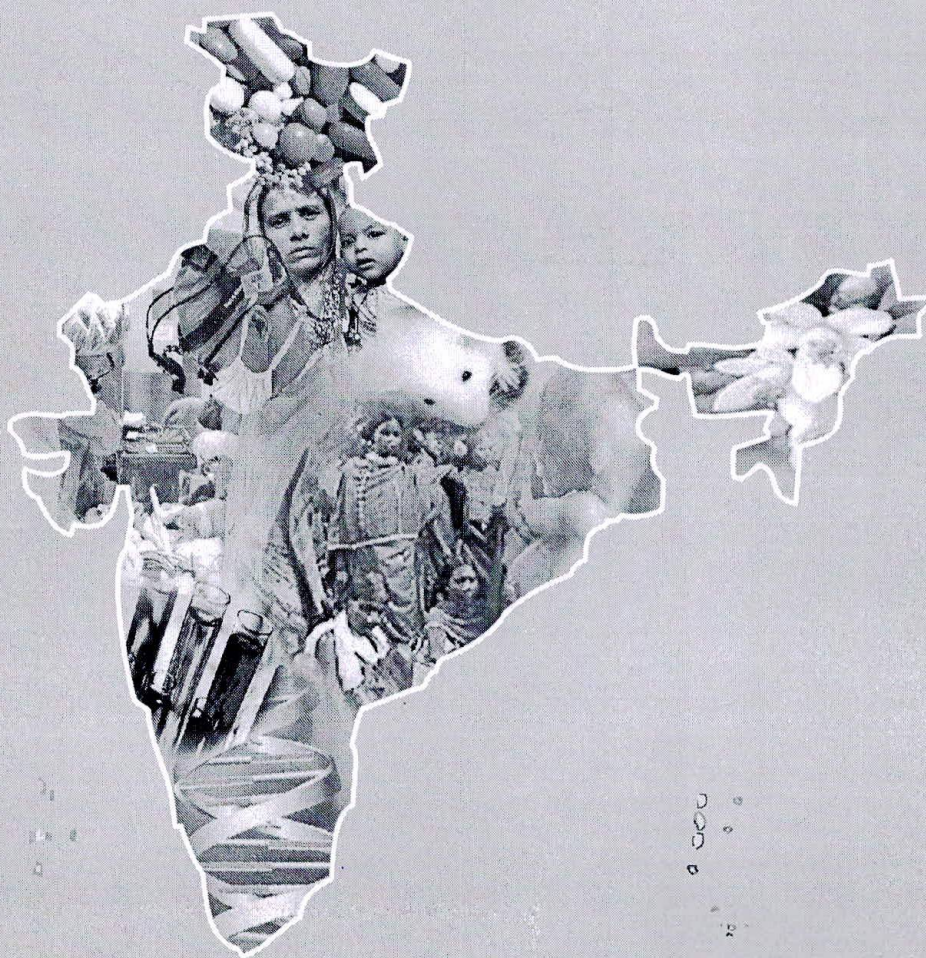


ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS



INDIAN COUNCIL OF MEDICAL RESEARCH
NEW DELHI

2006

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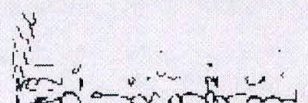
FOREWORD

The release of revised Ethical guidelines for Biomedical Research on Human subjects by the Council in 2000 was followed by a number of developments in science and technology. These have led to further widening of healthcare between the developed and developing countries. Due to globalization rapid techniques of diagnosis and therapy are now available through R & D. The advances in the area of genetics, genomics and molecular biology have grown by leaps and bounds with the resultant need to rein in these advances with sufficient safeguards to protect the rights and welfare of human participants subjected to biomedical research. Globally international agencies have been bringing out guidelines for researchers in their countries with relevance to developing countries. WHO and UNESCO are striving to bring a universal consensus to these guidelines in an attempt to reduce disparity across the world.

Considering the recent advances in the field of Assisted Reproductive Technologies, separate guidelines have been brought out by the Indian Council of Medical Research as "National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India"(2005). Since India is being projected as a global hub for clinical trials and the number of corporate hospitals with state-of-the-art facilities is growing, visits by foreign specialists using newer techniques or devices is increasing. Some Indian institutions are also involved in making indigenous devices, which have to be tried in Indian patients for safety and efficacy. Although a separate document has been made for regulating the medical devices under Indian Medical Devices Regulatory Authority (IMDRA) relevant portions have been included in this document. The guidelines for the important biotechnology areas like stem cell research and stored tissue including DNA banking have also been added in this revision. Taking into consideration the changing dimensions of ethical issues in the context of new technologies and evolving universal guidelines, the existing chapters on Clinical trials, Organ Transplantation, Human Genetics, Epidemiology and Assisted Reproductive Technologies have also been revised.

I hope the scientific community, the regulatory agencies and the public at large will be immensely benefited by this revised guidelines.

New Delhi
October 2006



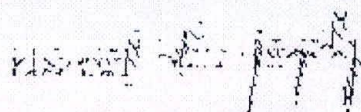
M. S. Valiathan
Chairman
Central Ethics Committee on Human Research
ICMR, New Delhi

PREFACE

It was proposed in the earlier revised "Ethical Guidelines for Biomedical Research on Human Subjects" of 2000, that the guidelines to each of the areas described would be updated periodically *pari passu* with the developments in the area of Biomedical Science. Hence revision has been undertaken in view of the recent development in the area of Science and technology. Further the points raised in several international and national meetings or workshops on bioethics have been taken into account for making the changes with relevance to Indian ethos in this third version of ethical guidelines now being released. The Bioethics Cell of the Division of Basic Medical Sciences has over the years acquired considerable expertise in addressing ethical queries in relation to advances made in biological sciences and biotechnology. This revision will address most of these in this version. The Statement of General principles remains almost the same as they continue to have relevance for future and are template for universal application for developing ethical guidelines in any area relevant to the Indian scenario. All the seven major Chapters, namely, Ethical Review Procedures, General Ethical issues, Clinical evaluation of drugs/ vaccines / devices/ diagnostics/ herbal remedies, Epidemiological studies, Human genetics and Genomics research, Transplantation research and Assisted reproductive technologies required updating as per the prevalent ethical debates around the globe. Care is taken to include new areas like stem cell research and therapy and biobanking while elaborating many existing topics to make it more user friendly.

As promised during the release of the ethical guidelines of 2000 about periodic update, the present version is being released. I hope this effort will continue to bring out future revisions to keep pace with the global developments in the area of Bioethics.

New Delhi
October 2006



N. K. Ganguly
Director General, ICMR

ACKNOWLEDGMENT

This is to acknowledge with gratitude the contributions made during the last five years by the professionals, public and the media through personal interaction during the innumerable workshops organized by the Bioethics Cell of the Council in bringing out these guidelines. We hope that this spirit of togetherness will continue to help us in updating these guidelines in the coming years to keep pace with further new developments.

The Bioethics Cell of the Council gratefully acknowledges the valuable contribution of all the members of the panel who reviewed this third version and provided continued guidance in drafting the new guidelines and finalizing them. Special thanks are due to Dr. U. M. Thatte and Dr. Reider Lie for their elaborate suggestions.

The patronage of Dr. N. K. Ganguly, the Director General, ICMR for his continued support for preparation of the third version of the Council's Ethical Guidelines is gratefully acknowledged.

The contribution of Dr. Geeta Jotwani, Dr. Roli Mathur, Dr. Hemalatha Somsekhar, Dr. Sanjeeva Majumdar, Dr. A. C. Kar, Mr. J. N. Mathur and Ms. Neelam Chaudhary is highly appreciated for the assistance given for updating these guidelines and bringing out the document.

New Delhi
October 2006

Vasanth Muthuswamy,
Senior Deputy Director General

Nandini K. Kumar,
Deputy Director General

INTRODUCTION

The Indian Council of Medical research brought out the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000 as the 'Ethical guidelines for Biomedical Research on Human Subjects'. Due to further rapid developments in science and technology in India after the release of the second version, it became necessary to update these guidelines to make adequate specific provision to meet ethical challenges posed by these advances. Necessitated by the globalization leading to increasing research in the developing world, the international guidelines released in 2002 by the developed countries including the revised CIOMS guidelines focused on observance of ethical norms relevant to different pluralistic cultural environment in these countries for the protection of the research participants in these regions. In India the challenge faced is to apply universal ethical principles to biomedical research in the multicultural Indian society with a multiplicity of health-care systems of considerably varying standards. The scope of this third version of the Council's guidelines takes note of these changes, and in keeping with the national policies and the demands of Indian culture, addresses ethical issues in specific situations to the extent possible. While on one hand, research involving human participants must not violate any universally applicable ethical standards, on the other hand, a researcher needs to consider local cultural values when it comes to the application of the ethical principles to individual autonomy and informed consent. In India, one will have to consider autonomy versus harmony of the environment of the research participant. In research on sensitive issues, this will have to be properly addressed in the research protocol to safeguard the human rights of the dependent or vulnerable persons and populations.

Some of the points in the international guidelines for biomedical research on human participants, which have relevance to international collaborative research initiatives, have been included in this version. Detailed description of vaccine trials, herbal products, biobanking, and stem cell research *etc.* has been provided to make the document reflect current ethical requirements, which can be applied to Indian circumstances from ethical, legal and social angle. The intention is to update this document at frequent intervals to keep the scientific community knowledgeable about the current concepts in bioethics, which is a dynamic process. Such an exercise is in keeping with similar trends seen in many countries and worked out by international agencies.

STATEMENT OF GENERAL PRINCIPLES IN BIOMEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS

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

- (a) Statement of General Principles on Research using Human Participants in Biomedical Research
- (b) Statement of Specific Principles on Research using Human Participants 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 shocking details of the post Second World War (1939-45) trial of German medical practitioners accused of conducting experiments on human participants without their consent and exposing them to grave risk of death or permanent impairment of their faculties raised grave concern about subjecting human subjects to medical research. Thus, the first International Statement on the ethics of medical research using human subjects namely, the **Nuremberg Code** was formulated in 1947. Although informed consent for participation in research was recorded in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of this consent. In 1948, **Universal Declaration of Human Rights** (adopted by the General Assembly of the United Nations) expressed concern about rights of 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 and specific guidelines on use of human subjects in medical 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 bioethics advisory bodies in national jurisdictions like Nuffield Council of Bioethics and European Commission on Ethics have also laid down general and specific principles in specific areas of scientific research involving human beings as subjects in medical research. These 'national' Codes drawn from the international codes and the universal principles therein provide the 'guidelines' that should be followed in their respective jurisdictions. Meanwhile the international studies conducted in developing countries sponsored or funded by developed countries highlighted the global health divide and the ethical issues related to the 10/90 gap. National Bioethics Advisory Bodies and Funding organizations of developed nations took note of this and to rectify the situation revised guidelines which had relevance to developing countries as evident from Report of National Bioethics Advisory Committee, USA, by 2000 and Guidelines by Nuffield Council of Bioethics, UK and CIOMS, Geneva by 2002. The Helsinki Declaration underwent changes five times, the last one being in 2004. Still the controversy about use of placebo and post-trial access as described in it is being debated. The most recent documents on ethics are those of UNESCO's **"The Universal Declaration on Human Genome and Human Rights"** (1997), **"The International Declaration on Human Gene Data"** (2003) and **"Universal Declaration on Bioethics and Human Rights"** (2005).

GENERAL STATEMENT

Medical and related research using human beings as research participants 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 participant is placed at no greater risk other than such risk commensurate with the well being of the participant in question in the light of the object to be 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 participants shall follow the principles given below –

- I. Principles of essentiality** whereby the research entailing the use of human participants is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.
- II. Principles of voluntariness, informed consent and community agreement** whereby research participants are fully apprised of the research and the impact and risk of such research on the research participant and others; and whereby the research participants retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human participants or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research participant, these principles of voluntariness and informed consent shall apply, *mutatis mutandis*, to the community as a whole and to each individual member who is the participant of the research or experiment. Where the human participant is incapable of giving consent and it is considered essential that research or experimentation be conducted on such

a person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research participants by someone who is empowered and under a duty to act on their behalf. The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applied use so that research participants are continually kept informed of any and all developments in so far as they affect them and others. However, without in any way undermining the cardinal importance of obtaining informed consent from any human participant involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall depend upon the degree and seriousness of the invasiveness into the concerned human participant's person and privacy, health and life generally, and, the overall purpose and the importance of the research. Ethics committee shall decide on the form of consent to be taken or its waiver based on the degree of risk that may be involved.

III. Principles of non-exploitation whereby as a general rule, research participants are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research participants kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born. Such human participants should be selected so that the burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice. Each research shall include an in-built mechanism for compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.

IV. Principles of privacy and confidentiality whereby the identity and records of the human participants of the research or experiment are as far as possible kept confidential; and that no details about identity of said human participants, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of

the human participant concerned, or someone authorised on their behalf; and after ensuring that the said human participant does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

V. Principles of precaution and risk minimisation whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research participant and those affected by it including community are put to the minimum risk, suffer from no known irreversible adverse effects, and generally, benefit from and by the research or experiment; and that requisite steps are taken to ensure that both professional and ethical reviews of the research are undertaken at appropriate stages so that further and specific guidelines are laid down, and necessary directions given, in respect of the conduct of the research 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, preferably through training, the ethical considerations to be borne in mind in respect of such research or experiment.

