Log books for the maintenance and periodic overhauling of all equipments should be maintained. The entire procedure from the ovarian stimulation protocol to the oocyte retrieval and oocyte and sperm preparation including evaluation of the morphology of the gametes, their number, timing of insemination, date of embryo transfer, number of embryos or gametes transferred and the fate of the gametes must be documented. Abnormal pre-embryos such as polyploid embryos should not be transferred. Cryopreserved material must be labeled indexed and stored properly. The laboratory personnel should be well versed with the techniques of cryopreservation. Batches of culture media must be identified. All agents used in the Laboratory must be entered in a Register and the date of their receipt entered on the box containing them. Asepsis should be maintained at all cost. Each couple undergoing treatment should undergo a minimal screening for HIV and Hepatitis. The laboratory personnel should be adequately protected which include screening and vaccinations.

It is essential that all documentation regarding every patient treated in the centre is maintained meticulously and all precautions are taken to ensure that confidentiality is maintained.

GENERAL PRINCIPLES

There is a certain element of risk associated with all AR procedures. It is, therefore, necessary to ascertain the therapeutic and research value of the AR procedure in each case.

Informed Consent : After duly counseling the couple / oocyte/semen donor, an informed and written consent should be taken from both the spouses as well as the donor, as the case may be. They should be explained the various risk factors associated with the procedures in simple language and the words that they can understand. These include risks associated with ovarian hyperstimulation, anaesthestic procedures, and invasive procedures like laparoscopy, aspiration of ovum etc. They should also be explained the possibility of multiple pregnancies, ectopic gestation, increased rate of spontaneous abortion, premature births, higher perinatal and infant mortality as well as growth and developmental problems. They should also be explained that there is no guarantee on the success / failure of the procedure.

Selection of Donor : The physician assumes the responsibility in selection of the suitable donor on following terms :

- Complete physical examination of the donor should be done to ascertain the good health of the donors of semen, oocyte or embryo.

- The donor should be healthy with reasonable expectation of good quality eggs or sperms and preferably with proven fertility record.

- The physical characteristic and mental make-up of the donor should match as closely as possible to that of the spouse of the recipient, specially with reference to colour of the skin, eyes and hair, height and build, religious and ethnic background, the educational level and ABO blood type.

- Blood group of the proposed donor and donee should be tested with respect to Rh compatibility.

- No person suffering from any sexually transmitted disease (e.g. syphilis, gonorrhea, chlamydia, herpes, HIV etc.), infectious disease (e.g. hepatitis B, HIV) or genetically transmissible disease should be used as donor. Sexually transmitted diseases should be ruled out within a week of obtaining the seminal fluid.

- It is essential that donated semen is cryo-preserved and used only after 6 months as this would enable the centre to retest the donor after 6 months for HIV and eliminate the potential risk of HIV transmission in the 'window' period of HIV infection.

- Identity of the donor as well as the recipient should be protected from each other. However, all the records of the donor must be preserved in order to trace him / her in case of any eventuality and should be confidential.

- Confidentiality of the entire procedure and its outcome is advisable and therefore, no relative should be accepted as a donor in order to avoid identification and claims of parenthood and inheritance rights.

- Written consent of the donor should be taken towards unrestricted use of sperms or oocytes for AR, as well as an undertaking from him / her that he / she will not attempt to seek the identity of the recipient. In case the donor is married, the written consent of the spouse should be taken, if possible.

- It is also desirable to restrict the use of semen from the same donor to a maximum of 10 pregnancies to avoid the possibility of an incestuous relationship occurring among the offsprings at a later date.

- In case of the oocyte donor, incurring any health problems related to the process of donation, the costs of the subsequent health care should be borne by the potential recipient couple irrespective of whether they receive oocyte donation as planned or not.

- In case of unused surplus / spare embryos, consent of the concerned couple should be obtained to cryopreserve such embryos for donation to other needy couples. Such embryo donations should be kept anonymous. The ownership rights of such embryos rest with the couple concerned.

