NATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL AND HEALTH RESEARCH INVOLVING HUMAN PARTICIPANTS



INDIAN COUNCIL OF MEDICAL RESEARCH
2017

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Government of India

सत्यमेव जयते

स्वच्छ भारत
एक कदम स्वच्छता की ओर

MESSAGE

I am happy to know that the Indian Council of Medical Research (ICMR) is bringing out the revised National Ethical Guidelines for Biomedical and Health Research Involving Human Participants – 2017.

ICMR is one of the oldest medical research bodies in the world and is the apex body in India for the formulation, cooperation and promotion of biomedical research. I understand that the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants – 2017 have been prepared considering the moral, ethical, social values and ethos of our diverse population. I applaud and commend the enormous efforts directed by ICMR to ensure that the biomedical and health research is carried out in an ethical manner to maintain and improve public trust towards biomedical research.

I congratulate ICMR for the release of these very important guidelines and feel confident that these will help improve the research scenario by imparting better protection of our population.

(Jagat Prakash Nadda)

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एवं
महानिदेशक, आई सी एम आर
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Department of Health Research
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&
Director-General, ICMR



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FOREWORD

I am very pleased that the ICMR ethical guidelines for research have been revised which were last brought out in 2006. ICMR has always been leading in developing ethical standards for human research in the country. These guidelines are well recognized in India and a number of other countries also.

Changes in biomedical health research and its environment have been very rapid in recent times. In India with its diverse population, it is very important to be sensitive to the needs and requirements for advances in medicine, while providing adequate protection to the vulnerable population. Medical research is the need of the hour and therefore it is important not only be responsive to emerging issues but to also build greater trust towards research. ICMR ethical guidelines have been developed after long and careful deliberations with experts and stakeholders, from various disciplines and constituencies across the country, who have carefully dealt with difficult topics, to prepare the document in line with national as well as international guidelines, frameworks and regulations. The revised guidelines are not only an update of the existing 2006 guideline but also address newer concerns, in accordance with the socio-cultural milieu of our country. For the first time, the guidelines have addressed concerns in subject areas where there is scanty guidance available such as public health research, socio behavioural research, conducting research during disasters or emergencies, dealing with vulnerable populations or conducting collaborative research. It is thus important that every stakeholder, whether a researcher or a member of an ethics committee, or a sponsor, is aware of the provisions made in the revised ethical guidelines, which would help improve the conduct of biomedical research in India.

I look forward to this document being widely referred to and used towards achieving high quality of conduct of ethical health research in the country.

Soumya

(Soumya Swaminathan)

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MESSAGE

I am glad to know that Indian Council of Medical Research (ICMR) is coming out with the revised National Ethical Guidelines for Biomedical and Health Research involving human participants, which is laudable step in the desired direction.

Over a period of time it has been established that the ICMR has always been on the forefront and has played a very decisive role in generating and promoting the highest ethical standards in Biomedical research in consonance with the global guidelines and also keeping in mind the social values and ethos of the diverse population in the country.

Ethicality, morality and Value basis is the 'trinity' on which the Biomedical research has to stand on. Without these important incorporations it will be rudderless and direction less ship wondering in the ocean without ever reaching its desired destination. The entire edifice on which Biomedical research has stands its total adherence to the ethical principles and considerations which add to its purity, sanctity, impact as well as relevance.

The laudable venture undertaken by the ICMR would definitely prove decisive in this direction and would go a long way in amalgamating Biomedical research with the desired ethical contours, faces and facets. I record my compliment for the same.

(Dr. Jayshree Mehta)

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PREFACE

Medical profession is probably the oldest one to prescribe ethical guidelines. Such guidelines for practically all aspect of professional conduct were provided both in Caraksamhita and Susrutasamhita. Rapid advances in the whole field of biomedical sciences have added newer responsibilities and complex dilemmas for medical persons – both practitioner and researchers. It would be correct to say that every advance in medical science results in added moral responsibility. ICMR has always been on the forefront to set the standards for ethics in biomedical and health research. The Council brought out a policy document in 1980, which was revised in 2000 and further revised in 2006. The latest version of guidelines has addressed the newer emerging ethical issues keeping in view the social, cultural, economic, legal and religious aspects of our country. Ethics is a subject of discussions and debates and each and every word and line in the revised guidelines have been deliberated upon by a group of experts and have gone through a process of consultation and debate before it has been finalized. The new expanded document has separate sections on Responsible Conduct of Research, Informed Consent Process, Vulnerability, Public Health Research, Social and Behavioural Sciences Research for Health, Biological materials, Biobanking and Datasets, International Collaboration and Research during Humanitarian Emergencies and Disasters. The guidelines also highlight the need for capacity building in the area of ethics in order to improve the ethical conduct of research. These Guidelines are a result of in-depth discussions and debates, involving the diverse stake-holders and also the public. The ICMR ethical guidelines are well respected not only in India but a number of other countries. The new "National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017" will serve as a guide to answer and meet the challenges and concerns raised by the emerging ethical issues.

I wish that the society will be enormously benefitted by these revised guidelines in general and biomedical scientist in particular.

Dr. P N Tandon
Chairperson
Central Ethics Committee on Human Research

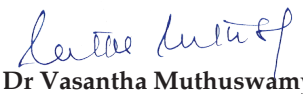
New Delhi
April 2017

MESSAGE FROM CHAIRPERSON ADVISORY GROUP

ICMR brought out the 'Policy Statement on Ethical Considerations Involved in Research on Human Subjects' in 1980 under the chairmanship of Hon'ble Justice H R Khanna. These guidelines were revised in 2000 as the 'Ethical Guidelines for Biomedical Research on Human Subjects' under the chairmanship of Hon'ble Justice M N Venkatachaliah. In view of the new developments in the field of science and technology, another revision was carried out as Ethical Guidelines for Biomedical Research on Human Participants in 2006. Bioethics is a dynamic area and over the last 10 years many new concerns and issues have evolved internationally over the ethical dilemmas faced by the scientific and ethics committees in the conduct and review of biomedical research; hence, an exercise was taken up over a period of one year with national and international consultation to come up with this new set of state of art guidelines. It was a challenging task to decide which of the best practices we should incorporate in this revised version. A wide range of stakeholders in the country consult the ICMR ethical guidelines as gold standard and these are also looked upon by many developing countries.

The new guidelines have many new sections added up and many changes incorporated in the existing sections. There are now a total of 12 sections including Responsible Conduct of Research, Informed Consent Process, Vulnerability, Public Health Research, Social and Behavioural Sciences Research for Health, Biological materials, Biobanking and Datasets and Research during Humanitarian Emergencies and Disasters. Many new issues have been added up as subsections e.g. sexual minorities (LGBT), multicentric studies, research using datasets etc. The section on ethics review process has been elaborated to help the many ethics committees who have doubt about the various procedures to be followed. The support given to the drafting committee by ICMR to complete the work within the stipulated time needs appreciation.

With the emergence of new technologies and knowledge that can potentially transform society, it has become necessary to constantly update the ethical guidelines to protect the rights and safety of the research participants involved in clinical research. I hope the scientific community, the regulatory agencies and all the stakeholders at large involved in biomedical research will be enormously benefitted by this revised new guidelines.



Coimbatore
September 2017

Dr Vasantha Muthuswamy
Chairperson, Advisory Group

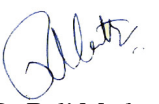
ACKNOWLEDGEMENT

We acknowledge with gratitude the inspiration and patronage of Dr Soumya Swaminathan, Director General ICMR and Secretary Department of Health Research, to update and revise the ICMR Ethical Guidelines for Biomedical Research on Human Participants 2006. The dynamic efforts and contributions of the Advisory Group consisting of Dr Vasantha Muthuswamy (Chairperson), Prof S D Seth, Dr Nandini K Kumar, Prof N K Arora and Prof Urmila Thatte are gratefully acknowledged. Special thanks are due to all the members of the 14 subcommittees who drafted the initial write up as well as all contributors who devoted their time and efforts towards these guidelines. The team of experts that was chosen provided a perfect blend of knowledge, experience and skill to prepare different sections of these guidelines. The inputs of stakeholders from all parts of the country in providing their valuable comments and suggestions in the Regional and National Consultation meetings and web based Public Consultation are duly acknowledged. The support from WHO – country office for India in their technical inputs and jointly hosting the consultation meetings in Bangalore and New Delhi is deeply appreciated and acknowledged. Special thanks are due to a team of very motivated persons especially Dr Rajib Hazam and Dr Kalyani Thakur who knew their job and provided technical and secretarial support and also assisted in coordination and communications involved in undertaking this exercise. This involved a very large number of consultations with experts and stakeholders who provided comments during face to face as well as online consultations. We are thankful to Dr Prashant Mathur, Director, National Center for Disease Informatics & Research (NCDIR), Bengaluru for guiding and facilitating the process. The administrative support extended by Mr Shyam Singh and Mr Santosh Saini from ICMR Headquarters and Mr N M Ramesha and Mr C Somasekhar from NCDIR, Bengaluru along with many others is duly recognised.

It is hoped that this document is able to address the ethical challenges involved in a variety of biomedical and health research areas and will be a useful document for the researchers, ethics committees, institution and sponsors engaged in the conduct of biomedical and health research involving human participants across the country.



