Draft
National Ethical Guidelines

for

Biomedical and Health Research involving Human Participants

Indian Council of Medical Research

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CONTENTS

Preamble

The code of conduct for physicians was well laid out in the Indian traditional systems of medicine and 'do no harm' was the underlying universal principle besides other principles applicable to the existing culture and the class systems of the society. The Indian Council of Medical Research (ICMR) issued the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980. Due to rapid advances in biomedical science and technology, a new ethical dimension necessitated further updation of these guidelines. Subsequently the 'Ethical Guidelines for Biomedical Research on Human Subjects' was released in 2000, followed by another revision in 2006 as 'Ethical Guidelines for Biomedical Research on Human Participants'. ICMR in the year 2007 jointly brought out a guideline with the Department of Biotechnology (DBT) on 'Guidelines for Stem Cell Research and Therapy', which was further revised in 2013 as the 'National Guidelines for Stem Cell Research'.

The Nuremberg Code (1947) was the first International document on the ethics of research in human subjects and highlighted the essentiality of obtaining voluntary consent. In 1964, the World Medical Association formulated guidelines on conducting research in humans, known as the Declaration of Helsinki. This has undergone seven revisions with the latest version issued in October, 2013 at Fortaleza, Brazil.

In 1979, the 'Belmont Report' (USA) released by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research for the first time enunciated the three basic ethical principles for research involving human subjects: Respect for Persons, Beneficence and Justice. The principle of Non Maleficence was added to the ethical principles later (1994). The Department of Health and Human Services (DHHS) of US released the Federal Policy for the protection of Human subjects as the "Common Rule" in 1991.The International Conference on Harmonization (ICH) brought out the Good Clinical Practice Guidelines E6 (R1) in 1996. The National Bioethics Advisory Commission, USA (2001), The Council for International Organizations of Medical Sciences (CIOMS), Geneva (2002) and the Nuffield Council of Bioethics, UK (2002) released guidelines relevant to research in developing countries. UNESCO's Universal Declaration on Bioethics and Human Rights (2005) and other international instruments on human rights further defined the universal codes of ethics to be adopted by the Member countries. Some of these guidelines are currently undergoing revision. The ICMR Ethical Guidelines have adapted

important guidance points from these International guidelines in accordance with the socio-cultural milieu of our country.

The socio-cultural ethos in India and its varying standards of health care today pose unique challenges to the application of universal ethical principles to biomedical and health research. The last decade has seen emerging ethical issues necessitating further revision as 'National Ethical Guidelines for Biomedical and Health Research on Human Participants 2016'. These Guidelines have covered some newer areas like Social and Behavioural Sciences, Responsible Conduct of Research and New Technologies, while a few other specialised areas like Informed Consent process, Biological Materials and Datasets, Vulnerability, International Collaboration, Research during Humanitarian Emergencies and Disasters have been expanded.

Scope

These guidelines are applicable to all biomedical, socio-behavioural and health research conducted in India involving human participants, their biological material and data. The PURPOSE of such research:

i. SHOULD be directed towards enhancing knowledge about the human condition in relation to its social and natural environment.
ii. CONDUCTED under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subjected 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.
iii. MUST be subjected to a regime of EVALUATION at all stages of the proposal i.e., research design and conduct with the objectives in mind, the means by which they are sought to be achieved, the anticipated benefits and harms, declaration of results and use of the results thereof.

1. Statement of General Principles on Ethical Considerations involving Human Participants

1.0 Research pertains to a broad range of scientific enquiry on human participants for developing generalisable knowledge that improves health, increases understanding of disease and is justified ethically by its social value. Every research has some inherent risk and probabilities of harm to participants/community. Therefore, protection of participants should be built in to the design of study. Do no harm (non maleficence) has been the underlying universal principle in all systems of medicine around the world for guiding health care. While conducting biomedical and health research, the four basic principles namely; **Respect for Persons (Autonomy), Beneficence, Non Maleficence** and **Justice** have been enunciated to govern research. These four basic principles have been expanded into 12 general principles described below, which are to be applied to all biomedical and health research involving **human participants** or research using their **biological material or data.**

1.1 General Principles

1.1.1 **Principle of biomedical and health research** whereby the rights, safety and well-being of research participants are the most important considerations.

1.1.2 **Principle of essentiality** whereby the research entailing the use of human participants is considered to be essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research. This should be duly vetted by an Ethics Committee (EC) independent of the proposed research.

1.1.3 **Principle of voluntariness** whereby the right of the participant to agree or not to agree to participate in research or to withdraw from research at any time is always respected. The informed consent process will ensure that this right is safeguarded.

1.1.4 **Principle of non-exploitation** whereby the research participants are equitably selected so that the burdens and benefits of the research are distributed fairly and without arbitrariness or discrimination. Sufficient safeguards shall be ensured to protect the vulnerable groups.

1.1.5 **Principle of ensuring privacy and confidentiality** whereby the identity and records of the human participants of research are kept confidential and access is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive etc) the information can be breached for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant.

1.1.6 **Principle of risk minimization** whereby due care is taken by all stakeholders (including but not limited to investigators, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and if any harm occurs appropriate care is given.

1.1.7 **Principle of Professional Competence** whereby the research is planned, conducted, evaluated and monitored at all times by persons who are competent and have the appropriate and relevant qualification and/ or experience and/ or training.

1.1.8 **Principle of Accountability** whereby all stakeholders involved in research, are accountable for their actions. The research is conducted in a fair, honest, impartial and transparent manner. The related records, data and notes should be retained for required period for possible external scrutiny.

1.1.9 **Principle of the Maximization of Benefit** whereby due care is taken that the research is designed and conducted in such a way so as to maximize the benefits to the research participants directly or indirectly and/ or to the society.

1.1.10 **Principle of Institutional Arrangements** whereby institutions where the research is being conducted should have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.

1.1.11 **Principle of Transparency** whereby the research plan and the outcomes emanating through such research are brought into the public domain through reports, registries, scientific and other publications while safeguarding the right to privacy of participants. All stakeholders involved in research should disclose any conflict of interest if any, and manage them appropriately.

1.1.12 **Principle of Totality of Responsibility** whereby the professional and moral responsibilities complying to ethical guidelines and related regulations is binding on all stakeholders directly or indirectly.

2. General Ethical Issues

2.0 All research involving human participants should be conducted in accordance with the four basic ethical principles as outlined in section 1.0. The researcher and her/ his team are responsible for protecting the rights, safety and well-being of the participants enrolled in the study. She/ he should have the appropriate qualifications and competence in biomedical research methodology and should be aware of and comply with the scientific, medical, ethical, legal and social requirements of the research proposal. The ECs have the responsibility to ensure that the research is conducted in accordance with the above mentioned principles.

2.1 Informed Consent Process

Informed consent protects the individual's autonomy to freely make a choice whether to participate in research or not. The process involves 3 components - providing relevant information, its comprehension and voluntariness.

The informed consent document (patient/ participant information sheet and informed consent form) should have the required elements. It should be reviewed and approved by the EC before enrollment of the participants. For all biomedical research involving human participants, it is the primary responsibility of the researcher to obtain the written, informed consent of the prospective participant. In the case of an individual who is not capable of giving informed consent, the consent of a legally acceptable/ authorised representative should be obtained. In certain circumstances audio/ audio-visual recording of the informed consent process may be required, e. g., in case of certain regulatory clinical trials.

Oral Consent/ waiver of consent/ reconsent may be obtained under certain conditions after due considerations and approval by the EC. Refer to section 4 on Informed Consent process for further details.

2.2 Payment For Participation

2.2.1 Participants may be reimbursed for expenses incurred in connection with their participation in research if required, e.g., for travel related expenses. Participants may also be paid for inconvenience incurred, time spent and other incidental expenses in either cash or kind or both as deemed necessary, e.g., loss of wages, food supplies etc.

2.2.2 The participant should not be made to pay extra for any of the research related activities including investigations, patient work up, any interventions and associated treatment.

2.2.3 They may also receive additional medical services at no cost.

2.2.4 When the LAR (Legally Acceptable Representative) is giving consent on behalf of a participant, no payments should be offered that may become an undue inducement except a reimbursement of the travel and other incidental expenses incurred for the participation in the research.

2.2.5 ECs must review and approve the payments (in cash or kind or both) and the processes involved, and also determine that this does not amount to 'undue inducement'.

2.3 Privacy and Confidentiality

Privacy is the right of an individual to control or influence what information can be collected and stored and by whom and to whom that information may be disclosed to or shared with. Confidentiality is the obligation of the researcher/ research team/ organisation to the participant to safeguard the entrusted information. It includes obligation to protect information from unauthorised access, use, disclosure, modification, loss or theft.

2.3.1 The investigator should safeguard the confidentiality of the participant's information and related research data.

2.3.2 The limits of the researchers' ability to ensure strict confidentiality must be explained to the participant.

2.3.3 Any publication arising out of research should consider upholding the privacy of the individuals by not publishing any photographs or revealing the individual's identity. If this is required for scientific reasons a specific re-consent would be required.

2.3.4 Some information may be sensitive and should be protected to avoid stigmatisation and/ or discrimination.

2.3.5 While conducting research with stored biological samples or medical records, coding or anonymisation of personal information should be done and access should be limited.

2.3.6 Data of individual participants/ community may be disclosed under the following circumstances (Table 2.1) –

Table 2.1

1. Under the orders of a court of law;
2. Threat to a person's life or community;
3. Public Health risk which would take precedence over personal right to privacy;
4. Serious adverse reactions which are required to be communicated to regulatory authority;
5. Requirements of government agencies or regulatory authorities.

2.4 Benefit-Risk Assessment

Benefits refer to any sort of favourable outcome of the research to the individual, community or society which can be direct or indirect and should justify the risks. Risk can be discomfort or harm which could be physical, psychological, social, economical or legal. It is defined as an aggregate of the probability and magnitude of injury or harm or discomfort anticipated in research.

2.4.1 All Research has potential benefits and risks, which can be at individual, societal or at community level. Mechanisms should be in place to maximize benefits and minimize risks to participants.

2.4.2 Researcher should ensure that reasonable benefit-risk ratio should be an integral part of the research design and state the plans to minimize the risks and discomforts and maximize the benefits, if applicable.

2.4.3 EC should assess the inherent benefit-risk ratio, plans for minimizing the risk and discomfort and decide on the merit of the research before approving it.

2.5 Compensation for Research Related Harms

Research participants who suffer from direct physical, psychological, social, legal or economic harm 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 such as medical care, referrals, clinical facilities etc. In case of death, their dependents are entitled to financial compensation. The research proposal should have an in-built provision for mitigating research related harms.

2.5.1 It is the responsibility of the investigator to report to the EC all serious adverse events (SAE) occurring within a period of 7 days along with a report on relatedness of

these to the research. In case of any death reporting should be done within 24 hours of occurrence or information.

2.5.2 It is the responsibility of the EC to review the relatedness of the SAE to the research as reported by the investigator and determine the quantum of compensation to be paid for research related injury or harm.

2.5.3 All adverse events (AE) should be recorded and reported to the EC according to a pre-planned timetable, depending on the risk level and as recommended by the EC.

2.5.4 In investigator initiated research and student research or when the research is funded, by the granting agencies, investigator/ institution where the research is conducted, becomes its sponsor.

2.5.4.1 The institution should have an in-built mechanism to be able to provide for compensation e.g. through a corpus fund created in the institution.

2.5.4.2 It is the responsibility of the host institution to provide compensation and/ or insurance for research related injury or harm as decided by the EC. Every institution should provide/ create funds for such purposes.

2.5.4.3 In the applications for research grants to funding agencies - National or International, Government/ Non Government agencies - the investigator should keep budgetary provision for insurance cover and/ or compensation.

2.5.4.4 Participants may be offered free medical care of co-morbid conditions (ancillary care) provided it does not amount to undue inducement.

2.5.5 For other sponsored research, it is the responsibility of the sponsor (Pharmaceutical Company, a Government or a Non Governmental organisation, National or International/ bilateral/ multilateral donor agencies/ institutions) to include in the budget to cover for insurance or compensation for research related injury or harm as decided by the EC.

2.6 Conflict of Interest

Conflict of Interest (COI) is a set of conditions where professional judgment concerning a primary interest like participants welfare or the validity of research tends to be unduly influenced by a secondary interest, non-financial (personal, academic or political) or financial. COI can be at the

level of researchers, EC members, institutions or sponsors. Some or the other COI are always present in research, however it is important to declare these at the outset and properly manage them.

2.6.1 Research institutions must develop and implement policies and procedures to identify, mitigate conflicts of interest and educate their staff about such conflicts.

2.6.2 Researchers must ensure that the materials submitted to EC include a disclosure of interests that may affect the research.

2.6.3 ECs must evaluate each study in light of any disclosed interests and ensure that appropriate means of mitigation are taken.

2.6.4 Conflict of interest within the ECs should be declared and managed in accordance with standard operating procedures (SOPs) of that EC.

2.7 Distributive Justice

2.7.1 Efforts must be made to ensure that individuals or communities invited for research are selected in such a way that the burdens and benefits of research are equitably distributed.

2.7.2 Those who are economically or socially disadvantaged or with any disability should not be used to benefit others who are better off than them.

2.7.3 Research should not lead to social, racial or ethnic inequalities.

2.7.4 Plans for benefit sharing with participants, donors of biological materials or data should be included in the study which has potential for commercialization.

2.7.5 This should be decided a priori in consultation with the stakeholders before it is evaluated by the ECs.

2.8 Selection of Vulnerable and Special Groups as Research Participants

Vulnerable groups and individuals “may have an increased likelihood of being wronged or of incurring additional harm”. In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests.

2.8.1 Characteristics that make individuals vulnerable are: Clinical conditions - Age and Medical condition or Situational conditions including but not limited to: economically

disadvantaged, socially disadvantaged individuals e.g. ethnic or religious groups, individuals/communities which have hierarchical relationships, institutionalised persons, humanitarian emergencies, language barrier and cultural differences.

2.8.2 In general, these participants should be included in research only when the research is directly answering the health needs or requirements of the group. However, vulnerable populations have an equal right to be included in research so that benefits accruing from the research apply to them too.

2.8.3 The EC should make a determination on vulnerability and ensure that additional safeguards and monitoring mechanisms are in place.

Refer to section 5 on Vulnerability for further details.

2.9 Community Engagement

Community can be defined as a group of people sharing the same geographical location, beliefs culture, age, gender, profession, lifestyle, or disease etc. Community should be meaningfully engaged before, during and after the research to mitigate culturally sensitive issues and ensure more responsiveness to their health needs and requirements.

2.9.1 Community can be engaged in many ways and can provide valuable opinion whenever research involves a particular community.

2.9.2 Community advisory board/ group (CAB/ CAG) can act as an interphase between the community (from which participants are to be drawn), the researchers and the concerned EC. Members from the community can also be represented in the EC as a member/ special invitee.

2.9.3 Community engagement does not replace individual informed consent. It ensures that 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.

2.9.4 After the study is completed, the community representative can help in dissemination of the results to the entire community.

Refer to section 7 on Epidemiological and Public Health Research and Section 8 on Research in Social and Behavioural Sciences for further details.

2.10 Post Research Access and Benefits Sharing

The benefits accruing from research should be made accessible to individuals, communities and populations whenever feasible. Sometimes more than the benefit to the individual participant, the community may be given benefit in an indirect way through improving their living conditions, establishing counselling centres, clinics or schools, and giving education on good health practices.

2.10.1 Efforts should be made to communicate the research findings of the study back to the individuals/ communities where ever feasible.

2.10.2 The research team should make plans for post research access and sharing of benefits (academic, intervention) with the participants.

2.10.3 Post-research access arrangements or other care must be described in the study protocol so that the EC may consider such arrangements during its review.

2.10.4 EC should consider the need for an *a priori* agreement between the investigators and sponsors regarding all the points mentioned above (from 2.10.1 to 2.10.3).

2.10.5 The studies with restricted scope e.g. student projects, post study benefit to the participants may not be feasible but conscious efforts should be made by the institution to take steps to continue to support and give better care to the participants

3. Ethical Review Procedures

3.0 It is necessary that all proposals on health, biomedical and behavioral research should be reviewed and approved by an appropriately constituted EC to safeguard the rights, safety and well-being of all research participants. ECs are entrusted not only with the initial review of research proposals prior to their initiation, but also have a continuing responsibility of regular monitoring of the approved research to ensure ethical compliance during the conduct of research. The EC should be competent and independent in its functioning.

3.0.1 The EC is responsible for scientific and ethical review of research proposals.

3.0.2 The Institution is responsible for establishing an EC to ensure an appropriate and sustainable system for quality ethical review and monitoring.

3.0.3 The Institution is responsible to make available required logistical support e.g. infrastructure, staff, space, funds and protected time for the Member Secretary.

3.1 Terms of Reference for Ethics Committees

3.1.1 The Terms of Reference for the EC and members should be clearly specified by the Institution in the EC Standard Operating Procedures (List of SOPs: given in Annexure 1).

3.1.2 Every EC should have written SOPs according to which the Committee should function. EC can refer to ICMR guidelines in preparing the SOP for all biomedical research and for industry sponsored drug and devise trials they can refer to CDCSO guidelines for relevant areas. The SOPs should be updated periodically based on the changing requirements. A copy of the latest version of SOPs should be made available to each member and they should be trained on the SOPs. The SOPs must be available in the Secretariat of the EC as hard and soft copies.

3.1.3 The scope of EC should be stated.

3.1.4 The tenure and renewal policy of the EC should be predefined.

3.1.5 The EC members should not have any known record of misconduct.

3.1.6 The EC should be registered with the relevant regulatory authorities as per updated requirements, e.g., ECs approving regulatory clinical trials should be registered with CDSCO.

3.2 Special Situations

3.2.1 Institutions can have multiple EC to review large number of research proposals/ different kinds of research. Each EC should function as a stand-alone committee which should follow all the SOPs and TORs of that institution.

3.2.2 Institutions could have subcommittees e.g., SAE subcommittee, Data Safety Monitoring Committee or expedited review committee. These should be part of the main committee and comprise chairperson/ member secretary and appropriate designated 1-2 members of the main EC. These subcommittees should report to the concerned main EC.

3.2.3 If an Institution wishes to utilize the services of the EC of another Institution relevant requirements must be fulfilled before they do so (Table 3.1) -

Table 3.1

1.	The institution should provide a "No Objection Certificate" and agree to be overseen by the other EC.
2.	Enter into an MoU with that institute.
3.	EC of the other institute should have access to all research records including the source documents, research participants and be able to monitor the research.

3.2.4 Stem cell proposals should be first reviewed and approved by Institutional Committee for Stem Cell Research (ICSCR) before they are submitted to the EC for consideration.

3.2.5 There are also independent ethics committees (Ind EC) functioning outside institutions for researchers who have no institutional attachments.

3.2.5.1 A registered legal entity must be first established, governed by individuals who will oversee and monitor the functioning of the Ind EC.

3.2.5.2 The Ind EC should function according to SOPs that follow national guidelines for functioning of ECs.

3.2.5.3 The Ind EC should not oversee proposals from investigators of/ affiliated to institutions, which have own ECs.

3.3 Composition of EC

3.3.1 The ECs should be multi-disciplinary and multi-sectoral.

3.3.2 There should be adequate representation of age and gender.

3.3.3 Preferably 50% of the members should be non-affiliated or from outside the Institution.

3.3.4 The number of members in an EC should preferably be between 7 and 15.

3.3.5 The EC should have a mix of medical and non-medical members.

The composition, affiliations, qualifications, roles and responsibilities may be as follows (given in Table 3.2)

Table 3.2

S. No.	Members of EC	Affiliation	Qualifications	Roles & Responsibilities of EC Members
1.	Chairperson/ Vice Chairperson (optional)	Non-institutional (Should not be currently affiliated to the Institution)	• An eminent person from any background • Preferably having experience of serving on an ethics committee	• Conduct EC meetings and accountable for functioning of the committee • Ensure active participation of all members (particularly non-affiliated, non-medical) in all discussions and deliberations. • Handling of complaints against Investigators, EC members, conflict of interest issues and requests for use of EC data etc. • Ratify minutes of the previous meetings. • Review SAE reports with causality assessment. • In case of anticipated absence of both Chairperson and Vice Chairperson at a planned meeting, the Chairperson should nominate a committee member as Acting Chairperson or the members present may elect an Acting Chairperson on the day of the meeting. The Acting Chairperson should be a non-affiliated person and will have all the powers of the Chairperson for that meeting.
2.	Member Secretary/	Institutional	• Should be a staff member of the	• Organize an effective and efficient procedure for receiving, preparing,

	Alternate member Secretary (optional)		institution. • Should have knowledge and experience in clinical research and ethics, have personal interest and good communication skills. • Should be able to devote adequate time to this activity which should be protected by the institution.	circulating and maintaining each proposal for review. • Schedule EC meetings, prepare the agenda and minutes. • Organise EC documentation, communication and archival. • Arrange for training of EC secretariat and EC members. • Ensure SOPs are updated as and when required. • Ensure adherence of EC functioning as per SOPs. • Prepare for and respond to audits and inspections.
3.	One - two persons from Basic Medical Science areas (for drug trials preferably Pharmacologist – Medical/ Non-medical)		• should be individuals with scientific qualification and expertise.	• Declare any conflict of interest to the Chairperson, if any, at each meeting which should be recorded in the minutes. • Review and attend EC Meetings and participate in discussions and deliberations. • Review the progress reports and final reports. • Review Serious Adverse Event reports and recommend appropriate action(s). • Carry out monitoring visits at study sites as and when needed. • Maintain confidentiality of the documents and deliberations of EC meetings. • Participate in continuing education activities in research ethics and get updated on relevant guidelines and regulations.
4.	One - two Clinicians		• should be individuals with qualification and expertise.	
5.	One Legal Expert		• should have a basic degree in law	
6.	One Social Scientist		• should be individuals with social/ behavioral science qualification and expertise	
7.	One Philosopher/ Ethicist/ Theologian		• should be individuals with qualification, training and/ or expertise and be sensitive to the local cultural and moral values.	
8.	One Lay Person from the community		A literate person from the public or community who is • Not qualified in medical/ health	

			sciences • not pursued a medical science/health related career in the last 5 years • is aware of the local language, cultural and moral values of the community. • Indulges in social and community activities • is willing to read and review the proposals specifically the informed consent document,	

3.3.6 The Quorum should be as specified in the Table 3.3.

Table 3.3

S. No.	Quorum Requirements
1.	The quorum of the EC should be a minimum of five or 50% percent of the members plus one whichever is more.
2.	No decision is valid without fulfilment of the quorum.
3.	The quorum should comprise of both medical and non-medical members.
4.	Minimum one non-affiliated member should be part of quorum.
5.	Quorum for regulatory clinical trials should be as per CDSCO requirements.

3.3.7 The Head of the Institution should not be part of the EC to maintain the independence and should act as an appellate authority in case of disputes.

3.3.8 The EC can also have a set of alternate members who can be invited as members with decision-making powers to meet the quorum requirements. These members have the same terms of reference and attend the meeting in absence of regular members.

3.3.9 The EC can maintain a panel of Subject Experts who are consulted for their subject expertise, for instance, a pediatrician for pediatric research, a cardiologist for research

on cardiac disorders etc. They may be invited to attend the meeting for opinion on specific proposal but will not have voting rights.

3.3.10 EC may include a representative from specific patient groups in the Committee as a member of EC/ special invitee, for opinion on specific proposal, for example HIV, genetic disorders, cancer etc but will not have voting rights.

3.4 Terms of Reference for EC members

3.4.1 The Head of the Institution should appoint all EC members, including the Chairperson.

3.4.2 The appointment letter issued to all members should specify the terms of references. The letter head issued by the Head of the Institution should include at the minimum, the following -

- Role and responsibilities of the member in the Committee
- Duration of appointment
- Conditions of appointment

3.4.3 Generally the term of membership may be for 2-3 years. The duration could be extended for further terms as specified in SOPs and a defined percentage of members could be changed on regular basis.

3.4.4 Members to be appointed on the EC should be willing to fulfil the EC requirements (given in table 3.4).

Table 3.4 Examples of EC requirements

S. No.	EC Requirements
1.	Submit a recent signed CV, training certificates on research ethics courses and GCP guidelines as required.
2.	If members are not trained in research ethics or GCP at the time of induction as member in the EC, the member must undergo training and submit training certificates within 6 months (or as per institutional policy) of appointment
3.	Be willing to place her/ his full name, profession and affiliation to the EC in the public domain.
4.	Sign a Confidentiality Agreement
5.	Read, understand, accept and follow the Conflict of Interest policy of EC and declare the Conflict of Interest if any at appropriate time.
6.	Willing to undergo training or update programmes during the tenure as EC member.
7.	EC members should be aware of relevant Guidelines and Regulations.

3.5 Criteria for selection of members of EC should be specified in SOPs

3.5.1 Members should be selected in their personal capacities based on their qualifications, experience, interest, commitment and willingness to volunteer the necessary time and effort for the EC. (Refer Table 3.2 for qualifications and roles and responsibilities of EC members).

3.5.2 Members are appointed in the EC for a particular role. They cannot substitute for any other absent member's role for a meeting.

3.6 Training

3.6.1 Members should be trained in research ethics, EC functions, SOPs and should be conversant with ethical guidelines and relevant regulations of the country.

3.6.2 EC members should undergo initial and continuing training in research ethics, regulatory requirements if any and applicable EC SOPs.

3.6.3 Any change in the relevant guidelines or regulatory requirements should be brought to the attention of all EC members.

3.6.4 EC members should be aware of local, social and cultural norms and emerging ethical issues.

3.7 Roles and Responsibilities of Ethics Committee

3.7.1 The basic responsibility of an EC is to ensure protection of the rights, safety and well being of the research participants.

3.7.2 The EC will perform this function through competent initial and continuing review of all scientific, ethical, medical and social aspects of project proposals received by it in an objective, timely and independent manner.

3.7.3 ECs should ensure the scientific soundness of the proposed research even if a scientific review committee has previously ratified it.

3.7.4 The AE/ SAE should be reviewed by EC and needful suggestions should be made to PI. EC may suggest appropriate compensation, wherever required.

3.7.5 Ensure that universal ethical values and international scientific standards are followed in terms of local community values and customs.

3.7.6 Assist in the development and education of the research community responsive to local health care requirements.

3.7.7 Responsibilities of Members should be clearly defined (details in Table 3). The SOP's should be given to the members at the time of their appointment.

3.7.8 Secretariat should support the Member Secretary and Alternate Member Secretary (if applicable) in all their functions and should be trained in documentation and filing procedures.

3.8 Submission and Review Procedures

3.8.1 Investigators should submit proposals to the Secretariat for review as per EC SOPs and timelines in the prescribed format along with required documentation. EC should prepare a checklist for the same (given in Table 3.5).

Table 3.5 Documents required for proposal submission

S. No.	Required Documents& Checklist
1.	Covering letter to the Member Secretary
2.	Project submission application form for initial review
3.	The correct version of the research proposal (see item 29)
4.	The correct version of the Informed consent Document (ICD) in English and local language(s)
5.	Brief Curriculum Vitae of all the study investigators (as specified in the SO
6.	Details of Funding agency/ Sponsor and fund allocation (if applicable)
7.	Amendments to the study (if any)
8.	Translation and Back translation certificates (if applicable)
9.	Amendments to the ICD (if any)
10.	Case Record Form/questionnaire
11.	Recruitment procedures: advertisement, notices, letters to docto applicable)
12.	Patient instruction card, identity card, diary etc. (if applicable)
13.	Investigator Brochure (if applicable)
14.	Regulatory permissions (as applicable)
15.	Regulatory Documents as needed (e.g. Investigator's Undertaking to DCGI)
16.	Relevant Administrative approvals (as applicable),
17.	Memorandum of Understanding (MOU) in case of studies involving collaboration with other institutions (if applicable)
18.	GCP training certificate (preferably within 5 years) of Principal Investigator and study team (recommended for clinical trials)
19.	A statement on conflict of interest (COI), if any
20.	Any other research ethics / other training evidence as required as per EC S
21.	List of ongoing research studies undertaken by Principal Investigat applicable)
22.	Investigator's Brochure (as applicable for Drug/ Biologicals / Device trials)
23.	Clinical Trial Agreement between the sponsors, investigator and the Head of the Institution(s) (if applicable)

24.	Insurance policy (it is preferable to have the policy and not only the insurance certificate)for study participants indicating conditions of coverage, date of commencement and date of expiry of coverage of risk (if applicable)
25.	Indemnity policy clearly indicating the conditions of coverage, date of commencement and date of expiry of coverage of risk (if applicable)
26.	Institutional Committee for Stem Cell Research approval (if applicable)
27.	Documentation of clinical trial registration (preferable)
28.	Any additional document (s), as required by EC
29.	Protocol should include the following - a) The face page with title of project with signatures of Principal Investigator (PI) and b) Sponsor (if applicable) c) Background with rationale of why a human study is needed to answer the research question d) Clear research objectives and end points (if applicable) e) Participant recruitment procedures f) Eligibility criteria g) Detailed description of methodology of the proposed research, including sample size (with justification), type of study design (observational, experimental, pilot, randomized, blinded etc.), types of data collection, intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures if any. h) Justification for placebo, benefit-risk assessment, plans to withdraw. If standard therapies are to be withheld, justification for the same i) Procedure for seeking and obtaining informed consent with sample of patient/participant information sheet and informed consent forms in English and local languages. AV recording if applicable j) Plan for statistical analysis of the study. k) The privacy and confidentiality of the study participants. l) For research involving more than minimal risk, an account of management of such risk or injury. m) Proposed compensation and reimbursement of incidental expenses and management of research related injury/ illness during and after research period. n) Provision of Ancillary care for unrelated illness during the duration of research. o) An account of storage and maintenance of all data collected during the trial. p) Plans for publication of results - positive or negative - while maintaining confidentiality of personal information/ identity.