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

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

IX. Principles of institutional arrangements whereby there shall be a duty on all

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

- X. Principles of public domain** whereby the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.
- XI. Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.
- XII. Principles of compliance** whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human participant to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

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

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 participants should be cleared by an appropriately constituted Institutional Ethics Committee (IEC), also referred to as Institutional Review Board (IRB), Ethics Review Board (ERB) and Research Ethics Board (REB) in other countries, to safeguard the welfare and the rights of the participants. There are also independent ethics committees [IEC(Ind)] functioning outside institutions for those researchers who have no institutional attachments or work in institutions with no ethics committee. 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 of the approved programmes to foresee the compliance of the ethics during the period of the project. Such an ongoing review shall be in accordance with the international guidelines wherever applicable and the Standard Operating Procedures (SOP) of the WHO available at www.who.int

BASIC RESPONSIBILITIES

The basic responsibility of an Institutional Ethics Committee (IEC) is to ensure a competent review of all ethical aspects of the project proposals received by it in an objective manner. 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 Committee. In institutions where this is lacking, the IEC may take up the dual responsibility of review of both, the scientific content and ethical aspects of the proposal. It is advisable to have separate Committees for each, taking care that the scientific review precedes the scrutiny for ethical issues. The scientific evaluation should ensure technical appropriateness of the proposed study. The IECs should specify in writing the authority under which the Committee is established.

Special situations

Small institutions could form alliance with other IECs or approach registered IEC(ind). Large institutions/Universities with large number of proposals can have more than one suitably constituted IECs for different research areas for which large number of research proposals are submitted. However, the institutional policy should be same for all these IECs to safeguard the research participant's rights. A sub-committee of

the main IEC may review proposals submitted by undergraduate or post-graduate students or if necessary, a committee may be separately constituted for the purpose, which will review proposals in the same manner as described above. 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

The IECs should be multidisciplinary and multisectorial in composition. Independence and competence are the two hallmarks of an IEC. The number of persons in an ethics committee should be kept fairly small (8 - 12 members). It is generally accepted that a minimum of five persons is required to form the quorum without which a decision regarding the research should not be taken. The IEC should appoint from among its members a Chairman who should be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary should be from the same Institution and should conduct the business of the Committee. Other members should be a mix of medical/ non-medical, scientific and non-scientific persons including lay persons to represent the differed points of view. The composition may be as follows:-

1. Chairperson
2. One - two persons from basic medical science area
3. One - two 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

As per revised Schedule Y of Drugs & Cosmetics Act, 1940, amended in 2005, the ethics committee approving drug trials should have in the quorum at least one representative from the following groups:

1. One basic medical scientist (preferably one pharmacologist).
2. One clinician
3. One legal expert or retired judge

4. One social scientist/ representative of non-governmental organisation/ philosopher/ ethicist/ theologian or a similar person
5. One lay person from the community.

The Ethics Committee (EC) can have as its members, individuals from other institutions or communities with adequate representation of age and gender to safeguard the interests and welfare of all sections of the community/society. If required, subject experts could be invited to offer their views, for instance, a pediatrician for pediatric conditions, a cardiologist for cardiac disorders etc. Similarly, based on the requirement of research area, for example HIV, genetic disorders *etc.* it is desirable to include a member from specific patient groups in the Committee.

TERMS OF REFERENCE

The Terms of References should include Terms of Appointment with reference to the duration of the term, the policy for removal, replacement, resignation procedure, frequency of meetings, and payment of processing fee to the IEC for review, honorarium/ consultancy to the members/ invited experts *etc.* and these should be specified in the SOP which should be made available to each member. Every IEC should have its own written SOPs according to which the Committee should function. The SOPs should be updated periodically based on the changing requirements.

The term of appointment of members could be extended for another term and a defined percentage of members could be changed on regular basis. It would be preferable to appoint persons trained in bioethics or persons conversant with ethical guidelines and laws of the country. Substitute member may be nominated if meetings have been continuously missed by a member due to illness or other unforeseen circumstances. For this the criteria for number of missed meetings may be defined in the SOP.

TRAINING

The EC members should be encouraged to keep abreast of all national and international developments in ethics through orientation courses on related topics by its own members or regular training organized by constituted body(ies), so that they become aware of their role and responsibilities. For drug trial review it is preferable to train the IEC members in Good Clinical Practice. Any change in the regulatory requirements should be brought to their attention and they should be aware of local, social and cultural norms, as this is the most important social control mechanism. .

REGULATION

Once the legislation of guidelines occurs which is currently under active consideration by the Ministry of Health, a Biomedical Research Authority will be set up under

the proposed Bill on Biomedical Research on Human Participants(Promotion and Regulation) which would require that all IECs register with this Authority. It will also evaluate and monitor functioning of the IECs, and develop mechanisms for enforcing accountability and transparency by the institutions.

REVIEW PROCEDURES

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

The IEC's member-secretary or secretariat shall screen the proposals for their completeness and depending on the risk involved categorise them into three types, namely, exemption from review, expedited review and full review (see below for explanation).

Minimal risk would be defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of general population or during the performance of routine physical or psychological examinations or tests. However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current every day life.

An investigator cannot decide that her/his protocol falls in the exempted category without approval from the IEC. All proposals will be scrutinised to decide under which of the following three categories it will be considered :

1. Exemption from review

Proposals which present less than minimal risk fall under this category as may be seen in following situations :

- i. Research on educational practices such as instructional strategies or effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exceptions:

- i. When research on use of educational tests, survey or interview procedures, or observation of public behavior can identify the human participant directly or through identifiers, and the disclosure of information outside research could subject the participant to the risk of civil or criminal or financial liability or

psychosocial harm.

- ii. When interviews involve direct approach or access to private papers.

2. Expedited Review

The proposals presenting no more than minimal risk to research participants may be subjected to expedited review. The Member- Secretary and the Chairperson of the IEC or designated member of the Committee or Subcommittee of the IEC may do expedited review only if the protocols involve -

1. Minor deviations from originally approved research during the period of approval (usually of one year duration).
2. Revised proposal previously approved through full review by the IEC or continuing review of approved proposals where there is no additional risk or activity is limited to data analysis.
3. Research activities that involve only procedures listed in one or more of the following categories :
 - a. Clinical studies of drugs and medical devices only when -
 - i. research is on already approved drugs except when studying drug interaction or conducting trial on vulnerable population or
 - ii. adverse Event (AE) or unexpected Adverse Drug Reaction (ADR) of minor nature is reported.
4. Research involving clinical materials (data, documents, records, or specimens) that have been collected for non-research (clinical) purposes.
5. When in emergency situations like serious outbreaks or disasters a full review of the research is not possible, prior written permission of IEC may be taken before use of the test intervention. Such research can only be approved for pilot study or preliminary work to study the safety and efficacy of the intervention and **the same participants should not be included** in the clinical trial that may be initiated later based on the findings of the pilot study.

- a. Research on interventions in emergency situation

When proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, physicians may use new intervention as investigational drug (IND) / devices/ vaccine to provide emergency medical care to their patients in life threatening conditions. Research in such instance of medical care could be allowed in patients -

- i. when consent of person/ patient/ responsible relative or custodian/ team of designated doctors for such an event is not possible. However, information about the intervention should be given to the relative/ legal guardian when available later;
 - ii. when the intervention has undergone testing for safety prior to its use in emergency situations and sponsor has obtained prior approval of DCGI;
 - iii. only if the local IEC reviews the protocol since institutional responsibility is of paramount importance in such instances.
 - iv. if Data Safety Monitoring Board (DSMB) is constituted to review the data;
- b. Research on disaster management

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

- i. Research planned to be conducted after a disaster should be essential culturally sensitive and specific in nature with possible application in future disaster situations.
- ii. Disaster-affected community participation before and during the research is essential and its representative or advocate must be identified.
- iii. Extra care must be taken to protect the privacy and confidentiality of participants and communities.
- iv. Protection must be ensured so that only minimal additional risk is imposed.
- v. The research undertaken should provide direct or indirect benefits to the participants, the disaster-affected community or future disaster-affected population and *a priori* agreement should be reached on this, whenever possible, between the community and the researcher.
- vi. All international collaborative research in the disaster-affected area should be done with a local partner on equal partnership basis.
- vii. Transfer of biological material, if any, should be as per Government rules taking care of intellectual property rights issues.

3. Full Review

All research presenting with more than minimal risk, proposals/ protocols which do not qualify for exempted or expedited review and projects that involve vulnerable population and special groups shall be subjected to full review by all the members. While reviewing the proposals, the following situations may be carefully assessed against the existing facilities at the research site for risk/benefit analysis:

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

7. mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
8. sputum collected after saline mist nebulization and bronchial lavages.
- b. Collection of data through noninvasive procedures routinely employed in clinical practice. Where medical devices are employed, they must be cleared/ approved for marketing, for instance -
 - i. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy;
 - ii. weighing or testing sensory acuity;
 - iii. magnetic resonance imaging;
 - iv. electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow,
 - v. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- c. Research involving clinical materials (data, documents, records, or specimens) that will be collected solely for non-research (clinical) purposes.
- d. Collection of data from voice, video, digital, or image recordings made for research purposes.
- e. Research on individual or group characteristics or behavior not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

SUBMISSION OF APPLICATION

The researcher should submit an application in a prescribed format along with the study protocol as prescribed in SOP of IEC concerned. The protocol should include the following :-

1. The title with signature of Principal Investigator (PI) and Co-investigators as attestation for conducting the study.
2. Clear research objectives and rationale for undertaking the investigation in human participants in the light of existing knowledge.

3. Recent curriculum vitae of the Investigators indicating qualification and experience.
4. Participant recruitment procedures and brochures, if any.
5. Inclusion and exclusion criteria for entry of participants.
6. Precise description of methodology of the proposed research, including sample size (with justification), type of study design (observational, **experimental, pilot, randomized, blinded** etc.), intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures if any.
7. Plan to withdraw or withhold standard therapies in the course of research.
8. Plan for statistical analysis of the study.
9. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and local languages.
10. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory, animal and human research.
11. For research involving more than minimal risk, an account of management of such risk or injury.
12. Proposed compensation and reimbursement of incidental expenses and management of research related and unrelated injury/ illness during and after research period.
13. An account of storage and maintenance of all data collected during the trial.
14. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.
15. A statement on probable ethical issues and steps taken to tackle the same like justification for washout of standard drug, or the use of placebo control..
16. All other relevant documents related to the study protocol like investigator's brochure for trial on drugs/ devices/ vaccines/ herbal remedies and statement of relevant regulatory clearances.
17. Agreement to comply with national and international Good Clinical Practices (GCP) protocols for clinical trials.
18. Details of Funding agency/ Sponsors and fund allocation.

19. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee(HMSC) or appropriate Committees under other agencies/ authority like Drug Controller General of India (DCGI)
20. For exchange of biological material in international collaborative study a MoU/ Material Transfer Agreement between the collaborating partners.
21. A statement on conflict-of-interest (COI), if any.

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, review serious adverse event (SAE) reports and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate. The following points should be considered while doing so :

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 to the PI.
2. If a member has conflict-of-interest (COI) involving a project then s/he should submit this in writing to the chairperson before the review meeting, and it should also be recorded in the minutes.,
3. If one of the members has her/his own proposal for review or has any COI then s/he should withdraw from the IEC while the project is being discussed
4. A negative decision should always be supported by clearly defined reason
5. An IEC may decide to reverse its positive decision on a study if it receives information that may adversely affect the risk/ benefit 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/ alternate Chairperson/ designated member of the committee.

REVIEW PROCESS

The method of review should be stated in the SOP whether the review should be done by all reviewers or by primary reviewer(s) in which case a brief summary of the project with informed consent and patient information sheet, advertisements or brochures, if any, should be circulated to all the other members.

The ethical review should be done in formal meetings and EC should not take decisions through circulation of proposals. The committee should meet at regular intervals and should not keep a decision pending for more than 3 - 6 months, which may be defined in the SOP.

PERIODIC REVIEW

The ongoing research may be reviewed at regular intervals of six months to one year as may be specified in the SOP of the ethics committee.

CONTINUING REVIEW

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

INTERIM REVIEW

Each IEC should decide the special circumstances and the mechanism when an interim review can be resorted to by a sub-committee instead of waiting for the scheduled time of the meeting like re-examination of a proposal already examined by the IEC or

any other matter which should be brought to the attention of the IEC. However, decisions taken should be brought to the notice of the main committee.

MONITORING

Once IEC gives a certificate of approval it is the duty of the IEC to monitor the approved studies, therefore an oversight mechanism should be in place. Actual site visits can be made especially in the event of reporting of adverse events or violations of human rights. Additionally, periodic status reports must be asked for at appropriate intervals based on the safety concerns and this should be specified in the SOP of the IEC. SAE reports from the site as well as other sites are reviewed by EC and appropriate action taken when required. In case the IEC desires so, reports of monitoring done by the sponsor and the recommendations of the DSMB may also be sought.