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INTRODUCTION

The code of conduct for physicians was well laid out in traditional Indian systems of medicine and do no harm was the underlying universal principle besides other principles applicable to the prevalent 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.[1] Due to rapid advances in biomedical science and technology, new ethical dimensions emerged which necessitated further updation of these guidelines. Subsequently the Ethical Guidelines for Biomedical Research on Human Subjects was released in 2000,[2] followed by the revised Ethical Guidelines for Biomedical Research on Human Participants in 2006.[3] In the meantime, the Central Drugs Standard Control Organization (CDSCO) also released the Indian Good Clinical Practice Guidelines (2001)[4] for clinical trials and revised Schedule Y of the Drugs and Cosmetics Act, 1940, in the year 2005[5] with several amendments in the Rules under Drugs and Cosmetics Act in the year 2013. ICMR and the Department of Biotechnology (DBT) jointly brought out Guidelines for Stem Cell Research and Therapy in 2007 and a further revision in 2013 which is now revised as National Guidelines for Stem Cell Research, 2017.[6]

The Nuremberg Code of 1947[7] was the first international treatise on the ethics of research involving human beings and highlighted the essentiality of obtaining voluntary consent. In 1964, the World Medical Association formulated guidelines on conducting research on humans, known as the Declaration of Helsinki. This has undergone seven revisions with the latest version being issued in October 2013 at Fortaleza, Brazil.[8]

In 1979, the Belmont Report released by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in the United States of America (USA), for the first time enunciated the three basic ethical principles for research involving human subjects: respect for persons, beneficence and justice.[9] The Department of Health and Human Services (DHHS), USA, released the Federal Policy for the Protection of Human Subjects as the 'Common Rule' in 1991 (revised in 2017).[10] The International Conference on Harmonization (ICH) brought out the Good Clinical Practice Guidelines E6 (R1) in 1996[11] revised as E6 (R2) in 2016.[12] The National Bioethics Advisory Commission, USA (2001),[13] the Council for International Organizations of Medical Sciences (CIOMS), Geneva (2002 revised in 2016),[14,15] and the Nuffield Council of Bioethics, United Kingdom (2002)[16] released recommendations/guidelines relevant

to research in developing countries. UNESCO's Universal Declaration on Bioethics and Human Rights (2005)[17] and other international instruments on human rights further defined the Universal Codes of Ethics to be adopted by the member countries. The revised ICMR ethical guidelines have adapted important guidance points from these international guidelines keeping in mind the diverse socio-cultural milieu of our country.

The socio-cultural ethos in India and its varying standards of healthcare 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 of the earlier guidelines and preparation of the current National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. These guidelines have covered some newer areas like public health research, social and behavioural sciences research for health and responsible conduct of research, and research during humanitarian emergencies and disasters while a few other specialized areas like informed consent process, biological materials, biobanking and datasets and vulnerability have been expanded into separate sections.

Scope

These guidelines are applicable to all biomedical, social and behavioural science research for health conducted in India involving human participants, their biological material and data. The purpose of such research should be:

i. directed towards enhancing knowledge about the human condition while maintaining sensitivity to the Indian cultural, social and natural environment;

ii. conducted under conditions such that no person or persons become mere means for the betterment of others and that human beings who are participating in any biomedical and/or health research or scientific experimentation are dealt with in a manner conducive to and consistent with their dignity and well-being, under conditions of professional fair treatment and transparency; and

iii. subjected to a regime of evaluation at all stages of the research, such as design, conduct and reporting of the results thereof.

STATEMENT OF GENERAL PRINCIPLES

1.0 Research on human participants pertains to a broad range of scientific enquiry aimed at developing generalizable knowledge that improves health, increases understanding of disease and is ethically justified by its social value. Every research has some inherent risks and probabilities of harm or inconvenience to participants/communities. Therefore, protection of participants should be built into the design of the study. Do no harm (non-maleficence) has been the underlying universal principle guiding health care in all systems of medicine around the world. While conducting biomedical and health research, the four basic ethical principles namely; respect for persons (autonomy), beneficence, non-maleficence and justice have been enunciated for protecting the dignity, rights, safety and well-being of research participants. These four basic principles have been expanded into 12 general principles described below, and are to be applied to all biomedical, social and behavioural science research for health involving human participants, their biological material and data.

1.1 General Principles

1.1.1 **Principle of essentiality** whereby after due consideration of all alternatives in the light of existing knowledge, the use of human participants is considered to be essential for the proposed research. This should be duly vetted by an ethics committee (EC) independent of the proposed research.

1.1.2 **Principle of voluntariness** whereby respect for the right of the participant to agree or not to agree to participate in research, or to withdraw from research at any time, is paramount. The informed consent process ensures that participants' rights are safeguarded.

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

1.1.4 **Principle of social responsibility** whereby the research is planned and conducted so as to avoid creation or deepening of social and historic divisions or in any way disturb social harmony in community relationships.

1.1.5 **Principle of ensuring privacy and confidentiality** whereby to maintain privacy of the potential participant, her/his identity and records are kept confidential and access

is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.) privacy of the information can be breached in consultation with the EC 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 researchers, ECs, sponsors, regulators) at all stages of the research to ensure that the risks are minimized and appropriate care and compensation is given if any harm occurs.

1.1.7 Principle of professional competence whereby the research is planned, conducted, evaluated and monitored throughout by persons who are competent and have the appropriate and relevant qualification, experience and/or training.

1.1.8 Principle of maximization of benefit whereby due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits to the research participants and/or to the society.

1.1.9 Principle of institutional arrangements whereby institutions where the research is being conducted, have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure, manpower, funds and training opportunities.

1.1.10 Principle of transparency and accountability whereby the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of the participants. Stakeholders involved in research should disclose any existing conflict of interest and manage it appropriately. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/ audit.

1.1.11 Principle of totality of responsibility whereby all stakeholders involved in research are responsible for their actions. The professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.

1.1.12 Principle of environmental protection whereby researchers are accountable for ensuring protection of the environment and resources at all stages of the research, in compliance with existing guidelines and regulations.

GENERAL ETHICAL ISSUES

2.0 All research involving human participants should be conducted in accordance with the basic and general ethical principles as outlined in section 1. The researcher and the team are responsible for protecting the dignity, rights, safety and well-being of the participants enrolled in the study. They should have the appropriate qualifications and competence in research methodology and should be aware of and comply with the scientific, medical, ethical, legal and social requirements of the research proposal. The ECs are responsible for ensuring that the research is conducted in accordance with the aforementioned principles.

2.1 Benefit-risk assessment

Benefits to the individual, community or society refer to any sort of favourable outcome of the research, whether direct or indirect. The social and scientific value of research should justify the risk, which is the probability of causing discomfort or harm anticipated as physical, psychological, social, economic or legal.

2.1.1 The researcher, sponsor and EC should attempt to maximize benefits and minimize risks to participants so that risks are balanced to lead to potential benefits at individual, societal and/or community levels.

2.1.2 The EC should assess the inherent benefits and risks, ensure a favourable balance of benefits and risks, evaluate plans for minimizing the risk and discomfort and decide on the merit of the research before approving it.

2.1.3 The EC should also assess any altered risks in the study at the time of continuing review.

2.1.4 The type of EC review based on risk involved in the research, is categorized as given in Table 2.1. Also see Table 4.2 for further details.

2.2 Informed consent process

Informed consent protects the individual's autonomy to freely choose whether or not to participate in the research. The process involves three components – providing relevant information to potential participants, ensuring the information is comprehended by them and assuring voluntariness of participation. Informed consent should explain medical terminology in simple terms and be in a language that the participant understands.

Table 2.1 Categories of Risk

Type of risk	Definition/description
Less than minimal risk	Probability of harm or discomfort anticipated in the research is nil or not expected. For example, research on anonymous or non-identified data/samples, data available in the public domain, meta-analysis, etc.
Minimal risk	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of an average healthy individual or general population or during the performance of routine tests where occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, physical examination, chest X-ray, obtaining body fluids without invasive intervention, such as hair, saliva or urine samples, etc.
Minor increase over minimal risk or Low risk	Increment in probability of harm or discomfort is only a little more than the minimal risk threshold. This may present in situations such as routine research on children and adolescents; research on persons incapable of giving consent; delaying or withholding a proven intervention or standard of care in a control or placebo group during randomized trials; use of minimally invasive procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress, such as drawing a small sample of blood for testing; trying a new diagnostic technique in pregnant and breastfeeding women, etc. Such research should have a social value. Use of personal identifiable data in research also imposes indirect risks. Social risks, psychological harm and discomfort may also fall in this category.
More than minimal risk or High risk	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study using a drug, device or invasive procedure such as lumbar puncture, lung or liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

2.2.1 The informed consent document (ICD), which includes patient/participant information sheet (PIS) and informed consent form (ICF) should have the required elements (see Box 5.1 for further details) and should be reviewed and approved by the EC before enrolment of participants. For all biomedical and health research involving human participants, it is the primary responsibility of the researcher to obtain the written, informed consent of the prospective participant or legally acceptable/authorized representative (LAR). In case of an individual who is not capable of giving informed consent, the consent of the LAR should be obtained. If a participant or LAR is illiterate, a literate impartial witness should also be present during the informed consent process.