455

456 3.8.2 The EC Member Secretary/ secretariat shall screen the proposals for their
457 completeness and depending on the risk involved categorise them into three types,

458 namely, exemption from review, expedited review and full committee review
459 (given in Table 3.6).
460
461
462 **Table 3.6 Types of review**

S. No.	Types of Review	
1.	**Exemption from review**	Proposals that can be exempt from review include those with less than minimal risk where there are no linked identifiers, e.g. • Research conducted on data that is in the public domain for systematic reviews or meta-analyses. • Observation of public behaviour when information is recorded without linked identifiers and disclosure would not harm the interests of the observed person. • Quality control and quality assurance audits in the institution. • Comparison among instructional techniques, curricula, or classroom management methods. • Consumer acceptance studies related to taste and food quality.
2.	**Expedited review**	Proposals that pose no more than minimal risk may undergo expedited review, e.g., • Research involving non-identifiable specimen and human tissue from sources like blood banks, tissue banks, left over clinical samples. • Research involving clinical documentation materials which are non identifiable (data, documents, records) • Modifications or amendment to approved protocol including administrative changes or correction of typographical errors and change in investigator(s). • Revised proposal previously approved through expedited review, full review or continuing review of approved proposals. • Minor deviations from originally approved research causing no risk or minimal risk. • Progress /Annual reports where there is no additional risk e.g. activity limited to data analysis. • Expedited Review will be conducted by Chairperson, Member Secretary and 1- 2 designated members. • Expedited review of SAEs/ unexpected AEs will be conducted by SAE subcommittee. • The approval granted through expedited review and the decisions of the SAE subcommittee must be ratified at the next Full committee meeting.

3.	**Full Committee Review**	All research proposals presenting more than minimal risk that are not covered under exempt or expedited review should be subjected to full committee review, e.g., • Studies involving vulnerable population even if the risk is minimal. • Studies involving intentional deception of participants. • Research proposals that have received exemption from review, or have undergone expedited review/ undergone subcommittee review should be ratified by the full committee. Full committee has a right to reverse/ or modify any decision taken by the subcommittee or expedited committee. • Amendments of proposals/related documents (including but not limited to informed consent documents, Investigators Brochure, advertisements, recruitment methods etc.) involving an increase in risk. • Major Deviations and violations • Any new information that has emerged during the course of the research must also be reviewed and decisions taken if necessary to terminate the study or not in view of altered benefit– risk assessment • Research during emergencies and disasters through unscheduled meetings.

3.8.3 An investigator cannot decide that her/ his proposal falls in the exempted or expedited category without approval from the EC and may request the EC for consideration. Final decision on the type of review rests with the EC and should be on case to case basis.

3.8.4 All EC members should review all proposals. EC may adopt different procedures for review of proposals as detailed in their SOPs.

3.8.5 The EC may adopt a system for pre-meeting peer review by subject experts and obtain clarifications from the researchers before the meeting in order to save time and make the review more efficient during the full committee meeting, especially in institutions where there are no separate scientific review committees.

3.8.6 The EC may have a system of appointing primary and secondary reviewers. Member Secretary in consultation with chairperson should identify the primary and secondary reviewers for reviewing the scientific content and the informed consent document.

3.8.7 Subject experts may be identified and requested to review the proposal. These experts may be invited to the EC meeting but will not participate in the final decision.

3.8.8 The designated primary reviewers and the subject experts should conduct the Initial review as per the pre-defined study assessment form**.**

3.8.9 Review of study protocol and study related documents should be done for Social value, Scientific design and conduct of the study, Benefit-risk assessment, Selection of study population and recruitment of research participants, Payment for participation, Protection of research participants' privacy and confidentiality, Community considerations, Qualifications of Investigators and assess adequacy of study sites, Disclosure or declaration of potential conflicts of interest, Plans for Medical management of and compensation for study related injury, Review of the Informed Consent Procedure, etc. (given in Table 3.7).

Table 3.7

1.	Social Values	• The basic requirement for health research to be ethically permissible is that it must have anticipated social value. The outcome of the research should be relevant to the health problems of the society. All stakeholders, including sponsors, researchers, and ECs must ensure that the planned research has social value.
2.	Scientific design and conduct of the study	• Valid scientific methods are essential to make the research ethically viable as poor science can expose research participants or communities to risks without any possibility of benefit. • Although ECs may obtain documentation from a prior scientific review, they should also determine that the research methods are scientifically sound, and should examine the ethical implications of the chosen research design or strategy.
3.	Benefit-risk assessment	• The benefits accruing from the planned research either to the participant or to the community or society in general must justify the risks inherent in the research. • Risks may be physical, psychological, economic, or social and harm may occur either at an individual level or at the family, community or population level. It is necessary to look first at the intervention under investigation and assess its potential harms and then consider the aggregate of harms and benefits of the study as a whole • EC should review plans of risks management, including withdrawal criteria with rescue medication or procedures.

		• EC should give advice regarding minimisation of risk/ discomfort wherever applicable. • The adequacy of provisions made for monitoring and auditing the conduct of the research, including the constitution of a data safety monitoring board (DSMB) if applicable (e.g. in clinical trials)
4.	Selection of study population and recruitment of research participants	• Recruitment should be Voluntary and non-coercive. There should be fair selection of participants as per inclusion exclusion criteria. However, selection of participants should be distributive and such that not a particular population or tribe or economic group is coerced to participate or benefit. • Participant should be given option to opt out without the routine care being affected. • No individuals or group of persons must bear the burdens of participation in research without any benefits except in studies where healthy volunteers are involved. • Vulnerable group will not be recruited unless proper justification is provided.
5.	Payment for participation	• EC should review plans for payment for participation, reimbursement of incurred cost (e.g. travel or lost wages) and inconvenience. • ECs should determine that payments are not so large so as to make prospective participants take part in the research without due consideration of the risks, against their better judgement (no undue inducement).
6.	Protection of research participants' privacy and confidentiality	• ECs should examine the processes that are put in place to safeguard participants' privacy and confidentiality.
7.	Community considerations	• The EC should consider that due respect is given to the community and their interests are protected and the research addresses its needs. • EC should see that no stigma or discrimination ensues from the proposed research and harm if any should be minimised. • EC should review plans for communication of results back to the community at the end of the study. • EC may examine how the benefits of the research will be disseminated to the community.

8.	Qualifications of Investigators and assess adequacy of study sites.	• The EC should look at the suitablility of qualifications and experience of the PI to conduct the proposed research along with adequacy of site facilities for participants
9.	Disclosure or declaration of potential conflicts of interest.	• The EC should review the declaration of COI by investigator if any and suggest ways to manage them
10.	Plans for Medical management of and compensation for study related injury.	• The EC should look at the proposed plan for tackling any medical injuries or emergencies
11.	Review of the Informed Consent Process	• The process for obtaining informed consent, including the identification of those responsible for obtaining consent and the procedures adopted for vulnerable population. • The adequacy, completeness, and understandability of the information to be given to the research participants, and, when appropriate, their legally acceptable representative(s)(LARs) o Contents of the patient/ participation information sheet including the local language translations (Details in section 4 on Informed Consent process). o Back translations of the informed consent document in English wherever required. o Provision for audiovisual recording of consent process if applicable as per relevant regulations. o If consent waiver or verbal consent request has been asked for, this should be reviewed by assessing whether the protocol meets the criteria (see section of guidelines on Informed Consent)

3.9 Decision Making Process

3.9.1 All proposals that are determined to undergo full committee review must be deliberated and the decision about the proposal taken at a full committee meeting.

3.9.2 EC members should be given enough time to review the documents sent. The period may vary between 1-2 weeks except for emergency research.

3.9.3 ECs should conduct regular full board meetings to deliberate proposals at pre-decided schedule, as described in the SOPs.

3.10 Full Committee Meeting

3.10.1 A meeting will be considered valid only if the quorum is fulfilled, which should be maintained throughout the meeting.

3.10.2 The chairperson welcomes the members. The member secretary introduces the agenda**.**

3.10.3 If a member has declared a conflict of interest (COI) for a proposal then this should be submitted in writing to the Chairperson before the meeting. This should be recorded in the minutes.

3.10.4 List of absentee members should be informed.

3.10.5 Proposals should be taken up as per agenda items.

3.10.6 Ratification of the minutes of the previous meeting, exempt review, expedited review.

3.10.7 The investigator may be called in to present a proposal or provide clarifications on the study protocol that has been submitted for review.

3.10.8 The primary reviewers should brief the members about the study proposal.

3.10.9 The comments of an independent consultant (if applicable) could be presented by the Member Secretary or 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.

3.10.10 Representative(s) of the study group population can be invited during deliberations to offer their viewpoint but should not take part in the decision making process.

3.10.11 The member who has declared COI should withdraw from the EC meeting, while the research proposal is being discussed and should be minuted.

3.10.12 The decision must be taken either by a broad consensus or majority vote (as per SOP) and should be recorded. Any negative opinion should be recorded with reasons.

3.10.13 The decisions may be as given in Table 3.8

Table 3.8

1. Approval – With or without suggestions or comments.
2. Minor modifications- Approval is given after examination by the member secretary or expedited review as the case may be.
3. Resubmission – Where major modifications are suggested which will be

	placed before the full committee for reconsideration.
4.	Not approved (or termination/ revoking of permission if applicable). Clearly defined reasons must be given for not approved/ termination/ revoking permission.

3.10.14 Approval may be granted for the whole duration of the proposed research. However, the validity of the approval letter is only up to one year. Depending on the risk involved the progress of the project may be monitored annually or at shorter period (quarterly, half yearly) as per EC SOP. The approval may be continued if progress is satisfactory.

3.10.15 An EC may decide to reverse its positive decision on a study if it receives information that may adversely affect the benefit/ risk assessment.

3.10.16 The Member Secretary (assisted by the Secretarial staff) should record the discussions and make the minutes which should be circulated to all the members for comments before final approval by the Chairperson/ Co- Chairperson/ Alternate Chair/ designated member of the committee.

3.10.17 It is good practice to get the minutes prepared and finalized at the end of the meeting and gets everyone's approval signed and dated on the spot.

3.10.18 The decision of the EC should be communicated to the researcher along with suggestions if any.

3.11 Continuing Review

3.11.1 The ongoing research should be reviewed at regular intervals of at least once a year (or more if deemed necessary depending on the level of risk) as may be specified in the SOP of the EC and at the time of according approval and indicated in the communication letter.

3.11.2 EC should evaluate annual progress of ongoing projects, review serious adverse event (SAE) reports at site and other sites, protocol deviations/ violations, any new information pertaining to the research and assess final reports of all research activities.

3.11.3 In the case of SAEs, for regulatory trials applicable regulations must be complied with. The EC should also ensure compliance by the Investigator. For non regulatory trials an institutional policy should be in place.

3.11.4 EC should examine the measures taken for the medical management of SAEs. Participants should not have to bear costs for the management of study related injury whether they are in the intervention arm or not. Compensation must be given for research related injuries if applicable, as determined by the EC and regulatory requirement where applicable.

3.11.5 For protocol deviations/ violations the EC should examine the corrective actions. If the violations are serious the EC may halt the continuation of the study. The EC may report to the Institutional Head/ Government authorities where there is continuing non-compliance to ethical standards.

3.11.6 Reports of monitoring done by the sponsor and DSMB reports may also be sought.

3.12 Site Monitoring

3.12.1 It is recommended that ECs should have mechanisms to monitor the approved study site, till completion of research to check for compliance or improve the function.

3.12.2 Monitoring can be 'not for cause' or 'for cause' and must be decided at a full committee meeting

- Routine monitoring: for example (not restricted to), for proposals that have a high risk, vulnerable participants. This can be decided at the initial review or continuing review.

Table 3.9 Examples of 'For cause' monitoring (not restricted to)

S. No.	Examples of For cause monitoring
1.	High number of protocol violations/deviations
2.	Large number of proposals carried out at the study site or by the same investigator
3.	Large number of Serious Adverse Events (SAE) reports
4.	High recruitment rate
5.	Complaints received from participants
6.	Any media report
7.	Adverse Information received from any other source
8.	Non compliance to EC directions
9.	Misconduct by the investigator
10.	Any other cause as decided by EC

3.13 Record Keeping and Archiving

3.13.1 Record Keeping

3.13.1.1 All documentation and communication of an EC should be dated, filed and preserved according to written procedures.

3.13.1.2 Strict confidentiality should be maintained during access and retrieval procedures.

3.13.1.3 All active and inactive (closed) files should be appropriately labelled and archived separately in designated areas.

The following records should be maintained (Table 3.10).

Table 3.10

Administrative Documents	• The constitution and composition of the EC • Signed and dated copies of the most recent Curriculum vitae of all EC members • Confidentiality agreement • COI declaration • Records of training of EC members • Financial records • Registration/ accreditation documents as required • A copy of national and international guidelines and applicable regulations • Regulatory Notifications • Meeting related documents • Agenda, minutes, all communications • SOPs
Project Related Documents	• One hard copy and a soft copy of initial research proposal and related documents • Decision letters • Any amendments submitted for review and approval • Regulatory approvals • SAE, AE reports • Protocol Deviations/ violation • Progress reports and continuing review activities. • All correspondence between the EC and investigators. • Record of notification issued for premature termination of a study with a summary of the reasons. • Final report of the study • Publications, if any.

3.13.2 **Archiving**

3.13.1 All records must be archived for a period of at least 3 years after the completion/ termination of the study.

3.13.2 Documents related to regulatory clinical trials must be archived for 5 years as per CDSCO regulation after the completion/ termination of the study.

3.13.3 Records may be archived for a longer period, if required by the sponsors/ regulatory bodies.

3.13.4 EC should have archival and retrieval mechanism described in SOPs.

3.13.5 Strict confidentiality should be maintained during access and retrieval procedures.

3.13.6 EC records should be accessible for inspection by authorized representatives of regulatory agencies

4. Informed Consent Process

4.0 For biomedical and health research involving human participants, the investigator must obtain written informed consent of the prospective participant. It is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not. Informed consent is a process that culminates with the individual accepting or refusing to participate in the study. It protects the individual's freedom of choice and respects the individual's autonomy.

4.1 Requisites

4.1.1 To consent, the participant must have the capacity to understand the proposed research, be able to make a decision whether or not to be enrolled and convey it to the researcher.

4.1.2 The consent should be given voluntarily and not be obtained under duress or coercion of any sort, or by offering any undue inducements.

4.1.3 In the case of an individual who is not capable of giving voluntary informed consent, the consent of a legally authorised/ acceptable representative (LAR) must be obtained (Refer to section 5 on vulnerability for further details).

4.1.4 It is mandatory for a researcher to administer consent before initiating any study related procedures involving the participant.

4.1.5 It is necessary to maintain privacy and confidentiality at all stages.

4.2 Essential information for prospective research participants

4.2.1 Before requesting an individual's consent to participate in research, the investigator must provide the individual with detailed information about the research in the language she/ he is able to understand which should not only be scientifically accurate but should also be sensitive to social and cultural context of the participant.

4.2.2 The informed consent document (ICD) has two parts- Participant Information Sheet (PIS) and the informed consent form (ICF). Information on known facts about the research, which has relevance to participation is included in PIS followed by ICF in which the participant acknowledges that she/ he has understood the information given in PIS and is now volunteering to be included in that research.

4.2.3 Adequate time should be given to the participant to read and understand before deciding to enroll in the research.

4.2.4 Wherever needed/ suggested by EC, a test of understanding can also be administered to ensure that the participant has really understood the procedures and extent of their involvement in the study.

4.2.5 Essential elements of an informed consent document (Table 4.1)

Table 4.1 Essential elements of an informed consent document

1.	Statement mentioning that it is research
2.	Purpose and methods of the research in simple language
3.	Expected duration of the participation and frequency of contact with estimated number of participants to be enrolled, types of data collection and methods
4.	Benefits that might reasonably be expected as an outcome of research to the participant or community or to others
5.	Any foreseeable risk, discomfort or inconvenience to the participant resulting from participation in the study
6.	Extent to which confidentiality of records could be maintained i.e., the limits to which the investigator would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality
7.	Freedom of individual to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to
8.	Free treatment and/ or compensation of participants for research related injury
9.	The identity of the research teams and contact persons with address and phone numbers (PI/ Co-PI for queries related to the research and Chairperson/member secretary or helpline for appeal against violations of ethical principles and human rights
In addition, the following elements may also be required depending on the type of study	
1.	Any alternative procedures or courses of treatment that might be as advantageous to the participant as the ones to which she/he is going to be subjected to.
2.	If the research could lead to any stigma, e.g. HIV and genetic disorders etc., there will be provision for pre test and post test counselling.
3.	Insurance coverage if any, for research related or other adverse events.

4.	Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research. Details in section 10 on Biological materials, Biobanking and Datasets . Other specifics are as follows - o Period of storage of the sample/data; o If the material is likely to be used for secondary purposes or would be; o If material is to be shared with others, this should be clearly mentioned; o Risk of discovery of biologically sensitive information and provision to safeguard confidentiality; o Right to prevent use of her/ his biological sample (DNA, cell-line, etc.) and related data at any time during or after the conduct of the research; and o Benefit sharing, if research on biological material and/ or data may lead to commercialization.
5.	Publication plan, if any, including photographs and pedigree charts.

692

693 **4.3 Responsibility of investigators**

694 4.3.1 Communicate to prospective participants all the information necessary for informed
695 consent in a language and manner easily understood by the prospective participants.

696 4.3.2 There should be no restriction on the participant's right to ask any questions related
697 to the study.

698 4.3.3 The possibility of unjustified deception, undue influence and intimidation should be
699 avoided at all costs. Although deception is not permissible, sometimes withholding
700 some information till the completion of the research would be required to validate
701 that research. However such research should be approved by the EC. For instance,
702 study on abortion practices, certain observational studies etc.; attempt should be
703 made to debrief the participants/ communities after completion of the research. Seek
704 consent only after the prospective participant is adequately informed.

705 4.3.4 The investigator should not give any unjustifiable assurances to prospective
706 participant, which may influence her/ his decision to participate;

707 4.3.5 Ensure that the participant is competent and has understood all aspects of the study
708 and that the consent is given voluntarily. Where the participant and/ or the LAR is
709 illiterate, an impartial literate person, not connected to the study should be present
710 throughout the consent process as witness.

711 4.3.6 Administer a Test of Understanding whenever possible for sensitive studies, if need
712 be the test may be repeated until the participant has really understood.

713 4.3.7 Verbal consent may be taken on approval by the EC when the participant refuses to
714 sign or give thumb impression or cannot do so, in presence of the impartial witness
715 who should sign and date the document. This can be documented through audio or

video recording; however verbal consent should be an exception for specific reasons carried out with the approval of EC and not to be followed routinely.

4.3.8 If circumstances allow only verbal or oral consent it is to be obtained in the presence of an impartial witness. Additionally this may be audio/ video recorded in the presence of impartial witness who also should be captured in the frame.

4.3.9 In the case of abandoned/ institutionalized individuals or wards under judicial custody take the consent of institutional head;

4.3.10 Renew or take fresh informed consent of each participant under circumstances described in section 4.7.

4.3.11 The investigator must assure prospective participants that their decision to participate or not will not affect their rights, the patient - clinician relationship or any other benefits to which they are entitled.

4.3.12 Re-imbursement may be given for travel and incidental expenses/ participation in research after approval by EC.

4.3.13 Ensure free treatment for research related injury (death, disability, chronic life-threatening disease and congenital anomaly or birth defect) and if required payment over and above medical management by the investigator and/ institution and sponsor(s).

4.3.14 Provide routine care as mentioned in the protocol during the period of study, even in the event of withdrawal of the participant.

4.3.15 Inform EC if there is any deviation or violation of the protocol.

4.4 Documentation of obtaining consent - Documentation of informed consent process is an essential part of this entire exercise.

4.4.1 Each prospective participant should sign the informed consent form after going through the informed consent process of receiving information, understanding it and voluntarily agreeing to participate in the research.

4.4.2 If the participant is unconscious or has lost insight (e.g. in psychosis), efforts must be made to get the consent of the participant when she/ he regains consciousness/ insight. There should be an institutional policy in place to deal with such situations in the absence of LAR.

4.4.3 The process of consent for an illiterate participant and/ or LAR should be witnessed by an impartial literate witness who is not a relative of the participant and in no way

connected to the conduct of research (e.g., other patients in the ward not in the study, staff from the social service department, counsellors etc). The witness should be a literate person who can read the participant information sheet and consent form and understand the language of the participant.

4.4.4 If the participant cannot sign then a thumb impression must be obtained.

4.4.5 The Investigator who administered the consent must also sign and date the consent.

4.4.6 In the case of abandoned institutionalized individuals (widows, elderly, orphans) who are incompetent to give consent of their free will, this may be obtained from the institutional head or appropriate LAR.

4.4.7 In the case of wards under judicial custody only the institutional head gives consent.

4.4.8 If a child participant becomes an adult during the course of the research, consent should be taken even though assent was obtained earlier.

4.5 Regulatory Clinical trials - Clinical trials that are conducted for regulatory purposes, e.g. for drug approval, need to follow all the requirements of the appropriate regulatory authorities. Refer to section 6 on clinical trials of drugs and other interventions for further details.

4.6 Waiver to obtain consent

The investigator can apply to the EC for waiver of consent if the research involves less than minimal risk to the participant and the waiver will not adversely affect the rights and welfare of the participants. The EC may grant waiver of consent in the situations described in Table 4.2 below –

Table 4.2 Conditions where consent waiver may be granted by ECs

1.	Research could not practically be carried out without the waiver
2.	Retrospective studies, where the participants are de-identified or cannot be contacted.
3.	Research on anonymised biological samples/ data.
4.	Surveillance programmes/programme evaluation studies (Refer to section 7 on Epidemiological and Public health research for further details)

5.	Research on data available in public domain.
6.	Prior approval of EC should be taken for research on humanitarian emergencies and disaster, as the participant may not be in a position to give consent. Attempt should be made to obtain participants consent at the earliest (Refer to section 13 on Research during Humanitarian Emergencies and Disasters for further details).

4.7 Re-consent or fresh consent

In the following situations a reconsent is required:

4.7.1 Availability of new information pertaining to the study, which changes the benefit-risk ratio.

4.7.2 When a research participant regains consciousness from unconscious state or becomes mentally competent after having suffered a loss of insight and is now regained insight and able to understand the study.

4.7.3 When an unmarried girl/ woman acquires marital status during the period of the research. In some type of research, the partner/ husband may also be required to give additional consent.

4.7.4 When research requires a long-term follow-up or requires extension.

4.7.5 When there is change in treatment modality, procedures, site visits, data collection method or change in tenure of participation.

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

4.8 Procedures after the consent process

After the consent is obtained, the participant should be given a copy of the PIS and signed ICF unless the participant is not willing to take these documents (which should be recorded). The investigator has an obligation to convey how the confidentiality will be maintained. The original PIS and ICF should be archived as per the requirements of guidelines and regulations.

4.9 Special situations

4.9.1 **Gatekeepers -** Permission of the “gatekeepers” i.e. the head/ leader of the group or culturally appropriate authorities may be obtained in writing or audio or video graphed on behalf of the group. This process should be witnessed.

Table 4.3

1.	When permission is obtained from an organisation that represents the community, the quorum required for such a committee must be met, e.g. in a village panchayat the number of members required ordinarily to conduct a meeting must be present while giving consent.
2.	Individual consent is necessary even if the community gives permission.

4.9.2 Community consent

In certain populations the community plays an important role in the consent process, especially when the participants may not take part in the research unless the community's consent is available. There may be situations when individual consent cannot be obtained as it will change the behaviour of the individual. Refer to section 7. on Epidemiological and public health research for further details). In such situations community consent is required -

4.9.3 Consent from Vulnerable groups

Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests and provide valid informed consent (Table 4.4). The list of vulnerable populations/ communities is given in Table 5.2 in section 5 on vulnerability.

Table 4.4

1.	Their consent to participate in the study may be unduly influenced either by the expectations of benefits or fear of retaliation in case they refuse to participate;
2.	Many of them are socially, economically or politically or situationally disadvantaged and therefore susceptible to being exploited and coerced to give consent.
3.	They are incapable of making a voluntary informed decision for their own self as their autonomy is compromised. An LAR is required to provide informed consent on their behalf. Where LARs are not available, the institutions should have policies in position to obtain alternate consent from appropriate authorities.

5. Vulnerability

5.0 The word vulnerability is derived from the Latin word "*vulnarere"* which means "to wound". Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens or social injustice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so. For example, those who –

Table 5.1

1.	consent to participate in the study on account of being unduly influenced either by the expectations of benefits or fear of retaliation in case they refuse to participate;
2.	are socially, economically or politically disadvantaged and therefore susceptible to being exploited;
3.	are incapable of making a voluntary informed decision for their own self or those whose autonomy is compromised;
4.	are temporarily or permanently unable to consent, e.g. unconscious, mentally differently abled; and
5.	are able to give consent, but whose voluntariness or understanding is compromised due to their situational conditions.

The key principle to be followed when research is planned in vulnerable persons is that, others will be responsible for protecting their interests because they cannot or are in a compromised position to protect their interests on their own.

Vulnerable populations or groups - The following (but not restricted to) populations or communities may be vulnerable at some or all times (Table 5.2)

Table 5.2

1.	Economically and socially disadvantaged,
2.	Children
3.	Women in special situations (e.g., Pregnancy, Lactation, poor decision making power/ poor access to health care)

4.	Tribal populations and marginalized communities;
5.	Sexual minorities (LGBT),
6.	Refugees, migrants, homeless, persons or populations in conflict zones, riot areas, disaster situations,
7.	Institutionalised individuals, Under trials and prisoners, orphans, abandoned widows, elderly.
8.	Mentally ill and cognitively impaired, mentally differently abled.
9.	Patients who are terminally ill or are in search of new interventions having exhausted all therapies
10.	Persons suffering from stigmatizing or rare diseases
11.	Lack of power due to dependency or being under a hierarchical system, e.g. students, patients, employees, subordinates, services personnel, healthcare workers etc.

5.1 Principles of Research in Vulnerable populations

If vulnerable populations are to be included in research, all stakeholders must ensure that additional protections are in place to safeguard the rights and welfare of these individuals.

5.1.1 Research must be planned in vulnerable populations only if that population will benefit from the research.

5.1.2 Vulnerable populations have an equal right to be included in research so that benefits accruing from the research apply to them too.

5.1.3 The participants must be empowered to the extent possible, to be able to take their own decisions.

5.1.4 In vulnerable populations, when the potential participants lack the ability to consent, a Legally Acceptable Representative (LAR) should be involved in decision making.

5.1.5 Special care must be taken to ensure the privacy and confidentiality of all participants in research.

5.2 Additional safeguards/ protection mechanisms

When potential participants are dependent on others, they may either feel intimidated and incapable of disagreeing with their caregivers, or feel a desire to please them. In the first case,

they may be subjected to (at least perceived) undue pressure, while in the second, they may be easily manipulated. If they perceive that their caregivers want them to participate in research, or if the caregiver stands to benefit from the dependent's participation, the feeling of being pressed to participate may be irresistible and undermine the potential voluntariness of consent to participate.

5.2.1 There should be no coercion, force, duress, undue influence, threat or misrepresentation during the entire research period.

5.2.2 There should not be any repercussions on participant's refusal to enter research or to withdraw from research, and this should be clearly stated in the informed consent form.

5.2.3 It is imperative that complete information about the research is given to the participant. Vulnerable persons may require significant and repeated education/ information about the research, benefits and risks, and alternatives, if any.

5.2.4 Steps should be taken to ensure privacy and confidentiality of vulnerable participants especially if the research participation may result in enhancement of their vulnerability.

5.2.5 Research on sensitive issues like mental health, sexual practices/ preferences, HIV/AIDS, substance abuse etc. may present special risks to research participants therefore protection of their privacy, confidentiality and rights at all times is required, during and even after completion of research.

5.2.6 Care should be taken that the participants are not exploited.

5.2.7 Special care must be taken to ensure that LAR/ caregivers are not induced to agree to participate.

5.2.8 LAR/ Caregivers should not be rewarded for encouraging the enrollment of their dependents.

5.2.9 Researchers should be cognizant of the possibility of conflicting interests between the prospective participant and LAR. Informed consent from such LARs who are apparently not acting in the best interests of the prospective participant should not be accepted. In such cases, an alternative LAR(s) may be invited to provide consent, as per local law or institutional policies.

5.2.10. Participation may make a person vulnerable to stigmatization and discrimination, which may affect even the person who is participating as a normal control or is recruited from the general population. Because of the magnitude and probability of harm, special protections should be meticulously undertaken to ensure privacy and confidentiality about their identity and data.

5.3 Obligations/ Duties of Stakeholders (Table 5.3)

Table 5.3

Researchers	Ethics Committees	Sponsors	Regulatory authorities
Responsibility of the researcher/ research team towards participants is total, irrespective of having obtained consent.	Determine during review whether the prospective participants for a particular research are vulnerable.	The sponsor, whether a pharmaceutical company, a government, or an institution, should justify the inclusion of vulnerable groups while developing the protocol and include provisions for protecting their safety.	Regulations should have safeguards to protect the vulnerability and rights of the participants. e.g. Audio- visual recording of the Informed consent process in regulatory clinical trials issued by the CDSCO. Research should be conducted within the purview of existing relevant guidelines/ regulations.
Justify inclusion of vulnerable population in the study.	Examine whether inclusion of the vulnerable population is justified.	The sponsor should ensure protection of the researcher in the case of research on sensitive topics.	
Conflicts of Interests (COI) issues must be addressed.	Ensure that COI do not increase harm or lessen benefits to the participants.		
The researchers must have well defined procedures to have a balanced benefit risk ratio.	Determine carefully the benefits and risks to the participants and advice risk minimization strategies wherever possible.		
Researchers must ensure that prospective participants are competent to give informed consent.	Suggest additional safeguards, like more frequent review and monitoring including site visits.	Enable monitoring and procedures in place for Quality Assurance (QA) and Quality Control (QC).	