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. The following records should be maintained for the following:

- i. the Constitution and composition of the IEC;
- ii. signed and dated copies of the latest the curriculum vitae of all IEC members with records of training if any;
- 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 a period of 3 years if it is not possible to maintain the same for more than that due to resource crunch and lack of infrastructure.

ADMINISTRATION AND MANAGEMENT

A full time secretariat and space for keeping records is required for a well functioning IEC. The members could be given a reasonable compensation for the time spared for reviewing the proposals. A reasonable fees can be charged to cover the expenses related to review and administrative processes. Every institution should allocate reasonable amount of funds for smooth functioning of the IEC.

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 participants 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. Details on these issues are described in the next Chapter on General Ethical Issues.

GENERAL ETHICAL ISSUES

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

I. INFORMED CONSENT PROCESS

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

1. Nature and purpose of study stating it as research
2. Duration of participation with number of participants
3. Procedures to be followed
4. Investigations, if any, to be performed
5. Foreseeable risks and discomforts adequately described and whether project involves more than minimal risk
6. Benefits to participant, community or medical profession as may be applicable
7. Policy on compensation
8. Availability of medical treatment for such injuries or risk management
9. Alternative treatments if available

10. Steps taken for ensuring confidentiality
11. No loss of benefits on withdrawal
12. Benefit sharing in the event of commercialization
13. Contact details of PI or local PI/Co-PI in multicentric studies for asking more information related to the research or in case of injury
14. Contact details of Chairman of the IEC for appeal against violation of rights
15. Voluntary participation
16. If test for genetics and HIV is to be done, counseling for consent for testing must be given as per national guidelines
17. Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipt of its results

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

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

Fresh or re-consent is taken in following conditions :

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

5. Before publication if there is possibility of disclosure of identity through data presentation or photographs (which should be camouflaged adequately).

Waiver of consent

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

- i. When it is impractical to conduct research since confidentiality of personally identifiable information has to be maintained throughout research as may be required by the sensitivity of the research objective, *eg.*, study on disease burden of HIV/AIDS.
- ii. Research on publicly available information, documents, records, works, performances, reviews, quality assurance studies, archival materials or third-party interviews, service programs for benefit of public having a bearing on public health programs, and consumer acceptance studies.
- iii. Research on anonymised biological samples from deceased individuals, left over samples after clinical investigation, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognised institutions or qualified investigators, samples or data from repositories or registries *etc.*
- iv. In emergency situations when no surrogate consent can be taken.

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

- i. communicate to prospective participants all the information necessary for informed consent. Any restriction on participant's right to ask any questions related to the study will undermine the validity of informed consent;
- ii. exclude the possibility of unjustified deception, undue influence and intimidation. Although deception is not permissible, if sometimes such information would jeopardize the validity of research it can be withheld till the completion of the project, for instance, study on abortion practices;
- iii. seek consent only after the prospective participant is adequately informed. The investigator should not give any unjustifiable assurances to prospective

- participant, which may influence the her/his decision to participate;
- iv. obtain from each prospective participant a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial, and in case the participant is not competent to do so, a legal guardian or other duly authorised representative;
- v. take verbal consent when the participant refuses to sign or give thumb impression or cannot do so. This can then be documented through audio or video means;
- vi. take surrogate consent from the authorized relative or legal custodian or the institutional head in the case of abandoned institutionalized individuals or wards under judicial custody;
- vii. renew or take fresh informed consent of each participant under circumstances described earlier in this chapter;
- viii. if participant loses consciousness or competence to consent during the research period as in Alzheimer or psychiatric conditions, surrogate consent may be taken from the authorized person or legal custodian.
- ix. The investigator must assure prospective participants that their decision to participate or not will not affect the patient - clinician relationship or any other benefits to which they are entitled.

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

- i. the aims and methods of the research;
- ii. the expected duration of the participation;
- iii. the benefits that might reasonably be expected as an outcome of research to the participant or community or to others;
- iv. any alternative procedures or courses of treatment that might be as advantageous to the participant as the procedure or treatment to which s/he is being subjected;
- v. any foreseeable risk or discomfort to the participant resulting from participation in the study;
- vi. right to prevent use of her/ his biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;
- vii. the extent to which confidentiality of records could be maintained ie., the limits

- to which the investigator would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality;
- viii. responsibility of investigators;
 - ix. free treatment for research related injury by the investigator and/ institution and sponsor(s);
 - x. compensation of participants for disability or death resulting from such injury;
 - xi. insurance coverage if any, for research related or other AEs;
 - xii. freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to;
 - xiii. the identity of the research teams and contact persons with address and phone numbers;
 - xiv. foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;
 - xv. risk of discovery of biologically sensitive information and provision to safeguard confidentiality;
 - xvi. publication, if any, including photographs and pedigree charts.

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

II. COMPENSATION FOR PARTICIPATION

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

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

- ii. when a participant is withdrawn from research for medical reasons related to the study the participant should get the benefit for full participation;
- iii. when a participant withdraws for any other reasons s/he should be paid an amount proportionate to the amount of participation.

III. CONFLICT OF INTEREST

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

Academic institutions conducting research in alliance with industries/ commercial companies require a strong review to probe possible conflicts of interest between ~~scientific responsibilities of researchers and business interests~~ (ownership or part-ownership of a company developing a new product). In cases where the review board/ committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, the board/ committee should advise accordingly. Significant financial interest means anything of monetary value that would reasonably appear to be a significant consequence of such research including salary or other payments for services like consulting fees or honorarium per participant; equity interests in stocks, stock options or other ownership interests; and intellectual property rights from patents, copyrights and royalties from such rights. The investigators should declare such conflicts of interest in the application submitted to IEC for review. Institutions and IECs need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. The IEC can determine the conditions for management of such conflicts in its SOP manual. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Those who have also to be informed of the secondary interest in financial terms should include the institution, IEC, audience when presenting papers and should be mentioned when publishing in popular media or scientific journals.

Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes. Undue compensation would include assistance to related person(s) for transport of body for cremation or burial, provision for insurance for unrelated conditions, free transportation to and fro for examination

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

IV. SELECTION OF SPECIAL GROUPS AS RESEARCH PARTICIPANTS

- i. *Pregnant or nursing women* : Pregnant or nursing women should in no circumstances be the participant of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be participants of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable participants.
 - a. The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting foetal abnormalities and for conditions associated with or aggravated by pregnancy etc. Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast-feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant. Compensation in terms of supplying supplementary food such as milk formula should be considered in such instances.
 - b. Research related to termination of pregnancy : Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made participants for such research as per The Medical Termination of Pregnancy Act, GOI, 1971.
 - c. Research related to pre-natal diagnostic techniques : In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, GOI, 1994 and not for sex determination of the

foetus.

- ii. **Children** : Before undertaking trial in children the investigator must 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 from the age of seven years up to the age of 18 years.;
 - e. research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;
 - f. interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child participant must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;
 - g. the child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/ tested, provided the consent has been obtained from parents / guardian;
 - h. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child participant as any available alternative interventions;
 - i. the risk presented by interventions not intended to benefit the individual child participant is low when compared to the importance of the knowledge that is to be gained.
- iii. **Vulnerable groups** : Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.
 - a. research on genetics should not lead to **racial inequalities**;
 - b. persons who are **economically or socially disadvantaged** should not be used to benefit those who are better off than them;
 - c. rights and welfare of **mentally challenged and mentally differently able persons** who are incapable of giving informed consent or those with behavioral disorders must be protected. Appropriate proxy consent from

the legal guardian should be taken after the person is well informed about the study, need for participation, risks and benefits involved and the privacy and confidentiality procedures. The entire consent process should be properly documented;

- d. adequate justification is required for the involvement of participants such as prisoners, students, subordinates, employees, service personnel etc. who have **reduced autonomy** as research participants, since the consent provided may be under duress or various other compelling reasons.

V. ESSENTIAL INFORMATION ON CONFIDENTIALITY FOR PROSPECTIVE RESEARCH PARTICIPANTS

Safeguarding confidentiality - The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual participants. Data of individual participants can be disclosed under the following circumstances :

- a. only in a court of law under the orders of the presiding judge or
- b. there is threat to a person's life or
- c. in cases of severe adverse reaction may be required to communicate to drug registration authority or
- d. if there is risk to public health it takes precedence over personal right to privacy and may have to be communicated to health authority.

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

VI. COMPENSATION FOR ACCIDENTAL INJURY

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

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

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

to oversee such claims, which would be common for projects being undertaken by it.

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

VII. POST - TRIAL ACCESS

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

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

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

sponsors (Governmental like National Institutes of Health, USA, non-Governmental like Bill & Melinda Gates Foundation, Ford Foundation or others like WHO, UNICEF, UNAIDS, etc.).

Special Concerns

1. Given the magnitude and severity of the health problems in different countries, capacity building to address ethical issues that arise out of collaborative research must be promoted on a priority basis. Strategies should be implemented so that various countries and communities can practise meaningful self-determination in health development and can ensure the scientific and ethical conduct of research.
2. The collaborating investigators, institutions and countries can function as equal partners with sponsors even when in a vulnerable position by building appropriate safeguards. Community representatives should be involved early enough while designing the protocol and in a sustained manner during the development, implementation, monitoring and dissemination of results of research.
3. Careful consideration should be given to protect the dignity, safety and welfare of the participants when the social contexts of the proposed research can create foreseeable conditions for exploitation of the participants or increase their vulnerability to harm. The steps to be taken to overcome these should be described and approval taken from concerned IEC/IndEC.
4. Every adult participant in the research should voluntarily give informed consent and child her/his assent as may be applicable.
5. As different kinds of research (epidemiological studies, clinical trials, product development, behavioural and social science oriented research *etc.*) have their own particular scientific requirements and specific ethical challenges, the choice of study populations for each type of study should be justified in advance in scientific and ethical terms regardless of the place from where the study population is selected. Generally, early clinical phases of research, particularly of drugs, vaccines and devices, should be conducted in communities that are less vulnerable to harm or exploitation. However, for valid scientific and public health reasons, if sufficient scientific and ethical safeguards are ensured it may be conducted in any phase after obtaining relevant regulatory clearances.
6. The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research programme should be specified in the research protocol and explained to the participants as fully as can be reasonably done. Moreover, the modalities by which to address these, including **provision**

for the best possible nationally available care to participants who experience adverse reactions to 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.

7. The research protocol should outline the benefits that persons / communities / countries participating in such research should experience as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation. The burden and the benefit should be equally borne by the collaborating countries.
8. Guidelines, rules, regulations and cultural sensitivities of all countries participating in collaborative research projects should be respected, especially by researchers in the host country and the sponsor country. These could be with reference to intellectual property rights, exchange of biological materials (human, animal, plant or microbial), data transfer, security issues, and issues of socially or politically sensitive nature. In this context, it is essential for researchers to follow the GOI notification on " Exchange of Human Biological Material for Biomedical Research" issued on 19.11.97 and obtain appropriate regulatory clearances as prevalent in the country for international collaboration and EC approval from all trial sites before the initiation of research.

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

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

Investigator's publication plans should not threaten the privacy or confidentiality of participants, for example publication of pedigrees in the report on research in

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

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

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

Human studies designed to evaluate the safety, effectiveness, or usefulness of an intervention includes 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, multifaceted and varied as the complexities of medical research have increased. It is clearly accepted that it is essential to carry out research on human participants to discover better medical and therapeutic modalities for the benefit of mankind. It is equally clear that such research on normal participants 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 participants including herbal remedies, in accordance with the basic ethical principles. These guidelines are important for the protection of research participants against any avoidable risk, guide the researchers in the preparation of research proposals/ protocols and facilitate ECs to review and approve such studies.. 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 participants should be conducted in accordance with the four basic ethical principles, namely autonomy or respect for person/ participant, beneficence, non-maleficence and justice. The guidelines laid down are directed at application of these basic principles to research involving human participants. An investigator is the person responsible for the research trial and for

protection of the rights, health and welfare of the participants recruited for the study. S/he 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 in these guidelines.

SPECIFIC PRINCIPLES

I DRUG TRIALS

As per the revised Schedule 'Y' of the Drugs & Cosmetic Act (2005), "a clinical trial is a systematic study of new drug(s) in human subject to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic, and pharmacokinetics), and/or adverse effects with the objective of determining the safety and/or efficacy of the new drugs". Clinical trial of drugs is a randomised single or double blind controlled study in human participants, 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:

- i. a new chemical entity (NCE);
- ii. 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;
- iii. 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.

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.