2.2.2 In certain circumstances audio/audio-visual recording of the informed consent process may be required, for example in certain clinical trials as notified by CDSCO.

2.2.3 Verbal/oral consent/waiver of consent/re-consent may be obtained under certain conditions after due consideration and approval by the EC. See section 5 for further details.

2.3 Privacy and confidentiality

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

2.3.1 The researcher should safeguard the confidentiality of research related data of participants and the community.

2.3.2 Potential limitations to ensure strict confidentiality must be explained to the participant. Researchers must inform prospective participants that although every effort will be made to protect privacy and ensure confidentiality, it may not be possible to do so under certain circumstances.

2.3.3 Any publication arising out of research should uphold the privacy of the individuals by ensuring that photographs or other information that may reveal the individual's identity are not published. A specific re-consent would be required for publication, if this was not previously obtained.

2.3.4 Some information may be sensitive and should be protected to avoid stigmatization and/or discrimination (for example, HIV status; sexual orientation such as lesbian, gay, bisexual, and transgender (LGBT); genetic information; or any other sensitive information).

2.3.5 While conducting research with stored biological samples or medical records/data, coding or anonymization of personal information is important and access to both samples and records should be limited. See section 11 for further details.

2.3.6 Data of individual participants/community may be disclosed in certain circumstances with the permission of the EC such as specific orders of a court of law, threat to a person's or community's life, public health risk that would supersede personal rights to privacy, serious adverse events (SAEs) that are required to be communicated to an appropriate regulatory authority etc.

2.4 Distributive justice

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

2.4.2 Vulnerable individuals/groups should not be included in research to solely benefit others who are better-off than themselves.

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

2.4.4 Plans for direct or indirect benefit sharing in all types of research with participants, donors of biological materials or data should be included in the study, especially if there is a potential for commercialization. This should be decided a priori in consultation with the stakeholders and reviewed by the EC.

2.5 Payment for participation

2.5.1 If applicable, participants may be reimbursed for expenses incurred relating to their participation in research, such as 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 (for example, loss of wages and food supplies).

2.5.2 Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including investigations, patient work up, any interventions or associated treatment. This is applicable to all participants, including those in comparator/control groups.

2.5.3 If there are provisions, participants may also receive additional medical services at no cost.

2.5.4 When the LAR is giving consent on behalf of a participant, payment should not become an undue inducement and to be reviewed carefully by the EC. Reimbursement may be offered for travel and other incidental expenses incurred due to participation of the child/ward in the research.

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

2.6 Compensation for research-related harm

Research participants who suffer direct physical, psychological, social, legal or economic harm as a result of their participation are entitled, after due assessment, to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, participant's dependents are entitled to

financial compensation. The research proposal should have an in-built provision for mitigating research related harm.

2.6.1 The researcher is responsible for reporting all SAEs to the EC within 24 hours of knowledge. Reporting of SAE may be done through email or fax communication (including on non-working days). A report on how the SAE was related to the research must also be submitted within 14 days.

2.6.2 The EC is responsible for reviewing the relatedness of the SAE to the research, as reported by the researcher, and determining the quantum and type of assistance to be provided to the participants.

- For clinical trials under the purview of CDSCO, the timeline and procedures as notified from time to time may be followed.
- All research participants who suffer harm, whether related or not, should be offered appropriate medical care, psycho-social support, referrals, clinical facilities, etc.
- Medical management should be free if the harm is related to the research.
- Compensation should be given to any participant when the injury is related to the research. This is applicable to participants in any of the arms of research, such as intervention, control and standard of care.
- While deliberating on the quantum of compensation to be awarded to participants who have suffered research-related injury, the EC should consider aspects including the type of research (interventional, observational, etc.), extent of injury (temporary/permanent, short/long term), loss of wages, etc.
- For other sponsored research, it is the responsibility of the sponsor (whether a pharmaceutical company, government or non-governmental organization (NGO), national or international/bilateral/multilateral donor agency/institution) to include insurance coverage or provision for possible compensation for research related injury or harm within the budget.

2.6.3 All AEs should be recorded and reported to the EC according to a pre-planned timetable, depending on the level of risk and as recommended by the EC.

2.6.4 In investigator initiated research/student research, the investigator/institution where the research is conducted becomes the sponsor.

- It is the responsibility of the host institution to provide compensation and/or cover for insurance for research related injury or harm to be paid as decided by the EC.

- The institution should create in-built mechanism to be able to provide for compensation, such as a corpus fund in the institution.
- In the applications for research grants to funding agencies – national or international, government or non-government agencies – the researcher should keep a budgetary provision for insurance coverage and/or compensation depending upon the type of research, anticipated risks and proposed number of participants.

2.7 Ancillary care

2.7.1 Participants may be offered free medical care for non-research-related conditions or incidental findings if these occur during the course of participation in the research, provided such compensation does not amount to undue inducement as determined by the EC.

2.8 Conflict of interest

Conflict of interest (COI) is a set of conditions where professional judgement concerning a primary interest such as participants welfare or the validity of research tends to be unduly influenced by a secondary interest, financial or non-financial (personal, academic or political). COI can be at the level of researchers, EC members, institutions or sponsors. If COI is inherent in the research, it is important to declare this at the outset and establish appropriate mechanisms to manage it.

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

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

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

2.8.4 COI within the EC should be declared and managed in accordance with standard operating procedures (SOPs) of that EC.

2.9 Selection of vulnerable and special groups as research participants

Vulnerable groups and individuals may have an increased likelihood of incurring additional harm as they may be relatively (or absolutely) incapable of protecting their own interests.

2.9.1 Characteristics that make individuals vulnerable are legal status – children; clinical conditions – cognitive impairment, unconsciousness; or situational conditions –

including but not limited to being economically or socially disadvantaged, (for example, certain ethnic or religious groups, individuals/communities which have hierarchical relationships, institutionalized persons, humanitarian emergencies, language barriers and cultural differences).

2.9.2 In general, such participants should be included in research only when the research is directly answering the health needs or requirements of the group. On the other hand, vulnerable populations also have an equal right to be included in research so that benefits accruing from the research apply to them as well. This needs careful consideration by researchers as well as the EC.

2.9.3 The EC should determine vulnerability and ensure that additional safeguards and monitoring mechanisms are established. It should also advise the researcher in this regard. See section 6 for further details.

2.10 Community engagement

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

2.10.1 The community can be engaged in many ways and can provide valuable opinions. The degree of community engagement should depend on the type of research that is being conducted.

2.10.2 Community advisory board/group (CAB/CAG) can act as an interface between the community (from which participants are to be drawn), the researchers and the concerned EC. Members of the CAB should be such that they do not coerce the members of the community to participate in the research and also protect the rights and serve the requirements of the group.

2.10.3 Members of the community can also be represented in the EC either as members or special invitees.

2.10.4 Community engagement does not replace individual informed consent. It ensures that the community's health needs and expectations are addressed, informed consent is appropriate, and access to research benefits are provided through research that is designed and implemented in the best interests of science and the community.

2.10.5 After the study is completed, the researcher may communicate with the community

representative, local institution or the government department from where the data was collected to help in dissemination of the results to the entire community.

See sections 8 and 9 for further details.

2.11 Post research access and benefit sharing

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

2.11.1 Efforts should be made to communicate the findings of the research study to the individuals/communities wherever relevant.

2.11.2 The research team should make plans wherever applicable for post-research access and sharing of academic or intervention benefits with the participants, including those in the control group.

2.11.3 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.

2.11.4 If an investigational drug is to be given to a participant post-trial, appropriate regulatory approvals should be in place.

2.11.5 The EC should consider the need for an a priori agreement between the researchers and sponsors regarding all the points mentioned above (from 2.11.1 to 2.11.3).

2.11.6 In studies with restricted scope, such as 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.

RESPONSIBLE CONDUCT OF RESEARCH

3.0 The value and benefits of research are dependent on the integrity of the researchers. Scientists have a significant social responsibility to prevent research misconduct and misuse of research. Responsible researchers abide by the standards prescribed by their professions, disciplines and institutions and also by relevant laws. All members of a research team are expected to maintain high standards and to uphold the fundamental values of research. The responsible conduct of research (RCR) involves the following major components: values; policies; planning and conducting research; reviewing and reporting research; and responsible authorship and publication.

Institutions conducting research must establish a research office within their institution to facilitate research, manage grants, and oversee all aspects of RCR. The research office must work closely with the EC and with all stakeholders, including undergraduate and postgraduate students. SOPs should be in place to address all the major components of RCR as outlined in the following sections.

3.1 Values of research

RCR is guided by shared values including honesty, accuracy, efficiency, fairness, objectivity, reliability, accountability, transparency, personal integrity, and knowledge of current best practices, and these should be reflected in the policies related to RCR.

3.1.1 The scientist as a responsible member of society

Scientific research is vital to improving our understanding of various health related problems and their solutions. All research components depend on cooperation and shared expectations as part of inter-professional ethics. Unethical behaviour in scientific research can destroy the public's trust in science and have a negative impact on the research team. Without trust between scientists and the public, or within research teams, meaningful research is compromised. Researchers should be aware that the resources of biomedical research are precious and to be used judiciously. Whereever possible they should also seek oppurtunities to plan translation of research findings into public health outcomes.