SPECIFIC PRINCIPLES

Legitimacy of the Child born through ART : A child born through AR is presumed to be the legitimate child of the couple having been born within the wedlock and with consent of both the spouses with all the attendant rights of parentage, support and inheritance. Sperm/ oocyte donor should have no parental right or duties in relation to the child and their anonymity should be protected.

IVF-ET (in-vitro fertilisation and embryo-transfer) and Surrogate Motherhood : There are no medico-legal problems posed by IVF-ET with egg and sperm of married couple. Donation of either egg or sperm is governed on the same lines as those for Artificial Insemination Donor with the married partner as the natural or biological mother. IVF-ET with donated egg or sperm or womb leasing will create two to three sets of parents, genetic, biological and natural. Following consensus has emerged universally with respect to surrogate motherhood :

1. It should be resorted to only when it is coupled with authorized adoption wherever applicable.

2. It should be rebuttably presumed that a woman who carries the child and gives birth to it is its mother.

3. The intending parents should have a preferential right to adopt the child subject to six week's postpartum delay for necessary maternal consent.

4. It should be resorted to only if medically certified as the only solution to infertility or any other medical bar on pregnancy, by the intending mother.

5. A qualified consultant should supervise to enforce adequate genetic screening.

6. The contract for surrogacy despite reasonable payment of compensation on completion of adoption would be valid subject to surrogate's right to retain the baby if she so desires.

7. The only remedy for the genetic parent would be to claim for custody on the grounds of the best interest of the child.

8. Abortion under the Abortion Law on the medical ground should be inviolate right of the surrogate and the adopting parents have no claim over the amounts already paid.

9. All expenses related to medical management during pregnancy, delivery, and immediate postpartum period till adoption should be borne by the intending couple.

Preservation, utilisation and destruction of embryos :

- Research is prohibited on embryos **of more than 14 days after fertilisation** excluding the period during which the embryo was frozen with maximum storage period of 10 years and a 5 yearly review of semen and embryo deposits as practised in other countries *eg*. U. K.

Spare embryos :

- Embryo-splitting may be resorted to in selected cases for overcoming the paucity of suitable embryos during ART in a couple. Child born of cryo-preserved embryos after divorce is deemed to be illegitimate.

Right of children / parents

Children born from use of donor gametes and their social/adopted parents have the right to know whatever medical or genetic information about the genetic parents that may be relevant to the child's health.

Pre-conceptional or pre-implantation sex selection is prohibited except for detecting specific sex- linked genetic disorders.

BIBLIOGRAPHY

1. The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Washington DC : US Government Printing Office, 1949; 2: 181-182.
2. World Medical Association. Declaration of Helsinki. Hong Kong : 41st World Medical Assembly; 1989.
3. Council for International Organizations of Medical Sciences (CIOMS). International Guidelines for Ethical Review of Epidemiological Studies. Geneva : 1991.
4. Council for International Organizations of Medical Sciences (CIOMS). International Guidelines for Biomedical Research involving Human Subjects. Geneva : 1993
5. Indian Council of Medical Research. Policy Statement on Ethical Considerations involved in Research on Human Subjects. New Delhi :1980
6. Council on Ethical and Judicial Affairs. Code of Medical Ethics - Current opinions with annotations. Chicago: American Medical Association ; 1997; 191
7. Office for Protection from Research Risks (OPRR), NIH. Institutional Review Board Guidebook. United States : Department of Health and Human Services ; 1993
8. National Commission for the Protection of Human Subjects. Belmont Report : Ethical and Guidelines for the Protection of Human subjects of Research. Washington DC : US Government Printing Office; 1978 (Summary and 2 volumes of appendices)
9. Nuffield Council on Bioethics. Genetic screening : Ethical issues. U.K : Nuffield Council Report ; 1993
10. Nuffield Council on Bioethics. Human tissue: Ethical and Legal issues. U.K : Nuffield Council Report ; 1995
11. Nuffield Council on Bioethics. Animal-to-Human Transplants : the Ethics of Xenotransplantation. UK : Nuffield Council Report ; 1996
12. Psychology Department. Ethical guidelines for research with human subjects. UK : University of Hertfordshire ; 1994
13. Network of European CNS Transplantation and Restoration (NECTAR). Ethical guidelines for the use of human embryonic or fetal tissue for experimental and clinical neuro-transplantation and research. Netherlands : 1991
14. United Nations Educational, Scientific and Cultural Organisation (UNESCO). Universal Declaration on the Human Genome and Human Rights. International Bioethics Committee; 1997
15. Department of Biotechnology. Guidelines for Gene Therapy. New Delhi : 1996
16. Government of India. Exchange of Human Biological Material for Biomedical Research. New Delhi : 1997
17. Indian National Science Academy. Guidelines for the Care and Use of Animals in Scientific Research. New Delhi : 1992
18. Government of India. Exchange of Human Biological Material for Biomedical Research Purposes. New Delhi : 1997
19. Guyer MS and Collins FS. The human genome project and the future of Medicine. Am J Dis Child 1993 ; 147 : 1145 – 52.