Special considerations

- i. Use of a placebo in drug trials and sham surgery has been intensely debated and even the fifth version of Helsinki Declaration has not been helpful in providing clarity in this matter. Each such protocol using placebo requires careful consideration before approval. Denial of the available treatment to control (placebo) group of patients is unethical.
- ii. Trials of drugs without the approval of the Indian Regulatory Authority and appropriate agencies should be dealt with according to the law of the land.
- iii. After the clinical trial is over, if need the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible. A suitable *a priori* agreement should be reached on post trial benefits.
- iv. 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.
- v. Issues of partner notification and discordant couples should be taken care of before initiating any HIV / AIDS related trial.
- vi. For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I through Phase III and data should be submitted as required under items 5, 6 and 7 respectively of Appendix I of revised Schedule 'Y' of Drugs and Cosmetics Act. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s).
- vii. For new drug substances discovered in countries other than India, Phase I data as required under item 5 of Appendix I, from other country(ies) should be submitted along with the application. After Phase I data generated outside India has been submitted to the Licensing Authority, permission may be granted to conduct Phase II and Phase III trials concurrently with other global trials for that drug.
- viii. In case of amendment or deviation in the protocol not only the approval of IEC may be obtained but also the Licensing Authority has to be notified of the same.

In order to optimize and expedite drug development for drugs indicated in life threatening/ serious diseases or specific diseases of relevance to India - the toxicological and clinical data requirements shall be decided on a case by case basis. In such cases, particular studies may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority and not by ECs.

The Indian Good Clinical Practices (GCP) based on the international guidelines issued by World Health Organization (WHO) and International Committee on Harmonization (ICH) 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. They may be accessed at <http://cdsco.nic.in/html/GCP.htm>.

The clinical trials usually are of 3 types –

- i. studies where intervention is clearly “demarcated research” such as phase I trial of a new compound;
- ii. studies with a mix of standard medical practices and specific research elements, *e.g.* trials of two competing anti-nausea drugs following standard chemotherapy;
- iii. studies involving research on therapeutic practices, such as the trial of two already approved anti-diabetic drugs.

Phases of Clinical Trials

All phases require approval from EC. The first three of the following four phases of clinical trials of drug require DCGI's clearance: -

Phase I (Human Pharmacology) - This is a non-therapeutic trial and the objective is to determine the safety of a new drug and determine the maximum tolerated dose as also to determine the nature of adverse reactions that can be expected. 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. These studies include both single and multiple dose administration and should ideally be carried out at a site that is adequately equipped. The following points should be considered before initiating the trial :

1. At least two participants should be administered each dose to establish the safe dose range using maximum tolerated dose, pharmacokinetic, pharmacodynamic effects, and adverse reactions, if any, with their intensity and nature.
2. As this involves testing in humans for the first time, it is safer to plan the study in cohorts of volunteers by starting from the lowest dose, which is increased to

higher doses only after the safety of the lower doses is clearly established.

3. Early measurement of drug activity as preliminary study of activity of potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage. This also can be carried on patients if the drug has cytotoxic potential as in case of cancer or if quicker results are needed as in case of HIV.
4. Pharmacokinetics i.e. characterization of a drug's absorption, distribution, metabolism and excretion (ADME), should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, and ethnic subgroups should also be considered.
5. Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies which relate to blood levels of drug to response (pharmacokinetic/ pharmacodynamic studies) may be conducted in healthy volunteers or in patients with the target disease. Such data obtained from patients may guide the dosage and dose regimen to be applied in later studies.
6. Investigator trained in clinical pharmacology should preferably carry out these studies.
7. 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.
8. Compensation is given by the sponsors of newly developed drugs. The amount may vary depending upon the discomfort experienced by the participant and the number of samples taken or being subjected to procedures. The EC has to examine this does not tantamount to undue inducement.
9. There should be adequate safeguards for management of adverse reactions, including resuscitative measures as in intensive care

Combined Phase I and Phase II - Such trials are conducted on populations for whom the therapeutic options are exhausted, as in the case of HIV/AIDS and cancer. Toxic drugs like anti-retroviral or anti-cancer drug, cannot be tested in normal healthy volunteers as in Phase I studies as the risk far outweighs any benefit. Hence such studies are planned in patients suffering from the disease so that the risk-benefit ratio is more favourable. Since here the patient population is a vulnerable group and trial on them has to be planned very carefully. The role of ethics committee

assumes great importance here as the weighing of the risk-benefit ratio influences the decision and participation in terminal stages may be considered to be inducement. The researcher also has to consider very carefully the risks involved.

Phase II (Therapeutic Exploratory Trials) - These are controlled studies conducted in a limited number of patients of either sex to determine therapeutic effects, effective dose range and further evaluation of safety and pharmacokinetics in patients. Generally due to selection of patients with narrow inclusion criteria to find effective dose the study population is more or less homogenous. The dose used is lesser than the highest dose used in phase I. Another objective of this Phase II is evaluation of potential study endpoints, therapeutic regimens including concomitant medications and target populations, and mild versus severe disease, for further studies in Phase II or III. These objectives may be served by exploratory analyses of subsets of data and by including multiple endpoints in trials. Normally 20 - 25 patients should be studied for assessment of each dosage. These studies are usually limited to 3 - 4 centres. It is advisable to include a clinical pharmacologist as a co-investigator in such studies.

Phase III (Therapeutic Confirmatory Trials) - The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of either sex 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. This is to validate efficacy and safety found in Phase II. On successful completion of phase III trials permission is granted for marketing of the drug.

Studies in Phase III may also further explore the dose-response relationship to drug concentration in blood and clinical response, use of the drug in wider populations, in different stage of disease, or the safety and efficacy of the drug in combination with other drug (s). For drugs intended to be administered for long periods, trial involving extended exposure to the drug are ordinarily conducted, although they may be initiated in Phase II. These studies carried out in Phase III complete the prescribing information needed to support adequate instructions for use of the drug.

These trials may be carried out by clinicians in the concerned therapeutic areas having facilities appropriate to the protocol. If the drug is already approved/ marketed in other countries, Phase III data should generally be obtained in sufficient numbers of patients distributed over adequate number of centers, primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Open non-comparative trials do not generate any generalisable data and therefore, are unethical. Studies in Phase III may also further explore the dose-response relationships, drug concentration in blood and clinical response, use of the drug in wider population, in different stage of disease, or the safety and efficacy of the drug in combination with other drugs.

Phase IV - The Phase IV studies should have valid scientific objectives. After approval of the drug for marketing, phase IV studies or post marketing surveillance is undertaken to obtain additional information about the risks and benefits resulting from long term usage of drug. 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**. There is a need to correlate the adverse events reported during Phase IV trials with the toxicity data generated in animals, to draw markers for future warnings of potential adverse events likely to occur with other drugs. These trials may not be necessary for approval of new drug for marketing but may be required by the Licensing Authority for optimizing its use. These studies also include those on specific pharmacologic effect, drug-drug interaction(s), dose-response studies, trials designed to support use under approved indication(s) e.g. mortality/morbidity studies, clinical trials in a patient population not adequately studied in the pre-marketing phase, e.g., children; and epidemiological studies etc. Bioequivalence and bioavailability study also falls under this category.

In addition there are Phase IV studies that are designed to evaluate the marketed drug in specifically designed studies, which have inclusion/exclusion criteria, objectives and end points. The drug is used for the labeled indication in these studies. Therefore Licensing Authority permission is not needed. However, EC permission is needed.

A third type of post-marketing study involves evaluation of the drug for a new indication of a marketed drug, eg. studies with letrozole. Here, DCGI permission and EC approval are needed which really makes the trial a Phase III study.

Special Studies

Bioavailability studies - For all new drug substances and for new dosage forms administered for systemic absorption which are approved elsewhere in the world, bioequivalence studies with the available formulation should be carried out wherever applicable. Data on the extent of systemic absorption may be required for formulations not meant for systemic absorption. Evaluation of the effect of food on absorption following oral administration should be carried out if the food absorption data is not submitted.

BA/BE (bioequivalence) studies are also clinical studies conducted most often in normal volunteers. Hence, all safeguards to protect participants must be in place, including ethical review of protocol, recruitment methods, compensation for participation, evidence of non-coercion and consent procedures. It is in such studies that volunteers often participate at short intervals and may participate at different centres within less than the prescribed period of three months between two studies.

Mechanisms to prevent this must be developed at the study site.

Dissolution studies: Data on dissolution of all solid oral dosage forms should also be submitted.

Dissolution and bioavailability data submitted in the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product.

Data regarding interaction of the new drug with drugs that are likely to be used concomitantly with it are required to be conducted and should be submitted from non-clinical studies and, if appropriate, from human studies.

Special Concerns

1. Multicentric Trials

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

- i. All the Investigators should give a written acceptance of the protocol provided by the sponsor which may be modified to suit the local requirements and should be followed for the trial duly approved by the ethics committee of the host institutes.
- ii. Meetings should be organised at the initial and intermediary stages of the trial to ensure uniform procedures at all centres.
- iii. Training should be imparted to research staff at the participating centres to familiarize them with the uniform procedures, data entry in the case record forms, ethics and GCP.
- iv. Standardisation of methods for recruitment and evaluation/monitoring of laboratory procedures and conduct of trial should be carried out.
- v. There should be monitoring of adherence to protocol including measures to terminate the participation of some centres, if necessary.
- vi. A Central monitoring committee could be set up for this purpose, which could include ethics committee members too.
- vii. Specific role of coordinators and monitors should be defined
- viii. Centralised data management and analysis should be planned as per WHO's "Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards".

- ix. 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.
- x. 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.
- xi. It is advisable to establish communication between ECs reviewing multi-centric studies in India to discuss ethical concerns of the trial. This is particularly important if any EC does not grant approval for a study at a site for ethical reasons.

2. Contraceptives

- i. All procedures for clinical trials are applicable. Participants should be clearly informed about the alternatives available.
- ii. In women where implant has been used as a contraceptive for trial, a proper follow up for removal of the implant should be done, after the trial is over or the participant has withdrawn from the trial.
- iii. 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.

3. Randomised Controlled Trial (RCT)

RCT reduces considerable bias but can also creates ethical problems when the comparative arm has placebo. Hence a proper justification should be provided for using the placebo. In keeping with the Declaration of Helsinki as far as possible standard therapy should be used in the control arm. In the following situations placebo can be used:

- i. self limited disease;
- ii. where no proven prophylactic, diagnostic or therapeutic method exists

Superiority and Non – inferiority trials – These terms have recently emerged as a result of newer application of statistical analysis for RCTs. When a trial is conducted to test if a new drug is superior to the existing one such a trial is termed superiority trial. When the trial is conducted to examine if the drug is as good as the existing one then it is called non-inferiority or active control equivalence trial (ACET). Such a concept evolved due to pitching of clinical reasoning against statistical thinking which earlier gave an indeterminate result when clinically small difference in beneficial effect was expected.

In superiority trials one of the arms can be placebo or active control but in equivalence trials use of placebo arm will be unethical as the drug's efficacy will have to be tested against a proven therapy.

In late 90s CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed to improve reporting of randomized controlled trials with primary focus on RCT with 2 parallel groups that assess the possible superiority of one treatment compared with another. This method of reporting has been modified to encourage reporting of non-inferiority or ACET trials which are lesser in number in medical literature. CONSORT guidelines are now being extended to other trial designs too.

Monitoring and reporting adverse reactions or events

Any adverse event or adverse drug reaction (AE/ ADR) can be expected and unexpected. These should be specified in the concerned SOP. Based on medical criteria they can be mild, moderate or severe/ serious and causality relationship should be examined. An AE or unexpected ADR requires expedited review by the ethics committee. Unexpected AE/ ADRs and all SAE (serious adverse event) should be reported to the sponsor by the investigator within 24 hours and to the ethics committee that accorded approval to the study protocol within seven days. In the event of death the EC should also be informed within 24 hours. Any unexpected SAE as defined in the Indian GCP (Good Clinical Practice) Guidelines occurring during a clinical trial should be communicated promptly within 14 calendar days by the Sponsor to the Licensing Authority and to the Investigator(s) of other trial sites participating in the study. The reporting of the SAE to the regulatory authority immediately is to enable it to stop the clinical trials of unapproved drugs or withdraw from market approved drugs based on report of Phase IV studies. All other serious unexpected reactions (ADRs) that are not fatal or life threatening must be filed as soon as possible but not later than 14 calendar days. 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.

The medical management of the adverse event is the responsibility of the investigator, and the protocol for adverse event management with allocation of responsibilities must be pre-defined in the protocol and submitted to the Ethics Committee. There must be a financial plan (including, if necessary, insurance) to manage adverse events and compensation for trial related injury. The Ethics Committee reviewing the protocol must review these aspects as well before giving approval.

II. VACCINE TRIALS

Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal participants, therapeutic or curative vaccines may be given to

patients suffering from particular disease. Many of the prophylactic vaccines are given to pediatric group. 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 participants**. For example, immunogenicity to hepatitis B vaccine should not be determined in high risk participants. Pharmacokinetic studies are generally not required for injectable characteristics of the immune response to the known or presumed action of vaccine. The class, subclass, and the function of specific antibody produced and the lag time for appearance and duration of adequate antibody titre is determined. Information about the induction of cell-mediated immunity, the cross reactive antibodies and/or interaction pre-existing antibodies which might affect immune system is also obtained.