3.1.2 Contemporary ethical issues in biomedical and health research

Emerging new areas of research give rise to new ethical issues. Among the contemporary

issues recently under debate are the use of underprivileged and vulnerable groups as participants, post-trial access of research benefits to participants and their communities, research on emerging technologies, etc. Continuing education is necessary to keep researchers apprised of contemporary issues.

3.1.3 Sensitivity to societal and cultural impact of biomedical and health research

To understand the social and cultural impact of research, one must analyse how the health sector and general public engage with the results of biomedical and health research. It is essential that researchers bear this in mind while planning, conducting and evaluating research as it will improve public accountability and enhance public, private and political advocacy.

3.1.4 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 guide researchers in ways above and beyond what can be gathered from reading textbooks. The relationship between mentors and trainees should enable trainees to become responsible researchers. Mentors should ensure their trainees conduct research honestly, do not interfere with the work of other researchers and use resources judiciously. A mentor should be knowledgeable, teach and lead by example and understand that trainees differ in their abilities. She/he should devote sufficient time and be available to discuss, debate and guide trainees ably. A mentor should encourage decision making by the trainees and the trainee should take an active role in communicating her/his needs.

3.2 Policies

3.2.1 The protection of human participants

Institutions must establish policies and mechanisms for the protection of human research participants. Such policies should assign responsibilities to the institution, the EC and the researchers. Additionally, there should be mechanisms and policies for monitoring research including data capture, management , conflicts of interest, reporting of scientific misconduct, and appropriate initial and continuing training of researchers and EC members. Policies can be made available on the websites of the institutes or organizations. Researchers should also follow their respective professional codes of conduct.

3.2.2 Animal experimentation

Those involved in experimentation on animals must follow all the existing regulations and guidelines including the Prevention of Cruelty to Animals 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, Committee for the Purpose of Control and Supervision of Experiments on Animals (CPSCSEA) Guidelines for Laboratory Animal Facilities, 2003[18] and Guidelines for Rehabilitation of Animals used in Research, 2010.

3.3 Planning and conducting research – Specific Issues

3.3.1 Conflict of interest issues

COI refers to a set of conditions whereby professional judgement concerning a primary interest, such as participant's welfare or the validity of research either is, or perceived to be unduly influenced by a secondary interest. The secondary interest may be financial or non-financial, personal, academic or political. This is not inherently wrong, but COI 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 COI which can be at the level of researcher, ethics committee or at the level of institution. Research institutions, researchers and research ECs must follow the steps given in Box 3.1.

Box 3.1 Identifying, mitigating and managing COI

The broad responsibilities of those involved in research, with respect to COI, are given below:

1. **Research institutions must:**
   - develop policies and SOPs to address COI issues that are dynamic, transparent and actively communicated;
   - implement policies and procedures to address COI and conflicts of commitment, and educate their staff about such policies;
   - monitor the research or check research results for accuracy and objectivity; and
   - not interfere in the functioning and decision making of the EC.
2. **Researchers must:**
   - ensure that documents submitted to the EC include disclosure of COI (financial or non-financial) that may affect their research;
   - guard against conflicts of commitment that may arise from situations that place competing demands on researchers' time and loyalties; and
   - prevent intellectual and personal conflicts by ensuring they do not serve as reviewers for grants and publications submitted by close colleagues, relatives and/or students.

(Contd.)

3. **ECs must:**
   - evaluate each study in light of any disclosed COI and ensure appropriate action is taken to mitigate this; and
   - require their members to disclose their own COI and take appropriate measures to recuse themselves from reviewing or decision making on protocols related to their COI; and
   - make appropriate suggestions for management, if COI is detected at the institutional or researchers level.

3.3.2 Data acquisition, management, sharing and ownership

- There is no single best way to collect data. Different collection techniques are needed for different types of research. Researchers should be sensitive to participants and use best practices for data collection.
- Data collection involves physical process of recording data in hard copy, soft or electronic copy, or other permanent forms. The physical formats for recording data vary considerably, from measurements or observations to photographs or interview recordings. To be valuable, research data must be properly recorded.
- Institutes receiving research funds have responsibilities for budgets, regulatory compliance and management of collected data with funded research. This means that researchers should obtain appropriate permissions/approvals to take their data and funding with them if they move to another institution.
- Ownership issues and responsibilities need to be carefully worked out well before data are collected and researchers should ensure clarity about data ownership, publication rights and obligations following data collection. MoUs vetted by the institution and/or EC should be in place.
- For biological samples, donors (participants) maintain the ownership of the sample. She/he could withdraw both the biological material and the related data unless the latter is required for outcome measurement and is so mentioned in the initial informed consent document.
- Institutes hosting/implementing the research are the custodians of the data/samples.
- Research must be conducted using appropriate and reliable methods to provide reliable data. The use of inappropriate methods in research compromises the integrity of research data and should be avoided.
- Quality research requires attention to detail at every step. Proper protocols need

to be established and the results accurately recorded, interpreted and published. Implementation of poorly designed research wastes resources and should be avoided.

In some cases, authorization is needed prior to data collection. Researchers are responsible for knowing when permission is needed to collect or use specific data in their research. See Box 3.2 for further details.

Box 3.2 Research requiring authorization prior to data collection

Data for the following types of research cannot be collected without getting prior authorization:

1. human participants and animals in research;
2. information posted on some websites;
3. hazardous materials and biological agents;
4. biological sample storage and future testing;
5. information from some libraries, databases and archives;
6. published photographs and other published information; and
7. other copyrighted or patented processes or materials.

- Data protection and storage is important and once collected, data must be properly protected, as it may be needed at a later stage to confirm research findings, establish priority, or be re-analysed by other researchers. Responsible data handling 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 back-up data saved in a secure place at a site that is different from the original data storage site.
- Data sharing is important as research data is valuable and needs to be shared, but deciding when and with whom to share may raise difficult questions. 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 or placed in a public domain in a de-identified/anonymized form, unless required otherwise, for which applicable permissions/re-consent should be sought unless obtained beforehand.

3.4 Reviewing and reporting research

The public's trust in published research is an essential component of ethical and responsible research.

3.4.1 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.

3.4.2 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.

3.4.3 Research that is completed, irrespective of results, must be published, since it would be unethical to expose another set of participant/patients/volunteers to the same risks to obtain the same results.

3.4.4 Researchers should provide results of study in the public database of the Clinical Trial Registry-India (CTRI).

3.5 Responsible authorship and publication

3.5.1 Authorship – The researchers should follow the guidance of International Committee of Medical Journal Editors (ICMJE) on authorship[23] which is largely accepted as a standard and is endorsed by the World Association of Medical Editors (WAME). See Box 3.3 for further details.

Box 3.3 Criteria for authorship (ICMJE)

According to the ICMJE, authorship entails the following criteria:

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 and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- 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.
- Authorship should never be gifted and 'ghost' authors are not acceptable. The authorship of research should be considered at the time of its initiation.
- The primary author should be the person who has done most of the research work related to the manuscript being submitted for publication. Research performed

as part of a mandatory requirement of a course/fellowship/training programme including student research should have the candidate as the primary author. All efforts must be made to provide the candidate with an opportunity to fulfil the second, third and fourth criteria of the ICMJE guidelines.

3.5.2 Peer review

Scientific disclosure and progress has been dependent largely on peers evaluating research and judging the quality and utility of conducting and publishing research.

- The present peer review system depends on fairness, honesty and transparency of all stakeholders – editors, reviewers and researchers. It can involve one or more reviewers and should be completed within a reasonable period of time.
- Researchers must avoid mentioning friends, well-wishers and mentors as reviewers and must decline to review research of close associates, friends and students.
- Funding agencies and journals must ask reviewers and researchers to inform them of COI, if any.
- Reviewers must maintain the confidentiality of manuscripts sent to them for review.
- If reviewers feel they are not competent to review papers, then they should inform editors immediately and should not pass on the manuscripts to friends and colleagues without seeking the consent of the editors.
- Reviewers who are researchers must not misguide editors in an attempt to self evaluate their research (using another email ID and profile).

3.6 Research misconduct and policies for handling misconduct

Research misconduct involves fabrication, falsification and plagiarism of data, which are serious issues both nationally and internationally. See Box 3.4 for further details.

3.6.1 Institutions should develop policies to address scientific/research misconduct.

3.6.2 Research misconduct, if suspected, needs to be investigated. An institution must investigate all allegations of misconduct as present or future participants' lives may be endangered if facts are not presented accurately. Such investigations must be done in a timely, fair and transparent manner and the results should be made available in the public domain.

3.6.3 It is important to establish institutional mechanisms for protection of both the whistle-blower and the person accused of research misconduct. This information must be kept

Box 3.4 Types of research misconduct

Research misconduct includes the following:

- 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 paper or another author's "language, thoughts, ideas, or expressions" and the representation of them as one's own original work or duplicating one's own publication (self plagiarism).

confidential until the enquiry is complete.

3.6.4 Simultaneous submission of the same grant application to different funding agencies or submitting papers/overlapping publications to journals is not acceptable, as this could lead to unnecessary duplication in review process or in meta analysis. .