20. Kjellstrand CM, Dosseter JB, (editors): Ethical Problems in Dialysis and Transplantation. Dordrecht : Kluwer Academic Publishers ; 1992 : p 163-168
21. Boer GJ: Ethical guidelines for the use of human embryonic or foetal tissue for experimental and clinical neurotransplantation and research. Network of European CNS Transplantation and Restoration (NECTAR). J Neurol 1994; 242 (1):1-13.
22. Council on Scientific Affairs and Council on Ethical and Judicial Affairs. Medical applications of fetal tissue transplantation. JAMA 1990; 263 (4):565-570.
23. Coutts MC. Fetal tissue research. Kennedy Institute of Ethics Journal 1993; 3(1) ; 81-101.
24. Keown J. The Polkinghorne Report on Fetal Research : nice recommendations, shame about the reasoning. J Med Ethics 1993 ; 19 (2): 114-120.
25. Meinke SA. Anencephalic infants as potential organ sources: ethical and legal issues. Scope Note 12. National Reference Center for Bioethics Literature. Washington, DC : 1989
26. Michaels MG, Frader J, Armitage G : Ethical considerations in listing fetuses as candidates for neonatal heart transplantation. JAMA 1993; 269: 401-403.
27. Robertson JA. Rights, symbolism and public policy in fetal tissue transplantation. Fetal tissue and organ transplantation : Hastings Center Report : 1988
28. Indian Standards Institute. Code for breeding, care, management and housing of laboratory animals. New Delhi : 1978.
29. Anonymous. The UFAW book on the care and management of laboratory animals. New York: Churchill Livingstone. 1987.
30. Baker HJ, Lindsey JR, Weisborth SH, editors. The laboratory rat, Volume II: Research application. New York: Academic Press. 1980.
31. Bhardwaj KR, Purohit DC, Dhawan BN editors. Laboratory animal ethics and technology. Lucknow : Central Drug Research Institute ; 1991.
32. Coats M.E. The germ free animals in research. New York: Academic Press. 1968.
33. Indian Council of Medical Research. ICMR Guidelines on Responsibility for Clinical trials of contraceptives conducted in India. New Delhi : 1994
34. National Advisory Board on Ethics in Reproduction (NABER). The work of the National Advisory Board on Ethics in Reproduction. Washington DC : NABER Report ; 1995 : 1 : 1- 5
35. American Fertility Society. Guidelines for human embryology laboratories. Fertil Steril 1992; 58 (4 Suppl 1): 1S-10S
36. American Fertility Society. Guidelines for Gamete Donation. Fertil Steril 1993 ; 59(2 Suppl 1) : 1S-9S
37. Human Fertilization and Embryology Authority. Code of Ethics. London : 1993.
38. American Fertility Society. Ethical Considerations of the New Reproductive Technologies : Ethics Committee Report ; 1987
39. World Health Organisation. Operational Guidelines for Ethics Committees That Review Biomedical Research. Geneva: 2000
40. Existing legal frame work
    - Code of Medical Ethics framed under section 33 of the Indian Medical Council Act, 1956
    - The Consumer Protection Act, 1986