Phase II : This refers to the initial trials examining effectiveness (immunogenicity) and dose range in a limited number of volunteers forming the target groups, like, children, adults or those at risk of exposure to pathogens. Pharmacokinetics and safety of the vaccine is also studied. Early Phase II is usually an exploratory trial while the late Phase II is known as pivotal efficacy study.

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) through multicentric studies. These studies determine the protection offered by the vaccine and provide pivotal data for licensure. Efficacy in vaccine trials means reduction in incidence of the disease after vaccination compared to the incidence that prevailed before vaccination. Effectiveness on the other hand provides information of protective rate conferred on a given population. It includes measurement of direct and indirect protection to a non - vaccinated person among the defined vaccinated population determined by vaccine coverage area, and correlation of vaccine strains with circulating strains.

Phase IV Studies (Post-Licensure Evaluation) : These studies are done in the entire population or a subgroup to detect the rarer or unexpected events that may not be seen in smaller Phase II/ III studies. Post-licensure studies of large populations, in a more heterogeneous group of people, over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness.

The pharmacodynamic studies provide information on the vaccines when other routes of administration are claimed eg oral vaccine, or when vaccine contains novel adjuvants or excipients. These are also done to conduct further research on

age at vaccination, effect of simultaneous administration of other vaccines, efficacy and adverse events due to changes in vaccine strain, and interchangeability of vaccine.

Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulation when there is change in vaccine composition with regard to adjuvant, preservative, or a change in manufacturing process, site or scale. These are performed either before or after product licensure. The rationale of bridging clinical studies is. The goal is to demonstrate product equivalency to that used in earlier pre-clinical or clinical testing. When serologic bridging studies are to be done, only comparison of sera with historical control from an efficacy trial is warranted, and no clinical trial need be undertaken.

Combination Vaccines

Combination vaccines are being used commonly at present. The main goal in efficacy trial design of such vaccines is to evaluate the efficacy of each antigenic component. When correlates of protection are validated for each component, immunogenicity end-points should be used. When they are not validated for each component, prospective controlled trial is required. Further, non-inferiority trials should be conducted to demonstrate that the combination vaccine is not inferior in terms of immunogenicity or efficacy, to vaccines with individual components.

Vaccines Administered Simultaneously with the Combination Vaccines

Immunogenicity and safety data should be obtained in Phase III (Pre-licensure) studies to support the simultaneous administration of a new vaccine with already licensed vaccines that would be given to the same target population using the same (or overlapping) schedule. With regard to immunogenicity, assessment should be performed to show that subjects still attain an acceptable immune response to both the combination vaccine and the other simultaneously administered vaccine. The immunogenicity obtained with such simultaneous administration should be evaluated early in clinical development for all components to detect any possible immunological interference and such assessment would be valuable before proceeding to a large-scale trial of the investigational vaccine. These studies will evaluate safety and interference of the new combination vaccine with one type of simultaneously administered vaccine, *e.g.*, for a new DTaP vaccine, safety and interference will be evaluated in a statistically valid manner with one type of simultaneously administered *Haemophilus influenzae* type b conjugate vaccine. If no such studies have been conducted, it should be stated in the package insert that no safety or immunogenicity data has been generated.

Special Concerns

- i. Some vaccines that contain active or live - attenuated micro-organisms can possibly possess a small risk of producing that particular infection. The participant to be vaccinated should be informed of the same.
- ii. The participants in control groups or when subjected to ineffective vaccines run a risk of contracting the disease. In such an event free treatment for the disease should be given and if it is a disease where lifelong treatment is required then this should be insisted upon by IEC/ IndEC.
- iii. 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.
- iv. Post trial access to the vaccine should be available to the control group. But if the vaccine is for pediatric age group and by the time the study gets over the children in the control arm may cross the age when the vaccine is supposed to be protective. In such instances the control arm could be some other alternative vaccine for that pediatric age group although this does not restore clinical equipoise. EC may examine the feasibility and ethical aspects on a case-to-case basis.
- v. Post trial access to the vaccine should be given first to the community from which the participants were drawn.
- vi. When a trial of HIV preventive vaccine is being conducted, positive serology may result after the vaccination. This may not indicate infection but may create problems for employment and travel purposes. To avoid confusion, a certificate stating that the person is a trial participant in an HIV vaccine trial may be issued.
- vii. Children being a vulnerable group, care should be taken to choose the particular age with regard to gender, ethnic background and health profile for testing vaccines for this age especially if they are from over-researched community. Vulnerable.
- viii. In RCTs if no effective vaccine exists as comparator then placebo can be used. The community should be involved to decide on the choice of comparator.

III. CLINICAL TRIALS WITH SURGICAL PROCEDURES / MEDICAL DEVICES

Medical and health care technology has undergone rapid transformation in the past two decades. Of late, a series of technological inventions have revolutionized the preventive, diagnostic, rehabilitative, therapeutic (life-supporting or life sustaining devices) capabilities of medical sciences and biomedical technology has made considerable progress in the conceptualisation and designing of bio-equipments.

Several biomedical devices and critical care equipment have been imported and successfully deployed in diagnostic and therapeutic services in the country. Similarly, various academic and research organizations as well as private entrepreneurs are taking active interest in the development and manufacture of medical devices. Several important devices such as cardiac valve and spin offs from defence research laboratories like Kalam-Raju Stent, cardiac catheters, eye lasers and external cardiac pacemaker have been successfully 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 large scale 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.

Some low technology devices such as thermometers and weighing instruments seek optional certification from Indian Standards Institute (ISI) as a proof of quality rather than as a pre-market approval requirement. The Bureau of Indian Standards (BIS) certifies and regulates few other low technology devices. However, these procedures are not adequate to assure the quality of high technology medical devices. It appears that some imported high technology devices, approved or cleared by the country of origin or by the Federal Drug Administration (FDA) of the United States of America (USA), are permitted for marketing in India. No regulatory mechanisms exist even with the Drug Controller General of India (DCGI) for certification, quality assurance and post market surveillance of both imported and indigenous medical devices. 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. Earlier only needles, syringes and blood bags were covered by the Drugs and Cosmetics Act, 1940. Now sterile devices like cardiac stents, drug eluting stents, catheters, intra-ocular lenses, IV cannulae, bone cements, heart valves, scalp vein set, orthopedic implants, internal prosthetic replacements have been included in the list with effect from 1.3.2006.

The attendant health risks through the errors caused by use of implantable devices require systematic and rigorous pre-clinical and clinical studies to evaluate their efficacy and safety besides the quality. In addition, every implant and installed diagnostic device needs to be assessed for its long term safety and/or performance through an appropriate mechanism. Execution of these measures, i.e. evaluation, certification, post-market surveillance and regulatory action in the event of any inadequacy, is possible only

through a well conceived regulatory agency, which is supported by adequate legislative safeguards.

All countries which have a medical device industry, have policies and regulatory processes or mechanisms in place. Most of these countries ((mainly USA, EU, Australia, and possibly Japan. China, South Korea and Brazil) are attempting to harmonize the medical device regulations of different countries with a view to enhance their export potentials. However, it should be borne in mind that not all the devices permitted for export by other countries have been approved for commercialisation in their own countries. Therefore, the Society for Biomedical Technology (SBMT), an inter-ministerial initiative to utilize defense research spin offs for health care sponsored a review of the existing certification procedures and regulatory mechanisms in other countries. As a second step in this direction, it was decided to conceptualize a framework for medical device regulation.

It is proposed to set up the Indian Medical Devices Regulatory Authority (IMDRA) which is being examined by the Health Ministry. Until the guidelines are formulated and implemented by this Regulatory Authority, bodies like Indian Standard Institute, Board of Indian Standards, Drug Controller General of India, and Nuclear Medicine Board of the BARC constituted for specific purposes under an Act or Administrative authorities should approve clinical trials with biomedical devices on case-to-case basis.

Definitions

Device : "An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* agent, or other similar or related article, including a component, part or accessory,

- ❖ intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or
- ❖ intended to affect the structure or any function of the body of man, and
- ❖ which does not achieve any of its primary intended purposes/ uses
- ❖ through chemical action within or on the body of man, or
- ❖ by being metabolized within the body."

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.

Medicated devices : These are devices that contain pharmacologically active substances which are treated as drugs.

Medical devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial

grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic accessories. Their purpose varies from being used primarily for specific affected parts of the body to being used as adjunct to primary therapies, for *eg.* lithotripsy with drug therapy for kidney stone. 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 participant - for example, pace markers, implants, internal catheters.

A more appropriate classification and the proposed regulatory and certification procedures for Indian devices are summarized in the table given below.

All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. As for the medicated devices, 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 trials of medical devices are different from drug trials, as they cannot be conducted in healthy volunteers. Hence Phase I trials are not necessary for trial on medicated 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.
- ❖ Safe 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 follow-up procedures to be adopted if the patient decides to withdraw from the trial.
- ❖ Study design of the intra body devices like implants can be very challenging and should have adequate protective safeguards. The study should be long enough to detect if there are any late onset ADRs.
- ❖ If full assessment of safety is not complete, the Phase III could extend to

Phase IV.

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 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 participants to more radiation than exposed normally.
- ❖ In the event of death of a participant with radiological implant, due precaution as per radiation guidelines may be taken not to expose the relatives or the close co-habitants to radiation till safe.
- ❖ Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes.
- ❖ Safety measures should be taken to protect research participants and others who may be exposed to radiation.
- ❖ The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo.
- ❖ Information must be given to participant about possible genetic damage to offspring.
- ❖ Non-radioactive diagnostic agents are considered as drugs and the same guidelines should be followed when using them.
- ❖ Ultrasound should be substituted wherever feasible.

V. CLINICAL EVALUATION OF TRADITIONAL AYURVEDA, SIDDHA, UNANI (ASU) REMEDIES AND MEDICINAL PLANTS

Self medication and greater orientation towards preventive health care, the growing desire of the aging population to stay young and healthy, and the increasing healthcare costs of therapy provided by Modern Medicine have led to more usage of traditional remedies. However, the improved research technology tools and growth deciders like new Biotechnology developments for producing the evidence, together with media publicity have catapulted traditional knowledge to the status

of a hidden treasure worth exploring. Nevertheless, subjecting traditional remedies to the same rigours that synthetic drugs undergo to establish their safety and efficacy is a difficult proposition, as most of them are complex combinations leading to difficulty in assessment of their activity and risk/benefit ratio. This involves four sets of issues - chemical-manufacturing-control (CMC) issues, non-clinical issues, clinical issues, and ethical issues.

The recognized traditional systems in India are *Ayurveda*, *Siddha* and *Unani* besides Yoga and Naturopathy and Homeopathy. The two unique features of herbal products used in the traditional Indian medical systems are that they are mostly used in compound forms and are multi-component mixtures including minerals in some of the formulations, and that substantial information is available regarding their prior human use vouchsafing safety and efficacy of these formulations. Therefore, an approach different from that for evaluation of synthetic drugs is required which concerns two groups, namely, clinical investigators evaluating the benefits and risks of herbal products and the regulatory authorities.

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* (ASU) drugs or formulations 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 ASU drugs include herbal and herbo-mineral formulations. The herbal products can belong to one of the three categories given below:-

1. A lot is known about the use of a plant or its extract, metals, minerals and animal products 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 and the substance is to be 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 and any

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compound formulation having plants, metals, minerals and animal products as ingredients 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 for synthetic products before it is cleared for clinical evaluation.

3. An extract or a compound isolated from a plant and any compound formulation having plants, metals, minerals and animal products as ingredients 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 ASU 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. Since traditional remedies have short life, increasing their stability and shelf life, and controlling their batch to batch variation could be challenging tasks for modern scientists and drug controllers to justify the beneficial effects of stored formulations.

Category I - For formulations belonging to this category, it may not be necessary to undertake phase I studies. In Phase II dose ranging should be explored to find the effective dose as also maximum tolerated dose. RCTs would be the preferable methodology to validate the claim with placebo or standard drug depending on the ethical requirement. The clinical trials would mostly fall in the non-inferiority group if literature is not available regarding the proven efficacy of the formulation. Superiority trial could be designed if the control arm is placebo or modern medicine, which is only weakly effective. Sometimes it would also be right to design pilot observational studies to explore feasibility of conducting larger trials for validation if the outcome is encouraging.

It needs to be emphasized 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. This is the unique **reverse pharmacology** approach for evaluating traditional formulations for traditional indication. If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months it would be necessary to undertake 4 - 6 weeks toxicity study in 2 species of animals in the circumstances described above or when a larger multicentric phase

III trial is subsequently planned based on results of phase II study. Clinical trials with ASU 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. However, Good manufacturing Practices (GMP) standards for the formulations to be tried would not be required for Phase I and II trials. But for Phase III GMP standards would be required for the formulations to be used in the trial as the number of participants would be larger and this will be followed by marketing approvals.

Category II and III : All the steps involved for regulatory approvals as in the case of synthetic drugs should be followed. However, for formulations falling under category two only limited toxicities as mentioned for category I would apply.