3.7 Registration with Clinical Trials Registry–India

The Clinical Trials Registry–India, linked to WHO registry, was launched on 20 July 2007 by ICMR, as a free and online public record system for registration of clinical trials, PG thesis and other biomedical research being conducted in the country. Trial registration in the CTRI was made mandatory by CDSCO on 15 June 2009 for clinical trials that are registered under the Drugs and Cosmetics Act and its Rules. Registration with CTRI is voluntary for other biomedical and health research. In addition, editors of major biomedical journals of India declared that only trials on any of the public databases would be considered for publication in journals. According to 64th WMA General Assembly, held at Fortaleza, Brazil, in October 2013, the Declaration of Helsinki clearly states that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." Under the aegis of WHO, a joint statement on public disclosure of results from all international trials was signed by ICMR and others in May 2017.

3.7.1 All clinical research involving human participants including any intervention such as drugs, surgical procedures, devices, biomedical, educational or behavioural research, public health intervention studies, observational studies, implementation research and preclinical studies of experimental therapeutics and preventives or AYUSH studies may be registered prospectively with the CTRI.

3.7.2 Trial registration involves providing information regarding the study, investigators, sites, sponsor, ethics committees, regulatory clearances, disease/condition, types of study, methodologies, outcomes, etc.

3.7.3 Registration of research in CTRI ensures that more complete, authenticated, readily available data on research is available publicly. This improves transparency, accountability and accessibility.

3.8 Collaborative research

Researchers are increasingly collaborating with colleagues who have the expertise and/or for resources needed to carry out particular research. This could be inter-departmental/inter-institutional or international and also multicentre involving public and/or private research centres and agencies. The main ethical issues surrounding collaborations pertain to sharing techniques, ownership of materials and data, IPRs, joint publications, managing research findings, managing COI and commercializing research outcomes. Researchers should familiarize themselves with all aspects including local, national and international requirements for research collaboration including necessary approvals, memorandums of understanding (MoUs) and material transfer agreements (MTA) and EC approval of collaborating institutes.

3.8.1 Ethical considerations in collaborative research

Collaborative studies should take into account the values/benefits expected from the research as compared to the risks involving the persons/population being studied.

- The participating centres should function as partners with the collaborator(s) and sponsor(s) in terms of ownership of samples and data, analysis, dissemination, publication and IPR as appropriate. There must be free flow of knowledge and capacity at bilateral/multilateral levels.
- Careful consideration should be given to protecting the dignity, rights, safety and well-being of the participants in cases where the social contexts of the proposed research can create foreseeable conditions for their exploitation or increase their vulnerability to harm.
- The nature, magnitude and probability of all foreseeable harm resulting from participation in a collaborative research programme should be specified in the research protocol and well explained to the participants.
- The benefits and burdens should be equally distributed amongst participants recruited by all collaborating institutions.
- All participants in collaborative research should have access to the best nationally

available standard of care.

- If there is exchange of biological material involved between collaborating sites, the EC may require appropriate MoU and/or MTA to safeguard the interests of participants and ensure compliance while addressing issues related to confidentiality, sharing of data, joint publications, benefit sharing, etc.

3.8.2 Responsibilities of ethics committees, researchers and institutions

The review, conduct and monitoring of collaborative research should be overseen and stakeholders must be aware of the requirements of various regulatory and funding agencies.

- An EC should review the protocols in the local social and cultural context and ensure respect for sensitivities and values of participants and communities at collaborative sites.
- A mechanism for communication between the ECs of different participating centres should be established. In case of any conflict, the decision of the local EC based on relevant facts/guidelines/law of the land shall prevail.
- An EC should examine whether the researcher has the required expertise and training in the area of collaboration.
- An EC should protect the interests and rights of the collaborating researcher(s) and ensure that they are not treated as mere collectors of samples or data.
- Participating researchers from collaborating sites should be adequately represented when designing the research proposal.
- Institutions are responsible for fair contract negotiation in collaborative research partnerships (including benefit sharing and avoiding unauthorized use of their expertise, biological samples and data) to safeguard the interests of participants, researchers and institutions.
- Institutions should provide opportunities for collaboration to build capacity and engage in research which is mutually beneficial.

3.8.3 International collaboration

The scope of international collaboration in biomedical and health research has gained such momentum in recent years that it could have potentially exploitative commercial and human dimensions. While on one hand collaboration in medical research could be seen as a humane interest in the health of civil society, on the other hand it could create the impression of exploitation by one country experimenting on the population of another

poorer one. Due to different levels of development in terms of infrastructure, expertise, social and cultural perceptions, laws relating to IPR, ethical review procedures, etc., an ethical framework based on equality and equity is required to guide such collaborations. The same is applicable to research undertaken with assistance and/or collaboration from international organizations (public or private). The collaboration may involve either implementation of multiple components of the research or even a single component like laboratory testing. To undertake a collaborative research in India, our country's ethical guidelines and relevant regulatory requirements should be followed and understood before the sponsor agency/country initiates collaboration.

- Indian participating centres should function as partners with the collaborator(s) and sponsor(s) in terms of ownership of samples and data, analysis, dissemination, publication and IPR related to research in India, as may be considered appropriate.
- There should be good communication between international participating centres and in case of any conflict, the decision of the EC of the Indian participating centre(s), based on relevant facts/guidelines/law of the land, shall prevail.
- The institution should protect against imposition of moral or ethical standards of the sponsoring country (ethical imperialism) which may not be in agreement with India's ethical and regulatory requirements.
- The institution/EC should not accept international proposals which cannot be conducted in the country of origin.
- Researchers and EC members should be trained to understand and recognize ethical perspectives that reflect India's best interests.

The types of international collaborations are mentioned in Box 3.5

Box 3.5 Types of international collaboration

International collaboration can include all or any of the following elements:

- funding by international agencies, such as UN Agencies, NIH, WHO, Wellcome Trust, World Bank and others;
- academic collaborations with foreign institutions, universities, organizations, foundations with or without external funding; and
- formal government inter-country bilateral/multilateral collaborative arrangements between Indian research bodies/institutions and similar bodies/institutions of other countries.

- All biomedical and health research proposals involving foreign assistance and/or collaboration should be submitted to the Health Ministry's Screening Committee (HMSC) for consideration and approval before initiation.[19] The secretariat for HMSC is located at the ICMR Headquarters, New Delhi. As per the requirements of HMSC, all research involving international collaboration – either technical, financial, laboratory or data management must be submitted to HMSC.
- The exchange of material envisaged as part of a collaborative research proposal must be routed through appropriate authorities. While 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 the Indian context may vary from other countries and agencies with respect to socio-cultural norms and needs of the country.
- Export of all biological materials will be covered under the existing Government of India (GOI) guidelines for transfer of human biological materials. Research proposals requiring biological material transfer may be considered by the EC on a case-to-case basis. Collaborators should obtain applicable regulatory clearances as mandated by laws such as the Environmental Protection Act, 1986[20], the Biological Diversity Act, 2002[21], 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 Centres/reference centres for specific purposes, and for individual cases of diagnosis or therapeutic purposes, may not require permission.
- Indian participating centre(s) must have appropriate regulatory approval and registration to receive foreign funds for research.[22]
- Any research involving exchange of biological material/specimens with collaborating institution(s) outside India must sign an MTA justifying the purpose and quantity of the sample being collected and addressing issues related to confidentiality, sharing of data, joint publication policy, IPR and benefit sharing, post analysis handling of the leftover biological materials, safety norms, etc.
- The guidelines, regulations and cultural sensitivities of all countries participating in collaborative research proposals should be respected by researchers in India and the sponsor country. An appropriate MoU should be in place to safeguard mutual interests and ensure compliance.

ETHICAL REVIEW PROCEDURES

4.0 It is necessary for all research proposals on biomedical, social and behavioural science research for health involving human participants, their biological material and data to be reviewed and approved by an appropriately constituted EC to safeguard the dignity, rights, safety and well-being of all research participants. ECs are entrusted with the initial review of research proposals prior to their initiation, and also have a continuing responsibility to regularly monitor the approved research to ensure ethical compliance during the conduct of research. The EC should be competent and independent in its functioning.

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

4.0.2 The institution is responsible for providing logistical support, such as infrastructure, staff, space, funds, adequate support and protected time for the Member Secretary to run the EC functions.

4.0.3 The EC is responsible for scientific and ethical review of research proposals. Although ECs may obtain documentation from a prior scientific review, they must determine that the research methods are scientifically sound, and should examine the ethical implications of the chosen research design or strategy.

4.0.4 All types of biomedical and health research (whether clinical, basic science, policy, implementation, epidemiological, behavioural, public health research, etc) must be reviewed by an EC before it is conducted.

4.1 Terms of reference (TOR) for ECs

4.1.1 The TOR for the EC and its members should be clearly specified by the institution in the EC SOPs (Annex 1 for the List of SOPs).

4.1.2 Every EC should have written SOPs according to which the committee should function. The EC can refer to ICMR guidelines in preparing the SOPs for all biomedical and health research and to CDSCO guidelines for drug and device trials under the purview of the licensing authority. The SOPs should be updated periodically to reflect 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 both hard and soft copies.