Researchers must take consent of the LAR when a prospective participant lacks the capacity to consent.	Only full committee should do initial and continuing review of such proposals. It is desirable to have representatives from specific populations during deliberations.		
Researchers must respect the dissent of the participant.			
Researchers must seek the informed consent of appropriate authorities for dependent mentally ill or cognitively impaired individuals in the absence of their caregivers	ECs have special responsibilities when research is on participants who are mentally ill and/ or cognitively impaired and should exercise caution when researchers will have to justify exceptions to the usual requirements of participation or where departure from the guidelines governing research are truly necessary. EC should ensure that these exceptions are as minimal as possible and clearly spelt out in the Informed Consent Documents.		

5.4 Women in special situations

Women have equal rights to take part in research and should not be deprived arbitrarily of the opportunity to benefit through research unless it precludes them for special reasons such as pregnancy and lactation. Informed consent process is important in Indian women because of a largely paternalistic culture in India. Hence, they should be allowed to consult husband/ family members, if necessary. Although autonomy of the woman is important, the researcher has to

follow the requirements of local cultural practices in order not to disturb the harmony in the household/ family.

5.4.1 Participation of women in Clinical Trials/ intervention study that may expose her to a risk (Table 5.4) –

Table 5.4

1.	Proper justification to include pregnant and nursing women in clinical trials designed to address the health needs of such women or their foetuses or nursing infants should be provided by the researchers for review by EC, e.g. a trial designed to test the safety and efficacy of a drug for reducing perinatal transmission of HIV infection from mother to child, a trial of a device for detecting foetal abnormalities or trials of therapies for conditions associated with or aggravated by pregnancy, such as nausea and vomiting, hypertension or diabetes.
2.	If women in reproductive age are to be recruited, they should be informed of the risk to the foetus if they become pregnant and should be asked to use an effective contraceptive method and be told about the options available in case of failure of contraception.
3.	If the woman becomes pregnant during the period of research she should be withdrawn from the study and followed up to see if the child *in-utero* has been affected, especially if the test product is known to be carcinogenic, mutagenic or teratogenic or there is failure of contraception in a contraceptive trial.
4.	Woman who becomes pregnant must not automatically be removed from the study when there is no evidence showing a potential harm to the foetus, but she must be offered the option to withdraw or continue. In case the woman opts for continued participation, researchers and sponsors must adequately monitor and offer support to the woman till necessary.

Refer to 6.18 on pregnancy and clinical trials for more details.

5.4.2 Prenatal Diagnostic studies - Research related to pre-natal diagnostic techniques in pregnant women should be limited to detect the foetal abnormalities or genetic disorders as per the Pre-conception and Pre-natal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994, amended in 2003 and not for sex determination of the foetus.

5.4.3 Research on sensitive topics

When research is planned on sensitive topics like domestic violence, genetic disorders, rape, etc. confidentiality should be strictly maintained and the privacy protected. In risk mitigation strategies, appropriate support systems such as

counselling centres, police protection, etc. should be put in place. At no time should information acquired from a woman participant be unnecessary, hurtful or appear voyeuristic. The EC should be especially vigilant regarding these sensitive issues.

5.5 Children

Children are individuals who have not attained the legal age for consent (18 years). They are considered vulnerable participants because their autonomy is compromised, as they do not have the cognitive ability to fully understand the minute details of the study and make decisions. Decision about participation and withdrawal of a child in research is expected to be taken by the parents/ LAR in the best interests of their children/ wards. However, there could be some extraneous factors that may force them to act otherwise, which should be carefully assessed by the researcher and the EC.

Research in children can be carried out in a situation, condition, disorder or disease (Table 5.5) –

Table 5.5

1.	Exclusively seen in childhood.
2.	Involving adults as well as children; but the issues involved are likely to be significantly different in these two populations.
3.	Involving adults as well as children and is of similar nature in terms of morbidity, severity and/ or mortality, wherever relevant, and studies involving adults have demonstrated required degree of safety and efficacy.
4.	In which 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.
5.	In which 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.

5.5.1 Additional safeguards/ Protections (Table 5.6)

Table 5.6

1.	Research is generally permitted in children only if the safety has been established in adult population or if the information likely to be generated cannot be obtained by other means.
2.	Research should be conducted in child friendly settings, in the presence of parent(s) where they can obtain adequate medical and psychological support;

3.	EC should do the risk benefit assessment to determine whether additional safeguards are required.
4.	EC should also take into consideration the circumstances of the children to be enrolled in the study including their age, health status, and other factors and potential benefits to other children with the same disease or condition, or society as a whole.

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932 **5.5.2 Consent of parent/ LAR (Table 5.7)**

933 **Table 5.7**

1.	EC should determine if consent of one or both parents would be required before a child could be enrolled.
2.	Generally, consent from one parent/ LAR may be considered sufficient for research involving no more than minimal risk.
3.	Permission from both parents should be obtained when the research involves potential direct benefit to the child or for research, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the child even if it involves more than minimal risk.
4.	Only one parent's consent is acceptable, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child irrespective of the risk involved.
5.	Whenever relevant the protocol should include a parent/ LAR information sheet that contains information about specific aspects relevant to children such as effects on growth and development, psychological well-being and school attendance, in addition to all components described under the participant information Sheet.
6.	When the research involves sensitive issues related to neglect and abuse of child the EC may waive the requirement of obtaining parental/ LAR consent and prescribe an appropriate mechanism to safeguard the interest of the child.
7.	Cognitively impaired children or children with developmental disorders form one of the most vulnerable populations. In fact their parents are also vulnerable, and there is a high likelihood of therapeutic misconception. Parents must be explained carefully about the potential risks and benefits to make them understand the proposed research.

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5.5.3 Assent

In addition to consent from parents/ LAR, an oral or written assent, as approved by the EC, should be obtained from children of 7-18 years of age. As children grow, their mental faculties develop and they will be able to understand and respond. Respecting the child's reaction, the child is made a party to the consent process by the researcher, who explains the proposed research in a very simple manner in a language the child understands the request to participate in research. A child's affirmative agreement to participate in research is called 'assent'. If the child objects, then that wish has to be respected. At the same time mere failure to object should not be construed as assent.

Table 5.8

1.	There is no need to document assent for children below 7 years of age
2.	For children between 7 – 12 years an oral assent must be obtained in the presence of parents/ LAR and should be recorded.
3.	For children over the age of 12 years a written assent must be obtained. This assent form has to be also signed by the parent/ LAR.
4.	Adolescents may have the capacity to give consent like adults. However, as they have not attained the legal age to provide consent, it is termed as Assent and the consent of the parent/LAR to be obtained. If the latter will affect the validity of the study, waiver of consent from the relevant adult should be taken and recorded with the approval of the EC.

5.5.4 Waiver of Assent (Table 5.9)

Table 5.9

1.	All the conditions that are applicable to the adults for waiver of informed consent also apply for children.
2.	If the intervention available is likely to benefit the child definitely and it is only available if the child participates in the study. This should be adopted only in exceptional cases where all forms of consent/assent have failed.
3.	The investigators will provide the care for the participant during the period of the study. They will follow the protocol as mentioned in the participant information sheet. If the participant withdraws from the study, her/ his care will not be compromised.

5.5.5 Assent form

Content of the assent form has to be in accordance with the developmental level and maturity of the child. The language of the assent form must be consistent with the cognitive, social and emotional status of the child. It must be simple and appropriate to the age of the child.

Points to be included in the assent form are as given below (but not limited to) Table 5.10.

Table 5.10

1.	An explanation about the study and how it will help the child.
2.	An explanation of what will be done in the study. It is essential to describe the discomfort that the child is likely to undergo.
3.	The assent form must contain the contact information of the person whom the child can approach if she/ he needs an explanation.
4.	A paragraph must emphasize that the child can refuse to participate in the study and if so, the treatment at the centre will not be compromised.

5.6 Research involving sexual minorities (LGBT) and sex workers

There are unique challenges associated with research on sexual minorities and sex workers like privacy, confidentiality, and possibility of stigma, discrimination, and exploitation resulting in increased vulnerability.

5.6.1 Protection of their dignity and quality health care under these circumstances should be well addressed in the research proposal, preferably in consultation with the community before the proposal is finalised.

5.6.2 It would be advisable to have a representative of the LGBT community as a special invitee/ member to participate in the meeting of the EC if there is a research proposal involving these participants.

5.6.3 Community advisory board should be set up to act as interphase between the researcher(s) and the community.

5.6.4 Elder members of this community could serve as LAR if required.

5.6.5 For HIV positive persons, any research may be misconstrued as research on anti-HIV treatment and make them willing to participate, therefore, the full implications in simple terms should be explained to them about any other research being done on them, e. g., research on hepatitis B.

5.6.6 Among the LGBT there are inhibitions between the different groups, so each group should be explained details of research separately.

5.6.7 Peer educators or champions among the LGBT community could be educated and sensitized first who would in turn explain about the details to the potential participants from the community who would then understand them better.

5.6.8 Support systems to deal with the associated mental conditions and addictions of this community should be in place.

5.6.9 Whenever possible, a school for unattended children of the participants, a hospital and counselling centre should preferably be set up as ancillary care.

5.7 Research on Tribal Population

Research on tribal populations should be conducted only if it is of a specific therapeutic, diagnostic and preventive nature with appropriate benefits to the tribal population.

5.7.1 Due approval from competent administrative authorities like Tribal Welfare Commissioner or District Collector should be taken before entering the tribal areas.

5.7.2 Whenever possible it is desirable to take the help of the government functionaries/ local bodies or registered NGOs working closely with the tribal groups, in whom the local population has confidence.

5.7.3 Where panchayat system does not exist tribal leader of that community or culturally appropriate authority or the person socially acceptable to the community may serve as gatekeepers, from whom permission to enter the premises should be sought.

5.7.4 Informed consent should be taken in consultation with the community elders and persons who know the local language/ dialect of the tribal population with appropriate witnesses.

5.7.5 Despite permission of the gatekeeper the individual consent process cannot be waived.

5.7.6 Additional precautions should be taken to avoid inclusion of children, pregnant women and elderly etc. belonging to particularly vulnerable tribal groups (PVTG).

5.7.7 For any research done using tribal knowledge, which may have commercial potential, benefit sharing with the tribal group should be ensured.

5.8 Research Involving Mentally Ill or Cognitively Impaired/ Affected Individuals

5.8.1 Mentally ill - According to the World Health Organization, mental disorders comprise a broad range of problems, with different symptoms. They are generally characterized by some combination of abnormal thoughts, emotions, behaviour and relationships with others. Under Section 2 (i) of the Person with Disabilities (Equal Opportunities, Protection of Rights and Full Participation) Act, 1995 mental illness has been defined as any mental disorder other than mental retardation. Colloquially these disorders are called 'mental illness' which will be used throughout this document. Presence of a mental disorder is not synonymous with incapacity of understanding or providing informed consent.

5.8.2 Cognitively affected or impaired - The conscious mental activities such as the activities of thinking, understanding, learning, and remembering are under the definition of cognition. Those in whom these activities are not fully functional are regarded as cognitively impaired. Such groups would include those without full intellectual potential (intellectually disabled, previously called mentally retarded), unconscious, those suffering from a number of neuropsychological disorders such as dementia or delirium and those who cannot fully comprehend or participate in the informed consent process, either temporarily or permanently. Other sources or reasons for cognitive impairment affecting the ability to give informed consent include, but are not limited to: being too young (children do not yet develop the necessary cognitive abilities to give informed consent); being in extreme pain; being under the influence of medication, illicit drugs, or alcohol; mental retardation; and traumatic brain injury (that causes unconsciousness or cognitive impairment while conscious).

5.8.3 Risk of harm to self - Some psychiatric conditions lead people to risk harm to

1030 themselves or others (Table 5.11).

1031 **Table 5.11**

1.	Prospective participants must be informed during the informed consent process how the investigator will address suicidal ideation or other risks of harm to self or others.
2.	It should be disclosed to the participant that her/ his confidentiality may be breached for reporting to family members, police, or other authorities or they may have to be admitted in the hospital upon expression of such thoughts of self-harm.
3.	While some interventions – like hospitalization and treatment for suicidality – may be primarily for the participants' own benefit, they themselves may not perceive it as such and may want to refuse to participate in a study if hospitalization and treatment may sometimes be required.
4.	A careful assessment of the individual's choices must be made by the investigators before recruiting such individuals.

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1033 **5.8.4 Risk of harm to others (Table 5.12)**

1034 **Table 5.12**

1.	Mechanisms have to be activated when a participant is detained and hospitalized because of the expression of homicidal ideas as she/ he may not want to participate in research if hospitalized.
2.	Such interventions should be of short duration and possibly least restrictive and invoked only when necessary, in accordance with relevant laws.

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1036 **5.8.5 Research involving concealment or deception (Table 5.13)**

1037 **Table 5.13**

1.	Some study designs may reduce or violate human participant protections/rights or specific requirements of informed consent. An example is studies involving deception either in recruiting participants, or in the study intervention, or both. In some studies a degree of deception – usually omitting to inform fully – is necessary if the study is to be accomplished at all. All such studies should have prior EC approval.

2.	Research involving any degree of deception should be justified only if it is clear that • Deception is truly necessary to accomplish the goals of the research • Partial disclosure/ authorized deception is a way of informing the participant that they would be deceived but the nature of the deception is not disclosed. This may be considered in the protocol. • There are no undisclosed risks to participants that are more than minimal, and • There is an adequate plan for debriefing participants, when appropriate, and for dissemination of research results to them.

5.8.6 Institutionalized participants

While reviewing protocols that include mentally ill prisoners or those who are incarcerated or involuntarily committed to psychiatric facilities, the EC must ensure the following (Table 5. 14)

Table 5.14

1.	Enrolling these participants is specifically pertinent to the research questions and is not merely a matter of convenience;
2.	It is possible for the participant to deny consent and later withdraw from the study without any negative repercussions on his care.
3.	Mechanisms to avoid coercion are described in the protocol.
4.	Those being invited to enroll are competent to give informed consent or refusal.
5.	LAR will give consent on behalf of participants who are not competent to give consent only if the research has substantial potential of therapeutic benefit over the risk and the research participation presents the only possible health care prospects.

5.8.7 Avoidance of Stigma (Table 5.15)

Table 5.15

1.	For some persons already under treatment for a psychiatric condition, research participation might not present a substantially greater burden of stigma. On the other hand, if the person is not symptomatic, diagnosed, or under treatment, research participation may be a primary source of stigmatising her/ him as mentally ill.
2.	The potentially greater risks of stigmatization should not prohibit recruitment of participants from the general, nonclinical population; instead, awareness of the risks imposed by research should prompt researchers to plan to minimize them.

5.9 Persons suffering from stigmatizing or rare diseases

In the case of stigmatizing **or rare diseases** where research cannot be delayed, and any surrogate/ next of kin or LAR may or may not be available to consult for consent, the incompetent participant may be enrolled in the study. Specific reasons for involving subjects with a condition that renders them unable to give informed consent should be stated in the research protocol and the study should be approved by EC.

The institutions should have in place policies for taking consent from appropriate authorized individuals who can give consent on behalf of such individual(s) in the absence of LARs.

5.10 Patients who are terminally ill

Terminally ill patients or patients who are in search of new interventions having exhausted all available therapies are vulnerable as they are ready to give consent for any intervention that can be a ray of hope for them. There should be appropriate consent procedures and the EC should carefully review such protocols and recruitment procedures. Additional monitoring should be done to detect any adverse event at the earliest. These studies are approved so that the scientific community or professional groups do not deny such patients the possible benefit of any new intervention that is not yet validated.

5.11 Other vulnerable groups

Other vulnerable groups include the economically and socially disadvantaged, homeless, refugees, migrants, persons or populations in conflict zones, riot areas, disaster situations, under trials and prisoners-institutionalised, those having lack of power due to dependency or being under a hierarchical system, e.g. students, patients, employees, subordinates, services personnel, healthcare workers etc.

5.11.1 Ideally, the individuals listed above should not be recruited as research participants.

5.11.2 Autonomy of such individuals is already compromised and the researchers have to justify their inclusion if there is no other option.

5.11.3 ECs have to satisfy themselves with the justification provided and record the same in the proceedings of the EC meeting.

5.11.4 Additional safety measures suggested as above in the guidelines to be strictly followed by the ECs.

5.11.5 The Informed Consent process should be well documented. There should not be any undue coercion or incentive for participation. The participant's refusal to participate should be respected and there should be no penalisation.

5.11.6 EC should also determine carefully the risks and benefits of the study and examine the risk minimization strategies.

6. Clinical Trials of drugs and other interventions

6.0 A clinical trial is any research/ study that prospectively assigns human participants or groups of humans to one or more health-related intervention/s to evaluate the effects on health outcomes. The intervention could be drugs, vaccines, biosimilars, biologics, phytopharmaceuticals, radiopharmaceuticals, diagnostic agents, public health interventions, socio-behavioral interventions, technologies, devices, surgical techniques or interventions involving traditional systems of medicine, etc.

Clinical trials are usually well-controlled studies, which use a design that allows a comparison of participants treated with an investigational product (IP)/ any intervention to a control population (receiving placebo or an active comparator), so that the effect of the IP/ intervention can be determined and differentiated from effects of other influences e.g. spontaneous change, placebo effects, concomitant treatment/ intervention, or observer expectations.

6.1 General guidelines

6.1.1 All clinical trials must be planned, conducted and reported in a manner that ensures that the rights, safety and well being of participants are protected.

6.1.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

6.1.3 All clinical trials must be conducted in accordance with The Indian Good Clinical Practices (GCP) Guidelines, the Declaration of Helsinki (2013, or later versions as applicable), National Ethical (ICMR) guidelines (2016) and other applicable guidelines. The Drugs and Cosmetics Act (1940), Rules (1945) and applicable amendments (including Schedule Y), and other relevant regulations should be followed wherever applicable

6.1.4 A participants' right to agree or decline consent to take part in a clinical trial must be respected.

6.1.5 At all times, the privacy of a participant must be maintained and any information gathered from the participant be kept strictly confidential.

6.1.6 Therapeutic misconception in potential participants must be avoided.

6.1.7 At least one member of the research team must have qualification in the subject on which the trial is planned.

6.1.8 Applicable regulatory approvals must be taken.

6.1.9 All clinical trials must be approved by an EC that is constituted and functions in accordance with these guidelines and applicable regulations.

6.1.10 All clinical trials must be registered with Clinical Trial Registry of India (CTRI; www.ctri.nic.in).

6.1.11 Ethical standards should be common for all clinical trials irrespective of whether they fall under the purview of regulators or not.

6.1.12 A written informed consent must be obtained from each participant before any study related procedure is performed.

6.1.13 Clinical trials should not be conducted involving vulnerable participants unless that is necessary for their welfare.

6.1.14 If the trial is planned in a vulnerable population it should be only undertaken with due justification, and all possible participant protections should be in place.

6.1.15 Procedures to assure the quality of every aspect of the trial should be implemented.

6.1.16 SAEs must be reported within 24 hours to the sponsor, EC and regulator if applicable, followed by a due analysis report in seven working days.

6.1.17 Medical management of AEs and SAEs, irrespective of relatedness to the clinical trial must be given free of cost.

6.1.18 In addition, compensation must be given if the SAE is proven to be related to the trial.

6.1.19 Medical care (ancillary care) should be provided to clinical trial participants for non-study/ trial related illnesses arising during the period of the trial.

6.1.20 Institutional mechanisms must be in place to allow for insurance coverage for trial related or unrelated illnesses (ancillary care) and compensation wherever deemed necessary by the EC.

6.2 Types of interventions/ trials:

6.2.1 Clinical Drug/ Vaccine Development

The broad aim of the process of clinical development of a new drug or vaccine, (referred to as investigational product, IP) is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the benefit-risk relationship is acceptable.

1153 **Table 6.1**

<table>
<tr><td>Phase 0
A Phase 0 study is an exploratory study, conducted to find out whether an investigational new drug (IND) can modulate its intended target in human beings, and to identify its distribution in the body, or describe its metabolism. This study involves very limited human exposure, and has no therapeutic or diagnostic intent. It is conducted early in the process of drug development and allows for human use of an IND with less pre-clinical data and in lower doses than is required for a conventional Phase I. This is invariably part of a regulatory study.</td><td>Phase I
Phase I starts with the initial administration of an investigational new drugs/ vaccines into humans. These studies usually have non-therapeutic objectives. Phase I studies are conducted in healthy participants or in patients, in the case of drugs with significant potential toxicity, e.g. cytotoxic drugs.
Studies conducted in Phase I typically involve
a) Estimation of Initial Safety and Tolerability
b) Pharmacokinetics
c) Assessment of Pharmacodynamics (biological effects for vaccines)
d) Early Measurement of Drug Activity (including immunogenicity in case of vaccines)</td></tr>
<tr><td>Phase II
Phase II starts with the initiation of studies in which the primary aim is to explore therapeutic efficacy (immunogenicity in case of vaccines) in patients/ participants. Phase II studies are conducted in a group of patients/participants who are selected by relatively narrow criteria, and are closely monitored. Early studies in Phase II are designed to estimate the dose response. Later studies are planned to confirm the dose response</td><td>Phase III
Phase III begins with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit or protection rate (in case of vaccines).
a) Designed to confirm the evidence from Phase II studies that about the safety and efficacy of a drug/ vaccine for use in the intended indication and recipient population.
b) Planned to provide an adequate basis for impact on clinical practice or for obtaining marketing approval, where applicable.
c) New use – clinical trials of an already marketed drug for a new indication, dosage form, dosage regimens, or routes of administration would technically be Phase III studies. If these studies are intended for ultimate commercial use of the drug, these require regulatory approval. Research on ‘Off label use’ comes under this category. (See 6.16)
d) Bridging trials and pivotal trials come under Phase III category.</td></tr>
<tr><td colspan="2">Phase IV
Phase IV begins after product approval and is related to the use of the intervention for the approved indications. These studies are important for optimising the use of the product. These include a variety of studies e.g.
a) Post-Marketing Surveillance - practice of monitoring the safety of a product after it has been released on the market.
b) Phase IV clinical trials - a study conducted to assess safety, tolerability and effectiveness of a marketed product is prescribed in the usual manner in accordance with the terms of the marketing authorization e.g. efficacy and safety conducted in special population.</td></tr>
</table>

c)	Outcomes research - aim to study the effectiveness and efficiency of the intervention after its introduction for human use.
d)	Registries - Registries set up prospectively to maintain data about patients with certain shared characteristics and who have received a particular intervention (e.g., stent) that collect ongoing and supporting data over time on well defined outcomes of interest.

6.3 Ethical consideration

All clinical trials should be scientifically sound. The sponsor of the study, the investigator, the institution, the EC, and the regulatory authority (if applicable) are responsible for ethical conduct of a study. Before any clinical trial is initiated, adequate data from pre-clinical investigations or previous clinical studies should be generated and be sufficient to indicate that the intervention is acceptably safe for the proposed investigation in humans.

6.3.1 Ethical considerations for Phase I (for drugs and vaccines) studies

6.3.1.1 All Phase I trials require EC approval and applicable regulatory approvals.

6.3.1.2 Phase I study is a non-therapeutic trial, in which there is no anticipated direct clinical benefit to the participant. Hence, it should be conducted in participants who can give voluntary informed consent themselves and who can sign and date the written informed consent form.

6.3.1.3 As Phase I studies are conducted most often in healthy volunteers, all safeguards to protect the participants must be in place, especially recruitment methods, payment for participation, evidence of non-coercion and consent procedures.

6.3.1.4 When a Phase I study is conducted in participants with a disease e.g. cancer, due consideration should be given to the seriousness of the medical condition and the study procedures planned.

6.3.1.5 The study protocol should describe measures to minimise the risks of Phase I clinical trial in healthy volunteers and patients. These include, but are not limited to (Table 6.2)-

Table 6.2

1. Exclusion of participants who may be at increased risk from the study.
2. Careful review of investigational procedures posing high risk of physical harm or serious discomfort.
3. Evaluation of available data to decide if the investigational product or procedures proposed in the protocol have been associated with serious adverse events and steps to prevent or minimise such risks.
4. Careful monitoring of the condition of participants and to intervene to manage adverse events.

6.3.1.6 Phase I study Unit must have robust and tested procedures for immediate resuscitation and maintenance of life support and onward transfer of subjects to hospital, if necessary.

6.3.1.7 The Phase I unit should have a formal arrangement/ agreement with a hospital for managing emergencies arising from their clinical trials.

6.3.1.8 A Phase I study with a high risk investigational product e.g. first-in-human, biologic should be carried out in a hospital where experienced personnel and facilities are immediately available to manage medical emergencies.

6.3.1.9 Medical Pharmacologist/ Physicians trained in clinical pharmacology should be involved in Phase I studies.

6.3.2 Ethical Considerations for Phase II, III and IV studies

6.3.2.1 All Phase II and III studies require EC approval and applicable regulatory approvals.

6.3.2.2 In the case of Phase IV studies the following require EC approval:

i. Phase IV clinical trials
ii. Outcomes research
iii. Registries
iv. If the data is used to answer any research question
v. New Use for non commercial purpose (academic research)

6.3.3 Ethical considerations for Vaccine Studies

Vaccines can be prophylactic and therapeutic in nature. 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:

6.3.3.1 Phase I for determination of its safety and biological effects including immunogenicity, includes study of dose and route of administration and should involve low risk.

6.3.3.2 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.

6.3.3.3 Combination Vaccines - The main goal in efficacy trial design of such vaccines is to evaluate the efficacy of each antigenic component. 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.

6.3.3.4 **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.

6.3.3.5 Types of Vaccines (Table 6.3)

Table 6.3

1.	Live and attenuated vaccines (measles, mumps, rubella and chickenpox)
2.	Inactivated vaccine (e.g. flu vaccine)
3.	Toxoid vaccines (e.g. diphtheria and tetanus vaccines)
4.	DNA vaccines
5.	Recombinant vector vaccines

6.3.3.6 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.

6.3.3.7 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.

6.3.3.8 For recombinant DNA vaccines and products applicable Governmental guidelines and regulations should be followed.

6.3.3.9 Post trial, the control group should receive the complete dose of an effective vaccine (either one that is already available or the investigational vaccine).

6.4 Bioavailability (BA)/ Bioequivalence (BE) Study

Bioavailability is the measurement of the proportion of the total administered dose of a therapeutically active drug that reaches the systemic circulation and is therefore available at the site of action.

Bioequivalence – it is a term used in pharmacokinetics when there are two (or more) medicinal products (proprietary preparations of a drug), containing the same active substance which need to be compared *in vivo* for biological equivalence. These comparative studies are used to assess that the new version (generic) produces the same concentration

in the systemic circulation when given to human participants. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same.

Bioequivalence studies are used as surrogates for clinical effectiveness data for generic drugs where no clinical difference is anticipated between the two compounds.

6.4.1 Ethical Issues

6.4.1.1 All BA/ BE studies should be scientifically sound and conducted in compliance with principles of ethical conduct described above for a Phase I study.

6.4.1.2 Ethical conduct of BA/ BE study requires evaluation of the risk-benefit profile of

a) The reference and generic product

b) The study procedures – indoor stay, fasting, screening, blood sampling.

6.4.1.3 Bioavailability and bioequivalence studies are usually conducted in healthy volunteers. Hence, they have no benefit to the participant but may pose risks due to the adverse effects of the drug. Hence, all safeguards to protect participants must be in place.

6.4.1.4 EC must review carefully the Recruitment methods, payment for participation, and consent procedures in detail. It is in such studies that volunteers often participate regularly at the cost of their health and care should be taken that taking part in multiple trials is avoided by maintaining volunteer registries, biometry, follow up, etc.

6.4.2 Study Designs and Ethical Implications -

Clinical trials have wide range of methodological approaches, EC need to look into the details of the ethical concerns involved:

6.4.2.1 In blinded studies, if a serious adverse event occurs, and it is imperative in the interest of managing the event, to know what the patient was receiving, unblinding should be done.

6.4.2.2 When an available therapy is effective in preventing serious harm e.g. death or irreversible morbidity in the clinical trial population, it is inappropriate to use a placebo control.

6.4.2.3 Placebo may be used as a comparator under the following conditions (Table 6.4)

Table 6.4

1. When there is no established effective therapy available.
2. When withholding an established effective therapy would not expose participants to serious harm, but may cause temporary discomfort or delay in relief of symptoms.
3. When the use of an established effective therapy as a comparator would not yield scientifically reliable results and the use of placebo would not add any risk of serious or irreversible harm to the participants.

6.4.2.4 If a placebo must be used for scientific reasons, then (Table 6.5)

Table 6.5

1. The protocol must have added safeguards to protect participants from harm, for example, but not restricted to, having clear-cut withdrawal criteria, intensive monitoring, rescue medications.
2. Use an "add-on" trial design where the IP or placebos are added to standard pre-decided therapy.
3. Expose fewer patients to placebo e.g. by having 2:1 randomization with 2 participants receiving IP against 1 getting placebo (unbalanced randomization).
4. An active comparator as an additional arm may also be included in such trials where randomization can be e.g. 2:2:1 (IP: Active comparator: placebo).

6.5 Multicentric Trials

Multicentric trials are carried out with a primary aim to provide a sound basis for the subsequent generalisation of its results. All sites should obtain approval from the respective EC.

6.5.1 The ECs of all sites should follow all applicable regulatory guidelines, including being registered with the regulator.

6.5.2 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.

6.5.3 The EC can suggest site-specific protocol and informed consent modifications.

6.5.4 The Sponsor should ensure that documented EC approvals from all sites are obtained before launching the study at the site.

6.5.5 All investigators (centres) should conduct the trial in strict compliance with the protocol, regulatory requirements and EC recommendations.

6.5.6 The implementation of the protocol procedures is similar at all centres.

6.5.7 Plans for manuscript publication and a common final report are decided before initiation of the study.

6.5.8 Meetings should be organised at the initial and intermediary stages of the trial to ensure uniform procedures at all centres.