All formulations involving herbal component should satisfy following criteria as prescribed by WHO document "Operational Guidance: Information needed to support clinical trials of herbal products (2005)":

a. For Phase I / II studies –

Herbal Substance:

- description of the plant: genus, species (cultivar where appropriate); region(s) and country(ies) of origin; time of harvest; parts to be harvested
- plant processing: drying, mechanical disruption, solvent extraction (aqueous or organic solvents, others)
- analytical procedures
- specification
- storage conditions/shelf life.

Herbal Product:

- amount of active ingredient
- list of excipients
- type of product (tablet, capsule, etc.) and its method of manufacture
- analysis of putative active ingredient(s) via chemical or biological parameters
- analysis of a sizeable chemical constituent (analytical marker compound)
- analysis via chemical fingerprint (analytical markers)
- analysis for lack of contamination by pesticides, herbicides, heavy metals, synthetic drug adulterants, microbials, toxins, etc.
- dissolution studies

- storage conditions and stability during the length of the trial
 - specification against which a certificate of analysis can be assessed before the clinical trial material is released.
- b. **For Phase III studies :** Performing generally the same procedures as for Phase I/II trials, but more extensively and with more stringent oversight.

Herbal Substance:

- as above for Phase I/II trials.

In addition:

- statement that the plant is cultivated according to Good Agricultural Practices or harvested according to Good Wildcrafting Practices
- reference batch.

Herbal Product:

- as above for Phase I/II trials

In addition:

- environmental impact statement.

On account of the substantial use of traditional ASU formulations both in animals and humans this relevant information should be included in the protocol for evaluation of these products. This helps in analysis of the chemistry, manufacturing, and control of the product. The manufacture of the product should ideally be as per traditionally processed formulation to endorse the claim for efficacy as seen in traditional practice.

As the extracts of herbal products and ASU formulations are mixtures of at least partially uncharacterized constituents it is claimed that such a mixture provides a therapeutic advantage, since the unknown constituents may be additive or synergistic in action or may produce a balance to counteract adverse effects of any one constituent. This may thus provide more efficacy than would be provided by the known constituent alone. Thus, purification of the medicines down to known or otherwise single chemical constituents is not required as it may lead to loss of the advantage provided by the mixture.

For standardization and quality control analysis of the active pharmaceutical ingredient(s) may be best approached by analysis of one or more active biomarker(s), analysis of a chemical constituent that constitutes a sizable percentage of the total ingredients, and a chemical fingerprint of the total ingredients. The latter two analyses would act as surrogates for analysis of the unknown constituents that contribute to efficacy. In order to have the best standards by minimizing variation of content from

batch to batch several analytical procedures may be needed to adequately quantify the constituents of herbal products or ASU formulations.

Quality Control

Contaminating herbicides and pesticides levels as well as toxic contaminations must be particularly addressed in maintaining the quality control of the herbal or herbo-mineral formulation. The presence of adulterants should also be ruled out.

For traditional ASU formulations extraction may be done as per classical method or by a special SOP prepared for it. Information on each individual plant species used as ingredient must be collected and authenticated and maintained as voucher specimens. The plant ingredient should be subjected to pharmacognosy and other relevant analysis in phytochemistry.

Formulations intended for administration in clinical trials should be prepared in bulk after standardization, and quality control. The stability and shelf life studies should also be carried out simultaneously for marketing purposes.

The recommendations made earlier regarding informed consent, inducements for participation, information to be provided to the participant, withdrawal from study and research involving children or persons with diminished autonomy, all apply to 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 *Ayurveda*, *Siddha* or *Unani* physician is a co-investigator in such a clinical trial.** It would neither be 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 by following the outcome parameters prescribed in each system.

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 which 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. Such studies are on large scale and assist in improving the public health, which includes both patients and healthy people and communities.

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 class population would mean that a significant number of life style related diseases such as Ischaemic Heart Disease are increasing. The Framingham Heart Studies in USA illustrates how epidemiological data collected on risk factors for cardiovascular diseases helped in planning measures to prevent and control them. Such information in India could be undertaken as 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. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health and the social milieu. 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 participants, 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 participants 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 : In observational studies predefined parameters in a defined population group over a specified period and frequency are recorded for studying exposure to risks affecting health. These may be of the following types :

- a. **Cross Sectional Studies (Surveys) :** This is primarily population based and involves selecting an entire population or random samples of the representative population based on census data and then using 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. The study participants are directly contacted only once in the defined period for which informed consent is required to be taken.
- 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 participants and informed consent to participate in the study is necessary. However, if it entails only a review of medical records, informed consent may not be required and indeed may very often not be feasible. But for such waiver of consent approval from IEC would be necessary.
- 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 participants for a long time and involves asking questions, checking of records, 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 on health. 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 maximize 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 assume that the individuals or populations 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.

Surveillance studies to obtain true disease burden rates most likely give rise to ethical dilemmas regarding maintenance of confidentiality and prevention of stigmatization. So is the case with studies on post – disaster events, mental health and evaluation of health programs. Wherever applicable anonymisation could solve these problems when the information is required to be placed in public domain.

SPECIFIC PRINCIPLES

1. **Informed Consent** : When individuals are to be included as participants 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 participants/ patients may not be fully aware of their rights. In this context, the role of investigator is crucial and s/he should remain vigilant and conscious of her/ his obligations towards the participants/ 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.* who are considered to be gate keepers of the society/ community
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. Steps should be taken to maintain utmost privacy which should be informed to the community.
6. **Maintaining confidentiality** of epidemiological data is absolutely essential. A particular concern is the fact that some population based data may also have implications on issues like national security and these need to be carefully evaluated at the beginning.

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. 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 instance, as in AIDS, STD etc. It may not always be possible to communicate study results to individuals but research findings and advice 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.
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, for eg., studies on outbreaks, epidemics, disasters and calamities, and epidemiological studies undertaken by providers of relief and rehabilitation.
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. Benefits : When epidemiological studies (like those on mortality and morbidity as a result of exposure to an agent) lead to long associations with the community, the results if released in timely manner could give improved health care facilities or educate the community to reduce the impact of adverse environment on health and tackle the problem at their end in time.
12. 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.
13. 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 cleared by IEC before initiation as is done in all epidemiological studies.

It is not always possible to know what will happen to the participants as unexpected results or undesirable events can sometimes occur. Very often the benefits and risks of the research pertain not only to the individual participants, but also the community from which they are drawn. Therefore, the participation of local community representatives in planning, conducting and monitoring research is important to avert circumstances which may be detrimental to the participants' welfare. This also helps in improving the vision of the researcher regarding the objectives and the design of study. The inclusion of a community representative to act on behalf of all participants involved in a research study. Communities should be informed of the research, possible outcomes (positive and negative), and the results of the research. Research findings belong to participants and their communities as well as the researchers and the research community. Community representatives and researchers can work together to make sure that research is conducted in the most appropriate way and the benefits if any, could be shared in a reasonable or workable manner.

Community Participation

A community can be defined as a group of people sharing the same location, beliefs, culture, ideals, goals, age, gender, profession, lifestyle, common interests, geographical locations or settings or disease. When research participants are drawn from a specific community, members of that community can be involved to discuss any concerns it may have regarding the research. In different ways such a dialogue can be facilitated. If an ethics committee does not have a member from the community, it may ask a local community representative to be the voice for all participants. On the other had, community representatives can formally join together to form a group termed as Community Advisory Board, Community Working Group, or Community Advisory Group, which takes part in the research at all stages of the study. In international studies, particularly on issues involving communities, representation from this body ensures that the community's health needs and expectations are addressed, informed consent is appropriate, and access to research benefits is provided through research that is designed and implemented in the best interests of science and community.

Community representation should be involved before, during and after the study. Before the study is initiated the community is informed to see if it agrees that the research addresses a need or problem relevant to that community and to confirm that the design is culture specific and brings some benefits to research participants

or the community. Since some risk may be associated the community representation is needed to assist in developing appropriate ways to protect the participants. During the study, the association with community representatives continues to educate others about the research and to alert the researcher to ethical issues related to the research. After the study is completed, community representatives can help in making the results known to the entire community. However, application of research findings may take a long time, which the community representatives should be made to understand. The benefits may be participants' and community's access to intervention. Whose responsibility and conditions under which this would be done, duration of availability of intervention, methods of improving the quality of health care in the community and any expected desirable behavioral change in the community should be clearly explained to community by the Ethics Committee or community representatives.

STATEMENT OF SPECIFIC PRINCIPLES FOR HUMAN GENETICS AND GENOMICS 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 practice of eugenics by nazis. 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 such information. With the successful completion of Human Genome sequencing in June 2000, clear-cut guidelines were laid and disseminated this information to all stakeholders through media and public debates for improving awareness and understanding of human genetic disorders amongst public, the majority of whom have little knowledge of genetics was initiated.

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 recent 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. Termination of pregnancy or selection of embryos to avert birth of a genetically abnormal child, possible discrimination by insurers and employers because of genetic trait, tailored development of stem cells from embryos created by conception, *in vitro* fertilisation or nuclear transfer for regenerative therapy or organ transplantation, and potential for producing designer babies as per whims and fancies of parents or even society have been subject of fierce public debate. Serious issues are raised by genetic research because it can potentially create conflict between the rights and freedoms of the individual versus that of the family and the society at large particularly when it involves human embryo and vulnerable population 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. Earlier experiments on cloning sheep and mice have

brought human cloning into the realm of active debate raising additional set of Ethical, Legal and Social Issues (ELSI). While there should be no restrictions in availing the gains of latest technology, which are beneficial to the mankind any potential harm should be contained. 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. Other issues relate to property rights on biological samples, patenting of DNA sequences and potential for bio-terrorism. In this rapidly evolving field there is a need to continuously monitor such developments and respond to emerging ethical issues promptly and judiciously.

GENERAL GUIDELINES

Clinical research in the area of human genetics and human genome, including gene therapy, is subject to general ethical considerations of protection from harm and voluntariness of participation. It concerns not only the individual but also the family, community or society from which s/he has been drawn. Therefore, the additional considerations are -:

- i. The harm may not only be physical, but also psychosocial which may produce anxiety and depression or damage familial relationship. This should be safeguarded. Appropriate communication skills are necessary for genetic counselling. There is a likelihood of social stigmatization and discrimination in schooling, employment, health and general insurance, which requires much greater care in recruiting participants 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). In 2003 this Act was amended to include the Preconceptual diagnostic technique also.

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 participant, 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.

Participant 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, out of personal interest s/he 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 participants certain special considerations have to be kept in mind while obtaining informed consent of the prospective participants enrolled in the study. These are in addition to general principles that are applicable to all medical research. Since genetic research gives rise to information applicable to the community from which the participants were drawn, 'group consent' will have to be taken from culturally appropriate authority like community head where there are no relevant authorities like village panchayat head. The ethic committees should ensure that this has been applied wherever applicable.

Confidentiality of data

This includes codification of the biological samples, where necessary.

- b. The investigator must establish secure safeguards for the confidentiality of the research data. Participants should be told of the limits of the investigator's ability to safeguard confidentiality and of the anticipated consequences of breach of confidentiality.
- c. Genetic data should be delinked to maintain confidentiality. If the result of the research is of benefit to the health of the participant then with the approval of ethics committee re-link could be established for communication of the result.
- d. When commercial companies, are involved in research, it is necessary to protect

researchers and participants from possible coercion or inducement to participate in the study.

- e. Academic institutions conducting research in alliance with industries or 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.
- f. 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.
- g. 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 participants. In genetic research, the primary the risks are psychosocial rather than physical. Adequate counseling should be given to participants 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 counselling.**

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 might vary, therefore, the need may be carefully evaluated 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;
 2. they must be made aware of any substantial risk;
 3. 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. Specific consent is required from the affected proband to share his/ her genetic information with family members who may be benefited from it. In case of refusal duty of confidentiality shall weigh higher than the duty for beneficence to family members unless sharing of information is vital to prevent serious harm to the beneficiary in the family. In such case appropriate precautions may be taken to ensure that only the genetic information needed for diagnosis / treatment is shared.
- ❖ 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.

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.

Screening new borns : Screening of newborns 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.

Screening of children : Children should not be screened merely at the request of their parents. The child's autonomy should dominate over parental autonomy. The genetic testing for children should be deferred until they are able to comprehend and are able to participate in the decision making process, unless the intervention based on result of the test is likely to be of direct therapeutic benefit to them.

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) was 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 counseling 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 scientific community should address the above – mentioned questions before application of this knowledge could be considered as ethically valid.

V. DNA AND CELL-LINE BANKING / REPOSITORY

A biobank/repository is collection of resources that can be accessed to retrieve human biological material and data. Human Tissue Repositories collect, store, and distribute human tissue materials for research purposes. Repository activities involve three components: (i) the **collectors** of tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators. The term biobank when broadly used may include physical samples but also databases, and involve bioinformatics.