4.1.3 The scope, tenure and renewal policy of the EC should be stated.

4.1.4 Members of the EC should not have any known record of misconduct.

4.1.5 The EC should be registered with the relevant regulatory authorities, for example, ECs approving clinical trials under the ambit of Drugs and Cosmetics Actshould be registered with CDSCO.

4.2 Special situations

4.2.1 Institutions can have one or more than one EC. They can have multiple ECs to review large numbers of research proposals. Each EC can function as a stand-alone committee which should follow all the SOPs and TORs of that institution.

4.2.2 An institution that does not have its own EC (user institution) may utilize the services of the EC of another institution (host institution) preferably in the adjoining/nearby area. Relevant requirements must be fulfilled before they do so. See Box 4.1 for further details.

Box 4.1 Utilizing the services of an EC of another institution

The following requirements must be fulfilled by institutions that use the services of an EC from another institution:

- The two institutions (host and user) should enter into an MoU for utilizing the services of the EC of the host institution or the user institution should provide a 'No Objection Certificate' and agree to be overseen by the EC of the host institution.
- The EC of the host institution should have access to all research records including the source documents and research participants for continuing review of the implemented project, including site visits.
- The EC of the host institution can undertake site monitoring and will have all the rights and responsibilities related to ethical review of the projects submitted by the user institutions.

4.2.3 For multicentric biomedical and health research, all participating sites may decide to utilize the services of one common EC from a participating site identified as designated main EC for the purpose of primary review. This EC should be located in India and registered with the relevant authority. However, the local site requirements, such as informed consent process, research implementation and its monitoring, etc. may be performed by the local EC. This would require good communication and coordination between the researchers and EC secretariats of participating sites. For clinical trials under the Drugs and Cosmetics Act, the requirements as stated by CDSCO must be followed. See section 4.10 for further details.

4.2.4 Stem cell proposals should be reviewed and approved by the institutional committee

for stem cell research (IC-SCR) before being submitted to the EC for consideration, in accordance with the National Guidelines for Stem Cell Research (2017).

4.2.5 Independent ECs (Ind EC) that function outside institutions can be used by researchers who have no institutional attachments. For these committees, the following essential conditions should be met:

- The Ind EC must be established as a registered legal entity, governed by individuals who are not members of the proposed EC and who will oversee and monitor the functioning of the Ind EC.
- It should function according to SOPs that follow the national guidelines for functioning of ECs.
- It should not accept research proposals from investigators affiliated to institutions that have their own ECs unless there is an MoU.
- It will have rights and responsibilities related to the projects submitted to it.
- It should have access to all research records, including the source documents and research participants.
- It should undertake continuing review of the implemented project including site visits.
- It should familiarize itself with local socio-cultural norms that may help to ensure protection of rights and wellbeing of research participants.

4.2.6 Institutions could have subcommittees such as the SAE subcommittee or expedited review committee. These should be part of the main committee and comprise Chairperson/ Member Secretary and one to two appropriate designated members of the main EC as defined in the SOPs. These subcommittees can report to the concerned main EC.

4.2.7 Institutions could have separate committee for SAE in which one or two members of EC could be included to facilitate continuity of EC activity and its report should be reviewed by main EC.

4.3 Composition of an EC

4.3.1 ECs should be multi-disciplinary and multi-sectoral.

4.3.2 There should be adequate representation of age and gender.

4.3.3 Preferably 50% of the members should be non-affiliated or from outside the institution.

4.3.4 The number of members in an EC should preferably be between seven and 15 and a minimum of five members should be present to meet the quorum requirements.

4.3.5 The EC should have a balance between medical and non-medical members/technical and non-technical members, depending upon the needs of the institution.

The composition, affiliations, qualifications, member specific roles and responsibilities are given in Table 4.1.

Table 4.1 Composition, affiliations, qualifications, member specific roles and responsibilities of an EC

S. No.	Members of EC	Definition/description
1.	**Chairperson/ Vice Chairperson** (optional) Non-affiliated Qualifications - A well-respected person from any background with prior experience of having served/ serving in an EC	• Conduct EC meetings and be accountable for independent and efficient functioning of the committee • Ensure active participation of all members (particularly non-affiliated, non-medical/ non- technical) in all discussions and deliberations • Ratify minutes of the previous meetings • 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. • Seek COI declaration from members and ensure quorum and fair decision making. • Handle complaints against researchers, EC members, conflict of interest issues and requests for use of EC data, etc.
2.	**Member Secretary/ Alternate Member Secretary** (optional) Affiliated Qualifications - • Should be a staff member of the institution • Should have knowledge and experience in clinical research and ethics, be motivated and have good communication skills	• Organize an effective and efficient procedure for receiving, preparing, circulating and maintaining each proposal for review • Schedule EC meetings, prepare the agenda and minutes • Organize EC documentation, communication and archiving • Ensure training of EC secretariat and EC members • Ensure SOPs are updated as and when required • Ensure adherence of EC functioning to the SOPs • Prepare for and respond to audits and inspections • Ensure completeness of documentation at the time of receipt and timely inclusion in agenda for EC review. • Assess the need for expedited review/ exemption from review or full review.

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	• Should be able to devote adequate time to this activity which should be protected by the institution	• Assess the need to obtain prior scientific review, invite independent consultant, patient or community representatives. • Ensure quorum during the meeting and record discussions and decisions.
3.	**Basic Medical Scientist(s)** Affiliated/ non-affiliated Qualifications - • Non-medical or medical person with qualifications in basic medical sciences • In case of EC reviewing clinical trials with drugs, the basic medical scientist should preferably be a pharmacologist	• Scientific and ethical review with special emphasis on the intervention, benefit-risk analysis, research design, methodology and statistics, continuing review process, SAE, protocol deviation, progress and completion report • For clinical trials, pharmacologist to review the drug safety and pharmacodynamics.
4.	**Clinician(s)** Affiliated/ non-affiliated Qualifications - • Should be individual/s with recognized medical qualification, expertise and training	• Scientific review of protocols including review of the intervention, benefit-risk analysis, research design, methodology, sample size, site of study and statistics • Ongoing review of the protocol (SAE, protocol deviation or violation, progress and completion report) • Review medical care, facility and appropriateness of the principal investigator, provision for medical car, management and compensation. • Thorough review of protocol, investigators brochure (if applicable) and all other protocol details and submitted documents.
5.	**Legal expert/s** Affiliated/ non-affiliated Qualifications - • Should have a basic degree in Law from a recognized university, with experience • Desirable: Training in medical law.	• Ethical review of the proposal, ICD along with translations, MoU, Clinical Trial Agreement (CTA), regulatory approval, insurance document, other site approvals, researcher's undertaking, protocol specific other permissions, such as, stem cell committee for stem cell research, HMSC for international collaboration, compliance with guidelines etc. • Interpret and inform EC members about new regulations if any

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6.	**Social scientist/ philosopher/ ethicist/theologian** Affiliated/ non-affiliated Qualifications - • Should be an individual with social/ behavioural science/ philosophy/ religious qualification and training and/or expertise and be sensitive to local cultural and moral values. Can be from an NGO involved in health-related activities	• Ethical review of the proposal, ICD along with the translations. • Assess impact on community involvement, socio–cultural context, religious or philosophical context, if any • Serve as a patient/participant/ societal / community representative and bring in ethical and societal concerns.
7.	**Lay person(s)** Non-affiliated Qualifications - • Literate person from the public or community • Has not pursued a medical science/ health-related career in the last 5 years • May be a representative of the community from which the participants are to be drawn • Is aware of the local language, cultural and moral values of the community • Desirable: involved in social and community welfare activities	• Ethical review of the proposal, ICD along with translation(s). • Evaluate benefits and risks from the participant's perspective and opine whether benefits justify the risks. • Serve as a patient/participant/ community representative and bring in ethical and societal concerns. • Assess on societal aspects if any.

4.3.6 The quorum should be as specified in Box 4.2.

Box 4.2 Quorum requirements for EC meetings

1. A minimum of five members present in the meeting room.
2. The quorum should include both medical, non medical or technical or/and non-technical members.*
3. Minimum one non-affiliated member should be part of the quorum.
4. Preferably the lay person should be part of the quorum.
5. The quorum for reviewing regulatory clinical trials should be in accordance with current CDSCO requirements.
6. No decision is valid without fulfilment of the quorum.

**Medical members are clinicians with appropriate medical qualifications. Technical members are persons with qualifications related to a particular branch in which the study is conducted, for example social sciences.*

4.3.7 So as to maintain independence, the head of the institution should not be part of the EC but should act as an appellate authority to appoint the committee or to handle disputes.

4.3.8 The Chairperson and Member Secretary could have dual roles in the ethics committee. They could fulfil a role based on their qualifications (such as that of clinician, legal expert, basic scientist, social scientist, lay person etc.) in addition to taking on the role of Chairperson or Member Secretary.

4.3.9 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 TORs as regular members and can attend meetings in the absence of regular members.

4.3.10 The EC can maintain a panel of subject experts who are consulted for their subject expertise, for instance, a paediatrician for research in children, a cardiologist for research on heart disorders, etc. They may be invited to attend the meeting to give an expert opinion on a specific proposal but will not have decision making power/voting rights.

4.3.11 The EC may invite subject experts as independent consultants or include a representative from a specific patient group as a member of the EC or special invitee, for opinion on a specific proposal, for example HIV, genetic disorders, or cancer, with appropriate decision making power.