6.5.9 There should be monitoring of adherence to protocol including measures to terminate the participation of some centres, if necessary.

6.5.10 All researchers should give a written acceptance of the protocol provided by the sponsor, which may be modified to suit local requirements and should be followed for the trial duly approved by the EC of the host institutes.

6.5.11 Site-specific data can be published only after appropriate authorities accept the combined report and appropriate permissions are obtained.

6.6 Phytopharmaceuticals drugs

The Drugs and Cosmetics Rules, 8th Amendment 2015 defines a new class of drugs called phytopharmaceutical drug as "purified and standardised fraction with defined minimum four bio-active or phyto-chemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route."

All ethical guidelines described in drug development section apply to this group of drugs.

6.7 Device trials

Devices could be used internally or externally. Depending upon risks involved devices are classified as follows:

Table 6.6

Critical devices	Non-critical devices
These present a potential serious risk to the health, safety or welfare of the participant –	These do not present significant risk to the patients e.g. Thermometer, BP

e.g., stents including medicated stents, pace makers, implants, internal catheter	apparatus, mobile based Pulse Oximeter or Ultrasound.

6.7.1 Clinical trials of medical and dental devices (whether notified by CDSCO or not) should be conducted in accordance with all the ethical principles described in these guidelines, Indian GCP as well as applicable regulations of the country for medical devices.

6.7.2 Before approving clinical trials on medical devices (notified/ not notified by CDSCO) the EC should evaluate all available and relevant data on the device so as to be able to make a thorough risk benefit assessment.

6.7.3 Medicated devices should be evaluated as though the trial is on the drug(s) contained within them.

6.7.4 Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.

6.7.5 Apart from safety considerations of the device, the procedures to introduce the medical device in the patient should also be evaluated for safety.

6.7.6 If the participant wants to withdraw from a trial, it may not be possible to remove the internal device. This must be explained to the participant before enrolling her/him. The participant however should be allowed to opt out of continuing on the trial without prejudice to his/her ongoing treatment.

6.7.7 The duration of follow up should be long enough to detect late onset adverse reactions especially when the device is implanted within the body.

6.8 Biologicals, biosimilars

Biologics (biopharmaceutical drug) can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living cells or tissues. This section applies to products that are produced by means of biological processes with or without recombinant DNA technology. All aspects that are described in Section 6.1 are also applicable.

6.8.1 As these are biologic substances, special care must be taken to review all data so far generated. Special expertise may be sought for such reviews so that foreseeable risks are well identified.

6.8.2 A thorough risk benefit assessment must be carried out with available data.

6.8.3 If the study involves biosimilars, the product quality (manufacturing & characterization), preclinical data and bioassay must demonstrate similarity with a reference biologic.

6.8.4 All applicable and current regulations must be followed.

6.9 Stem cells and cell derived therapies

In recent years, the area of stem cell research has undergone rapid developments promising new leads in the treatment of several incurable diseases. According to the source and the degree of expected risk to human participants, stem cell research is categorised into permissible areas of research (adult and cord blood), restricted areas of research (embryonic) and prohibited areas of research (reproductive cloning). To address the issues related to stem cell research, Indian Council of Medical Research (Department of Health Research) and Department of Biotechnology, Government of India have published National Guidelines for Stem Cell Research in the year 2007, modified in 2013 (http://icmr.nic.in/guidelines/NGSCR%202013.pdf).

6.9.1 The source of cells is limited to human subjects for these guidelines. In case of allogenic donation there is no direct benefit to the donor *per se*. Source of the cell procurement process such as ovum donation or bone marrow donation are invasive and may carry risk to the donor. Extra care has to be taken in providing appropriate information while taking consent for donation. The donor may need to be investigated for potentially transmittable infections and also some genetic diseases, results of which, the donor may or may not like to know.

6.9.2 The donor also needs to be informed that cell lines may be derived from the donated tissue, which may be banked and shared with others. They may also undergo genetic manipulation, and have potential for development of commercial products. In the later case, the intellectual property rights will not be of the donor. Also while confidentiality and privacy are sacrosanct, a provision needs to be kept for traceability in a contingency situation. The donor might need to be contacted in future as well.

6.9.3 The two basic characteristics of stem cells *viz*. potential for unlimited proliferation and ability to differentiate into a variety of cells of all three germ layers, which has made them the darling of regenerative medicine, incidentally are also their biggest distracters. For example, one of the signatures of the stem cells is their ability to

produce teratoma, which is totally unacceptable in terms of safety of any therapeutic product. Also, once introduced into body, they may survive indefinitely and what type of cells they may produce could be unpredictable. Special care should be taken when cells are obtained from embryos and fetuses. It is necessary to ensure that donors are not exploited and commodifed.

6.9.4 Except haemopoietic cell transplantation, all the other uses of stem cells fall under the category of research and must be conducted as a clinical trial, and needs the approval of EC, Institutional Committee for Stem Cell Research (ICSCR), National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and the Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) of Central Drugs Standard Control Organisation (CDSCO) as the case may be. Use of stem cells outside the domain of a clinical trial for any purpose will be considered unethical and hence not permissible.

6.9.5 Each institution should maintain a registry of its investigators who are conducting stem cell research and ensure that all are kept updated in accordance with changes in guidelines and regulations regarding use of these cells. It shall also be the responsibility of the institution to ensure that all current standards are applied.

6.9.6 All clinical trials with any stem cells shall have prior approval of IC-SCR and Institutional Ethics Committee (IEC). Prior approval of Drug Controller General of India (DCGI) will also be required for stem cell based IND products & new drug applications (cells for therapy are deemed as drugs). Clinical trials with clinical grade SSCs processed as per National GLP/GMP/GTP guidelines as applicable to be carried out.

6.9.7 All clinical trials shall be registered with the NAC-SCR through IC-SCR. All such studies should also be registered with the Clinical Trials Registry of India (CTRI). It has to be ensured that no unproven stem cell therapy is offered outside of the well-controlled clinical trials.

6.9.8. International Collaborations shall have prior approval of respective funding agency as per its procedure or Health Ministry's screening committee (HMSC).

6.9.9 Clinical trials using stem cells need to be planned carefully with follow-up periods suitable for the subject being evaluated and should also include appropriate end points.

6.9.10 Specific principles related to clinical trials with stem cells are to be followed as per the National guidelines, 2013. An extra layer of oversight by those who are knowledgeable about the special issues to be put in place. The institutions/Sponsors conducting clinical trial should be responsible for insurance and compensation of the subjects recruited under the trial.

6.9.11 Establishing and licensing Umbilical cord stem cells falls under the purview of the DCGI. The guidelines notified by CDSCO available at http://cdsco.nic.in/html/GSR%20899.pdf should be followed.

6.9.12 The physician/scientist engaged in stem cell research should avoid any activity that leads to unnecessary hype or unrealistic expectation in the minds of study subjects or their family members. They should be given adequate unbiased information about the limitations and potential adverse effects. There should be suitable mechanisms for creating awareness and communicating scientific evidence to the public.

6.10 Surgical interventions

Surgical interventions that are being studied systematically must be considered as research and follow all general principles described in these guidelines.

6.10.1 In any protocol where an established surgical intervention is to be studied, the investigator must provide references for the procedure and describe the most likely complications (with frequency of each complication) in the protocol for the EC to review and perform risk benefit assessment.

6.10.2 In trials where a modification of the established surgical intervention is to be tested the protocol and ICD must specify the need for this modification and the expected complications if any. It is preferable that a comparative study be conducted where the conventional method is compared to the test surgical intervention.

6.10.3 Trials where an entirely new surgical intervention is being tested, the EC may insist on some animal data, which establishes the efficacy and safety of the technique.

6.10.4 During the conduct of a surgical interventional trial all adverse events must be reported to the EC (and sponsor as applicable) within the specified timelines as described for drug trials.

6.10.5 Provision for free treatment and compensation for study related injury must be made available to the trial participant and the EC must determine the amount after the investigator has described the relatedness.

6.10.6 Sham surgery should not be included in design of clinical trials due to inherent ethical issues. However, in exceptional cases, and for strong scientific reasons these methods can be used under following conditions (Table 6.7) -

Table 6.7

1.	There has to be a clear description of these justifications in the protocol, which must be assessed by the EC.
2.	There should be no irreversible harm caused by the sham surgery.
3.	The participant must get access to appropriate intervention at the end of his participation in the trial.

6.11 Community trials (Public Health Interventions)

Community trials are the studies involving whole communities and are conducted to evaluate preventive strategies like Mass Drug Administration (MDA) trials, fortification of food etc. Such studies typically involve the whole community (study unit could be a group, area, institution, village, block, district etc.) and the whole population is expected to participate in the study. In such studies, different communities are randomized and allocated to different arms (refer to section 7 on Epidemiological & Public Health Research).

6.12 Clinical trials of Interventions in HIV/AIDS

Clinical trials in HIV positive patients could be for the evaluation of new drugs, vaccines, other preventive measures and diagnostic tests. Apart from the general ethical principles that apply to all clinical trials, some special issues need to be addressed when clinical trials are planned in patients with HIV/AIDS e.g. the social stigma and culturally embedded myths about HIV, marginalization and lack of legal status or criminalization of some communities that are susceptible to HIV or the disparity in standard of care in different parts of the world.

6.12.1 Global studies in HIV/ AIDS in specific communities should receive approval from the relevant national authority [NACO] and any other relevant authority (for example the Health Ministry Screening Committee HMSC where applicable) apart from approval from the EC.

6.12.2 When testing for HIV is done, consent and pre test and post test counseling should be done as per NACO guidelines.

6.12.3 Issues that may arise because of discordant couples should be addressed before initiating any study in HIV/AIDS.

6.12.4 As HIV is a sexually transmitted disease and is potentially life-threatening, the right to life of the sexual partner must be respected over the right to the privacy of the HIV positive individual..

6.12.5 Phase I studies are permissible in patients with HIV/AIDS if the drug under study cannot be tested in normal, healthy participants due to expected toxicity of the IP.

6.12.6 A combined Phase I/II or Phase II study can be conducted in this population when other therapeutic options in them have been exhausted.

6.12.7 When a trial with a preventive HIV vaccine is conducted, it can result in a positive serology. This does not indicate HIV infection but can create problems for travel and employment. Under such circumstances, the project investigator should issue a certificate stating that the person in question was a participant in a vaccine trial and provide clarification on the results.

6.12.8 Research that involves sexual minorities (MSM, LGBT and intravenous drug users) should have community engagement [community leaders] throughout the life of the project till completion and dissemination of results.

6.12.9 The EC may also consider co-opting a member from this community, if relevant for initial and continuing review of proposals.

6.12.10 Where possible, the EC should ensure post trial access of the IP for the participants.

6.13 Clinical Trials on Traditional Systems of medicine

Although Traditional Systems of medicine (termed Complementary and Alternate Systems in the West) are known for their long history of safe and effective use, validation of safety and efficacy using scientific and evidence-based methodologies is needed for the purpose of universal acceptability, gaining confidence of practitioners and satisfaction of end users in the products.

Government of India (GOI) has recognised Ayurveda, Siddha, Unani, Yoga and Naturopathy, as traditional Indian systems of medicine besides adding Homeopathy to it. In 2012, Sowa Rigpa (Amchi or Tibetan medicine) also has been added to the list. Department of AYUSH used to govern and regulate these systems, which has been taken over by the newly created Ministry of AYUSH. Drugs under Ayurveda, Unani and Siddha systems come under Drugs and Cosmetics Act, 1940 as ASU drugs. The products under these systems of medicine are classified into two groups (Table 6.8) –

Table 6.8

1. Classical products are those that are to be clinically evaluated for same indication for which it is being used or as has been described in the classical authoritative texts. These classical drugs are manufactured and named in accordance with the formulations described in the authoritative texts.	2. Patent or Proprietary products are formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda (or Siddha or Unani Tibb systems as the case may be) of medicine specified in the First Schedule, but differ to create a new combination, or use innovation or invention to manufacture products different from the classical medicine. However, this group does not include a medicine, which is administered by parenteral route.

6.13.1 Research on AYUSH and ASU interventions of Traditional Medicines (TM), Folk Medicines, and Patent and Proprietary Medicines of TM involving human participants should be conducted in accordance with all the ethical principles described in these guidelines including SAE reporting and compensation, AYUSH GCP Guidelines as well as other applicable regulations of the country.

6.13.2 If investigational products/ comparator of more than one Traditional Systems of medicine are to be investigated, then investigator(s) from all the respective systems should be included in the study as Co-investigator(s).

6.13.3 The EC must co-opt a person with relevant expertise (an expert of that traditional system of medicine) to review the proposal, especially the risks and benefits of the intervention, the eligibility criteria, the doses of the interventions, the outcomes planned and the traditional method of evaluation if necessary.

6.13.4 When a Folklore medicine/ ethnomedicine is ready for commercialization after it has been scientifically found effective, benefit sharing should be ensured, and 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.

6.13.5 While conducting trials using intervention(s) of TM, the investigator must ensure the quality of the interventional product.

6.14 Trials of Diagnostic agents

A diagnostic agent refers to any pharmaceutical product used as part of a diagnostic test (i.e. together with the equipment and procedures that are needed to assess the test

result) and that is either administered into or onto the human body. Diagnostic agents must be considered as new drugs and therefore clinical trials involving diagnostic agents should be conducted in accordance with all the ethical principles described in these guidelines, Indian GCP Guidelines as well as applicable regulations of the country.

6.14.1 Risk benefit assessment involving diagnostic agents additionally includes the assessment of benefits (technical performance, diagnostic performance, impact on diagnostic thinking and impact on patient management/ outcome) and the risks related to the agent itself (e.g. immunogenicity, allergic reactions) but also risks related to incorrect handling of test procedures or incorrect diagnosis induced by its use.

6.14.2 The EC must review the pharmacology, toxicology, pharmacokinetics and safety data (preclinical and clinical data as applicable) especially for diagnostic agents which come in contact with skin or mucosal surfaces in human body (*in vivo* use). Special expertise may be co-opted in the EC for review of such products.

6.14.3 These trials are usually comparative, the comparator being the reference/ gold standard test to diagnose the disease. Hence, the protocol must state clearly the choice of the reference with justification. Likewise, omission of a reference standard as comparator must also be justified.

6.14.4 A placebo may be used as comparator when the response to a diagnostic test is being assessed using subjective evaluation criteria (e.g. skin changes in a skin prick test) or for the assessment of tolerability. There have to be clear justifications in the protocol for the use of a placebo, and no irreversible harm should occur to the participant. Post-trial access to the standard of care diagnostic test must be assured.

6.14.5 Safety follow-up of patients in these trials should not be limited to the duration of the diagnostic procedure but may be extended for a longer period according to the pharmacokinetic and pharmacodynamic properties of the diagnostic agent.

6.14.6 Long-term safety (when appropriate) should be assessed especially for agents accumulating in the body (e.g. deposits of gadolinium in bones and skin).

6.15 Radio - active materials and X-rays

Radioactive substances contain a radioactive isotope, and may be used for therapeutic or diagnostic purposes. If the radioactive substance is to be tested as a drug then all the ethical considerations described in Section 6.3 (for drug trials) will apply and if it is to be

evaluated as a diagnostic agent then Section 6.15 applies. Additionally, the following considerations must be applied. The permissible radiation limits when radioactive materials and X-rays are being evaluated must comply with regulatory authority guidelines. In India the agency that regulates radioactive materials is the Bhabha Atomic Research Centre (BARC), Mumbai.

6.15.1 The investigator site should have license from the competent authority to store, handle and dispense the radioactive substance.

6.15.2 The investigator and clinical trial team must be competent and should have received appropriate training to handle radioactive substances and X-rays.

6.15.3 The protocol and ICD should clearly state the potential radiation exposure in quantitative terms to the whole body or per organ that participants are likely to be exposed to. This exposure must be within acceptable limits.

6.15.4 The EC may co-opt relevant expertise to review such protocols

6.15.5 When a trial involving radioactive substances is planned in healthy participants, they must be preferably over 50 years old and receive radiation in a dose as low as permitted

6.15.6 Women of childbearing age, children, radiation workers or any individual who has received more than the permissible amount of radiation in the past 12 months should be excluded from trials involving radioactive materials or X-rays.

6.15.7 In the event of death of a participant with a radiological implant, due precautions must be taken as per the prescribed radiation guidelines so as to not expose relatives or close co-habitants to radiation.

6.15.8 The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo and information must be given to the participant in the ICD about possible genetic damage to offspring.

6.16 Investigator Initiated Clinical Trials

Academic institutions routinely carry out investigator initiated clinical trials.

6.16.1 All the ethical principles applicable to clinical trials described in this section will also apply to investigator initiated trials.

6.16.2 The Investigator has the dual responsibility of being an investigator as well as the sponsor.

6.16.3 Financial arrangements must be made by the institution/investigator to pay for free management of research related injury and compensation if the injury is related to the intervention.

6.16.4 Funds should be made available or appropriate mechanisms put in place for Ancillary care to trial participants during the trial.

6.16.5 Policies must be made by the institution to put in place mechanisms to ensure quality of the data generated and safety of the intervention, e.g., monitoring, auditing, Data Safety Monitoring Committee

6.16.6 It is desirable to have a medical pharmacologist as a member in the EC reviewing such clinical trials.

6.16.7 When research is planned on an "off-label" use of a drug (when a drug that is marketed is being used for a new indication/new dose/formulation/ route) for purely academic purposes and not for commercial use, then these clinical trials designed by investigators/ academicians, do not currently require regulator approval. However, an EC has to approve such studies after due considerations of benefits and risks and all other ethical aspects.

6.17 Clinical Trials on contraceptives

Several methods are available today for contraception including, barrier methods, hormonal methods, emergency contraception, Intra-uterine and surgical methods. Since these studies are conducted in healthy participants, all efforts to minimise risks must be in place and the proposed benefits must justify the foreseeable risks. The following issues must be addressed while undertaking research on contraceptives be they drugs, devices or surgeries.

6.17.1 All procedures for clinical trials will be applicable.

6.17.2 For a new contraceptive method, non-comparative studies can be accepted. However, a sufficient number of cycles should be studied to obtain the desired precision of the estimate of contraceptive efficacy.

6.17.3 The comparator should, whenever possible, be chosen among marketed products with a similar mechanism of action and schedule of use.

6.17.4 In women where a non-biodegradable implant has been used, 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.

6.17.5 The educational and socioeconomic level of women participants may be considered as to whether they will be able to comprehend the use and risks associated with the particular contraceptive.

6.17.6 Participants should be clearly informed about the alternatives available for contraception.

6.17.7 Any pregnancies occurring during a contraceptive trial should be followed up for final outcome to mother and child.

6.17.8 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.

6.17.9 A compensation policy must be in place at the beginning of the trial in case this occurs.

6.18 Pregnancy and clinical trials

Any clinical trial conducted in women of childbearing age raise ethical issues that need to be addressed. Similarly, studies conducted in women who are pregnant need to be evaluated with care and ethical issues addressed.

6.18.1 When clinical trials are conducted in women of childbearing age, they must be counselled to use effective contraceptive methods. These must be stated in the protocol and the ICD and the PI must ensure that these methods are understood and followed by the woman participant.

6.18.2 In clinical trials, which include women of reproductive age, there may be occasional inadvertent pregnancy exposure to the medicinal product. In such instance woman should be withdrawn from the study and efforts should be made to collect data on the drug effects as well as the outcome for both mother and foetus. This follow up plan of pregnancy and care of fetus must be stated in protocol and ICD. A plan for compensation of a participant under such circumstances must be prepared and approved by the EC.

6.18.3 If during research participation, the female sexual partner of a male participant gets pregnant, the protocol and ICD must have a plan to document this and both pregnant partner and fetus must be followed for outcome and reported.

6.18.4 Pregnant women have the right to participate in clinical research relevant to their health care needs e.g. gestational diabetes, pregnancy induced hypertension, HIV etc.

6.18.5 Risk benefit assessment must be done at all stages for both the mother and the fetus.

6.18.6 Pregnant or nursing women should in no circumstances be participants of any clinical trial unless the research carries no more than minimal risk to the mother, fetus or nursing infant and the object of the research is to obtain new knowledge relevant directly to the foetus, the pregnancy or lactation.

6.18.7 Research involving pregnant women and fetuses must only take place when (Table 6.9) –

Table 6.9

1. Appropriate studies on animals and non-pregnant individuals have been completed
2. The risk to the fetus is the least possible risk for achieving the objectives of the trials, including when the purpose of the trial is to meet the health needs of the mother or the fetus, or the risk to the fetus is minimal
3. Researchers should not take part in decisions making regarding any termination of a pregnancy.
4. No procedural changes, which will cause greater than minimal risk to the woman or fetus, will be introduced into the procedure for terminating the pregnancy solely in the interest of the trial.

6.18.8 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.

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

6.19 Clinical trials in Oncology

Clinical trials in oncology have associated with them several ethical issues that need to be addressed during their planning, conduct, oversight and publication. Three primary factors motivate participation in oncology clinical trials: hope for a cure; altruism that even if the patient did not benefit, it may ultimately help others; and trust that the physician would not recommend a treatment (the investigational drug) unless she/ he thought it might be helpful.

All criteria described in Section 6.1 apply to oncology clinical trials stated in drug trials, biologics and radioactive substances. In addition, while reviewing oncology studies, the following should be addressed -

6.19.1 Phase I studies with oncology drugs are conducted in patients. However, there may or may not be any benefit and there may be a high degree of therapeutic misconception. Further, there will be foreseeable and unforeseeable risks that need to be considered before a protocol is approved.

6.19.2 This patient population is vulnerable as they are often terminally ill. Economically disadvantaged populations may take part in the research to allow free access to an intervention. It is important to ensure that the participant has understood that this is research and the benefits expected may be small or they may not occur at all.

6.19.3 Participants must be made to understand that they may be randomized to a placebo group and therefore receive an inert drug, in case of a placebo-controlled study.

6.19.4 If the trial is a placebo- or active-controlled trial, all the groups must be given the current standard of care to which the Investigational Product (IP), placebo or active control is added.

6.19.5 Perceptions of benefits and risks of patients, healthcare workers, as well as EC members may be different. All these perspectives must be taken into consideration while reviewing the protocol.

6.19.6 Undue inducement must be avoided.

6.19.7 Patients should not be charged for any intervention including standard of care if they are participating in trial.

6.19.8 Post trial access plan must be in place, for patients who show benefit with an IP. In case it is a placebo controlled trial, those participants who have been in the placebo group may be offered post-trial access to the IP if found effective in other patients.

7. Epidemiological & Public Health Research

7.0 Epidemiology and Public Health are distinct entities requiring generation of evidence, although they do overlap and the terms are often used interchangeably. Public health ethics can be applied to practice and research and utilizes epidemiological tools to recognize and simplify principles and values to ensure better societal conditions for healthier lives through collective actions aimed at the community. It involves protection of both, the welfare of the individual as in clinical medicine, and the protection of the population at large since the benefits and risks are not limited to an individual but influence communities, populations and environment and such studies form the basis of health related policies and programs. It is important to realize that public health interventions have the potential to expose the vulnerabilities of the communities and segments of the population, therefore, public health investigations and interventions should be conducted ethically with appropriate protections and oversight procedures put in place.

Defining the boundary between public health practice and research remains a critical challenge within the evolving field of public health ethics. Intent of investigators is critical to determine whether the activity is part of the public health program or research. Public health practice relates to collection of data through surveillance, vital statistics, disease reporting and registries; investigation of outbreaks including contact tracing, use preventive interventions and provide health education; and enforce mandatory requirements like screening, treatment, immunization, notifying diseases and sometimes quarantine depending upon the situation. By using the same epidemiological design, sampling techniques and analysis; some of these activities could create the 'generalizable knowledge' same as the primary intent of research. Since it would be difficult to distinguish the boundary between practice and research, ethical oversight is required for both. This section highlights the specific ethical issues pertaining to research in epidemiology or public health for researchers, EC reviewers and decision-makers.

- **Principle of autonomy** – It is a 'relational' autonomy since interests of an individual as part of a community are relational in nature. Therefore, sometimes individual autonomy may not be appropriate for application at community level for their welfare. Community engagement is important in research on epidemiological and public health aspects. The conventional method of informed consent from individual may get replaced with alternative methods as described below at point 7.2.

- **Principle of beneficence** – Since this for a societal benefit it may be considered as 'social beneficence', which requires that potential benefits to individuals and to society be maximized and that potential harms and risks at individual level be minimized. The expected benefits may be to the individual and/ or community, which may be direct/ indirect sometimes with the interests being shared or competing as the case may be. The process of recruitment of subjects and participation in such studies should avoid excessive incentives and should strive to maintain voluntary nature of enrollment.
- **Principle of proportionality** where the probable public benefits may outweigh the breach of autonomy and privacy of individuals.
- **Principle of non-maleficence** – There should not be harm done to others while collecting data and during its disclosure, e.g. stigma, poverty, and discrimination that affect both the transmission and the outcome of 'social' diseases like HIV, STD, TB, mental disorders etc. There could be indirect harm to individual/ community, harm to relationships and loss of benefit. Wherever possible, these harms should be mitigated or minimised. But sometimes it is inevitable that some degree of harm to few may occur while increasing more benefit to larger groups of people by reducing their exposure to greater harm, e.g. restricting smoking to confined spaces may be more harmful to the smokers but more beneficial to the non-smokers.
- **Principle of justice** – It would be 'social justice' as the burden and benefits of research should be equitably distributed in all study groups, the context being 'health equity' especially when vulnerable or disadvantaged population is involved. Research that retains or enhances existing inequities should be avoided. The principle of reciprocity requires that the individuals or communities, which bore disproportionate share of burden or risks for the benefit of others be given back some form of benefit or compensation in kind. There is need for sensitivity to ethnic and cultural habits and norms while considering the health concerns/ burdens and self-defined information needs of the target population rather than overriding these in favor of professional pre-occupations and concerns.
- **Principle of Solidarity** – The intra- and interdependence among members of communities leads to solidarity for collective welfare or common good.

Table 7.1 Points for designing or review of proposal

1.	Are the objectives of the initiative scientifically sound and linked to potential improvement in public health?
2.	Are the objectives achievable using the design of the research?
3.	Are alternatives to informed consent required?
4.	Is there a requirement for community engagement? If so, the methodology to be used.

5.	Who are the beneficiaries and the expected benefits?
6.	What are the potential harms? Who would be harmed? Any measures to mitigate/ minimize?
7.	Can harm over-ride the benefit? If so, can it be compensated in kind?
8.	Is selection of participants justified?
9.	Are burdens and benefit-harm ratio justified?
10.	Is there social justice implied?

7.1 Ethical Issues of Epidemiological and Public Health Research Study Designs

These researches involve use of different study methods and tools on a large number of research subjects in single or multiple settings. Ethical issues emerge from the quality of scientific merit of the research proposal and its implementation. Thus, the research proposal must be scientifically sound and of high quality.

7.1.1 Observational studies

These include cross sectional studies, case control studies, cohort studies, case reports, case series, and other descriptive studies.

7.1.2. Experimental studies

These include field trials and cluster randomized controlled trials, stepped-wedge designs (a type of cluster randomized trial) and quasi-experimental methods. Public health interventions are delivered to groups, geographic areas, institutions or system collectively rather than individually.

7.1.3. Administrative data for research

Administrative data refer to systematically collected or compiled information designed to assist in organizational operations. There is shift in use of these data from primarily managing and monitoring programs and performing audits to conducting research and informing policy. Large volume of data may be accessible from state health departments, national surveys, commercial sources and other data repositories and big data sources. In recent years, administrative data have been more widely used for research and the increase is attributed to: technology improvements that permit easier data compilation and access; its use is time- and cost-effective; data files are often population based, providing large numbers of subjects; and they permit longitudinal analysis over multiple years. While such data can provide quick and easy access to information for secondary analysis, possibilities of misinterpretation of the data, violations of terms of conditions for which data was allowed access, compromising data security, confidentiality of information;

disclosure permissions, unauthorized and misappropriate use of the data, and publication pose ethical concerns. Partnership between the investigator(s) and the representation from the department or the organization from where data is sourced is considered an important strategy to take care of some of these concerns. For ECs, it is important to clearly understand the data and the context in which it was collected and compiled before permitting research on the administrative data.

7.1.4. Surveillance, Program Monitoring Data and Program Evaluations

A fundamental public health activity is to measure and monitor changes in health status, risk factors, and health service access and utilization. Surveillance is an ongoing, systematic collection, analysis, and interpretation of outcome-specific data, with the timely dissemination of these data to those responsible for preventing and controlling disease or injury. These data may be used by investigators for generating new evidence to improve program performances, and for more generalizable application at other sites and contexts. Program evaluation, refers to the systematic application of scientific and statistical procedures for measuring program conceptualization, design, implementation, and utility; the comparison of these measurements; and the use of the resulting information to optimize program outcomes. Evaluation research may or may not involve human subjects (health personnel, patients, community members, other stakeholders) besides screening the documents and observations of various activities at different levels. These studies may be placed under 'Exempt' category under specific situations where the sole purpose of the exercise is refinement and improvement of the program or where an unspecified but large number of stakeholders are to be interviewed spread across large geographic area. Proper ethical review must be done for program evaluation research activities. The review process should ensure the scientific soundness, public health value and potential harm inherent in the protocol and the need to have permission from relevant public health authorities.

The ethical concerns for managing data are similar to that mentioned under the section of administrative data.

7.1.5 Demographic Surveillance Sites and Registries

Demographic surveillance site is a geographically defined population under continuous demographic monitoring, with timely production of data on all births, deaths, and migrations. This monitoring system should provide a platform for assessing a wide

range of health-system, social and economic interventions. In addition, these sites can also be used to monitor developmental and environmental parameters and determine their interaction with and impact on human health. The sites are used as platforms for the testing of new health and non-health interventions; and can provide feedback on programs' effectiveness. The aim of a surveillance site is to improve the lives of people living in developing countries by informing and influencing existing as well as future policy. They can also help define a relevant research and development agenda.