- The Fatal Accidents Act, 1855
- The Indian Majority Act, 1875
- The Medical Council OF India Act, 1956
- The Legal Representative's Suits Act, 1855
- The Medical Termination of Pregnancy Act, 1971
- The (Extract of) Mental Health Act, 1987
- The Pre-natal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994
- The Transplantation of Human Organs Act, 1994

LIST OF MEMBERS OF CENTRAL ETHICAL COMMITTEE

Chairman

1. Hon. Justice M.N. Venkatachaliah
   (Former Chief Justice of India and Chairperson
   National Human Rights Commission),
   Vigyan Bhawan Annexe
   New Delhi-110 001

Members

2. Dr. G.V.Satyavati
   Former DG, ICMR
   'Prasada Nilaya'
   D-55/82, East End (B)
   Main Road, 9th Block, Jayanagar
   Bangalore-560 069

3. Dr. S.P. Agarwal
   Director General of
   Health Services,
   Nirman Bhawan,
   New Delhi-110011

4. Dr. L.H. Hiranandani
   A-3, Amarchand Mansion
   Opposite Gowasji
   Jahangir Hall
   Next to Y.W.C.A.
   Madam Cama Road
   Bombay - 400039

5. Dr. M.S. Valiathan
   Former Vice-Chancellor
   Manipal Academy of Higher Education,
   Manipal - 576119

6. Dr. Ranjit Roy Chaudhury
   Emeritus Scientist,
   National Inst. of Immunology
   Aruna Asaf Ali Road, New Delhi-110 067

7. Dr. B.N. Dhawan,
   Former Emeritus Scientist, CDRI
   No.3, Ramakrishna Marg
   Lucknow-226007

8. Dr. J.S. Guleria,
   K-11, Green Park Extension
   New Delhi

9. Dr. P.N. Tandon
   Emeritus Professor,
   Deptt. of Neurosciences,
   All India Institute of Medical
   Sciences, New Delhi

10. Dr. B.N. Tandon
    M-52, Greater Kailash Part II
    New Delhi

11. Dr. Indira Nath
    Emeritus Scientist
    Deptt. of Biotechnology,
    All India Institute of Medical
    Sciences, New Delhi

12. Dr. Saraswati Swain
    General Secretary
    National Institute of Applied
    Human Research
    and Development,
    Kalyani Nagar,
    Cuttack - 753013

13. Dr. Channabasavanna
    Former Director
    NIMHANS,
    Bangalore - 560012

14. Dr. Gourie-Devi
    Director
    NIMHANS
    Bangalore – 560012

15. Dr.P.K.Dave,
    Director,
    All India Institute of
    Medical Sciences,
    New Delhi – 110 029

16. Dr. Kamala Gopala Rao
    1017, 25th Main
    Banashankari, 2nd Stage
    Bangalore-560070

17. Smt.Rami Chhabra,
    B-5/19, Safdarjung Enclave,
    New Delhi- 110029

18. Dr. Manju Sharma
    Secretary
    Deptt. of Biotechnology
    C.G.O Complex,
    Lodhi Road
    New Delhi- 110003

19. Smt. Shailaja Chandra
    Secretary
    Department of ISM
    Ministry of Health and Family
    Welfare, Nirman Bhawan,
    New Delhi-110011

20. Dr. P. Das Gupta,
    OSD, DGHS
    Nirman Bhawan,
    New Delhi-110011
21. Dr. Y.S. Rajan,
    Senior Adviser (Technology),
    Confederation of
    Indian Industry,
    India Habitat Centre,
    Lodi Road,
    New Delhi-110003