4.3.12 As far as possible a separate scientific committee should priorly also review proposal before it is referred to EC. EC can raise scientific queries besides ethical ones as both good science and ethics are important to ensure quality of research and participant protection.

4.4 Terms of reference for EC members

4.4.1 The head of the institution should appoint all EC members, including the Chairperson.

4.4.2 The appointment letter issued to all members should specify the TORs. The letter issued by the head of the institution should include, at the minimum, the following:

- Role and responsibility of the member in the committee
- Duration of appointment
- Conditions of appointment

4.4.3 Generally, the term of EC membership may be 2–3 years. The duration could be extended as specified in the SOPs. A defined percentage of EC members could be changed on a regular basis.

4.4.4 EC members may be given a reasonable honorarium for attendance at the meeting.

4.4.5 Members to be appointed on the EC should be willing to fulfil the EC requirements as given in Box 4.3.

Box 4.3 Requirements for EC members

Every EC member must:

1. provide a recent signed CV and training certificates on human research protection and good clinical practice (GCP) guidelines, if applicable;
2. either be trained in human research protection and/or GCP at the time of induction into the EC, or must undergo training and submit training certificates within 6 months of appointment (or as per institutional policy);
3. be willing to undergo training or update their skills/knowledge during their tenure as an EC member;
4. be aware of relevant guidelines and regulations;
5. read, understand, accept and follow the COI policy of the EC and declare it, if applicable, at the appropriate time;
6. sign a confidentiality and conflict of interest agreement/s;
7. be willing to place her/his full name, profession and affiliation to the EC in the public domain; and
8. be committed and understanding to the need for research and for imparting protection to research participants in research.

4.5 Criteria for selection of members of an EC

4.5.1 Members should be selected in their personal capacities based on their qualifications, experience, interest, commitment and willingness to volunteer the required time and effort for the EC. See Table 4.1 for further details.

4.5.2 Members are appointed to the EC for a particular role. They cannot substitute for the role of any other member who is absent for a meeting. The role of Chairperson/ Member Secretary is an additional activity to their primary responsibility based on their qualifications. Hence, if the Chairperson is a lawyer, she or he can serve as both the lawyer and the Chairperson.

4.5.3 These criteria should be specified in SOPs.

4.6 Training

4.6.1 Members should be trained in human research protection, EC functions and SOPs, and should be conversant with ethical guidelines, GCP guidelines (if applicable) and relevant regulations of the country.

4.6.2 EC members should undergo initial and continuing training in human research protection, applicable EC SOPs and related regulatory requirements. All trainings should be documented.

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

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

4.7 Roles and responsibilities of the EC

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

4.7.2 The EC must ensure ethical conduct of research by the investigator team.

4.7.3 The EC is responsible for declaration of conflicts of interest to the Chairperson, if any, at each meeting and ensuring these are recorded in the minutes.

4.7.4 The EC should perform its function through competent initial and continuing review of all scientific, ethical, medical and social aspects of research proposals received by it in an objective, timely and independent manner by attending meetings, participation in discussion and deliberations.

4.7.5 The EC must ensure that universal ethical values and international scientific standards are followed in terms of local community values and customs.

4.7.6 The EC should assist in the development and education of the research community in the given institute (including researchers, clinicians, students and others), responsive to local healthcare requirements.

4.7.7 Responsibilities of members should be clearly defined (details in Table 4.1). The SOPs should be given to EC members at the time of their appointment.

4.7.8 The 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 under confidentiality agreement.

4.7.9 The EC should ensure that privacy of the individual and confidentiality of data including the documents of EC meetings is protected.

4.7.10 The EC reviews progress reports, final reports and AE/SAE and gives needful suggestions regarding care of the participants and risk minimization procedures, if applicable.

4.7.11 The EC should recommend appropriate compensation for research related injury, wherever required.

4.7.12 The EC should carry out monitoring visits at study sites as and when needed.

4.7.13 The EC should participate in continuing education activities in research ethics and get updated on relevant guidelines and regulations.

4.7.14 The EC may see that conduct of same/similar research by different investigators from same institution is harmonized. 'Me too' research (replicative) should not to be encouraged and submission of same research to different funding agencies should not be accepted.

4.8 Submission and review procedures

4.8.1 Researchers should submit research proposals as soft or hard copies to the Secretariat for review in the prescribed format and required documents as per EC SOPs. The EC should prepare a checklist for the required documents as given in Box 4.4 (a) and 4.4 (b). This list is subject to modifications, depending on the type of research, EC SOPs and institutional policies.

Box 4.4 (a) Details of documents to be submitted for EC review

1. Cover letter to the Member Secretary
2. Type of review requested
3. Application form for initial review
4. The correct version of the informed consent document (ICD) in English and the local language(s). Translation and back translation certificates (if applicable)
5. Case record form/questionnaire
6. Recruitment procedures: advertisement, notices (if applicable)
7. Patient instruction card, diary, etc. (if applicable)
8. Investigator's brochure (as applicable for drug/biologicals/device trials)
9. Details of funding agency/sponsor and fund allocation (if applicable)
10. Brief curriculum vitae of all the study researchers
11. A statement on COI, if any
12. GCP training certificate (preferably within 5 years) of investigators (clinical trials)
13. Any other research ethics/other training evidence, if applicable as per EC SOP
14. List of ongoing research studies undertaken by the principal investigator (if applicable)
15. Undertaking with signatures of investigators
16. Regulatory permissions (as applicable)
17. Relevant administrative approvals (such as HMSC approval for International trials)
18. Institutional Committee for Stem Cell Research (IC-SCR) approval (if applicable)
19. MoU in case of studies involving collaboration with other institutions (if applicable)
20. Clinical trial agreement between the sponsors, investigator and the head of the institution(s) (if applicable)

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21. Documentation of clinical trial registration (preferable)
22. 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)
23. Indemnity policy, clearly indicating the conditions of coverage, date of commencement and date of expiry of coverage of risk (if applicable)
24. Any additional document(s), as required by EC (such as other EC clearances for multicentric studies)
25. Protocol

Box 4.4 (b) Details of documents to be included in the protocol

The protocol should including the following:

1. the face page carrying the title of the proposal with signatures of the investigators;
2. brief summary/ lay summary;
3. background with rationale of why a human study is needed to answer the research question;
4. justification of inclusion/exclusion of vulnerable populations;
5. clear research objectives and end points (if applicable);
6. eligibility criteria and participant recruitment procedures;
7. detailed description of the 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;
8. duration of the study;
9. justification for placebo, benefit–risk assessment, plans to withdraw. If standard therapies are to be withheld, justification for the same;
10. procedure for seeking and obtaining informed consent with a sample of the patient/participant information sheet and informed consent forms in English and local languages. AV recording if applicable; informed consent for stored samples;
11. plan for statistical analysis of the study;
12. plan to maintain the privacy and confidentiality of the study participants;
13. for research involving more than minimal risk, an account of management of risk or injury;
14. proposed compensation, reimbursement of incidental expenses and management of research related injury/illness during and after research period;
15. provision of ancillary care for unrelated illness during the duration of research;
16. an account of storage and maintenance of all data collected during the trial; and
17. plans for publication of results – positive or negative – while maintaining confidentiality of personal information/ identity.
18. ethical considerations and safeguards for protection of participants.

Table 4.2 Types of review

S. No.	Types of review	
1	**Exemption from review**	Proposals with less than minimal risk where there are no linked identifiers, for example; • research conducted on data available in the public domain for systematic reviews or meta-analysis; • observation of public behaviour when information is recorded without any linked identifiers and disclosure would not harm the interests of the observed person; • quality control and quality assurance audits in the institution; • comparison of instructional techniques, curricula, or classroom management methods; • consumer acceptance studies related to taste and food quality; and • public health programmes by Govt agencies such as programme evaluation where the sole purpose of the exercise is refinement and improvement of the programme or monitoring (where there are no individual identifiers).
2	**Expedited review**	Proposals that pose no more than minimal risk may undergo expedited review, for example; • research involving non-identifiable specimen and human tissue from sources like blood banks, tissue banks and left-over clinical samples; • research involving clinical documentation materials that are non-identifiable (data, documents, records); • modification or amendment to an approved protocol including administrative changes or correction of typographical errors and change in researcher(s); • revised proposals 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, for example activity limited to data analysis. Expedited review of SAEs/unexpected AEs will be conducted by SAE subcommittee; and • for multicentre research where a designated main EC among the participating sites has reviewed and approved the study, a local EC may conduct only an expedited review for site specific requirements in addition to the full committee common review. • research during emergencies and disasters (See Section 12 for further details).

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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, some examples are; • research involving vulnerable populations, even if the risk is minimal; • research with minor increase over minimal risk (see Table 2.1 for further details); • studies involving deception of participants (see section 5.11 for further details); • research proposals that have received exemption from review, or have undergone expedited review/undergone subcommittee review should be ratified by the full committee, which has the 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, investigator's brochure, advertisements, recruitment methods, etc.) involving an altered risk; • major deviations and violations in the protocol; • any new information that emerges during the course of the research for deciding whether or not to terminate the study in view of the altered benefit–risk assessment; • research during emergencies and disasters either through an expedited review/ scheduled or unscheduled full committee meetings. This may be decided by Member Secretary depending on the urgency and need; • prior approval of research on predictable emergencies or disasters before the actual crisis occurs for implementation later when the actual emergency or disaster occurs.