Biobanks serve as an important resource for studies on understanding the population dynamics and the pathogenesis of a large number of diseases. Human biological samples in biobanks include organs (heart, liver, kidney, lung, pancreas, etc.), tissues, cells (somatic and gonadal), body fluids or samples like serum, buffy coat, DNA, hair, nails, excreta, sweat, buccal scrapings *etc.* Research on banked human tissue samples is conducted in a laboratory, hence it does not directly involve the individuals. The steps involve the initial process of collecting, processing, freezing, "anonymizing", and storing tissue with its corresponding clinical information in a database. As tissue banking concerns research at a later time, the ethical issues pertain to consent requirements for the banking and further uses of tissue and DNA samples, their control and ownership, and the benefit sharing to the individual or community. Therefore, to prevent any exploitation and protect the rights of participants, the three main requirements are individual **informed consent**, approval of the IEC and the **Repository Ethics Committee, wherever applicable**.

Repository Collections

Unidentified Specimens: Identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository.

Identified Specimens: These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by

name, patient number, or clear pedigree location (*ie.*, his or her relationship to a family member whose identity is known).

Research Samples

Unidentified Samples: Sometimes termed "anonymous," these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

Unlinked Samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

Coded Samples: Sometimes termed "linked" or "identifiable," these samples are supplied by repositories to investigators from identified specimens with a code rather than with personally identifying information such as a name or other identifying number.

Identified Samples: These samples are supplied by repositories from identified specimens with a personal identifier (such as a name of person/patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.

The sample collector must obtain informed consent of the donor for DNA banking or for cell-line transformation and banking. The process of seeking informed consent for purposes of banking must clearly be stated in addition to possible risks and benefits, the conditions under which samples from the Repository shall be provided to other researchers, how long the samples shall be preserved in the Repository and what will be the costs to individual researchers in obtaining samples from the Repository. The sample collector must also clearly inform every donor that he reserves the right to order destruction of his sample from the Repository at any time.

1. If any commercial use is made of the samples in the Repository, appropriate written benefit-sharing agreements, consistent with the policies stated earlier, must be jointly signed by the donor, sample collector and Repository in-charge. It is also desirable that community consultations are held prior to collection of samples to be stored in a Repository, and group consent is obtained before individual consent.
2. Any researcher who intends to use samples from a Repository must submit a Statement of Research Intent, which must be approved by the Ethics Committee of the Repository, which shall be responsible for determining whether the intended research is consistent with the informed consent provided by the donor, and, where applicable, of the group.

3. Unless scientifically essential, the Repository must not provide to an individual researcher any information linked to the samples. When linked information is to be provided, only the minimal information as required for the intended research shall be provided.
4. There should be appropriate Material Transfer Agreements with the Repository for depositing samples as well as for taking them out with clear reasons. Third parties must be allowed to take samples only after approval from Repository ethics committee.
5. The identity of the Repository from which samples were obtained must be revealed in all reports, patents or copyrights arising out of these samples.
6. Due intellectual property rights should be given while granting access to samples, through a contractual agreement.
7. For any publication resulting out of research from samples taken from repository, appropriate acknowledgement should be given to the original contributor of samples, sponsors of research, repository, donors and participants.

Detailed guidelines are also given in a separate booklet on biobanking or stored biological materials released by the Council in 2006.

General Principles

An Ethics Committee exclusive to the Repository, the Repository Ethics Committee constituted as per the guidelines in the Chapter on Ethics Review Mechanism, should play an important role in looking at the issues related to informed consent, privacy and confidentiality, risk-benefit analysis, benefit sharing, maintain linkages with other biobanks and repositories while adhering to the basic principles of bioethics *viz.* Autonomy, Justice, Beneficence and Non-maleficence.

Primary use

By primary use it is meant that the biological material will be used for the intended purpose as described in the protocol submitted for approval from Ethics Committee. Ownership of the sample lies with the individual, family or community as the case may be. Local Ethics Committee should consider following points for approving primary use :

- i. consent should be in written form, given voluntarily by the donor who has the capacity to do so. The use of the samples shall be reserved for the defined purpose only;
- ii. participants have the right to withdraw at any time. This does not apply to anonymised samples;

- iii. if sample is inadequate or contaminated re-contact is necessary for fresh and specific consent. This should be incorporated in the prior consent form;
- iv. while obtaining data/samples from vulnerable subgroups with reduced autonomy, Ethics Committee should ensure that informed consent be obtained from legally authorized representatives in the presence of impartial witness. The risks and benefits should be adequately explained;
- v. when samples have to be obtained for specific research from participants belonging to specified communities, permission of the group leader/local leader/authorities must also be obtained. However individual consent should never be compromised even if permission of the gatekeepers/village panchayat
- vi. group consent of the population/community should be obtained through its culturally appropriate authorities before sampling starts, particularly so for group specific research like genetic research;
- vii. samples obtained for archival purposes in a prospective study.

Secondary Use:

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

- i. the proposed use does not transgress the original consent given for the earlier study and the validity of the objectives of the new study;
- ii. provisions for ensuring anonymity of the samples for secondary use are stated;
- iii. after anonymising sample, results are not communicated to the donor;
- iv. for postmortem uses of samples the permission of the next of kin, legally authorized representative should be obtained; and
- v. waiver of consent is given whenever the donor is not traceable or the sample is anonymised.

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 preceded 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. 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.

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.

STATEMENT OF SPECIFIC PRINCIPLES FOR RESEARCH IN 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. Transplantation raises some specific ethical aspects, and these will have to be weighed in the light of ethical guidelines as applicable to Indian ethos. 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 may have lost 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: Specified in 'Transplantation of Human Organs Act, 1994' with 'Transplantation of Human Organs' Rules, 1995' the salient features are as 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, pupil 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, which on removal will not greatly alter, physiological functions, as in the case of 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 participant 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 as the participant 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 participants 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 s/he 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 her/ his 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 her/ his 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. If consent for organ donation is given prior to death in the presence of two or more witnesses, consent for transplantation of organs should be presumed and permissible without seeking further consent from relatives
3. 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.
4. It is important that the medical team uses the body only for the purpose for which consent has been given.
5. 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 unless anonymised.
6. Under no circumstances should financial gain be made from any such procedure.
7. There shall be no coercion and no monetary inducements offered to the family of the prospective cadaver donor.
8. Confidentiality of the donation must be maintained on both sides: the recipient and her/ his 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 participant 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

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. 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 resumed 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).

1. **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.
2. **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 baby of any gestation period up to one and a half months after birth.

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 Institutional Committee for Stem Cell Research and Therapy (IC-SCRT) and ethics committees and referred to National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) for final approval

in case of restrictive research as defined in the Stem Cell Research and Therapy Guidelines.

2. All centres doing research on stem cell should be registered with NAC-SCRT.
3. 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.
4. 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.
5. No research is permitted on the live aborted foetus.
6. Tissue for transplantation or research may be obtained from dead embryos or fetuses, 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.
7. 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.
8. Termination of pregnancy should not be sought with a view to donate foetal tissue in return for possible financial or therapeutic benefits.
9. 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.
10. The mother will not dictate who shall receive the foetal tissue taken for transplantation.
11. Anonymity of donor and recipient will be maintained so that neither party is aware of the identity of the other.
12. 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.
13. 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.
14. The procurement of embryos, fetuses or their tissue for commercial purposes will not involve profit or remuneration.
15. **Intact embryos or fetuses will not be kept alive** artificially for the purpose of removing usable material.
16. **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 ICSCRT and ethical committees.

17. **Cells obtained from fetuses will not be patented** for commercial considerations for their subsequent usage.
18. **Use of umbilical cord blood from a live fetus or neonate** for transplantation : The fundamental principle in any operation on a live fetus or neonate will be to ensure that no harm will occur to the fetus 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 fetus.
19. **Use of tissue or organs from dead anencephalic fetus or neonate** (fetus 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 fetus are ethically permissible only after such diagnosis of death is made.
20. 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 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 participants and also treat completely any complication that may follow their study even if it appears several years after the conclusion of the study.
 - viii. The research group will provide the human participants a printed document explaining in simple, non-technical language, the purpose of the study, details of the procedures the human participant 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 participant must certify in writing that he has studied and understood the contents of this document and that s/he is willing to participate in the study.
 - ix. 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.
21. 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 NAC-SCRT should be kept informed.
 22. 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 realized 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. Species-specific infective diseases are limited to those 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 are those causing Lassa Fever, the Marburg virus and the Ebola virus. 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.
6. Research involving the **transplantation** of human embryonic cells (*hESc*), human embryonic germ cells (*hEGc*) or human somatic cells (*hSSc*) of a pluripotent or multipotent nature into **animals** may be done provided that:
 - i) The research is designed to reconstitute a specific tissue or organ to derive a pre-clinical model.
 - ii) There is evidence from prior studies that the cells are not likely to contribute to gametes.

These animals transplanted with human stem cells will not be used for reproductive purposes and fall under restricted areas of research as described in the Stem Cell Guidelines for Research and Therapy. Such research after getting approved from IC-SCRT and ethics committee are required to be submitted for clearance from NAC-SCRT before initiation of the research.

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 participant 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 participants 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.

V. STEM CELL RESEARCH AND THERAPY

The stem cell research holds great promise of improving human health by control of degenerative diseases and restoration of damage to organs by various injuries; but at the same time it also raises several ethical and social issues such as destruction of human embryos to create human embryonic stem (hES) cell lines, potential for introducing commodification in human tissues and organs with inherent barriers of access to socioeconomically deprived and possible use of technology for germline engineering and reproductive cloning. The research in this field, therefore, needs to be regulated to strike a balance.

Definitions

Adult Stem Cell: a stem cell derived from the tissues or organs of an organism after birth (in contrast to embryonic or fetal stem cells)

Blastocyst: a hollow ball of 50-100 cells reached after about 5 days of embryonic development. It consists of a sphere made up of an outer layer of cells (the trophoectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells in the interior (the inner cell mass)

Cell Line: cells of common descent continuously cultured in the laboratory is referred to as a cell line

Cell Nuclear Replacement (CNR): The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryo without the fusion of sperm and egg. **It is also known as Somatic Cell Nuclear Transfer (SCNT).**

Clone: a cell or organism derived from, and genetically identical to another cell or organism

Clonal: Derived from a single cell

Cloning: creating an organism that is genetically identical to another organism, or a cell that is genetically identical to another cell provided that the so-called mother and daughter cells are subsequently separated (see also reproductive and therapeutic cloning)

Reproductive Cloning : The embryo developed after Somatic Cell Nuclear Transfer (SCNT) is implanted into the human uterus (of the donor of the ovum or a surrogate recipient) and allowed to develop into a fetus and whole organism. The organism so developed is genetically identical to the donor of the somatic cell nucleus.

Therapeutic Cloning: The development of the embryo after Somatic Cell Nuclear Transfer (SCNT) is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells could be differentiated into desired tissue using a cocktail of growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection

Cord Blood Stem Cell: Stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body (hematopoietic).

Embryo: in humans is the developing stage from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.

Early embryo: the term "early embryo" covers stages of development up to the appearance of primitive streak until 15th day after fertilization which marks the development of foetal body plan.

Embryonic germ cell: embryonic germ cells are primordial germ cells isolated from the gonadal ridge of 5-10 weeks fetus.

Embryonic stem cell: embryonic stem cells are derived from the inner cell mass up to the stage of blastula. These cells can be cultured indefinitely under *in vitro* conditions that allow proliferation without differentiation, but have the potential of differentiating into any cell of the body

Foetal stem cell: a stem cell derived from fetal tissue, including placenta. A distinction is drawn between the fetal germ cells, from which the gametes develop, and fetal somatic cells, from which rest of the organism develops.

Germ cells: ova and sperm, and their precursors

Implantation: the embedding of a blastocyst in the wall of uterus. In humans implantation takes place between 7-14 days after fertilization.

Mesenchymal stem cells: Rare stem cells present in human bone marrow and lining of umbilical cord that have been shown to differentiate into a variety of cell types in culture

Multipotent: Multipotent stem cells are those which are capable of giving rise to several different types of specialized cells constituting a specific tissue or organ.

Pluripotent stem cell: has the ability to give rise to various types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) Pluripotent stem cell has the potential to generate into every cell type in the body, but cannot develop into a embryo on its own.

Somatic cell: cell of the body other than egg or sperm

Somatic stem cell: an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ.

Somatic cell nuclear transfer: the transfer of a cell nucleus to an egg (or another cell) from which the nucleus has been removed.

Stem cells: Cells capable of self-replication, proliferation and differentiation.

Supernumerary embryo or spare embryo: an embryo created by means of *in vitro* fertilization (IVF) for the purpose of assisted reproduction but subsequently not used for it.

Totipotent: At two to three days after fertilization, an embryo consists of identical cells, which are **totipotent**. That is to say that each cell could give rise to an embryo on its own producing for example identical twins or quadruplets. They are totally unspecialized and have the capacity to differentiate into any of the cells, which will constitute the fetus as well as the placenta and membranes around the fetus.

The stem cell guidelines for research have been categorized into mainly three areas, namely, permissible, restrictive and prohibited areas. All centres doing research on stem cell should be registered with NAC-SCRT.