Prior approval is required to set up the demographic surveillance sites (with or without the use of GIS facilities) from competent state/national authorities and from the community leadership. Setting up such sites need not be subject to prior review and approval by an ethical review committee but research studies undertaken at these sites will have to undergo regular ethical review process. To safeguard the confidentiality of personally identifiable records, the collected data at demographic sites must be stored in encrypted format and primary identifiers accessible only to restricted designated individuals who are bound by confidentiality agreement.

Registries that are setup as part of research projects require prior approval of EC. On the other hand, registries may be set as part of the public health programs, which may be exempt from ethical review process. Certificate from EC secretariat should be obtained if the data is de-identified. But when the data emerging from these registries is proposed to be used for research, approval of EC will be required. The ethical concerns are similar to that mentioned under administrative data.

7.1.6. Implementation Research

At local, national, and global levels, a persistent challenge is to effectively implement and scale up policies, programs, and interventions that can save lives and improve health. A new approach to achieve these goals is through implementation research (IR), which raises unique challenges for research ethics committees particularly when the research is co-designed and co-implemented with implementers and end users i.e. community.

IR is a type of health policy and systems research that draws on many traditions and disciplines of research and practice. It builds on operations research, participatory action research, management science, quality improvement, implementation science, and impact evaluation. Implementation research requires flexible designs to account

for the changing contexts and interventions. IR may involve simple methods that implementers can use to identify and apply to solve problems. It may also involve more sophisticated research designs and specialized analyses to explain how and why a policy works, how best to scale a program, or how to introduce and expand an innovation. Implementation science involves the partnership of researchers and stakeholders, for attempting to understand and encourage uptake of piloted or completed research or program. A co-creation approach involves collaboration between researchers and end users from the onset, in question framing, research design and delivery, and influencing strategy, with implementation and broader dissemination strategies as part of its design from gestation. A defining feature of co-creation is its emergent and adaptive nature, making detailed pre-specification of interventions and outcome measures impossible. This methodology sits oddly with EC protocols that require precise pre-definition of interventions, mode of delivery, outcome measurements, and the role of study participants. Implementation research uses theory of change, examining natural diversity and the interaction of the intervention in the context to produce actionable knowledge. It often uses mixed (quantitative and qualitative) methodologies, and analyses in terms of 'intention to reach', rather than 'intention to treat', for equitable population health impact. This requires the ECs to better understand the approach of co-creation and co-participatory nature of the research design, wherein consultations and refinement of programs and policies during the course of their implementation become research.

It is important for ECs to acknowledge the need for flexibility in these studies, but they need to ensure not to allow loopholes that will permit partisan interests to 'move the goalposts' in more conventional research designs. With co-creation design, there is a move from protection of individual participants to the development of a relationship between researchers, implementers and community partners, which is mutually advantageous. The participant on whom research is done is actively engaged in designing and implementing the research process. Here there is distribution of power between 'researchers' and other stakeholders including those 'researched' at least to certain extent. ECs should acknowledge these aspects of implementation research and delivery sciences – both formally (by undergoing training) and informally (by encouraging discussion and debate). Researchers should establish partnership governance and outline the core components of a planned intervention before the ethics application is submitted. The theoretical 'core' of a complex intervention, must

be kept constant, and its local application and implementation can and should be flexible across sites and settings, within a broad conceptual framework. This will allow implementation elements open to modification based on evolving local situations and contexts. The ethics for the co-creation and co-participation aspects of implementation research are an emerging area and shall keep growing as more experience accumulates.

7.2 Informed Consent

7.2.1 Waiver of Consent - Most epidemiological and public health research would follow standard informed consent guidelines. The EC can consider the risks and benefits involved in using clinical details and biological samples and take a decision whether consent waiver can be granted in following conditions (Table 7.2) –

Table 7.2

1. On routinely collected data under program conditions: This includes research involving linkage to large anonymous databases of information that has been routinely collected (including administrative data, surveillance activities).
2. In circumstances when obtaining consent is impractical (e.g. stored anonymous data/biological samples, surveillance and administrative data) or use of personal non-identifiable data/material available from public health programs is proposed, the risks are minimal and societal needs override individual rights, risks and benefits of research.
3. Studies performed within the scope of regulatory and public health authorities for e.g., process and impact evaluations of national policies and programs, neonatal screening programs, diabetes screening as part of national program activities etc.
4. Studies that are not being done with the intent of research and the primary purpose is refinement and improvement of the public health programs.
5. Studies using health related registries that are authorized under national regulations.
6. Not practical to obtain consent in large geographical clusters in cluster randomisation trials and several implementation research.

7.2.2 Alternatives to consent (Table 7.3)

Table 7.3

1.	These may be broad consent, opt-out option, consultation with only a small representative group of the population of interest
2.	For research on sensitive topics verbal consent or pseudonyms may be

	suitable.
3.	Cluster randomized trials (CRT) and implementation researches are examples where ECs will have to decide on the complex issues of feasibility and type of consent to be obtained from the participants.

7.2.3 Re-consenting in longitudinal studies (Table 7.4) –

Table 7.4

1.	If there is no change in the study protocol there is no need for re consenting
2.	There is need for re-consenting when there is change in protocol, new information is sought/ or intervention is introduced/ or new information is available which has likely influence on the study participants.
3.	Other guidelines for re-consent as described in Section 4 Informed Consent Process should be followed.

7.3 EC's role

7.3.1 ECs should ensure data security, confidentiality of information, disclosure permissions and appropriate use of the accessed data.

7.3.2 EC members need to give sufficient weight to the importance of social benefit and the public health impact these studies may be addressing. In both cluster randomisation trials and implementation studies, obtaining participant informed consent raises logistic and methodological concerns. Sometimes participants in randomized clusters or area with implementation activity cannot avoid certain interventions, which imply that participant informed consent refers only to data collection, not administration of an intervention. Occasionally, complete participant information may be a source of selection bias, which then raises methodological concerns. Participant informed consent should therefore be reviewed by EC differently in both these types of research than in individually randomized trials because of methodological consequences. The hierarchical structure of such trials implies the consideration of two levels of consent. The first level is the 'gatekeeper(s)' who could be the 'guardian,' or the local authorities who are normally responsible for their well-being, who give permission for the participation and randomization of individual participation. The other level is individual participants, consent from whom can cover different aspects: (i) consent that routinely held data on individuals be collected, (ii) consent regarding the collection of supplementary data and (iii) consent for active participation. The ECs will have to take decisions regarding the consent on case-to-case basis.

7.3.3 There may be selective withholding of the information/ hypothesis of the study in the consent form for achieving public good without influencing the outcome of the study (e.g. psychology, neuro-behavioural, behaviour intervention trial). This may be permitted by the ECs with the provision that complete transparency will be maintained for sharing of the withheld information with the participants after completion of the study (debriefing of participants post-research) whenever possible. Authorized deception (AD) unlike active deception is another method of informing participants prior to the study that it will not be described accurately or that some procedures will be deceptive. Such revelation provides the participants an opportunity to decide whether or not to participate on these terms. AD must receive the explicit approval of the ethical review committee after it has reviewed the necessity of the withholding of information, minimization aspects of attendant risks to participants, and the adequacy of the procedures for "debriefing" the participation after completion of the study. If research involves incomplete disclosure but no deception then it falls within one or more of the categories of 'exempt from consent' research. Research employing deception may not be reviewed as exempt from consent and if that involves mild deception where the topic is not sensitive and the participants are not vulnerable it can be categorized under 'Expedited review'.

7.4 Protecting participants and communities

Special provisions in the design and execution of the epidemiological/ public health studies that are likely to have the potential of exploitation of research participants: socioeconomically deprived people; people who have limited access to health care may misunderstand the research as an opportunity to receive medical care and other benefits; financial incentives for participants. ECs have to consider these proactively. Specific measures should also be in place to protect the welfare of related community members who have not participated.

7.5 Declaration of conflict of interest

Conflicts of interest can affect public trust and support for public health research, and scientific judgment and thus harm scientific objectivity. Researchers are therefore, to be encouraged to explicitly disclose conflict of interest both financial and non-financial.

8. Research in Social and Behavioral Sciences

8.0 The context of research on Social and Behavioral Sciences is often different from the clinical/ biomedical research as these research initiatives may not have immediate tangible 'social relevance and benefits' yet would be relevant in the mid/ long term to science and society. Many research efforts will also have scholarship value besides relevance for policy and program development. More recently, such studies are done as a precursor to the execution of major implementation research projects. Similarly community behavioral studies are conducted before introduction of new interventions and refinement of existing ones. Thus, depending upon the context, social science studies can also have immediate and immense relevance to program and policy. With greater confidence developing among community of academics and program managers, social science and behavioral science methods are becoming integral part of evaluation of several public health programs to determine the processes and client as well as provider behavior. To be judicious and ethical in judging human behavior, the details of symbolic communication of culture, which includes a group's skills, knowledge, attitudes, values, and motives has to understood as it influences a participant's response to research. 'Ethical relativism' implies to moral diversity among culture and people. In view of the above, the ECs should be aware of the challenges that may be encountered in the process of conducting such studies.

8.1 Some of the key features of research proposals in Social and Behavior Sciences are

8.1.1 There is an ever-increasing need of interdisciplinary approach to biomedical research. The conventional social science research in health underscores the importance of bringing contemporary context to biomedical research.

8.1.2 It has now emerged as a cross cutting area of enquiry relevant to almost every medical/ biomedical research – clinical trials, epidemiological research, program evaluations, implementation research, genetics, research in disaster and conflict contexts.

8.1.3 There are specific ethical challenges involved in social and behavior sciences studies (Table 8.1) –

Table 8.1

1. Non-tangible risks which might be misconceived as no/ minimum risks research;
2. Perceptions of risks and benefits would be different which may transcend physical and mental safety to social risks and safety;
3. Data sharing related research ethics obligations; and

4. What would constitute ancillary care during such research;

8.1.4 Ethical challenges are more pronounced in international collaborative research due to possible inequity of expertise and knowledge access between partnering institutions and investigators. Refer to the section 11. International Collaboration for further details.

8.1.5 Appropriate experts/ expertise of EC members in social and behavior sciences domain is an essential aspect to address the above challenges.

8.2 Ethical Challenges and Strategies to Address -

8.2.1 Scientific design and conduct of the study (Qualitative Studies) -

Table 8.2

1. Like any other research the investigators must ensure that the proposed studies are scientifically sound, built on an adequate prior knowledge base, and are likely to generate valuable information.
2. When research involves patriarchal or restrictive communities, the attitude and attire of research team should respect that community's cultural norms/ practices, e.g. male member of research team as lead discussant; welcome offerings practiced by that community to gain entrance in its territory.
3. Field work challenges for research team – women may not be allowed to come out of the house in the open for responses or access may be denied to men external to the family or interviewers not belonging to same caste are subject to humiliating situations. Training would be required for the research team to meet such challenges without getting affected by them or if affected appropriate counseling be provided.

8.2.2 Ethical Review

There are some unique features of qualitative research, which need to be appreciated by the EC on a case-to-case basis.

Table 8.3

1. Social sciences are not positivist and therefore articulation of a hypothesis may not be possible at the beginning of the study. Instruments/ documents are developed during the course of the study, are reflective and may keep changing as the study progresses. The EC must be kept informed about the changes in the study protocol and instruments as the study progresses.
2. The investigator must take a prior permission from EC with justifiable reasons for audio/ video recording of the interview of the participants.

8.2.3 Risks Assessment

Participants of research in behavioral and social science face the potential of being

exposed to some risks greater than that during quantitative research protocols. The investigators and research team must understand the dignity of the community and the cultural context to avoid hurting and transgressing concepts of dignitary, social, and informational harms.

Dignitary harm is likely to occur when individuals are not treated as persons with their own values, preferences, and commitments, but rather as mere means, not deserving respect. This is also sometimes classified as another form of negligence. This may result in individuals feeling hurt at the core of their being, humiliated, excluded, dismissed or treated unfairly.

Social harm is non-medical adverse consequences of study participation, including difficulties in personal relationships and stigma or discrimination from family or community. Social harms can be related to personal relationships, travel, employment, education, health, housing, with government establishment and others.

Informational risk is the potential for harm from disclosure of information about an identified research participant. For much of social and behavioral research, informational risk is one of the primary risks, so social and behavioral research is particularly concerned with its management. Data sharing, which is common in social and behavioral research and is becoming increasingly common in biomedical research, requires specific plans for managing informational risk. Changing circumstances and technology can create new challenges for managing informational risk. The aggregate risks of the proposed studies must be considered appropriate in light of the potential benefits to participants and the social value of the research.

Table 8.4

1.	**Risk mitigation** against the potential risks mentioned above and minimizing their negative impacts (like short and long term adverse impacts on the participant e.g. abortion, sexual abuse studies and other sensitive areas) should be incorporated in to research methods.
2.	**Community engagement for pitching on to methods and interpretation of observations -** Investigators should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, and monitoring of research,

and in the distribution of its results.

2072

2073 **8.2.4 Informed Consent**

2074 Human participants in proposed research study must be informed about the nature of
2075 research project, and investigators/ research team must obtain their consent prior to their
2076 participation in study.

2077 **Table 8.5**

1. **Community consent/ Gatekeeper consent/ Individual consent on key behavioral studies -** In some circumstances individual informed consent has to be taken after obtaining the permission of 'gatekeepers' community heads or leaders/ culturally appropriate local authorities/ healthcare givers/Institutions or organizations responsible for child welfare or appointed advocates. Such procedures must respect local cultural customs. This may be a community tradition but does not substitute individual consent unless a waiver has been granted.
2. **Participant consent -** Investigators must develop culturally appropriate ways to communicate information necessary for adherence to the standard required in the informed consent process. The ECs may permit selective withholding of the information/ hypothesis of the study in the consent form for achieving over all social and public good without influencing the outcome of the study. On completion of the research the participants should be de-briefed if applicable. Authorized deception (AD) as described in 7.3.3 is applicable here also.
3. **Relational autonomy -** As in research on epidemiology or Public health the participant is part of the family or community and therefore culturally is not autonomous in decision-making. EC may take into account the context with due diligence regarding their vulnerable status during review e.g. a woman asking her husband or family before giving consent;
4. Waiving Informed consent - If the research has **important social and public health value** and poses no more than minimal risks to participants the EC may waive off individual informed consent if it is convinced that the research would not be feasible or practicable to carry out without a waiver e.g. research on illegal and harmful practices. Refer to the section 4 on informed consent Process for specific examples of waiver.

8.2.5 Privacy & Confidentiality (Table 8.6)

Table 8.6

1. Appointments for interviews with specification of place and setting may be obtained to maintain privacy and confidentiality of the research participants.
2. Sensitive research areas specific contexts and settings: In some circumstances women become more vulnerable in research because of heightened psychological, social, physical or legal risks. Examples include surveys and interviews regarding intimate partner violence and rape; social and behavioral research involving sex workers or gender identity; substance users; and the studies that solicit information about sexual behavior. Breach of confidentiality in these types of research may cause serious harms to women and other vulnerable participants. It is important to protect study participants to future risks and harms with culturally sensitive and context specific safeguards in place.
3. If findings have to be reported to authorities the participants should be informed of it prior to taking informed assent/ consent and also told what part of the information will be communicated.

8.2.6 Duty to disclosure (Table 8.7)

Table 8.7

1. In some specific circumstances researchers may come across situations where research participants carry a potential to harm to self or others, e.g. suicidal tendency, drug resistant health condition. In such a situation researchers should disclose this information to relevant authorities to avert untowardly incidents.
2. 'Incidental findings' during the study may be disclosed to the individual, family, community as required during post interview/study debriefing, e.g., HIV positivity. This debriefing reporting to the relevant stakeholder ensures that such strategies will not contribute to generating trust deficit between study communities and researchers.
3. Investigators and EC should have the basic understanding of the legal provisions in the related area.

8.2.7 Sharing qualitative research data

Sharing raw data and notes with repositories, investigators, peer community, institutions, and funders is increasingly becoming a requirement across the globe. Special care should be taken to maintain confidentiality of individual, location and research setting.

Community Authorization - Investigators should share research findings in aggregated form and relevant information in a client friendly format with community leaders, gatekeepers and communities without disclosing individual identity**.**

8.2.8 Etic and Emic issues

There are two perspectives – emic and etic – pertaining to society's cultural system, which have a bearing on the research on social and behavioral science. The emic perspective focuses on the intrinsic cultural distinctions that are meaningful to the members of a given society. The native members of a culture are the sole judges of the validity of an emic description which is observed by a researcher from outside as a non-participant.

The etic perspective relies upon the extrinsic concepts and categories that have meaning for scientific observers (e.g., per capita energy consumption). Here the scientists are the sole judges of the validity of etic account i.e. scientific determinations of a fact.

These perspectives should be appreciated in the following context (Table 8.8) -

Table 8.8

1. Data collection, interpretation, language nuances and interpretation require deep understanding of the context and cultural dimensions.
2. Investigators must explicitly declare their etic/ emic status and should consider these while interpreting the data and presenting the results;
   - In case the main investigators have etic background, local investigators with emic perspective should also be involved
   - As quality assurance measures, strategies for data triangulations including engagement of multiple investigators with diverse perspectives may be desirable
3. Investigators should declare upfront the limitations and validity of the research findings.

8.2.9 Safety of participants (Table 8.9) –

Table 8.9

1. Support systems like counseling centres, rehabilitation centres, police

protection etc. should be in place when research is on sensitive issue, e.g. woman abuse, child abuse;
2. Public policies and social programs could provide ancillary care to participants as the case may be.

8.2.10 Safety of research teams in the field (Table 8.10)

Table 8.10

1. The safety of the research team is the responsibility of institutions and investigators particularly in projects dealing with sensitive topics or sensitive research settings
2. Institutions should take measures to provide safety to the team members including insurance coverage and community engagement (Having SOPs for handling deteriorating situations, having a line of communication, communication plan).

8.2.11 Communication

The investigator(s) and research teams will have to spend time in understanding and establishing communication with the community where the research is to be conducted. Institutions should develop or have the SOPs for handling deteriorating situations, including a pre-tested communication plan.

9. Human Genetics Testing and Research

9.0 In no other area of biomedical research has there been a greater concern for ethical issues than in the field of human genetics. In recent years this concern has grown even further because of direct to consumer testing and the possibilities of embryo manipulations. While the recent DNA technology has provided one of the most powerful tools in the hands of mankind to unravel the mysteries of the human genome and manipulate the genome, it has also led to a great deal of concern about our ability to handle such information. This is another area where the gap between routine genetic testing and research is very narrow. There are several Ethical, Legal and Social Issues (ELSI) which are raised by genetic testing and research which warrant continuous monitoring and responding to emerging ethical issues promptly and judiciously.

General Issues

• The harm may not be physical but can be psychosocial and may produce anxiety, depression of affect family relationships
• Appropriate communication skills are required for genetic counselling which is akin to therapy
• 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 is more important as genetic disorders are generally a societal taboo
• There is a very thin line of distinction and often an overlap between genetic research and services for the physician as well as the patient and therefore adequate safeguards are needed.
• Genetic manipulations may have known or unknown consequences for the future and therefore greater care towards potential dangers is necessary
• Emerging genetic/ genomic technologies bring to the fore newer ethical concerns and issues. There is a need for professionals to keep abreast with knowledge and understand implications of these technologies
• The EC reviewing genetic research should have necessary expertise to understand the ethical implications and provide safeguards for research participants

9.1 Privacy and confidentiality

The investigator should explain to the patient/ participant the specific nature of the confidentiality of the data generated through genetic testing/ research. Disclosure of genetic diagnosis has the potential to cause psychosocial harm in the form of anxiety and depression or familial disharmony, discrimination and stigmatisation of individuals, families or communities, population groups and therefore, needs careful handling.

9.1.1 The investigator must understand that the results generated for health care and for research from the same patient should be kept separately.

9.1.2 Participants should be told of the limits of the investigator's ability to safeguard confidentiality and the anticipated consequences of breach of confidentiality.

9.1.3 The investigator must delink data (in various ways described below) for maintaining the confidentiality to securely safeguard the information. If the result of the research is of benefit to the health of the participant, then with the approval of EC, data could be re-linked for communication of the result.

9.1.4 Pre- and post-test counselling is a must to minimize psychosocial harm and stigmatisation.

9.1.5 Genetic research requires collection of family history and details about other members of the family leading to involvement of secondary participants, which will require informed consent from the latter as information identifies them.

9.1.6 An individual has the right to keep her/ his information generated by screening/testing confidential and not share it with family members to avoid possibility of domestic disputes if the genetic information is damaging (e.g., results revealing non-paternity, disease carrier status or others).

9.1.7 The investigator can not reveal the genetic information to family members without her/ his permission.

9.1.8 If family members are recruited/ tested then their information should be kept confidential from each other by the physician/ investigator.

9.1.9 If disclosure is absolutely warranted to provide treatment or counselling, the physician has to first obtain informed consent from the family member concerned.

9.1.10 If the family member does not consent then the physician should weigh the risks of non-disclosure vs breach of confidentiality and take appropriate decision.

9.1.11 Care must be taken to respect the privacy of all the individuals, especially if large data is generated (Clinical diagnosis, genetic test results).

9.1.12 Methods to mitigate these harms should be described in the proposal.

9.1.13 When predictive and presymptomatic genetic testing is involved or individualised genetic medicine is practiced, there is a need to have a team of Clinicians, Geneticist, Genetic counsellor and Laboratory personnel who should work together.

9.1.14 Storage of samples with potential for future genetic research should be done with appropriate consent and EC review.

9.1.15 Transfer to or sharing of biological material and/ or data with other laboratories within or outside the country should be done as per relevant guidelines.

9.1.16 Handling Intellectual Property Rights (IPR) related to gene patenting and development of newer technologies for commercial gains should follow the applicable National policy/ regulations

9.1.17 Newer genomic techniques for research like Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) may create uncertain evidence at the present level of knowledge, therefore, the confidentiality of data, and pre-test and post-test counselling need to be revisited with an entirely new perspective.

9.2 Informed consent

More stringent norms and highest standards of caution should be followed in the consent process when done for research purposes.

9.2.1 For routine genetic diagnostic testing, written consent may or may not be needed as per institutional policies; however it is required for any research. Informed written consent is a must for presymptomatic testing and Next Generation Sequencing (NGS).

9.2.2 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.

9.2.3 Specific consent is required from the affected proband to share her/ his genetic information with family members who may be benefited from it.

9.2.4 If the research or testing involves a child, appropriate age specific assent (oral/ written) should be obtained (refer section 5 on Vulnerability for further details).

9.2.5 Specific Consent: In addition to the general contents specified under section 4 on Informed Consent Process, the consent form for genetic testing for research should have the following additional elements:-

- The nature of information that would be generated, and the complexity in the generated information

- The nature and consequences of return of results should be clearly explained and specified in the informed consent document (ICD) and the participant offered a choice whether to receive or not that information and incidental findings, if any.
- Direct/ indirect benefits to the participants and their implications. If there are no direct benefits to the participants it should be mentioned in the ICD.
- How the data/ samples will be stored and shared and for how long, procedures involved anonymisation Refer to details in section 10 on Biological materials, Biobanking and Datasets).
- The participants should be given the choice to opt out of testing/ withdraw from research anytime they would want to.
- Sharing of samples with other researchers/ laboratories, ownership rights, IPR concerns, commercialization aspects, benefits sharing, consent types and procedures (refer to Section 10. Biological materials, Biobanking and Datasets for further details)

9.3 Group Consent/ Community Consent

9.3.1 Genetic research on community or population groups generate information applicable to the community/ populations from which the participants were drawn, and therefore, 'group consent' must be taken from the community head and/ or the culturally appropriate authority.

9.3.2 Even if group consent is taken, it will not be a replacement for individual consent. Refer to Section 4 on Informed Consent for further details.

9.4 Storage of samples for future genetic research

Rapid advances in Science and Technology have necessitated the storage of biological materials for future research. The samples from patients with rare genetic conditions, ethnic groups/ tribes/ populations on the verge of extinction, endogamous groups and others have great value and need to be preserved for future research. Refer to details on issues related to biobanking and data sets in Section 10 on Biological materials, Biobanking and Datasets.

9.5 Return of Results

9.5.1 Results cannot be returned for the advantage of participants when the research is done using irreversibly anonymised samples or data as identifying the individuals is not possible.

9.5.2 If there is possibility of returning the results, the report should clearly mention that the test has been done only for research purposes.

9.5.3 Return of the results depends on the research findings. If results are anticipated to be 'actionable', leading to potential benefits of improving health outcome through correction of diet as therapy or prevention (e.g. phenyl ketonuria) by delaying onset or reduction of disease burden, they need to be communicated to the participants. This should also be reported to the participants if they wish to know the results and this must be specified in the ICD. For this, their contact details should be available to do so.

9.5.4 The investigator should work with the local EC to decide on the validity of the research finding and the magnitude of the severity of the potential disease in order to return the results which should be avoided if the logical outcome of the research is expected to be inconclusive and the participants informed about it in the ICD.

9.6 Consanguinity

9.6.1 Consanguineous marriages are in practice in some communities. If there are inherited diseases detected in the family, it is the responsibility of the health professionals/ researchers to inform them regarding the possible implications that may arise due to consanguinity.

9.6.2 Appropriate pedigrees need to be prepared and stored as these can reveal a lot regarding the disease inheritance in affected families.

9.7 Publication Aspects

9.7.1 Publication of pictures, pedigrees or other identifying information about individual or family members or secondary participant(s) should be done with fresh or re-consent.

9.7.2 Features on the face should be masked to prevent identification. If these features have to be revealed for scientific reasons, this fact should be stated clearly in consent form and fresh or re-consent must be obtained.

9.8 Culturally Sensitive Issues

9.8.1 Transmission of the genetic abnormality from parents especially the mother to the fetus could be culturally a very sensitive issue. Such possibility arises when the wife is found to be a carrier of X-linked or recessive disease during routine testing or pre-

natal diagnosis reveals an affected fetus or as a carrier of fatal or late onset disease conditions (e.g. haemophilia, nonsyndromic deafness, mitochondrial conditions where female fetus could transmit the abnormality to next progeny etc. or Huntington's disease etc).

9.8.2 In view of the cultural background of our society, woman is still a vulnerable and exploited participant. Revealing information to the husband or other members of the family that his wife is the carrier of chromosomal abnormality (e.g. balanced chromosomal translocation) leading to recurrent abortions or a genetic syndrome in her child or that she is a carrier of a single gene abnormality 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.

9.9 Conflict of Interest

9.9.1 Direct to Consumer Testing (DTC) in laboratories offering a battery of genetic tests is rapidly growing. While this ensures patient's autonomy to undergo testing, it is important that the sensitivity and specificity of these investigations and the ability of the laboratory personnel to interpret the result is ensured before arriving at a diagnosis. A researcher's alliance with such a laboratory would constitute conflict of interest.

9.9.2 When research is conducted by commercial companies, steps should be taken to protect researchers and participants from possible coercion or inducement. Academic or research institutions involved in such an alliance 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).

9.9.3 An EC should determine if the conflict of interest could 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.

9.9.4 Prospective participants in research should also be informed of the sources of funding of research, so that they become aware of the potential conflicts of interest and commercial aspects of the research.

9.10 Defining risks and benefits

9.10.1 Potential risks and benefits should be discussed thoroughly with prospective participants.

9.10.2 In genetic research, the primary risks are psychosocial rather than physical.

9.10.3 Adequate counselling should be given to participants on the implication(s) of genetic information they receive.

9.10.4 Pre- and Post-test non-directive counselling should be given by those persons who are qualified and experienced in communicating the meaning of genetic information as some conditions may require termination of pregnancy or selection of embryos to avert birth of a genetically abnormal child/ fetus. Appropriate options should be provided to the family to come to a decision while disclosing the result.

9.10.5 While general principles of counselling require presence of both the spouses, necessary care and caution must be taken not to end up breaking the families. Truthful counselling with extreme caution and patience is essential to explain the situation in a proper perspective in order to minimize the psychosocial harm.

9.10.6 Genetic testing and research should be preceded and followed with non directive genetic counselling as some conditions may require termination of pregnancy or selection of embryos to avert birth of a genetically abnormal child/ fetus. Appropriate options should be provided to the family to come to a decision while disclosing the result.

9.11 Vulnerability

9.11.1 Genetic testing and research often require dealing with persons who are unable to protect their rights and safety and may be vulnerable like children, mentally and cognitively impaired individuals, people with rare diseases and others.

9.11.2 General and specific guidelines have to be followed as per section 5 on Vulnerability.

9.12 Fetal Autopsy

9.12.1 Fetal autopsy should be done after informed consent, preferably from both parents.

9.12.2 Relevant samples may be stored for possible future use following the guidelines of Biological materials, Biobanking and Datasets Section 10.

9.12.3 Adequate genetic counselling should be done to explain the requirements and benefits of autopsy to the family.

9.13 Issues related to Adoption

9.13.1 There will be occasions when the prospective adoptive parents desire to screen a child for genetic diseases before they reach a decision to adopt that child. In such situations, indications for pre-adoptive screening will be similar to screening of children of biological parents.

9.13.2 Applying the "Principle of Justice" for equitable distribution, the adoptive parents need not know more information at the time of adoption than a biological parent would know at the time of birth. This stems from the concern that the harm of screening should not be more than the benefit it might cause.

9.14 Role of Medical Team in Genetic testing and research

9.14.1 Adequate awareness should be created by professional societies and universities regarding genetic diseases, their prevention, screening and prenatal diagnosis amongst the Obstetrician, Geneticists, Paediatricians, Neonatologists, radiologists, laboratory professionals and others.

9.14.2 The laboratory personnel, attending physician and the counsellors should possess a formal qualification/ sufficient experience in genetics or should have undergone training in genetics and also inter-professional relationship if possible.