22. Dr. Badri N. Saxena
Former Additional
Director General,
Indian Council of
Medical Research,
New Delhi-110 029

23. Dr.Kalyan Banerjee
Suruchi Cooperative
Housing Society Ltd,
Gulmohar Path,
Law College Road,
Pune – 410 004

24. Sh.Rajeev Dhavan,
Senior Advocate,
Supreme Court of India
A-131, New Friends Colony,
New Delhi-110065

25. Dr. S.K. Bhattacharya,
Director,
National Inst. of Cholera &
Enteric Diseases,
Calcutta - 700010

26. Dr. N. Medappa
Sr. DDG and Chief,
Division of Publication and
Information,
Indian Council of
Medical Research,
New Delhi-110 029

27. Dr. R. Ravi
Deputy Director
General (SG)
Indo-Foreign Cell
Indian Council of
Medical Research,
New Delhi-110 029

Member-Secretary

28. Dr. Vasantha Muthuswamy
Deputy Director General and Chief
Division of Basic Medical Sciences
Indian Council of Medical Research
New Delhi-110 029

MEMBERS OF SUB-COMMITTEES

For General Principles

1. Dr. Rajeev Dhavan, Supreme Court of India, New Delhi.
2. Dr. Vasantha Muthuswamy, Indian Council of Medical Research, New Delhi.

For Specific Principles

I. Statement on Specific Principles for Clinical Evaluation of Drugs / Devices /Diagnostics/ Vaccines / Herbal Remedies

1.	Dr. Ranjit Roy Chaudhury, NII, New Delhi	Chairman
2.	Dr. B.N. Dhawan, CDRI, Lucknow	Member
3.	Dr. S.S. Handa, RRL, Jammu	Member
4.	Dr. C.D. Tripathi, MAMC, New Delhi	Member
5.	Dr. Usha Gupta, MAMC, New Delhi	Resource Person
6.	Dr. S.B. Lall, AIIMS, New Delhi	Resource Person

II. Statement on Specific Principles for Epidemiologicial Studies

1.	Dr. V.I. Mathan, Bangla Desh	Chairman
2.	Dr. P.S.S. Sundar Rao, Karigiri, Tamily Nadu	Member
3.	Dr. R. Prabhakar, Chennai	Member
4.	Dr. M.D. Gupte, NIE, Chennai	Member

III. Statement on Specific Principles for Human Genetics Research

1.	Dr. P.N. Tandon, AIIMS, New Delhi	Chairman
2.	Dr. S.S. Agarwal, SGPGI, Lucknow	Member
3.	Dr. Manorama Thomas, St. J.M.C., Bangalore	Member
4.	Dr. I.C. Verma, New Delhi	Member

IV. Statement on Specific Principles for Research in Transplantation Including Foetal Tissue Transplantation

1.	Dr. M.K. Mani, Apollo Hospital, Chennai	Chairman
2.	Dr. Sunil Pandya, KEM Hospital, Mumbai	Member
3.	Dr. R.P. Shanmugam, MMC, Chennai	Member
4.	Dr. Vinod Kochupillai, AIIMS, New Delhi	Member
5.	Dr. J. Amalorpavanathan, MMC, Chennai	Resource Person

V. Statement on Specific Principles for Assisted Reproductive Technologies

1.	Dr. R.P.Soonawalla, Mumbai	Chairman
2.	Dr. Sadhana K Desai, Mumbai	Member
3.	Dr. Mehroo D.Hansotia, Mumbai	Member
4.	Dr. H.S.Juneja, Mumbai	Member
5.	Ms.Kusum Kumar, Mumbai	Member
4.	Dr. Pritam Phatnani, Mumbai	Member
5.	Dr. Firuza Parikh , Mumbai	Member
6.	Dr. Mahendra Parikh, Mumbai	Member
7.	Dr. Somnath Roy, New Delhi	Member
8.	Dr. Prema Ramachandran, New Delhi	Member
9.	Dr. S.L.Chauhan, New Delhi	Member
10.	Dr. B.N. Saxena, New Delhi	Member