Permissible Research Areas

1. *In vitro* studies on established cell lines from any type of stem cell viz. *hES, hEG, hSS* or fetal/adult stem cells may be carried out with notification to ICSCRT, provided the cell line is registered with the IC-SCRT/NAC-SCRT and GLP is followed.
2. *In vivo* studies with established cell lines from any type of stem cells viz., *hES, hEG, hSS*, including differentiated derivatives of these cells, *on animals other than primates* with prior approval of IC-SCRT, provided such animals are not allowed to breed. This includes pre-clinical evaluation of efficacy and safety of human stem cell lines.
3. *In vivo* studies on experimental animals (other than primates) using *fetal/adult somatic stem cells* from Bone marrow, peripheral blood, umbilical cord blood, skin, limbal cells, dental cells, bone cells, cartilage cells or any other organ (including placenta), with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.
4. Establishment of new *hES* cell lines from spare, supernumerary embryos with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines given below. Once the cell line is established it shall be registered with the IC-SCRT and NAC-SCRT.
5. Establishment of fetal/adult *hSS* cell lines with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.
6. Establishment of Umbilical Cord stem cell bank with prior approval of the ICSCRT and IEC provided guidelines given in this document for collection, processing, and storage etc of the umbilical cord blood are followed. Appropriate SOPs shall be approved by the IC-SCRT and IEC.
7. Clinical trial with clinical grade stem cells, following ICMR Guidelines for Biomedical Research and GCP guidelines of the GOI, may be carried out with prior approval of IC-SCRT, IEC and DCGI. Clinical grade stem cells are required to be produced under international GMP/GTP conditions. The cells should be well characterized about their stemness and safety as per guidelines given in Annexure II. The headings under which the clinical trial protocols should be written are given in Annexure III. All clinical trials on stem cells shall be registered with NAC-SCRT through IC-SCRT.

Restricted Areas of Research

1. Creation of a zygote by IVF, SCNT or any other method with the specific aim of deriving a *hES* cell line for any purpose.

- ❖ Specific justification would be required to consider the request for approval by the NAC-SCRT through IEC and IC-SCRT.
 - ❖ It would be required to establish that creation of zygote is critical and essential for the proposed research, and no other alternative will serve the purpose.
 - ❖ Informed consent procedure for donation of ova, sperm, somatic cell or other as detailed in these guidelines would need to be followed.
2. Clinical trials sponsored by multinationals, involving stem cell products imported from abroad. Such collaboration shall require prior approval of the NAC-SCRT through IC-SCRT, IEC, DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC)
 3. Research involving introduction of hES/hEG/hSS cells into animals, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into non-human animal tissues.
 - ❖ If there is a possibility that human cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be strong. The animals derived from these experiments shall not be allowed to breed.
 - ❖ Such proposals would need approval of the NAC-SCRT through Institutional Animal Ethics Committee (IAEC) and IC-SCRT.
 4. Studies on chimeras where stem cells from two or more species are mixed and introduced into animals, including primates, at any stage of development viz., embryonic, fetal or postnatal, for studies on pattern of development and differentiation.
 5. Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

Prohibited Areas of Research

1. Any research related to germ line genetic engineering or reproductive cloning.
2. Any in vitro culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier.
3. Transfer of human blastocysts generated by SCNT or parthenogenetic or androgenetic techniques into a human or non-human uterus.
4. Any research involving implantation of human embryo into uterus after in vitro manipulation, at any stage of development, in humans or primates.

5. Animals in which any of human stem cells have been introduced at any stage of development should not be allowed to breed.
6. Research involving directed non-autologous donation of any stem cells to a particular individual is also prohibited.

Research Using Umbilical Cord Blood Stem Cells

Cord blood stem cell banking is permissible. All Cord blood banks have to be registered with the Drug Controller General of India (DCGI) as per the guidelines of blood banks. Purpose of banking should be clearly explained to couples interested in storing cord blood. The ethical issues include concern about ownership and risk of transmission of potential genetic disorders, besides other general issues of confidentiality, justice and beneficence. When it comes to registries and banking, the commercial aspects pose additional problems. The advertising involved in getting and collecting samples, conflict of interest, utility of samples, accessibility and affordability should also be carefully looked into. The following points should be considered while collecting umbilical cord blood as specified in "Ethical Guidelines for Biomedical Research in human Subjects" 2000 of ICMR:

1. No harm should occur to the fetus or the neonate.
2. Exact timing of the clamping of the umbilical cord should be defined in the clamping protocol.
3. Parents should be informed regarding risks and benefits involved.
4. Free informed consent from parents' should be obtained. If there is disagreement between the parents, the mother's wish shall prevail.
5. ID card should be issued for voluntary donation to enable access/benefit in future in case required for self/relative.
6. Standard Operative Procedures for collection, transportation, processing, storage, pre- preservation and clinical use should be laid down with approval of the IC-SCRT and IEC.
7. Detailed protocol for isolation and characterization of mesen chymal and/or stem cells should be approved by IC-SCRT and IEC.
8. Period of preservation for self- use later in life should be prescribed.
9. Detailed protocol for clinical use of stem cells should be in place.
10. Follow up plans for assessing safety and efficacy of cord blood stem cell therapy should be incorporated.

Research Using Fetal Stem Cells/Placenta

All proposals involving foetuses or foetal tissue, for research or therapy are permissible. However,

1. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.
2. Consent to have a termination of pregnancy and the donation of fetal material for purpose of research or therapy should be taken separately.
3. The medical person responsible for the care of the pregnant woman planning to undergo termination of pregnancy and the person who will be using the fetal material should not be the same. The women shall not have the option to specify the use for a particular person or in a particular way.
4. The identity of the donor and the recipient should be kept confidential.

Approval for Derivation of a New *hES* Cell Line

Whether new *hES* cell lines are derived from spare embryos or embryos created for the purpose, such research shall consider the following:

1. that the goal of research cannot be achieved in any other way even by research on adult stem cells;
2. there is no existing stem cell line that would be suitable for the purpose;
3. will increase knowledge about embryo development and causes of miscarriages and birth defects;
4. increasing the number of ethnically diverse *hES* cell lines;
5. advance knowledge, which can be used for infertility treatment or improving contraception techniques;
6. increase knowledge about serious diseases and use this knowledge to develop treatments including tissue therapies;
7. develop methods of therapy for diseased or damaged tissue or organs;
8. justification for the minimum number of embryos/ blastocysts required must be clearly defined;
9. research teams involved should have appropriate expertise and training in derivation and culture of human/non-human ES cells.

This however is not an exhaustive list.

Responsibility of Investigators and Institutions

1. The investigators and the institutions where the stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. In particular, scientists whose research involves *hES* cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for SCNT, and be sensitive to public

concerns about research that involves human embryos.

2. Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of hES cells.
3. Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for its functioning.

International Collaboration

4. National guidelines of respective countries should be followed.
5. Collaboration will be permitted as per existing procedures of funding agencies (DBT, ICMR etc) or the Health Ministry's screening committee, even if no funding is involved after the joint proposal with appropriate MOU is approved by NAC-SCRT.
6. Export of cell lines will be covered under GOI guidelines for Transfer of Biological materials.
7. If there is a conflict between scientific and ethical perspectives of the International collaborator and the domestic side then Indian Ethical guidelines or law will prevail.

Commercialization and Patent Issues

Research on stem cells/lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on merits of each case. If the IPR is commercially exploited, a proportion of benefits shall be ploughed in to the community, which has directly or indirectly contributed to the IPR. Community includes all potential beneficiaries such as patient group, research group etc.

Detailed guidelines have been provided in a separate booklet on 'Stem Cell research and Therapy' as national guidelines.

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) from the late '70s has not only enhanced the possibility of pregnancy but have also made women conceive in situations which would not have been possible decades 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. 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. National guidelines for Accreditation, Supervision and Regulation of ART Clinics have been formulated by ICMR in 2005 to provide optimum benefit of these newer technologies to appropriate persons by skilled team of experts, at affordable health and economic cost, in all public and private facilities in our country. A national registry pertaining to all centres that are accredited by the licensing authority shall be maintained at ICMR and shall contain records of treatment cycles and outcome. Equally important are issues related to the conduct of research with material obtained as byproducts from the clinical activity. These include the follicular fluid, oocytes, spare embryos, semen samples which can be used by researchers in basic or molecular science.

Definition

This includes fertilization involving manipulation of gametes outside the human 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, anaesthetic procedures, and invasive procedures like laparoscopy, aspiration of ovum *etc.*
- ❖ They should 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, possible side-effects (e.g. of the drug used) and the risks of treatment to the women and the risks associated with multiple pregnancy.
- ❖ They should also be explained that –
 - i. there is no guarantee on the success / failure of the procedure and the need to reduce the number of viable foetuses, in order to ensure the survival of at least two fetuses;
 - ii. there may be possible disruption of the patient's domestic life which the treatment may cause;
 - iii. about the possible deterioration of gametes or embryos associated with

- storage, and possible pain and discomfort;
- iv. about the cost (with suitable break-up) to the patient of the treatment proposed and of an alternative treatment, if any (there must be no other "hidden costs").
 - v. about the importance of informing the clinic of the result of the pregnancy in a pre-paid envelope; and
 - vi. about the advantages and disadvantages of continuing treatment after a certain number of attempts.
- ❖ 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 afresh in writing on the above issues at every stage.
 - ❖ Consent may be withdrawn at any time before implantation.
 - ❖ Specific consent must be obtained from couples who have their gametes or embryos frozen, with regard to what should be done with them in case of death, or if any of the parties becomes incapable of varying or revoking her or his consent.
 - ❖ Investigators should clarify the ownership of the embryos that they belong to the genetic mother or the laboratory. Abortions should never be encouraged for research purposes.
 - ❖ No AR procedure will be done without the consent of the spouse or partner.
 - ❖ There is no ethical objection at the moment for IVF or any other related procedure for research or for clinical application.

Selection of Donor : The semen bank 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 and C, 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 for at least 10 years in order to trace her / him 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.
- ❖ Any information about clients and donors must be kept confidential. No information about the treatment of couples provided under a treatment agreement may be disclosed to anyone other than the accreditation authority or persons covered by the license, except with the consent of the person(s) to whom the information relates, or in a medical emergency concerning the patient, or a court order. It is this person(s)' right to decide what information will be passed on and to whom.
- ❖ 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.

Gametes and embryos : 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 on embryo up to **14 days' growth** 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.

With regard to use of gametes or embryo -

- ❖ no woman shall be treated with gametes or embryos derived from gametes of more than one man or woman;
- ❖ no ART clinic shall mix semen from two individuals before use;
- ❖ no ART clinic shall provide a couple with embryo of desired sex;
- ❖ no gametes shall be stored for more than 10 years;
- ❖ an embryo shall be stored for not more than five years;
- ❖ sale, transfer or use outside India is prohibited;
- ❖ the donor shall relinquish all parental rights over the child which may be conceived from her or his gamete.

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. The choice is more than the absence of legal prohibition or coercion and 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,

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research on cloning with intent to produce an identical human being, as of today, is prohibited.

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. Surrogacy is an arrangement in which a woman agrees to carry a pregnancy that is genetically unrelated to her and her husband, with the intention to carry it to term and hand over the child to the genetic parents with whom she enters into a contract for surrogacy.
2. It should be resorted to only when it is coupled with authorized adoption wherever applicable.
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. Genetic parent's claim for the custody of the child in its the best interest through adoption would be, to establish that the child is theirs through genetic (DNA) fingerprinting, of which the records will be maintained in the clinic, .
5. Surrogacy 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. Abortion under the Abortion Law on the medical ground should be inviolate right of the surrogate and the genetic parents have no claim over the amounts already paid.
8. The contract for surrogacy is legally enforceable. It shall provide for all expenses related to medical management during pregnancy, delivery, and immediate postpartum period till adoption and should be borne by the intending couple. Monetary compensation for agreeing to be the surrogate may also be specified in

the agreement.

9. Information about the surrogate shall be kept confidential except with the consent of the person whom the information relates to or by court order.
10. ART clinics shall not provide surrogate mothers or information on potential surrogate mothers to couples or individuals.

Preservation, Utilisation and Destruction of Embryos:

- ❖ Research is prohibited on embryos **of more than 14 days after fertilization** 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 practiced 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 if existing law does not permit it.

Right of Children / Parents:

- ❖ A child born through ART shall be presumed to be the legitimate child of the couple, having been born in wedlock and with the consent of both the spouses. Therefore, the child shall have a legal right to parental support, inheritance, and all other privileges of a child born to a couple through sexual intercourse.
- ❖ Children born through use of donor gametes and their social/adopted parents have the right to know the medical or genetic information about the genetic parents that may be relevant to the child's health.
- ❖ The child's has a right to seek information on genetic parent(s) or surrogate mother (including a copy of the DNA fingerprint, if available) on reaching 18 years, except for information on the personal identity of the gamete donor or the surrogate mother unless when required in threatening medical conditions.
- ❖ The couple is not obliged to provide the information to the child on their own when s/he reaches the age of 18, but no attempt must be made by the couple to hide this information from the child should an occasion arise when this issue becomes important for the child.

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

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