9.14.3 The concerned specialists dealing with genetic disorders should ideally undergo training in genetic counselling and devote time to enable them to handle sensitive issues appropriately.

9.15 Quality standards of the laboratory

9.15.1 Any misinterpretation of genetic results or misdiagnosis may lead to psychological harm, and unnecessary or inappropriate intervention. Hence it is important to set standards for laboratories to ensure that the test results are reliable, the manpower is competent and the care provider is updated in developments in genetics.

9.15.2 All laboratories offering genetic testing should consider undergoing quality accreditation standards which are specific to genetic testing laboratories.

9.16 Genetic Diagnosis/ Testing and Screening

History and 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. Privacy and confidentiality issues involved in this process are given in detail at 9.2.

9.17 Predictive Genetic testing

The results of genetic test in diseases which are multifactorial in origin, have a polygenic basis, involve multiple genes or gene – environment interaction, must be communicated carefully so that unnecessary worry or fear is not created in the mind of individuals.

9.18 Genetic Screening

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

9.18.1 It is essential that screening must be purposive. Besides validation of screening tests, it shall also be ensured that a suitable intervention and counselling is made possible.

9.18.2 Those being screened are entitled to receive sufficient information about what is proposed to be done, reliability of the screening test, and what will be done with the collected samples.

9.18.3 Although screening may be permissible to allay anxiety, the response of different individuals might vary, which should be borne in mind by the health care provider.

9.18.4 Depending on the nature and pattern of inheritance of the genetic defect the implication for other relatives, children and future offsprings should be understood.

9.18.5 Confidentiality should be maintained in handling of results with emphasis on responsibility of individuals with an abnormal result to inform partners and family members. 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.

9.18.6 Screening tests should be sensitive enough to identify a significant proportion of affected persons (the detection rate) with minimal misidentification of unaffected persons (the false positive rate). Screening tests do not aim to make a diagnosis, but rather rationalise the use of more accurate confirmatory tests.

9.19 Prenatal Screening

It is aimed to screen mothers and fetuses who are at high risk of having functional or structural defects including chromosomal and single gene disorders. There are many screening tests which are recommended in routine practice.

9.19.1 Biochemical and ultrasound screening-Using various combinations of serum screening and ultrasound, screening tests are done either during first (dual marker) or second trimester (triple or quadruple screening) for aneuploidy screening. It is important to discuss about detection rates, false positive and negative results.

9.19.2 Ideally all antenatal mothers (not only high risk) should be offered screening routinely.

9.19.3 It is to be noted that a positive screening test does not mean that the fetus is affected nor does a negative test confirm an unaffected fetus.

9.20 Newborn screening (NBS) – NBS is a robust modality of secondary prevention leading to early diagnosis with timely intervention and should ideally be in a program mode and not offered as a 'test'.

9.20.1 Screening of newborns is ideal to detect those genetic diseases the serious effects of which could be prevented by a suitable intervention such as a special diet or drug e.g. hypothyroidism, phenylketonuria and many other inborn errors of metabolism.

9.20.2 It should not be generally done when there is no existing therapeutic modalities available (e.g., special diets) or treatment is very expensive or its cost is not provided routinely by the government and is not affordable by most families (e.g., Lysosomal storage disorders) or there is no known intervention for management.

9.20.3 Community education regarding NBS should precede the initiation of the program.

9.20.4 Availability of facilities for confirmatory diagnosis and experts for management of the disorders has to be in place before initiating the program.

9.20.5 Use of advanced technologies like chromosomal micro array (CMA) and Whole Exome sequencing (WES) for NBS will generate many new dimensions for debate in this area.

9.21 Screening of children

9.21.1 Children should not be screened for carrier status or disease merely at the request of their parents.

9.21.2 The child's autonomy should dominate over parental autonomy.

9.21.3 Testing of children should be deferred until they are able to comprehend and are able to participate in the decision making process, unless early intervention based on result of the test is likely to be of direct therapeutic benefit to them.

9.21.4 Screening for late onset diseases should not be done in children.

9.22 Screening for carrier status

9.22.1 Single gene – If there is a family history of a single gene disorder (Autosomal recessive, X linked), the individual should be tested after administering informed consent when she/ he is able to comprehend the risks and benefits of screening. Stigmatization for carrier status is common; therefore, the information should be kept confidential.

9.22.2 Chromosomal- If there is a family history of balanced translocation in any individual, then immediate relatives may be at risk. The same principles as for carrier testing should be followed.

9.23 Population screening – Genetic disorders can be population specific (e.g. recessive disorders in Ashkenazi Jews, Cystic fibrosis in many European countries) or even within a country or region (e.g. thalassemia and Sickle cell disease in some population groups).

9.23.1 Population screening should not be undertaken without prior education of the population to be screened and counselling should be integrated with the program.

9.23.2 Screening test should be robust with acceptable sensitivity and specificity.

9.23.3 Community permission/ group consent as well as individual informed consent should be taken.

9.23.4 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 EC.

9.24 Invasive Testing for Prenatal Diagnosis

9.24.1 Preliminary genetic counselling of the women for invasive prenatal diagnosis should include the following –

- Risk of fetus being affected
- Natural course and prognosis of the specific disorder
- Risks and limitations of the invasive procedures to be used
- Time required before a report can be issued
- Possible need for a repeat procedure in the event of a failed attempt
- Limitation of a test due to laboratory error

9.24.2 Utmost caution should be taken while reporting the fetal status after prenatal testing. In India carrier status of a female fetus for X- linked disorder should not be reported

as even revealing that for a recessive disorder can make the couple anxious because of its future implications. Using the terms “fetus likely to be affected” or “unlikely to be affected” in the report are more acceptable.

9.25 Pre-implantation genetic screening and diagnosis (PGS and PGD)

In this technique, *in vitro* screening is done on early embryos for a panel of common genetic disorders (e.g., aneuploides), specific disorder (if there is a family history or proven carrier status in parent(s) and unaffected embryos are implanted.

9.25.1 This obviates the need for invasive testing and risks associated with it and also termination of affected fetus which is traumatic for the family.

9.25.2 More recently advanced techniques like CMA are being used for PGS and NGS for screening which might theoretically raise the ethical issues regarding eugenics and designer babies based on selection of embryos.

9.26 Non Invasive Prenatal screening/ Testing (NIPS/ NIPT)

Recent advances in genomic technologies have resulted in the shift of antenatal aneuploidy screening towards the development of non-invasive pre-natal screening (NIPS) methods by using cell-free fetal (CFF) DNA sequences isolated from a maternal blood sample. As the test is done on maternal blood, the risk of invasive procedure is avoided and many high risk mothers opt for it. However there are several limitations which should be clearly explained.

9.27 Gene Therapy

9.27.1 Somatic cell gene therapy is 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.

9.27.2 Prior to obtaining approval for initiating a gene therapy trial, an approval from Department of Biotechnology (DBT) has to be obtained for the gene construct and the local EC.

9.27.3 If the trial is for a product for commercial use or for marketing purpose approval needs to be taken from CDSCO.

9.27.4 All gene therapy trials should have the provision for long term surveillance.

9.27.5 Informed consent must be taken especially regarding uncertainties about outcome.

9.27.6 Children could be candidates for therapy, if the therapy is meant for a childhood disorder.

9.27.7 Germ Line Therapy is prohibited under the present state of knowledge.

9.27.8 Eugenic Genetic Engineering for changing/ selecting/ altering genetic characteristics (so called designer babies) is prohibited. These 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.

9.27.9 The influence of environmental interaction on the expression of genetic characters is poorly understood. It would be unethical to use genetic engineering for improvement of intelligence, memory, personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics etc. even if specific gene/ genes are identified in future.

9.28 Use of new technologies

New technologies like Chromosomal Micro array (CMA), Whole Exome Sequencing and Whole Genome Sequencing (WES & WGS) and Clustered regularly interspaced short palindromic repeat (CRISPR) technology have unmasked new knowledge that could find solutions to diseases or inherited disorders but could also create ethical debates due to uncertain future. These techniques have made it possible to study genome. Each individual's genome is a unique and definite identity, which in spite of anonymisation of such data will always be associated with individual's identity, and this would be in conflict with the principle of privacy. With the advent of digitised medical records of such sophisticated data, additional efforts should be made to maintain confidentiality.

9.28.1 **Chromosomal Micro array (CMA) –** Interpretation of CMA results should be done carefully since on many occasions the Copy number variation (CNV) identified may be variation of unknown significance (VOUS) reported or unreported which may not explain the phenotype.

9.28.2 **Whole Exome Sequencing and Whole Genome Sequencing (WES & WGS)**

These high through put Next Generation Sequencing techniques are used for sequencing all the exons (WES) or the whole genome including introns (WGS). These techniques are increasingly being used in clinical practice, particularly WES and have opened up a new challenge for the counsellors as well as patients.

9.28.2.1 These genomic techniques identify pathogenic mutations or variations of unknown significance in many other genes, hidden genetic disorders or

cancers which may manifest later. The individual should be informed and asked whether she/ he will like to know about unrelated genetic mutations.The results should always be interpreted keeping in mind the coverage of genes of interest.

9.28.2.2 Families/ individuals opting for the test should be counseled before conducting the test regarding grey areas in these upcoming technologies. They should be aware that WES/ WGS may not give conclusive results.

9.28.3 **Clustered, regularly interspaced, short palindromic repeat (CRISPR) technology**

This is a powerful technology which efficiently edits plant and animal DNA. Researchers are hoping to use this genome editing technique to alter human genes to cure and eliminate certain genetic based diseases. Experiments done so far have shown that technique can be used to rapidly, easily and efficiently modify genes in a wide variety of cell types and in organisms. CRISPR works as a pair of DNA scissors, and Cas9 is the protein in the system that unzips DNA and finds the target by matching the DNA sequence against a snippet of its guide RNA. When Cas9 finds its target and snips it, there are concerns about its risks, which blur the excitement about its usefulness.

9.28.3.1 Despite the promise of the technique there could be a possibility of encountering error in genetic engineering.

9.28.3.2 It could be used for bioterrorism.

9.28.3.3 It could be used to change harmless genes as for eye colour leading to designer possibilities.

9.28.3.4 Cas9 will sometimes identify a wrong target even when up to five of the guide RNAs do not match the DNA—hence the off-target mutations may cause disease; alter germline or DNA of future generations of humans.

9.29 Permanent genetic modification of human embryos

The concerns are more social, including questions about the right of unborn babies and the roles of humans in making permanent genetic changes.

9.30 Genome-wide association study (GWAS)

Genetic epidemiology, also known as whole genome-wide association study, involves an examination of many common genetic variants in different individuals to see if any variant is

associated with a trait. GWASs typically focus on associations between single- nucleotide polymorphisms (SNPs) and traits like major diseases particularly multifactorial disorders.

9.30.1 As in other techniques there is a possibility of getting variations of known or unknown significance and participants should be aware of these facts.

9.31 Misuse of genetic technology

Prenatal Sex Selection - To prevent misuse of genetic tests, particularly pre-selection of sex, the Government of India has enacted "The Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition of Sex Selection) Act 1994, amended in 2003". All researchers in this area shall follow the provisions of this Act. Prenatal Sex determination is prohibited by law for sex selection of the foetus.

9.31.1 Misuse of genetic information by insurers or employers: Knowledge of genetic information of an individual/ family/ community/ population might be misused by the insurers/ employers leading to discrimination and psychosocial harm. Hence, the information about patient's disease and investigations must not be shared with anyone without the consent of the individual concerned.

9.31.2 Genetic manipulations fall under the area of genetic research. All protections for the participants including ethical review and informed consent have to be in place. EC must carefully examine such proposals and issues related to conflicts of interest between an individual, the family and society at large.

10. Biological Materials, Biobanking and Datasets

10.0 Biological materials or biospecimens include biological fluids such as blood, dried blood spots, body fluids, urine, tissues, organs, cord blood, ovary, semen or embryo. These may be stored or prospectively collected. A repository or biobank is an organized collection of resources that can be accessed to retrieve human biological material and data. The bioresources would therefore, be left over samples after clinical investigations or research project, biopsy material, surgical or autopsy specimens/ tissues, embryo or foetus, cell lines, waste materials like abandoned organs/ tissues. Repository activities involve three components: Collection of biospecimens and/ or data; Storage of biospecimens and data including its management; and Retrieval and disbursement to the investigators.

A Dataset is an organized collection of data and information maintained in physical and/ or electronic/ digital form that can be used for biomedical and health research. Besides data related to biospecimens as in biobanks, there are other repositories like disease registries, health surveys, disease surveillance, census data and even personal health records in healthcare institutions which may have huge potential for subsequent research. The data may be based from small numbers to whole population or major parts of it, e.g. Iceland decode biobank, Euro BioBank, Estonian Biobank, UK Biobank, GenomEUtwin etc.

10.1 Biobanking

A biobank is an organized collection of human biological materials with usually associated dataset stored for years in appropriate facilities for research and potential commercial purposes. The space occupied by organized collection of these materials and data is termed biorepository. Research on such biospecimens and/ or related datasets may not directly involve the individuals. Biobanks involve governance of collection of biological material, processing, storage with associated data, and dissemination of samples and/or data through sharing with other researchers and overarching ethical oversight. The biological materials could be kept for research, assisted reproductive technology (ART) purposes or for forensic purposes. The stored samples in these biobanks can range from small numbers in researcher's refrigerator to Departments, research institutions including Universities and non-profit organisations, judiciary custody, pharmaceutical companies and may extend into large warehouse like facilities at single site or a chain of facilities with central co-ordination. These give medical,

genetic and life-style related data.

Biobanks can also store non-human materials such as plant, animal, microbes, and parasites etc., but for the purpose of these guidelines this section will only pertain to human biomaterials and/ or related data.

As biobanking concerns storage and research at a later time, the ethical issues pertaining to consent requirements for the collection and banking and further uses of tissue and DNA samples and/ or data are same but with greater responsibilities concerning their ownership, access and benefit sharing to the individual or community. Therefore, to prevent any exploitation and protect the rights of donors, the main requirements are individual informed consent, approval of the EC and the Repository Governance Committee and post research benefit sharing, wherever applicable.

10.1.1 Types of Samples (Table 10.1)

Table 10.1

Identifiable	Direct link of sample/ data to the participant's identity.
Coded	Indirect link of sample/ data to the participant's identity with restricted access. This link could be relinked if required; therefore, it may also be termed reversible anonymisation.
Anonymised	Systematic de-identification, reversible or irreversible: Link of samples/data to personal identity is reversibly or irreversibly cut.
Anonymous or unidentified	No identifiers are present from the start or if collected is not maintained. Such samples are received by Biobanks without any identifiers and supplied to researchers.

10.1.2 Privacy of donor and confidentiality related to biological materials and/ or data

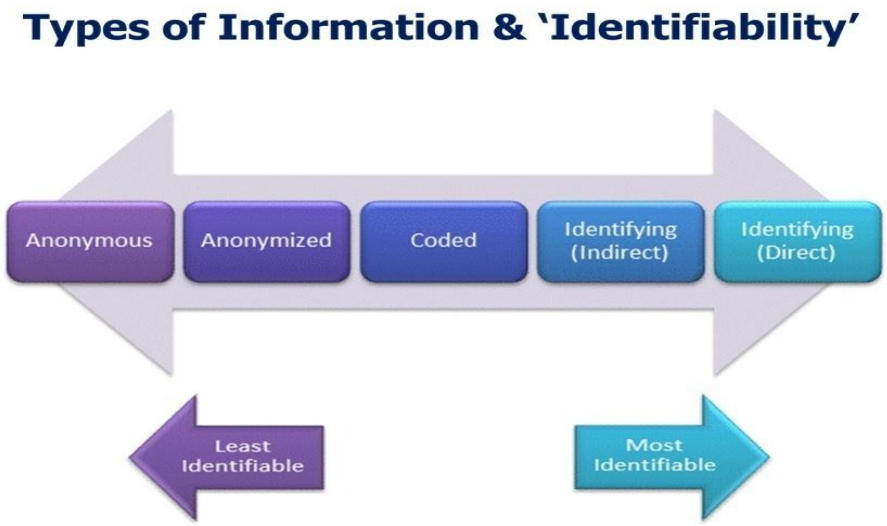
This pertains to both personal identifiers and the related data of the participant (Table 10.2).

Table 10.2

1. Procedure of anonymisation minimizes the connection between the identifiers and the stored sample or medical data by delinking the person from her/ his biological material.
2. Maintaining confidentiality of data and respecting ethnic identity is of prime importance especially in population based genetic studies.
3. More precaution should be sought when the research pertains to research on stigmatizing diseases.
4. Maintaining confidentiality of data and respecting ethnic identity is of prime importance especially in population based studies or genetic studies.
5. When data pertains to epidemiological and public health practice or research, it may be dealt in the manner described under section 7. Epidemiological & Public Health

Research for details.

The following spectrum shows how the possibility or degree of ease to obtain information on personal attributes of biospecimens and/ or data is dependent on the confidentiality aspect of identifiability, which increases as the shift to right occurs:



10.2 Storage of Biospecimens and Data with their Personal Identifiers

Informed consent, confidentiality, privacy, and re-consent are largely influenced by degree of identifiability, whether the biospecimens and data are anonymised or not. As a general principle, research must be conducted as far as possible on least identifiable data. However, under certain circumstances, some degree of identifiability may have to be retained for reasons related to the research. For example, anonymised data or specimens will not allow later withdrawal of consent by an individual, while in the coded category, this will be possible. In the latter scenario, the custodians of the respective biorepository or biobank have greater responsibility to take adequate measures to safeguard the codes and the data so as to respect the privacy and confidentiality of individual research participants. Permissibility of a certain research design, acceptability of risks versus benefits, and adequacy of the informed consent, will thus have to be assessed by EC on a case to case basis, taking into account specific contextual and potential vulnerability factors of the participants and the sensitivity of the proposed research.

10.3 Ethical issues related to Donors

10.3.1 Informed consent for biobanking poses specific ethical issues as the aims of scientific study based on which biospecimens are collected and stored in biorepository are not defined clearly at the time of collection when there are no specific end points and there is a time lag between the collection of the sample and its use in research.

10.3.2 The issues involve multiple stages when consent needs to be administered – storage analysis of the biospecimens use of data linked to the sample incidental findings return of results to the participant sharing of the sample/ data with other investigators/ national or international institutions multicenter and multinational collaborations and potential commercialization raising issues of access and benefit sharing.

Following are examples of different types of consent process and their implications (given in Table 10.3) -

Table 10.3

1. Blanket or Broad consent It is an open consent given only once to collect the sample, store it and use it for any research at any time in future without the need to get back to the individual for a re-consent. A consent model that allows for current and future access and use of samples or data for research without necessarily specifying what the focus of such studies might be.
2. Tiered Consent This model of consent offers several options to the participants to choose. It includes opt-in option for future use specifying general permission, or use only related to the original topic, or use for topics unrelated to the original one for which specific consent would have to be taken. This process is considered dynamic. They can opt out anytime if they do not wish to continue their participation without assigning reasons. It also takes into consideration return of results for which also options are provided for consent.
3. Specific Consent Participants are re-contacted for every new use of their stored samples/ data if the scope of research is outside what they had originally consented for.
4. Delayed consent It may be administered in the post-medical procedure period when biospecimen or data may be collected for appropriate research from critically ill patients who may not have given prior consent for research. Consent may be taken from the participant or LAR when it is practical. Such research can be done only after approval from the EC if convinced about benefit to the individual or society.
5. Presumed consent At the time of collection of samples participants are told that these would be used for all future research unless they explicitly deny permission to do so.
6. Withdrawal of consent or destruction of sample The donor has the right to ask for destroying her/ his collected sample(s) and discontinue/ withdraw from participation in the research. In longitudinal studies participant may withdraw from one component of the study like continued follow-up/ data collection when withdrawal may be referred to as partial.

7. Waiver of the Consent

While using anonymised (de-identified) samples/ data, researchers should seek the approval of the EC of the institution or the repository for waiver of consent from the donors.

8. Re-consent

- **Secondary or extended uses of stored samples/ dataset:** In such an instance one of the preliminary considerations for ECs must be to identify the circumstances under which the research requires re-use of collected identifiable biological material to generate the data or utilize the pre-existing identifiable dataset. This must also include review of the informed consent obtained originally to see if re-consent is warranted. There may be situations where consent would be impossible or impracticable to obtain for such research, in which case the research may be done only after independent evaluation by an EC." (Declaration of Helsinki, October 2013)
- **Pediatric donors:** In longitudinal studies once the child donor attains the legal age of consent a re-consent should be sought for the storage and use of her/ his tissue or sample. In pediatric biobanks or biobanks with pediatric samples it is important to address the issue of children reaching legal age of consent. Sometimes re-contact may lead to withdrawal resulting in limited data analysis which may lead to bias or it could evoke emotional distress about the past research. On the other hand re-consent may give the participant a power to agree. A biobank should decide the policy it would like to adopt for re-contact.

10.4 Ethical issues related to Research

The biobanks can use the stored material/ data for doing research themselves or they can outsource or supply the samples/ data to other researchers or institutions.

10.4.1 Transfer of Biospecimens

Material transfer agreement (MTA) should be executed, if the biospecimens are likely to be shipped from host institution to collaborating institutions within country or abroad. EC should oversee the process of the in-country and international material transfer. Mandatory regulatory clearances with appropriate MOU are required if biospecimens are to be sent overseas.

10.4.2 Secondary or extended uses of stored samples/ Reconsent

EC will examine circumstances under which originally the data or the biological material was collected and informed consent obtained. Then it will decide on a case-to-case basis about anonymisation/ informed consent waiver or re-consent. The EC must examine that (Table 10.4)

Table 10.4

1. the proposed use is in line with the original consent given for the earlier study and look at the validity of the objectives of the new study;
2. provisions for ensuring anonymity of the samples for secondary use are stated;
3. for postmortem uses of samples the permission of LAR should be obtained; and
4. waiver of consent is given whenever the donor is not traceable, the sample/ data is anonymised or it is impractical to conduct the research.

10.4.3 Return of research results

There are several possibilities which should be enlisted in the participant information sheet/ informed consent document for biobanking (Table 10.5).

Table 10.5

1. If the findings are in an aggregate form, the participants will receive no feedback on individual data.
2. There is also the risk of "informational arm" which can occur if participants are provided feedback when they are not prepared to face it or it is not actionable or when such information is unrelated since this could lead to distress in the absence of appropriate mechanism to deal with the situation.
3. Research findings in aggregate form must be discussed with the community before wider dissemination wherever applicable especially in research involving populations who may face particular vulnerabilities e.g. tribal populations' ethnic groups people living with certain diseases etc.
4. It may be a good approach to inform donors at the time of sample collection that novel information beneficial or non-beneficial may emerge from the study on their sample for which options must be offered whether to receive such information. Participants may also choose not to be contacted about their results. Another alternative is to give participants the option of receiving an aggregate report of all the results of the study through a newsletter email, phone call, which however does not reveal individual results. Such information may be released to the donor healthcare provider or the donor's family. This becomes a shared benefit for the community. The aforementioned options may be incorporated in a tiered consent.

10.4.4 Ownership of the biological samples and data: The donors maintain ownership and should be able to withdraw both their biological material donated to the biobank and the related data unless the data is required for outcome measurement. Complete anonymisation would practically make biological materials ownerless as the original donor loses the right of ownership. Biobanks/ Institutes are the custodians or trustees. Researchers have no claim for either ownership or custodianship.

10.4.5 Benefit sharing (Table 10.6) –

Table 10.6

1.	The informed consent document should address the use of biospecimens and/or data by private or for-profit entities and the possibility of research leading to future development of commercial products. The document should describe whether donors, their families, or communities would receive any financial or non-financial benefits by having access to the products, tests, or discoveries resulting from the research.
2.	The benefits accrued, if any, should be returned to the communities from where the donors were drawn in community based studies. This should be mentioned in the original consent form.
3.	To the maximum extent possible, benefits should be indirect or in kind.

10.4.6 Role of Ethics Committee

Research proposals, which require biorepository services including material transfer, should be reviewed by EC, either an institutional one or that of the biorepository.

10.5 Biological material/ data in forensic departments of laboratories

Specimens collected for forensic purposes and related or unrelated data (DNA profiling) offer a good source for academic research after the initial purpose has been served. Data sharing with researchers across the globe is a common practice for refining techniques to develop biomarkers, which could identify missing persons in most difficult circumstances (e.g. highly decomposed bodies, disaster situations etc.). In academic institutions there is a demand for organs and tissues for education, training and research purposes.

10.5.1 Informed consent – If written consent by the deceased person permitting use of organ or tissue is not there, family can be approached for consent for use of left over organ or tissue.

10.5.2 No consent would be required if sample or data is anonymised or if the deceased has no claimant.

10.5.3 Forensic official will be authorized to give permission for use of material/ data from its sources and be responsible for use of unclaimed cadavers.

10.5.4 The quantity of tissue taken should ideally be minimal if possible, particularly if it is seen externally on the body in order to preserve the dignity of the dead and be culturally acceptable by the next of kin or closest relative or friend.

10.5.5 The information in the informed consent document should state what tissue/ organ will be retained, who will be the custodian, duration of storage of sample, what type

of research would be conducted and how the remains will be disposed.

10.5.6 Genetic research or revelation of any other stigmatizing factors like HIV etc. in the deceased may have implication for family members. All ethical requirements as in the case of live participants should be followed.

10.5.7 Role of EC - The type of consent – broad with or without option to opt-out or specific - and from whom whether the family, closest relative or friend or anonymisation should be approved by EC.

10.6 Governance of Biobank/ Biorepository

Institutions where data are collected and archived must have a governance structure in place with following requirements for regulation:

10.6.1 Biorepository should have its own Technical authorization committee with representation of both science and ethics and external members. This committee should function in tandem with EC.

10.6.2 A Technical authorization committee, indigenous to biorepository, should govern disbursement of biospecimens and data to researchers. The same committee should also oversee regulatory aspects like execution of MTA (Material Transfer Agreement) or DTA (Data Transfer Agreement) for transfer of biospecimens to other institutions.

10.6.3 Stand-alone huge repositories should have separate Technical Authorization and ECs to undertake above mentioned tasks.

10.6.4 Biobank should have well-structured SOPs and clear guidelines for collection, coding, anonymisation, storing, access, retrieval and sharing of biospecimens and data.

10.7 Special issues related to datasets

10.7.1 While the primary objective of data collection and storage in some of these databases may not be research, these repositories or datasets offer a huge potential for subsequent research. With advances in Information Technology (IT) and decreasing costs, such repositories and datasets are increasingly being sought after for research purposes. Along with the increasing ease of establishing and maintaining such repositories for prospective research, there is also a proliferation of tools for data mining and other data science tools that can be employed on existing databases for research purposes. Irrespective of whether health research was initially an objective of collecting data and storing in databases, whenever such repositories are used for

other purposes of research, it must follow the expected requirements of any other health related research with due diligence, including review by an EC.

10.7.2 Databases maintained in electronic/digital formats, linked by internet or other networks, maintained using cloud computing technologies, and those associated with 'Big Data' initiatives, may pose additional risks to privacy and confidentiality than what is described under biobanks or traditional paper based data repositories. Hence, in such situations all reasonable measures must be adopted to respect and protect privacy and confidentiality of individuals. These include (Table 10.7) –

Table 10.7

1. ensuring physical safety and security of the involved devices and computer servers; ,
2. data security measures such as password protection;
3. differential and role-based access to data elements for members of the research team;
4. use of data encryption when data is transferred from one location/device to another;
5. Benefit sharing with owners and related legal Issues since unlike some other countries India does not have a Data Protection Act.as yet.

10.8 Contingency Plan

One of the important but often neglected ethical issues related to biorepository is legacy or contingency plan. Institutions should develop the contingent plans for sustainability of the biobanks.

11. International Collaboration

11.0 The scope of international co-operation and collaboration in biomedical and health research has gained momentum in recent years to such proportions that it could potentially have exploitative connotations with commercial and human dimensions. On the one hand, collaboration in medical research is underpinned by a humane interest for the health of civil society by adapting uniformly applicable universal ethical principles; while on the other hand, it could be seen as exploitative, by giving the impression of unnecessary 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, ethical review procedures etc., necessitate an ethical framework that is based on equality and equity to guide such collaborations . The same is applicable to research undertaken with assistance and/or collaboration from international organisations (public or private).The collaboration may involve either implementation of multiple components of the research or even a single component like laboratory testing. There are formal inter-country bilateral/ multilateral collaborative arrangements between Indian research bodies/institutions and similar bodies/institutions of several other countries. The review, conduct, monitoring of international collaborative research in India should be guided by ECs which should be aware of different requirements of various funding and regulatory agencies.

Types of International Collaboration (Table 11.1)

Table 11.1

1. Funding by International Agencies e.g. UN agencies, NIH, Welcome Trust, World Bank, Bill and Melinda Gates Foundation and others.
2. Academic Collaborations with Foreign Institutions, Universities, Organisations, Foundations with or without external funding.

All biomedical research projects involving foreign assistance and/or collaboration should be submitted to the Health Ministry's Screening Committee (HMSC) for consideration and approval before initiation (details can be accessed at http://www.icmr.nic.in/guide.htm). The secretariat for HMSC is at the Indian Council of Medical Research (ICMR) Headquarters, New Delhi. According to the guideline, all research involving international collaboration; either technical, financial, laboratory or data management must be submitted to HMSC. Autonomous institutions including

Institutes of national stature (like All India Institute of Medical Sciences, Post Graduate Institute of Medical Education and Research, Jawaharlal Institute of Postgraduate Medical Education and Research, Sanjay Gandhi Post Graduate Institute, Sri Chitra Tirunal Institute of Medical Sciences and Technology) and institutions under the administrative control of Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare (MoHFW) and State health authorities, as well as Deptts like Indian Council of Medical Research (ICMR), Council of Scientific and Industrial Research (CSIR), Indian Council of Agricultural Research (ICAR), and Departments like Department of Biotechnology (DBT) and Department of Science and Technology (DST) for their respective institutions may take in-house decisions on their proposals for foreign collaboration involving transfer of human biological material by following the guidelines in this regard and then sending the proposals to the HMSC for final endorsement [Ref. F. No. L. 19015/53/97 IH (Pt) dt 19/11/1997]. The exchange of material is envisaged as part of a collaborative research proposal as a whole must be routed through appropriate authorities. While the ethical review and approvals are subject to the national regulatory framework, international collaborations are subject to appropriate considerations of universal ethical principles. The finer specifics recommended in Indian context may vary from other countries and agencies.

11.1 Special Considerations

11.1.1 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.

11.1.2 The Indian participating centres should function as equal partners with the collaborator(s) and sponsor(s) in terms of ownership, analysis, dissemination, publication and intellectual property rights as may be appropriate. There must be bilateral/multilateral free flow of knowledge and capacity.

11.1.3 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 EC of Indian collaborator's institution and that of foreign collaborator.

11.1.4 Different kinds of research have their own particular scientific requirements and specific ethical challenges. The selection of study population should be justified in scientific and ethical terms. Generally, early phases of clinical trials, particularly of drugs, vaccines and devices, and research on other interventions, should be conducted in communities that are less vulnerable to harm or exploitation. However, for valid scientific and public health reasons, if sufficient ethical safeguards are ensured, it may be conducted on them after obtaining relevant regulatory clearances.

11.1.5 The nature, magnitude, and probability of all foreseeable harms resulting from participation in a collaborative research programme should be specified in the research protocol and explained to the participants reasonably well.

11.1.6 The research protocol should outline the benefits that persons/ communities participating in such research should get. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation.

11.1.7 All participants in the research should have access to the standard of care available in India.

11.1.8 The IEC should ensure and monitor the clinical care, compensation, insurance cover and other supports provided to the participants, as may be applicable.

11.1.9 The burden and the benefit should be equally distributed amongst participants recruited by all collaborating institutions.

11.1.10 Research that will be conducted in India should be relevant to the health needs of India and should not have any bearing on sensitive, religious, regional and other relevant issues.

11.1.11 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. An appropriate Memorandum of Understanding (MOU) should be in place to safeguard the interests and ensure compliance.

11.1.12 Any research involving exchange of biological material/ specimens to the collaborating institution(s) outside India must have a Material Transfer Agreement (MTA) which should include justification for the purpose, quantity, issues related to

confidentiality, IPR, post analysis handling of the leftover biological materials, safety norms etc.

11.1.13 Export of all biological materials will be covered under existing GOI guidelines for Transfer of Human Biological Materials. Research projects requiring transfer of biological material transfer, may be considered by the EC on case-to-case basis. Collaborators should obtain appropriate regulatory clearances that may be applicable, e.g., Environmental Protection Act, 1986, The Biological Diversity Act 2002 of Ministry of Environment and Forests, Drugs and Cosmetics Act 1940 and Rules 1945 and the relevant amendments. Such exchange of material from and to WHO collaborating/ Reference Centres for specific purposes and for individual cases for diagnosis or therapeutic purposes need no permission.

11.1.14 The Indian participating centre(s) must have appropriate regulatory approval and registration for receiving foreign funds for research (under Foreign Contribution Regulation Act- FCRA).

11.1.15 There should be a mechanism for communication between the ECs of different International participating centres. In case of any conflict, the decision of the EC in the Indian participating centre(s) and the law of the land shall prevail.

12. New Technologies

12.0 New Technologies offer a significant improvement over the established medical therapies and technologies for a given process in a specific context. The field is complicated by highly uncertain scientific assumptions and most often inconclusive evidence. Therefore, ethical positions in this regard are still evolving and some more experience will be required to consolidate them on firmer terms. Health technologies may work on new technological principle(s); new application of an existing technology; extension of existing technology, not currently used on body parts/ organs/ patient population; or new interface with any other medical device/ medical IT system. The guidelines in this section have covered the following new technology segments viz. Synthetic Biology, Medical Devices including implants and IT and Nano-technology.

12.1 Synthetic Biology

Synthetic biology is the application of science, technology and engineering to 'facilitate and accelerate the design, manufacture and/ or modification of genetic material of living organisms'. The ethical, legal and social issues pertain to impact of this science on society, biosafety, biosecurity, intellectual property rights, governance of such research and socio-economics.

Creation of organisms, molecular compounds and biological systems by manipulating biology through standardized engineering techniques has led to the rise of biotechnology industry which includes genetically modified organisms, stem cells, cloning, artificial life forms like bio fuels, bio weapons, vaccines, diagnostics etc. Software and bioinformatics as design tools along with the constructional and diagnostic tools play a major role in the synthesis. EC review, pre-market approval and registration should be aimed at protection of human beings and environment.

12.2 Medical Devices including implants & Medical IT

The ethical issues in medical devices and IT (in medical technology) research are broadly the same as for any other research. However, there are important differences in the regulatory context, research environment and methodology, and particularly in the area of investigation design, given the complexity there is a well-established system for evaluation of newly developed medical devices.

12.2.1 Medical Devices

Any instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or other similar or related article, intended by the

manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of (Table 12.1)

Table 12.1

1.	diagnosis, prevention, monitoring, treatment or alleviation of disease;
2.	investigation, replacement, modification, or support of the anatomy or of a physiological process;
3.	supporting or sustaining life;
4.	control of conception;
5.	disinfection of medical devices; and
6.	providing information by means of *in vitro* examination of specimens derived from the human body.

It does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. They may be critical or non-critical, intrinsic or extrinsic. Only some devices are notified. They are classified as given below from regulatory point of view (Table 12.2).

Table 12.2

Class	Level	Devices examples
A	Low risk (Class A)	Bandages/ tongue depressors
B	Low-moderate risk (Class B)	Hypodermic Needles/ suction equipment
C	Moderate-high risk (Class C)	Lung ventilator/ bone fixation plate
D	High risk (Class D)	Cardiac stents/ implantable defibrillator

12.2.1.1 **IT in medical technology**

Computer hardware and software that deals with the storage of data, retrieval, sharing, and use of information on health care and research and knowledge for communication and decision making. Refer Section 10. on Biological materials, Biobanking and Datasets for further details.

12.2.1.2 Adverse effects including causality - A separate program for this has been launched by the Indian Pharmacopeia commission along with technical

support from National Health Systems Resource Centre and Sri Chitra Thirunal institute of Medical Sciences & Technology called the Materovigilance Program of India (MvPI). This program intends to track all adverse events due to medical devices, so that appropriate corrective and preventive actions may be taken after a causality assessment has been duly made.

12.2.1.3 All adverse events related to the conduct of the study product or unanticipated problems involving risks of harm to the participants or others should be promptly reported to MvPI and/or other relevant authorities. Any recommendations provided by MvPI in response to such reporting should be immediately implemented.

12.3 Nano-technology

Nanotechnology is defined as technology associated with fabrication of any material, particle and/ or device in nanodimension, which acquire unique novel properties. The applications include drugs, cosmetics, diagnostics, imaging, tissue engineering, wound dressing and many other areas related to health and medical practice. Multifunctional nanoparticles can be fabricated and used simultaneously for molecular imaging (diagnosis) and therapy with lesser toxicity leading to new area of theragnosis (therapy and diagnosis). It helps in early non-invasive detection of biomarkers of diseases in urine, saliva or other body fluids, which can help in low cost mass screening even in rural areas. Booster free single dose vaccine is possible using nanoadjuvant which can solve the rural vaccination problem. The area of nano-biosensors are developing at rapid pace with feasibility of in-vivo implant and monitoring of cardiac, renal, neural and other vital organ functions with interface of remote control devices.

12.4 Special considerations

12.4.1 GLP, GMP, Good clinical practice (GCP), and ethical principles should be observed when conducting clinical trials.

12.4.2 Before use of a new technology product in an individual, pre-clinical studies should be carried out whenever applicable.

12.4.3 Adverse events/ severe adverse events will have to be reported and compensation paid as per the related regulations.

12.4.4 The new technology/ related products should be contained and released in environment in stepwise manner after clearance from appropriate authority regarding its safety.

12.4.4 Differing process based technology can result in similarly functioning biological product which can be debated for assigning intellectual property rights.

12.4.5 Training should address user's issues regarding safe research, handling of products, clinical trials and community misconceptions.

12.5 Distribution and service delivery

12.5.1 Biological material and distribution

12.5.1.1 The complexity of biomaterials varies widely depending on the duration of time and area of contact with the body. In order to comply with all the safety requirements and sets of universal standards, testing of biomaterials and biocompatibility should be as per relevant Indian regulatory standards or American Society for Testing and Materials (ASTM) International standards until Indian standards for biomaterials are in place. The testing of such standards shall be done in a NABL (National Accreditation Board for Testing and Calibration Laboratories) or COFRAC (Le Comité français d'accréditation) certified laboratory till then.

12.5.1.1 Devices must be approved by relevant regulatory authorities for quality and safety.

12.5.1.2 Nanoparticles - Materials can be converted into nanodimension from metals like gold, silver, iron, non-metal like carbon, ceramics, polymers, protein, lipid, carbohydrate and synthetic substances like dendrimer, aptamer and so on. The nanomaterials used for research purposes are mostly fabricated in the laboratories and are used in several industries and agriculture. The personnel involved in production, fabrication and handling of nanomaterials have a potential for occupational exposure.

12.5.2 **Pre-market approval and registration**

Approval should be based on the ethical acceptability of the research, including its social value and scientific validity, and ethical principles related to clinical trial. The review must take into account any prior scientific reviews and applicable laws/ regulations or legal judgment of court of Law on any new or existing technology.

12.5.3 Safety of use and monitoring

Prior scientific review, good clinical practice and application of ethical guidelines in conduct of clinical trial should be adhered to when studying safety of synthetic

biology products, medical devices and nanoparticles should determine safety (Table 12.3).

Table 12.3

1. For medical devices, they should be tested for EMI/ EMC (Electro-magnetic Interference and Electro-magnetic compatibility) at an NABL accredited laboratory prior to use.
2. Nanomaterial characterization and analysis should critically answer its biocompatibility and degradability.

12.6 Risks

12.6.1 **Precautionary principle** – The intention of this principle is to prevent harm to humans, environment and ecosystem because development of new technology emits hazardous elements in the environment, which may be unclear during the time of research but may manifest later. Environmental hazards may range from X-Ray radiation, electro-magnetic currents and non-ionizing magnetic waves. Safety measures should be followed as per the Environmental Protection Act (1986), Atomic Energy Act, Biomedical Waste Management Rules and other relevant laws.

12.6.2 Risks to the participants should be minimized and should be reasonable in relation to the potential benefits of the research as is expected in any human research. Refer to details in the section 2 on General Ethical Issues.

12.6.3 The research on new technologies should have well-established mechanism or system for assessing the risk, both on the scale of severity and temporality. The unpredictable metabolic behaviour of nanoparticles in human system during clinical trials cannot exclude long term sequestration leading to side effects which may manifest later depending on its time of degradation. This is important from the point of compensation of adverse reactions.

12.6.4 Biosecurity: Sometimes, the product can have dual use i.e. one useful for a particular purpose and the other use could be unintentionally or intentionally harmful in another aspect, e.g. use as a biological weapon. Therefore, to maintain security, the ICMR Code of conduct for researchers involved in life sciences should be followed along with creation of a system for reporting and vigilance to be followed to avoid misuse. There should be effective partnership between researchers involved and policy makers to place a secure system.

12.6.5 Distributive justice should be borne in mind when selecting participants.

12.6.6 Healthcare worker safety and occupational risk –

12.6.6.1 Collateral injury among healthcare workers and employees should be considered.

12.6.6.2 Precautions should be exercised as in the case of handling dangerous materials.

12.6.6.3 The safety aspect for healthcare workers should cover Personal Protective Equipment (PPE), exposure response and hazardous waste disposal.

12.6.6.4 Manufacturer's cleaning and maintenance instructions should be strictly followed and training given to everyone involved in the research about following these instructions.

12.6.6.5 Suspicion of equipment contamination with microorganisms that might pose a transmission risk in healthcare settings (e.g., those requiring contact precautions) may be treated seriously according to the manufacturer's warning.

12.6.6.6 Periodic health check up of researchers and handlers is important.

12.7 Benefits

12.7.1 Products should be cost-effective alternatives especially considering the resource poor situation in India leading to limited access and availability.

12.7.2 Reducing morbidity and mortality through targeted application and delivery

12.7.3 Reducing cost - Application of nanotechnology may be more cost effective than conventional medical management practices. Nanocarrier based targeted drug delivery system may be more effective in rapid cure, thus reducing hospital stay, e.g. application in cancer treatment.

12.6.7 Compensation **-** There could be error in desired body function and biological program design, faulty execution, and external interference of infectious agents with biological program (design/ execution and traumatic injury. In the event of research related injury, adequate compensation as described for regulatory drug trials should be adopted as detailed under Section 6 (Clinical Trials of drugs and other interventions) of these guidelines. In the case of nanoparticles, long term management should also be borne in mind.

13. Research during Humanitarian Emergencies and Disasters

13.0 For the purpose of these guidelines, humanitarian emergencies include both man-made and natural emergencies and disaster. During humanitarian emergencies such as an earthquake, floods, mass migration, conflicts, and outbreaks leading to substantial material damage affecting persons, communities, society and state(s). It may be of periodic frequency as in most natural disasters or caused by humans and creates an imbalance between capacity and resources to meet the needs of the survivors or the people whose lives are threatened during the emergency period. Research is necessary in such circumstances to enable provision of efficient and appropriate health and humanitarian response during the ongoing emergency; and to be able to plan for future emergency situations.

Humanitarian emergencies raise complex issues. The health system, research infrastructure and research governance frameworks may be adversely affected during such situations, which create challenges regarding the feasibility and oversight of conduct of research. While there might be a need to undertake research quickly, this should not impact scientific validity and the need to uphold ethical requirements. Close attention should be paid to the effect of the emergency on perceptions of ethical questions, altered or increased vulnerabilities, **provider – patient** and researcher-participant relationships, issues related to integrity of studies and ethical review processes. The unique challenge here is responsive requirement to rapidly evolving health needs or priorities of those impacted by the humanitarian emergency and the research cannot be conducted outside the humanitarian emergency situation.

Ethical Challenges are to undertake relevant research, which should be designed/ innovated/ adopted so as to yield scientifically valid results under the uncertain and often rapidly evolving conditions of a humanitarian emergency. The role of ECs in such circumstances is very important in reviewing protocols prepared for such emergency situation(s).

13.1 Pre-emptive research preparation for future humanitarian emergency

Natural disaster of cyclical frequency is an expected phenomenon the following will be acceptable if a research is planned to study various implications on humans and ecological effects on humans in these circumstances.

13.1.1 Researchers and sponsors could make arrangements about research questions to be addressed in the design, collection of samples and data, and sharing mechanisms far

in advance of the future humanitarian emergency,

13.1.2 Researchers could screen available and/ or relevant draft research protocols to expedite review process.

13.1.3 EC could review the proposals prior to occurrence of the emergency and determine who could be LAR in the absence of intended LARs in such situations.

13.2 Informed consent requirements

13.2.1 Feasibility of obtaining valid informed consent in the given circumstances as the participants would not be in a sane state of mind to differentiate between reliefs offered and research components.

13.2.2 Safeguards are required for all the participants due to additional vulnerability of all involved in the emergency, e.g. counselling, psychological help etc.

13.2.3 The potential research participants might be under duress and traumatized so researchers should be sensitive to this situation and are obligated to ensure that the informed consent process is conducted in a respectful manner.

13.2.4 Researchers should strive to identify and address barriers to voluntary informed consent and not resort to inducements for research participation.

13.2.5 Every effort must be made in the informed consent process to make research participants aware of the difference between participating in a study and receiving humanitarian aid. The different roles of the researchers, caregivers, and volunteer workers must always be clarified, and the potential conflicts of interest declared.

13.2.6 If research involves incompetent individuals (such as minors), then LAR should give consent. Additional protections might be required in special cases, for example, children with untraceable or deceased relatives. In these situations the consent should be obtained from individual/ institution who is not part of the research team.

13.2.7 Waiver of consent - Investigators should give the rationale to justify the waiver. EC should approve such a waiver after considerable discussion on the issue. For details refer to section 4 on Informed consent Process.

13.2.8 When assent/ consent of participant/ consent of LAR is not possible due to the situation and a test intervention is used with prior EC approval, attempts should be made to administer informed consent to participant when mentally able or LAR if available later.

13.3 Risk-minimization and equitable distribution of risks and benefits

13.3.1 Fair selection of Participants (Table 13.1)

Table 13.1

1.	The overall effort is not to over-sample, particularly vulnerable segments of population.
2.	Explicit selection criteria or prioritization of participants with proper justification should be provided in the protocol.
3.	Efforts should be taken to ensure that the research participants are not exploited in any way during the research project. The research should not impose additional burdens or if not possible minimal additional risk on people who are already traumatised, and on the local infrastructure.
4.	Research on interventions to be used in such a situation should first be a pilot study or preliminary work to examine the safety and efficacy of the intervention and same participants should not be included in the clinical trial that may be initiated later based on the findings of the pilot study.
5.	It is desirable to set up a Data safety Monitoring Board to review the data.

13.3.2 It should be ensured that the potential benefits of research do not convince potential research participants to take undue risks (undue inducement) of enrolling.

13.3.3 Efforts should be made to see that the positive results of a specific research are applicable to future similar disaster situations.

13.3.4 Whenever possible, *a priori* agreement could be reached between researcher(s) and disaster affected communities for benefit sharing which could be extended to future disaster affected communities wherever applicable.

13.4 Post research benefit - Sponsors and researchers should strive to continue to provide beneficial interventions, which were part of the research initiative after the completion of research as well as till the local social support system develops the capacity to provide services.

13.5 Privacy and confidentiality

Disruption of governance, infrastructure, and communication network, and inflow of visitors during emergencies can lead to the possibility of stigmatization and discrimination.

13.5.1 Special efforts (culturally appropriate and scientifically valid) are required to maintain dignity, privacy and confidentiality of individuals and the communities**;**

13.5.2 Utmost attention must be paid to prevent stigmatization, ostracisation, and other harm to individuals and communities at all stages in the research process.

13.6 Ethics Review Procedures

13.6.1 Ethics review should be conducted in a timely manner. Expedited ethical review is recommended in such circumstances. The full ethical review should follow as soon as possible. Following steps could expedite the process (Table 13.2).

Table 13.2

1. Measures such as virtual or tele-conferences should be attempted when face to face meetings are not possible.
2. In exceptional situations, preliminary research procedures including but not restricted to data/ sample collection that are likely to rapidly deteriorate or perish.

13.6.2 In situations where members of the local ECs are unavailable due to the emergency, the ethics review may be conducted by any other EC within India for initiating the study, till the local EC is able to convene its meeting ECs should develop procedures to ensure appropriate timely review and monitoring of the approved research. On case-to-case basis, some protocols may require re-review as the emergency situation may change.

13.7 Special Considerations

Humanitarian emergencies lead to fragile political environment, with disruption of health systems and social situations.

13.7.1 The investigators should undertake steps to maintain participant and community trust.

13.7.2 Efforts should be made to engage community in the conduct of research in a culturally sensitive manner to ensure public trust.

13.7.2.1 The research team should preferably describe a preliminary community mapping/ scoping exercise.

13.7.2.2 Where possible, community representatives or advocates should be involved in conceptualization, review, research and dissemination of research results in such settings.

13.8 Continuation of ongoing research when a humanitarian emergency occurs:

13.8.1 The investigators must go back to the EC for guidance.

13.8.2 Amendments might be incorporated in the project(s) to align to the research needs arising from the emergency including issues related to re-consent from participants.

13.8.3 EC may decide if more frequent monitoring is required.

13.9 International participation in research

13.9.1 Conduct of research in a humanitarian emergency, which involves a foreign researcher/ institution, must involve local partner(s).

13.9.2 Existing guidelines on international collaboration for biological samples, data and intellectual property related issues will be applicable.

13.9.3 Permission should be obtained from relevant national and local authorities, wherever applicable. The research should help in developing the capacity of local researchers, and sites and provide key learning points to the policy makers, and the community.

13.9.4 All publications must be jointly authored.

14. Responsible conduct of Research

14.0 The value and benefits of research are essentially dependent on the integrity of research in which scientists have a significant social responsibility in preventing misuse of research. 'Responsible' researchers abide by the standards set by their professions, disciplines and institutions and also by relevant laws. All the members of the team doing research are expected to maintain high standards to uphold the fundamental values of research and the principles arising out of those values for 'Responsible conduct of research' (RCR). The major components of RCR are values, policies, planning and conducting, reviewing and reporting research, and responsible authorship and publication.

14.1 Values of Research

Morally correct judgment, shared values like honesty, accuracy, efficiency, fairness, objectivity, reliability, accountability and transparency in research binding researchers together, personal integrity and knowledge of current best practices guide RCR. These factors should be respected and policies drawn for upholding them. Trust is built upon these values, which involves self, colleagues, mentors, peer reviewers and sponsors.

14.1.1 The Scientist as a Responsible Member of Society

Scientific research is a social activity to achieve common goals of improving the understanding of various health related problems and their solutions. All the facets of research depend on co-operation based on shared expectations as part of inter professional ethics. Unethical behavior in scientific research can destroy the trust that holds the research team together and would make future meaningful research impossible.

14.1.2 Getting updated on contemporary ethical issues in biomedical research

Emerging new areas of research give rise to new ethical issues. Mushrooming of contract research organizations, use of underprivileged and vulnerable groups as participants, post trial access to the benefits of the research interventions are some of the contemporary issues being debated and consensus is yet to evolve on these issues. Therefore, the researchers need to be constantly updated about application of ethical principles in such situations.

14.1.3 Sensitivity to Societal and cultural Impact of Biomedical Research

To analyze social and cultural impacts one must analyze how the health sector and general public engage with the results of biomedical and health research. It is essential that the researchers be aware of the importance of societal and cultural

impact of research while planning, conducting and evaluating that research. This will improve public accountability and enhance public, private and political advocacy.

14.1.4 Mentoring

Mentoring is one of the primary means for one generation of scientists to pass on their knowledge, values and principles to succeeding generations. Mentors through their experience can help a researcher much more than reading textbooks. The relationship between mentors and trainees should enable development of trainees into responsible researchers. A mentor should be knowledgeable, teach and lead by example, understand that trainees differ in their abilities, encourage decision making by the trainees and be available to discuss, debate and guide.

14.1.4.1 Mentor's expectations from trainees would be to see that the trainee conducts research honestly, does not interfere with the work of other researchers and uses resources judiciously.

14.1.4.2 The trainee should take an active role in communicating her/his needs and be able to express own opinion freely without any fear of getting reprimanded.

14.2 Policies

14.2.1 The Protection of Human Participants

There should be institutional policies for human research participant's protection, which ascribes responsibilities to institutions, EC and the researchers. Additionally, there should be mechanism and policies for monitoring of the research including data capture and management and safety of the participants. Policies pertaining to reporting of scientific misconduct, conflict of interest, etc. should be in place. Researchers should also follow their respective Professional Codes of Conduct and should have personal conviction about ethically conducting and reporting research. Policies should be in place for appropriate initial and continuing training of researchers and EC members.

14.2.2 Animal experimentation

Those involved in experimentation on animals must follow all the existing regulations and guidelines including 'The Prevention of Cruelty to Animal Act, 1960', amended in 1982, The Breeding and Experimentation Rules,1998, amended in 2001 and 2006,

The *Guidelines for care and use of animals in scientific research,* (Indian National Science Academy, 1982, amended in 2000), ICMR guidelines on Humane care and use of laboratory animals (2006), CPCSEA guidelines for Rehabilitation of animals used in research (2010)and CPCSEA guidelines for laboratory animal facilities (2002/2012).

14.2.3 Collaborative research

Researchers are increasingly collaborating with colleagues who have the expertise and/or resources needed to carry out a particular research involving sharing techniques, data, and intellectual property rights. This could be inter-departmental/ inter-institutional and international and also multi centric involving public and/ or private research centres/ agencies. The main ethical issues in such collaborations pertain to ownership of materials and data, IPR, joint publications, managing research findings, managing conflict of interest (COI) and commercializing research outcomes etc. The researchers should familiarise themselves with all the local, national and international requirements for such collaboration including necessary approvals, MoU, MTA (Material Transfer Agreement) etc.

14.3 Planning and conducting Research

When research involves human participants, their biological materials and /or data, it is the responsibility of the researchers to comply with the existing ethical guidelines and relevant regulations in order to ensure rights, safety and well-being of the participants while planning, conducting and reporting research. In this context, issues related to conflict of Interest **(COI)**, data acquisition, its management, sharing and ownership should be addressed.

14.3.1 Ensuring safety, rights and well-being of the participants – all applicable ethical guidelines should be applied including the use of independent peer review and consent process.

14.3.2 Conflict of Interest issues

The complex and demanding nature of research today inevitably gives rise to competing interests. This is not inherently wrong but conflicts of interest can influence the choice of research questions and methods, recruitment and retention of participants, interpretation and publication of data, and the ethical review of research. It is therefore, necessary to develop and implement policies and

procedures to identify, mitigate, and manage such conflicts of interest. Research institutions, researchers and research ECs must take the following steps (Table 14.1) –

Table 14.1

1. Research institutions • They must develop and implement policies and procedures to address conflicts of interest, conflict of commitment and educate their staff about such policies.
2. Researchers • Must ensure that the materials submitted to a research EC include a disclosure of conflict of interests that may affect the research. • Conflicts of commitment may arise from situations that place competing demands on researchers' time and loyalties. • Intellectual and Personal conflicts: Researchers should not serve as reviewers for grants and publications submitted by close colleagues, relatives and students.
3. Ethics committees • Must evaluate each study in light of any disclosed interests and ensure that appropriate means of mitigation are taken in case of a conflict of interest. • Must require their members to disclose their own COI and take appropriate measures.

14.3.3 Management of COI

"Managing" a conflict means finding a way to assure that the COI do not adversely influence the research. Some options are given below (Table 14.2) –

Table 14.2

1. Full disclosure of all interests so that others are aware of potential conflicts and can act accordingly.
2. Monitoring the research or checking research results for accuracy and objectivity;
3. Not involving the person in the research from the crucial steps such as interpretation of data or participating in a particular review decision or removal of the person from the research depending on the extent of COI.
4. Policies and measures for managing conflicts of interest must be dynamic, transparent and actively communicated to those affected.

14.4 Data Acquisition, Management, Sharing and Ownership

Collection of data is a major component of research. Four important aspects of data management – ownership, collection, storage and sharing need to be addressed.

14.4.1 Data ownership and custodianship (Table 14.3)

Table 14.3

1.	The usual understanding is that the person who conducts the research should own the data but conditions imposed by funders can and do vary considerably and so researchers and institutions must be aware of their obligations to them before they begin collecting data.
2.	Institutes receiving funds for the research have responsibilities for budgets regulatory compliance and data management and so they claim ownership rights over data collected with funded research. This means that researchers cannot automatically assume that they can take their data with them if they move to another institution.
3.	The ownership issues and the responsibilities that come with them need to be carefully worked out well before any data are collected. Before undertaking any work researchers should ensure clarity about data ownership publication rights and obligations following data collection.
4.	For biological samples donors (participants) maintain the ownership of the sample. Institutes hosting/ implementing the research are the custodians of the data/ samples. Researchers have no claim for ownership or custodianship of biological samples.

14.4.2 Data collection

There is no single best way to collect data. Different collection techniques are needed for different types of research. The important considerations to ensure the overall integrity of both the process and the information collected are:

14.4.2.1 Appropriate methods

Reliable research conducted using appropriate and reliable methods provide reliable data. The use of inappropriate methods in research compromises the integrity of research data and should be avoided.

14.4.2.2 Attention to detail

Quality research requires attention to detail at every step. Proper protocols need to be established and the results accurately recorded, interpreted, and published. Sloppy research wastes resources and should be avoided.

14.4.2.3 Authorization

Authorization is needed for the following prior to data collection (Table 14.4)

Table 14.4

1.	human participants and animals in research;
2.	information posted on some web sites;
3.	use of hazardous materials and biological agents;
4.	Biological sample storage & future testing;
5.	information in some libraries, databases, and archives;
6.	published photographs and other published information; and
7.	other copyrighted or patented processes or materials.

Researchers have a responsibility to know when permission is needed to collect or use specific data in their research.

14.2.2.4 Recording

The final step in data collection is the physical process of recording the data in hard copy, soft copy, or other permanent forms. The physical formats for recording data vary considerably, from measurements or observations to photographs or interview recordings. To have and hold their value, research data must be properly recorded.

14.4.3 Data protection and storage

Once collected, data must be properly protected, as it may be needed later to confirm research findings, to establish priority, or to be re-analyzed by other researchers.

The responsible handling of data begins with proper storage and protection from accidental damage, loss, or theft. Care should be taken to reduce the risk of fire, flood, and other catastrophic events. Computer files should be backed up and the backup data saved in a secure place at a site that is different from the original data.

14.4.4 Data Sharing

There is no doubt that research data should be shared, but deciding when and with whom to share may raise difficult questions. Researchers can withhold confirmed or validated data until they have had time to establish their priority for their work through publication. Once a researcher has published the results of an experiment, it is generally expected that all the information about that experiment, including the final data, should be freely available for other researchers to check and use. Data should be shared/ put in public domain in a de-identified /anonymized form, unless required otherwise for which applicable permissions/ re-consent should be sought.

14.5 Reviewing and Reporting Research

The trust of the public in published research is an essential component of ethical and responsible research.

14.5.1 The basic premise of all reviewers and editors evaluating research is that the work has been performed honestly, its reporting is transparent and truthful, and the researchers' integrity is beyond doubt.

14.5.2 Transparency pertains to both the research site and the researcher(s). This would require disclosure of the location of the research as well as the collaborating sites/institutions and the authors of that research.

14.6 Responsible Authorship and Publication

14.6.1. **Authorship** - The International Committee of Medical Journal Editors (ICMJE) guidance on authorship is largely accepted as a standard which is endorsed by the World Association of Medical Editors (WAME). The ICMJE recommends that the authorship be based on the following four criteria (Table 14.5)

Table 14.5

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
2. Drafting the work or revising it for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

14.6.1.1 The authorship of research should be considered at the time of its initiation.

14.6.1.2 Institutions and departments should have authorship policies. Editors of journals do not adjudicate on authorship disputes and would almost always refer these to the institution/ researchers themselves to resolve.

14.6.1.3 Authorship should never be gifted and 'ghost' authors are not acceptable.

14.6.1.4 The primary author should be the person who has done the most research work related to the manuscript being submitted for publication. Research performed as part of a mandatory requirement of a course/fellowship/training program should have the candidate as the primary author. All efforts must be made to provide the candidate an

opportunity to fulfil the second, third and fourth criteria of the ICMJE guidelines.

14.6.2 **Peer Review**

Scientific disclosure and progress has been dependent largely on peers evaluating research and judging the utility of conducting and publishing research.

14.6.2.1 The present peer review system depends on fairness, honesty and transparency of all stakeholders' – editors, reviewers and researchers.

14.6.2.2 The process of peer review must be clearly stated, whether blinded or open, involving one or more reviewers and should be completed within a reasonable period of time.

14.6.2.3 Researchers must avoid mentioning friends, well-wishers and mentors as reviewers.

14.6.2.4 Reviewers must decline to review research of close associates, friends and students.

14.6.2.5 The funding agencies and journals must ask reviewers and researchers to inform them of conflict of interest, if any.

14.6.2.6 Reviewers must maintain confidentiality of manuscripts sent to them for review.

14.6.2.7 If they feel that they are not competent to review papers they should inform editors immediately and should not pass on the manuscripts to friends and colleagues, without seeking the consent of the editors.

14.6.2.8 Reviewers must not use the data available to them from an unpublished manuscript for any purpose and should complete the review in a reasonable period of time.

14.6.2.9 Researchers must not create fake email ids and profiles to misguide editors in an attempt to self-evaluate their research.

14.7 Research Misconduct and Policies for Handling Misconduct

Research misconduct involves fabrication, falsification and plagiarism of data, which are serious issues. The Committee on Publication Ethics (COPE), UK provides guidance to handle different types of misconduct. The ICMJE and WAME support this guidance. Researchers, reviewers and editors should therefore use this guidance to avoid the problems of scientific misconduct.

• Fabrication is the intentional act of making up data or results and recording or reporting them.
• Falsification is manipulating research materials, equipment, or processes, or changing or omitting/ suppressing data or results without scientific or statistical justification, such that the research is not accurately represented in the research record.
• Plagiarism is the "wrongful appropriation" and "stealing and publication" of another author's "language, thoughts, ideas, or expressions" and the representation of them as one's own original work.

14.7.1 Misconduct, if suspected, needs to be investigated. The role of institutions in this is paramount and they must investigate all allegations of misconduct. This is imperative as the lives of patients may depend on the research in question. Such investigations must be done in a timely, fair and transparent manner and the results should be made available in the public domain.

14.7.2 Simultaneous submission and overlapping publications are not acceptable. If multiple journals were to accept the submitted research it would result in competing claims for publication. Even if the research was not accepted, it would lead to unnecessary review of the work by different groups of reviewers. Overlapping publication would result in infringement of copyright laws if the copyright for the same article were to be owned by two different publishers. This is also ethically incorrect because the reader would believe the work to be original while it was previously published. Also if the overlapping publication had original data it could lead to the same data being counted twice during a meta-analysis.

14.8 Reporting results

14.8.1 Research once done, irrespective of results, must be published according to Helsinki Declaration, since it would be unethical to expose another set of patients/volunteers to the same risk to obtain the same results.

14.8.2 As part of trial registration, reporting of results has been mandated by law in some countries. Where it is not legally required, researchers should provide results of registered trials in public databases wherever these are available. In India it will have to be reported in the Clinical Trial Registry of India.

S. No.	List of Standard Operating Procedures (SOPs)	SOP Code
1.	Writing, Reviewing, Distributing and Amending Standard Operating Procedures for ECs	**SOP/001**
2.	Constituting an Ethics Committee	**SOP/002**
3.	Confidentiality Agreements	**SOP/003**
4.	Conflict of Interest Agreements	**SOP/004**
5.	Training Personnel and EC	**SOP/005**
6.	Selection of Independent Consultants	**SOP/006**
7.	Procedures for allowing Guest or Observer	**SOP/007**
8.	Categorization of Submitted Protocols for Ethics Review	**SOP/008**
	A. Initial Full Board Review of New Research Study Protocols	**SOP/008 A**
	B. Expedited Review of Research Study Protocols	**SOP/008 B**
	C. Exemption from Ethics Review of Research Study Protocols	**SOP/008 C**
9.	Agenda Preparation, Meeting Procedures and Minutes	**SOP/009**
10.	Review of New Medical Devices Studies	**SOP/010**
11.	Review of Resubmitted Protocols	**SOP/011**
12.	Review of Protocol Amendments	**SOP/012**
13.	Continuing Review of Study Protocols	**SOP/013**
14.	Review of Final Reports	**SOP/014**
15.	Review of Serious Adverse Events (SAE) Reports	**SOP/015**
16.	Review of Study Completion Reports	**SOP/016**
17.	Management of Premature Termination, Suspension, Discontinuation of the Study	**SOP/017**
18.	Waiver of Written or Verbal Informed Consent	**SOP/018**
19.	Site Monitoring Visit	**SOP/019**
20.	Dealing with Participants' Requests and Complaints Coming to Ethics Committee	**SOP/020**
21.	Emergency Meeting	**SOP/021**
22.	Communication Records	**SOP/022**
23.	Maintenance of Active Study Files	**SOP/023**
24.	Archive and Retrieval of Documents	**SOP/024**
25.	Maintaining Confidentiality of EC's Documents	**SOP/025**
26.	Reviewing Proposals involving Vulnerable Populations	**SOP/026**
27.	Audit and Inspection of the EC	**SOP/027**
28.	Audio Visual Recording of Informed Consent Process	**SOP/028**

Glossary		
1.	**Accountability**	The obligation of an individual or organization to account for its activities, accept responsibility for them, and to disclose the results in a transparent manner.
2.	**Adult Stem Cell**	A stem cell derived from the tissues or organs of organism after birth (in contrast to embryonic or fetal stem cells).
3.	**Adverse Drug Reactions (ADR)**	All noxious and unintended responses to a medicinal product related to any dose used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. ADRs are classified into six types: dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure).
4.	**Adverse event**	Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a casual relationship with this treatment. The adverse event can therefore be any unfavourable or unintended sign or experience associated with the use of the investigational product, whether or not related to the product
5.	**Alternative Medicine**	Alternative medicine is any practice that is put forward as having the healing effects of medicine, but does not originate from evidence gathered using the scientific method, is not part of biomedicine, or is contradicted by scientific evidence or established science.
6.	**Appellate authority**	An appellate authority decides on the appeal filled for a judgment of the lower authority. The mandate of appellate authority is to ensure that due process of law is followed and the information which is rightfully to be disclosed in not denied on flimsy and useless ground.
7.	**Assent**	To agree or approve after thoughtful consideration of an idea or suggestion. In these guidelines it means agreement or approval which has to be corroborated with informed consent of LAR.
8.	**Assessment Form**	An official record of the review decision along with comments and dated signature of the reviewer.
9.	**Audit**	A systematic and independent examination of trial activities and documents to determine whether the review and approval activities were conducted and data were recorded and accurately reported according to the SOPs, GCP, Declaration of Helsinki and applicable guidelines and regulatory requirements.
10.	**Authority**	Authority means the Biomedical and Health Research Authority established under this Act.
11.	**Autonomy**	It is the ability and capacity of a rational individual to make an independently informed decision to volunteer as a research

		participant.
12.	**Ayurvedic, Siddha or Unani (ASU) drug**	Includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani Tibb system of medicine and corresponding pharmacoaepias specified in the First Schedule. These are also called as classical drugs which are manufactured and named in accordance with the formulations described in the authoritative texts.
13.	**AYUSH intervention**	Includes any existing/ new intervention with drug, therapeutic or surgical procedure or device in the recognized traditional systems of India as per Ministry of AYUSH, Govt. of India (including Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy and SOWA RIGPA).
14.	**Behavioral research**	Refers to studies of the behaviour of individuals, or of groups, organizations or societies.
15.	**Beneficence**	Beneficence is a concept in research ethics, which states that researchers should weigh the risks against benefits bearing in mind the welfare of the research participant(s) as a goal in any type of research.
16.	**Bioequivalence**	Bioequivalence is a term in pharmacokinetics used to assess the expected *in vivo* biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same.
17.	**Biomedical and Health Research**	Includes basic, applied and operational research designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioral), their detection, cause and strategies for health promotion, prevention, or amelioration of disease and rehabilitation and includes clinical research.
18.	**Biologicals or biopharmaceutical drug**	Any pharmaceutical drug product manufactured in, extracted from, or semi synthesized from biological sources (human, animal, or microorganism). These include vaccines, blood, or blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein, and living cells used in cell therapy.
19.	**Biosimilars**	A biosimilar (also known as follow-on biologic or subsequent entry biologic) is a biologic medical product which is almost an identical copy of an original product that is manufactured by a different company.
20.	**Blinded studies**	A **blind** or **blinded study** is an experiment in which information about the test is masked (kept) from the participant, to reduce or eliminate bias, until after a trial outcome is known. Double blinded means even the researcher does not know which is the test intervention.

21.	**Bridging study**	A supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region. It is an additional study executed in the new region to "build a bridge" with the foreign clinical data on safety, efficacy, and dose response. This bridging of clinical studies is usually made by allowing extrapolation of the foreign clinical trial data to the population in the new region. (ICH E5)
22.	**Caregivers**	A **caregiver** or carer is an unpaid or paid person who helps another individual with impairment with her or his activities of daily living.
23.	**Case control studies**	A study that compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls), and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease.
24.	**Case Report Form (CRF)**	Case record form or case report form is printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial participant.
25.	**Case series**	A case series (also known as a clinical series) is a type of medical research that tracks participants with a known exposure, e.g., patients who have received a similar treatment, or examines their medical records for exposure and outcome.
26.	**Cell Line**	Cells of common descent continuously cultured in the laboratory are referred to as a cell line.
27.	**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.
28.	**Clinical Research**	It is research that directly involves a particular person or group of people to study effect of interventions, or uses materials from humans indirectly, such as their behaviour or samples of their tissue for prevention, treatment and diagnosis of a disease condition/ health disorder.
29.	**Clinical Trial Registry**	A clinical trials registry is an official platform for registering a clinical trial.
30.	**Clinical trial**	Systematic study of new drug in human participant to generate data for discovering or verifying it's clinical, pharmacological (including pharmacodynamic and pharmacokinetic) or adverse effects with the objective of determining safety, efficacy or tolerance of the new drug and regulated under Drugs & Cosmetics Act and its Rules.
31.	**Cognitive**	Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect

	impairment	their everyday life.
32.	**Cohort**	A cohort is a group of participants who have shared a particular event together during a particular time span (e.g., people born in Europe between 1918 and 1939; survivors of an air crash; truck drivers who smoked between age 30 and 40).
33.	**Collaborative Research**	Collaborative Research is an umbrella term for methodologies that actively engage researchers, communities and/ or policy makers in the research process from start to finish.
34.	**Community**	A community is a social unit of any size that shares common values, or that is situated in a given geographical area (e.g. a village or town).
35.	**Comparator (Product)**	An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.
36.	**Compensation**	Means provision of financial payment or reimbursement to the research participants or medical and/ or financial management when temporary or permanent injury occurs due to participation in the biomedical and health Research.
37.	**Compliance**	Compliance means conforming to a rule, such as a specification, policy, standard or law.
38.	**Confidentiality Agreement**	Secrecy or Nondisclosure agreements designed to protect trade secrets, information and expertise from being misused by those who have learned about them.
39.	**Confidentiality breach**	Unauthorized release of confidential information.
40.	**Confidentiality**	Refers to keeping information which an individual has disclosed in a relationship of trust and with the expectation that it shall not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure with reference to the specific research undertaken for which the consent is obtained.
41.	**Congenital anomaly**	Structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life. Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations.
42.	**Consanguinity**	Descendent from the same ancestral family or related by blood.
43.	**Contract research organization (CRO)**	An institution or service organization, which represents a sponsor, in providing research support/ services on a contractual basis nationally or internationally.
44.	**Cytotoxic drugs**	A group of medicines that contain chemicals which are toxic to cells, preventing their replication or growth, and so are used to treat cancer. They can also be used to treat a number of other disorders such as

		rheumatoid arthritis and multiple sclerosis.
45.	**Debriefing**	A process of (1) receiving an explanation, (2) receiving information and situation-based reminders of context, (3) reporting of measures of performance, and/ or (4) opportunities to further investigate the results of a study, investigation, or assessment of performance after participation in an immersive activity is complete.
46.	**Delirium**	Delirium is a serious disturbance in mental abilities that results in confused thinking and reduced awareness of environment.
47.	**Dementia**	A chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning.
48.	**Demographic surveillance system**	Demographic surveillance systems (DSS) are one of the cornerstones of public health research in countries where lack of comprehensive and reliable data systems are non-existing.
49.	**Descriptive studies**	Any study that is not truly experimental, e.g., in human research, it can provide information about the naturally occurring health status, behaviour, attitudes or other characteristics of a particular group.
50.	**Deviation/Non-compliance/Violation**	The EC monitors whether investigators do not perform the study in compliance with the approved protocol, ICH GCP, FDA regulations and/ or fail to respond to the EC's request for information/action.
51.	**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.
52.	**Direct To consumer Testing**	Direct-to-consumer genetic testing refers to genetic tests that are marketed directly to consumers via television, print advertisements, or the Internet. This form of testing, which is also known as at-home genetic testing, provides access to a person's genetic information without necessarily involving a doctor or insurance company in the process.
53.	**Distributive Justice**	Distributive justice is fair distribution of burden, resources and benefits. In research it means fair selection of participants.
54.	**Epidemiological studies**	Epidemiology is the study of the patterns, causes, and effects of health and disease conditions in defined populations.
55.	**Epidemiological Tools**	Epidemiological tools are used to select study samples, estimate risk and evaluate associations.

56.	**Ethicist**	An **ethicist** is one whose judgment on ethics and ethical codes has come to be trusted by a specific community, and (importantly) is expressed in some way that makes it possible for others to mimic or approximate that judgement.
57.	**Ethics Committee**	Refers to a multidisciplinary committee of an institution responsible for safeguarding the rights, dignity, welfare and safety of research participants by carrying out independent review of research prior to its approval and then monitoring its conduct, and may also be referred to as Institutional Ethics Committee (IEC).
58.	**Ethics**	Ethics or moral philosophy is the branch of philosophy that involves systematizing, defending, and recommending concepts of right and wrong conduct.
59.	**Expedited approval**	An EC approval granted only by the Chairman of the Institute Committee or a designated Institute Committee member (not the full Committee) for minor changes to current EC approved research activities and for research which involves no more than minimal risk.
60.	**Exploitation**	The action or fact of treating someone unfairly in order to benefit from their work
61.	**Exploratory research**	Research conducted for a problem that has not been clearly defined.
62.	**Fabrication**	Fabrication is the intentional act of making up data or results and recording or reporting them.
63.	**Falsification**	Falsification is manipulating research materials, equipment, or processes, or changing or omitting/suppressing data or results without scientific or statistical justification, such that the research is not accurately represented in the research record.
64.	**Field trials**	Involve people who are disease-free but presumed to be at risk, used to evaluate interventions that reduce exposure without measuring the occurrence of health effects.
65.	**Folklore medicine**	It is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, societies, communities, folklores in India, used for the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses, and which may not find a mention in the list of authoritative texts listed under First Schedule of Drugs and Cosmetics Act 1940.
66.	**Funding agency**	Refers to both governmental and non-governmental agencies that provide research grants through competitive means to an investigator or an institution for carrying out Biomedical and Health Research.
67.	**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.
68.	**Generic product**	A product that is sold under the general name for a type of product, rather than a brand name.
69.	**Genetic Engineering**	It is the process of creating new DNA 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.
70.	**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'.
71.	**Guideline**	Any suggestion or recommendation intended as a guide for specific practice.
72.	**Host country**	Nation in which individuals or organizations from other countries or states visit as researcher(s) under international collaboration, which is India under the context.
73.	**Human participant(s)**	A person(s) or group(s) enrolling in research.
74.	**Incarcerated**	To imprison; confine or to enclose; constrict closely.
75.	**Incompetent**	Lacking necessary ability or skills or inadequate to or unsuitable for a particular purpose or unable to function properly.
76.	**Independent consultant**	An expert who gives advice, comments and suggestion upon review of the study protocols with no affiliation to the institute or investigators proposing the research protocols.
77.	**Individualized medicine**	Personalized or customised medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions with regard to the prevention, diagnosis, and treatment of disease. Same approach is adopted in traditional medicine but on clinical basis.
78.	**Inducement**	A motive or consideration that leads one to action or to additional or more effective actions.
79.	**Informed Consent Document (ICD)**	Written signed and dated paper confirming participant's willingness to voluntarily participate in a particular trial, after having been informed all aspects of the trial that are relevant for participant's decision to participate.

80.	**Inspection**	The act by a regulatory authorities of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authorities to be related in the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CRO) facilities, office of ethics committees or at other establishments deemed appropriate by the regulatory authorities.
81.	**Institution**	Refers to an individual or establishment or an organization (public or private), such as a university, college, hospital, clinic or a research institute (including its relevant officials, designated ethics committee, researchers, and any other employees or agents involved in research), CRO or others conducting biomedical and health research involving human participants.
82.	**Interdisciplinary**	Involving more than one branch of knowledge.
83.	**Interventional Trials**	Intervention trials consist of trials to prevent disease (field trials) or trials to treat established disease processes (clinical trials).
84.	**Investigational New Drugs (IND)**	Substance which may be a new chemical entity, a new combination, new dosage form, new dosage regime or to be used for a new indication or new route of administration, being studied to verify their potential effects and safety for human use and to get approval for marketing.
85.	**Investigational Product (IP)**	A pharmaceutical product (including the Comparator Product) being tested or used as reference in a clinical study, which may be an active chemical entity, a new combination, an IND or a marketed drug/Device (Check).
86.	**LAR**	Legally authorised representative under applicable law or judicial authority or legally acceptable representative (LAR) responsible for the participant who consents on behalf of a prospective participant to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol duly approved by the Institutional Ethics Committee;
87.	**Longitudinal studies**	A longitudinal study is an observational research method in which data is gathered for the same subjects repeatedly over a period of time.
88.	**Majority vote**	A motion is carried out if one half plus one member of the required quorum votes in its favour.
89.	**Maleficence**	The act of committing harm or a harmful act.
90.	**Man- Made emergencies**	Disasters caused by humans. Examples of man-made hazards include Airline disaster, Biological agents, Disruptions in Services - Water, sewer, communications, travel, etc; Hazardous materials - truck, rail, and pipeline; Mass Gatherings, Transportation - truck and rail,

		Weapons of mass destruction
91.	**Marginalized communities**	A group of people is actively separated or excluded from the rest of society.
92.	**Medicated devices**	These are devices that contain pharmacologically active substances, which are treated as drugs.
93.	**Mental illness**	A condition which causes serious disorder in a person's behaviour or thinking.
94.	**Mental health**	Mental **health** is a level of **psychological** well-being, or an absence of a mental disorder; it is the "**psychological** state of someone who is functioning at a satisfactory level of emotional and behavioral adjustment"
95.	**Meta-analysis**	Meta-analysis is a statistical technique for combining the findings from independent studies.
96.	**Minimal Risk**	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 since it would be undertaken as part of current everyday life.
97.	**Minutes**	An official record of the business discussed and transacted at a meeting, conference, etc.
98.	**Multifactorial Diseases**	Conditions caused by many contributing factors are called complex or multifactorial disorders.
99.	**Mutation**	A process by which the nucleotide of an organism changes permanently 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.
100.	**Natural emergencies**	A natural disaster is a major adverse event resulting from natural processes of the Earth; examples include floods, volcanic eruptions, earthquakes, tsunamis and other geologic processes.
101.	**New chemical entity of an ASU drug**	When an extract of a plant or a compound isolated from the plant and any 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) or 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.
102.	**New drugs including Investigational New Drugs (IND)**	Defined under Rule 122-E of Drugs and Cosmetics Rules include unapproved drugs, modified or new claims, namely, indications, dosage forms (including sustained release dosage form) and route of administration of already approved drugs and combination of two or more drugs or new combination of approved FDC. A new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.
103.	**Non- Therapeutic trial**	A non-therapeutic trial is one which is unlikely to produce any direct benefit to the participants involved. The aim of a non-therapeutic trial is to obtain knowledge which may contribute towards the future development of new forms of treatment or procedure.
104.	**Observational studies**	In an **observational** study investigators observe subjects and measure variables of interest without assigning treatments to the subjects.
105.	**Ostracisation**	To exclude, by general consent, from society, friendship, conversation, privileges, etc.
106.	**Pedigree studies**	Pedigree studies have been used to identify genes influencing a wide range of monogenic, highly penetrant traits of biomedical importance, including a variety of inborn errors of metabolism and other genetic diseases (e.g., cystic fibrosis, Duchene muscular dystrophy, Huntington disease).
107.	**Pharmaceutical Product(s)**	Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.
108.	**Pharmacodynamics**	Study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.
109.	**Pharmacokinetics**	It is a branch of pharmacology involving the study of the absorption, distribution, metabolism, and elimination of drugs from the body.
110.	**Pilot Studies**	A pilot study, pilot project or pilot experiment is a small scale preliminary study conducted in order to evaluate feasibility, time, cost, adverse events, and effect size (statistical variability) in an attempt to predict an appropriate sample size and improve upon the study design prior to performance of a full-scale research project.
111.	**Pivotal trial**	A clinical trial or study intended to provide evidence for a drug marketing approval from the licensing authority. Usually a phase III study which presents the data that the licensing authority uses to

		decide whether or not to approve a drug. A pivotal study will generally be well-controlled, randomized, of adequate size, and whenever possible, double-blind.
112.	**Polymers**	Polymers are substances whose molecules have high molar masses and are composed of a large number of repeating units.
113.	**Population Screening**	Population screening refers to a test that is offered to all individuals in a target group, usually defined by age, as part of an organised program.
114.	**Populations**	The total number of inhabitants constituting a particular race, class, or group in a specified area.
115.	**Post-Marketing surveillance**	The practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance.
116.	**Pre-clinical study**	*in vitro* and animal studies provide information on possible toxicities and mechanisms of action, and starting doses for human studies.
117.	**Predictive genetics testing**	A form of genetic testing, also known as presymptomatic testing. These types of testing are used to detect gene mutations associated with disorders that may appear after birth, often later in life, but it is not certain whether these will manifest later
118.	**Principal investigator**	Means an individual or the leader of a group of individuals who initiates and takes full responsibility for the conduct of biomedical and health research; if there are more than one such individuals they may be called Co-Principal Investigators.
119.	**Professional competence**	Professional competence is the broad professional knowledge, attitude, and skills required in order to work in a specialized area or profession.
120.	**Proprietary Medicine**	A proprietary medicine is a non-secret compound which is marketed under the maker's name.
121.	**Psychosocial Harm**	Research, particularly psychology studies, can put participants in situations that may make them feel uncomfortable while learning about their reaction to a situation. The result can be psychological harm that can manifest itself through worry (warranted or unwarranted), feeling upset or depressed, embarrassed, shameful or guilty, and/or result in the loss of self-confidence.
122.	**Public Health Studies**	Public health is defined as the science of protecting the safety and improving the health of communities through education, policy making and research for disease and injury prevention.
123.	**Quasi-experimental**	Design where there is an intervention, but it is often not completely planned by the person doing the research. This design falls between observational and experimental studies.

124.	**Quorum**	Number of EC members required to act on any motion presented to the Board for action
125.	**Randomised Controlled trials**	A **randomized controlled trial** (or **randomized control trial**; **RCT**) is a type of scientific experiment, where the people being studied are randomly allocated to one or other of the different treatments under study.
126.	**Randomization**	Randomization is the process of making something random, in various contexts this involves, for example selecting a random sample of a population (important in statistical sampling); allocating experimental units via random assignment to a treatment or control condition, etc.
127.	**Reference Biologic**	It is used as the comparator for head-to-head comparability studies with the similar biologic in order to show similarity in terms of safety, efficacy and quality. Only a product that is licensed on the basis of a full registration dossier can serve as reference biologic.
128.	**Regulations**	Mean the Regulations framed under an Act.
129.	**Reproductive cloning**	Reproductive cloning involves creating an animal that is genetically identical to a donor animal through somatic cell nuclear transfer. In reproductive cloning, the newly created embryo is placed back into the uterine environment where it can implant and develop.
130.	**Reproductive health**	Reproductive health is a state of complete physical, mental and social well-being in all matters relating to the reproductive system.
131.	**Reproductive toxicity**	A hazard associated with some chemical substances that they will interfere in some way with normal reproduction; such substances are called reprotoxic. It includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.
132.	**Research related injury**	Means harm or loss that occurs to an individual as a result of participation in research, irrespective of the manner in which it has occurred, and includes both the expected and unexpected adverse events and serious adverse events related to the intervention, whenever they occur, as well as any medical injury caused due to procedures.
133.	**Research**	Means a systematic investigation for gathering information and its analysis designed to develop or contribute to knowledge.
134.	**Retrospective studies**	A retrospective study looks backwards and examines exposures to suspected risk or protection factors in relation to an outcome that is established at the start of the study.
135.	**Risk minimisation**	The identification, analysis, assessment, control, avoidance, minimization, or elimination of unacceptable risks.

136.	**Risk**	The probability of injury or harm or discomfort to study participants. Acceptable risk differs depending on the conditions for which the product is being tested. A product for sore throat, for example, will be expected to have a low incidence of side effects. However, unpleasant side effects may be an acceptable risk when testing a promising treatment for a life-threatening illness.
137.	**Scientists**	Professionals with advanced training and expertise in the medical or non-medical areas related to the protocol being reviewed.
138.	**Serious Adverse Event (SAE)**	The adverse event is Serious and should be reported when the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly, and requires intervention to prevent permanent impairment or damage.
139.	**Sexual minorities**	A sexual minority is a group whose sexual identity, orientation or practices differ from the majority of the surrounding society. It can also refer to lesbian gay, bisexual and transgender (LGBT), gender queer (including third gender) or intersex individuals.
140.	**Similar biologic**	A biological product/ drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier, and with a history of safe use in India. The products, where the reference biologic is not authorized in India shall be considered on a case by case basis if such products have been granted marketing approval in countries with well established regulatory systems such as US FDA, EMA etc. and have been in wider use for a minimum of four years. Such products are also referred as biosimilars, similar biotherapeutic products, subsequent entry biologics or follow on biologics in various countries.
141.	**Social Benefit**	Social benefit is the total benefit to society from producing or consuming a good/ service.
142.	**Social Scientist**	A person who is an expert on societal and social behaviour.
143.	**SOP (Standard Operating Procedure)**	Detailed written instructions, in a certain format, describe all activities and action undertaken by an organization to achieve uniformity of the performance of a specific function.
144.	**Sponsor country**	When a country supports negotiations to fund research.
145.	**Sponsor**	Means a person who initiates the research and is responsible for its management and funding who could be an individual, institution, private company, government or non-governmental organization
146.	**Stent**	A tube designed to be inserted into a vessel or passage way to keep it open allay obstruction or aid in healing
147.	**Stepped Wedge**	A cluster randomised trial design involving random and sequential

	design	crossover of clusters from control to intervention until all clusters are exposed.
148.	**Stepped wedge Trial**	A stepped-wedge trial is a form of randomised controlled trial that involves sequential but random rollout of an intervention over multiple time periods.
149.	**Stigmatisation**	The assignment of negative perceptions to an individual because of pe rceived difference from the population at large; itmay occur on the bas is of physical appearance (including race or sex), of mental or physical i llness, or of various other qualities.
150.	**Suicidality**	The act or an instance of intentionally killing oneself.
151.	**Surrogate**	A surrogate is a substitute or deputy for another person in a specific role.
152.	**Theologian**	A person who is an expert on theology (theology - the study of religious faith, practice, and experience the study of God and God's relation to the world, a system of religious beliefs or ideas).
153.	**Therapeutic efficacy**	The effectiveness of a particular therapeutic method.
154.	**Therapeutic misconception**	When a research participant fails to appreciate the distinction between the imperatives of clinical research and of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures. It describes the assumption of research participants that decisions about their care are being made solely with their benefit in mind It is not a misconception to believe that participants probably will receive good clinical care during research. But it is a misconception to believe that the purpose of clinical trials is to administer treatment rather than to conduct research.
155.	**Traditional medicine**	It Is the sum total of the knowledge, skills, and practices indigenous to a country based on the theories, beliefs, and experiences, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.
156.	**Transgender population**	They experience a mismatch between their gender identity, gender expression or their assigned sex.
157.	**Transparency**	Transparency implies openness, communication, and accountability and operating in such a way that it is easy for others to see what actions are performed. It has been defined simply as "the perceived quality of intentionally shared information from a sender".
158.	**Undue inducement**	Offer of a desirable good in excess such that it compromises judgment and leads to serious risks that threaten fundamental interests.
159.	**Unexpected ADR**	An adverse reaction, the nature or severity of which is not consistent with the informed consent/ information sheets or the applicable

		product information (e.g., investigator's brochure for the unapproved investigational product or package insert/ summary of product characteristics for an approved product.

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