4.8.2 The Member Secretary/Secretariat shall screen the proposals for their completeness and depending on the risk involved categorize them into three types, namely, exemption from review, expedited review, and full committee review. See Tables 2.1 for risk categorization and 4.2 for further details regarding types of review.

4.8.3 A researcher cannot decide that her/his proposal falls in the exempted, expedited or full review category. All research proposals must be submitted to the EC. The decision on the type of review required rests with the EC and will be decided on a case-to-case basis. Researchers can approach the EC with appropriate justification for the proposal to be considered as exempt, expedited or if waiver of consent is requested.

4.8.4 Expedited review can be conducted by Chairperson, Member Secretary and one or two designated members or as specified in SOPs.

4.8.5 Approval granted through expedited review and the decisions of the SAE subcommittee must be ratified at the next full committee meeting.

4.8.6 EC members should be given enough time (at least 1 week) to review the proposal and related documents, except in the case of expedited review.

4.8.7 All EC members should review all proposals. However, the EC may adopt different procedures for review of proposals in accordance with their SOPs.

4.8.8 The EC may adopt a system for pre-meeting peer review by subject experts and obtain clarifications from the researchers prior to 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.

4.8.9 The EC may have a system of appointing primary and secondary reviewers. The Member Secretary should identify the primary and secondary reviewers for reviewing the scientific content and the ethical aspects in the proposal as well as the informed consent document, depending upon their individual expertise.

4.8.10 The Member Secretary may identify subject experts to review the proposal as per need. These experts may be invited to the EC meeting or join via video/tele conference but will not participate in final decision making.

4.8.11 The EC should meet regularly, adopt best practices, try to reduce turnaround time or have procedures in place for early decision making so that research is not delayed.

4.8.12 The designated (primary and secondary) reviewers and subject experts should conduct the initial review of the study protocol and study related documents as per the pre-defined study assessment form and for factors as described in Table 4.3.

Table 4.3 Ethical issues related to reviewing a protocol

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 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.

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		• 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. • The EC can raise scientific concerns (even if the study has prior approval of a scientific committee) if it may affect quality of research and or safety of research participants.
3	**Benefit-risk assessment**	• The benefits accruing from the planned research either to the participants or to the community or society in general must justify the risks inherent in the research. • Risks may be physical, psychological, economic, social or legal and harm may occur either at an individual level or at the family, community or societal level. It is necessary to first look at the intervention under investigation and assess its potential harm and benefits and then consider the aggregate of harm and benefits of the study as a whole. • The EC should review plans for risk management, including withdrawal criteria with rescue medication or procedures. • The EC should give advice regarding minimization of risk/ discomfort wherever applicable. • Adequate provisions must be made for monitoring and auditing the conduct of the research, including the constitution of a Data and Safety Monitoring Board (DSMB) if applicable (for example in clinical trials)
4	**Selection of the study population and recruitment of research participants**	• Recruitment should be voluntary and non-coercive. Participants should be fairly selected as per inclusion and exclusion criteria. However, selection of participants should be distributive such that a particular population or tribe or economic group is not coerced to participate or benefit. • Participants should be able to opt out at any time without their routine care being affected. • No individual or group of persons must bear the burden of participation in research without accruing any direct or indirect benefits. • Vulnerable groups may be recruited after proper justification is provided.
5	**Payment for participation**	• Plans for payment for participation, reimbursement of incurred costs, such as travel or lost wages, incidental expenses and other inconveniences should be reviewed.

(Contd.)

		• There is a need to determine that payments are not so large as to encourage prospective participants to participate in the research without due consideration of the risks or against their better judgement. No undue inducement must be offered.
6	**Protection of research participants' privacy and confidentiality**	• ECs should examine the processes that are put in place to safeguard participants' privacy and confidentiality. • Research records to be filed separately than routine clinical records such as in a hospital setting.
7	**Community considerations**	• The EC should ensure that due respect is given to the community, their interests are protected and the research addresses the community's needs. • The proposed research should not lead to any stigma or discrimination. Harm, if any, should be minimized. • Plans for communication of results to the community at the end of the study should be carefully reviewed. • It is important to examine how the benefits of the research will be disseminated to the community.
8	**Qualifications of researchers and adequacy assessment of study sites**	• The EC should look at the suitability 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 COI**	• The EC should review any declaration of COI by a researcher and suggest ways to manage these. • The EC should manage COI within the EC and members with COI should leave the room at the time of decision making in a particular study.
10	**Plans for medical management and compensation for study related injury**	• The proposed plan for tackling any medical injuries or emergencies should be reviewed. • Source and means for compensation for study related injury should be ascertained.
11	**Review of the informed consent process**	The informed consent process must be reviewed keeping in mind the following: • the process used for obtaining informed consent, including the identification of those responsible for obtaining consent and the procedures adopted for vulnerable populations; • the adequacy, completeness and understandability of the information to be given to the research participants, and when appropriate, their LARs;

(Contd.)

		• contents of the patient/participation information sheet including the local language translations (See section 5 for further details); • back translations of the informed consent document in English, wherever required; • provision for audio-visual recording of consent process, if applicable, as per relevant regulations; and • if consent waiver or verbal/oral consent request has been asked for, this should be reviewed by assessing whether the protocol meets the criteria. See section 5 for further details.

4.9 Full committee meeting

4.9.1 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.

4.9.2 ECs should conduct regular full committee meetings to deliberate proposals in accordance with a pre-decided schedule, as described in the SOPs.

4.9.3 A meeting will be considered valid only if the quorum is fulfilled. This should be maintained throughout the meeting and at the time of decision making.

4.9.4 If a member has declared a COI for a proposal then this should be submitted in writing to the Chairperson before beginning the meeting and should be recorded in the minutes.

4.9.5 The member who has declared COI should withdraw from the EC meeting (leave the room) while the research proposal is being discussed upon. This should be minuted and the quorum rechecked.

4.9.6 A list of absentee members as well as members leaving or entering in-between the meeting should be recorded.

4.9.7 Proposals should be taken up item-wise, as given in the agenda.

4.9.8 No of proposals reviewed in a meeting should justify that there is ample time devoted for review of each proposal. If there are more number of proposals for consideration per meeting either meetings may be more frequent or more EC's to be constituted as per requirement of the institution.

4.9.9 Time allotted for the meeting should be reasonable to allow ample discussion on each agenda item.

4.9.10 The minutes of the previous meeting and list of protocols that were exempt from review or underwent expedited review should be ratified.

4.9.11 The researcher may be called in to present a proposal or provide clarifications on the study protocol that has been submitted for review but should not be present at the time of decision making.

4.9.12 The primary and secondary reviewers can brief the members about the study proposal and review carried out as per EC SOPs.

4.9.13 The comments of an independent consultant (if applicable) could be presented by the Member Secretary or subject experts could be invited to offer their views, but they should not participate in the decision-making process. However, her/his opinion must be recorded.

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

4.9.15 The EC may utilize electronic methods such as video/conference calls for connecting with other subject experts/independent consultants during the meeting.

4.9.16 All members of the EC (including the Chairperson and the Member Secretary) present in the room have the right to vote/express their decision and should exercise this right.

4.9.17 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.

4.9.18 The decisions may be as shown in Box 4.5.

Box 4.5 Types of decisions by EC

An EC can give one of the following decisions:

- approved – with or without suggestions or comments;
- revision with minor modifications/amendments – approval is given after examination by the Member Secretary or expedited review, as the case may be;
- revision with major modifications for resubmission – this will be placed before the full committee for reconsideration for approval; or
- not approved (or termination/revoking of permission if applicable) – clearly defined reasons must be given for not approving/terminating/revoking of permission.

4.9.19 Approval may be granted for the entire duration of the proposed research or can be subject to annual review depending on the type of study. The EC should review the annual report (counted from the day of approval or date of actual start of the study) for continuation as per SOP.

4.9.20 Depending on the risk involved, the progress of the proposal may be monitored annually or at shorter intervals (quarterly, half yearly) as per EC decision. Approval may be continued if progress is satisfactory.

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

4.9.22 The Member Secretary (assisted by the Secretariat) should record the discussions and prepare the minutes which should be circulated to all the members for comments before final approval by the Chairperson/Vice-Chairperson/designated member of the committee.

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

4.9.24 The researcher should have an opportunity to reply/clarify to EC comments or to discuss or present her/his stand.

4.9.25 The researcher can also approach the head of the institute who serves as an appellate for EC matters.

4.9.26 The head of the institute as appellate has the power to dissolve the EC or reappoint an EC.

4.10 Review of multicentric research

Multicentre research is conducted at more than one centre by different researchers usually following a common protocol. A large number of clinical trials, clinical studies and public health research including surveys are conducted at several research centres within the country or at international sites. Multicentric research studies are carried out with the primary aim of providing a sound basis for the subsequent generalization of its results. All sites are required to obtain approval from their respective ECs, which would consider the local needs and requirements of the populations being researched and safeguard the dignity, rights, safety and well-being of the participants. There are concerns, however, related to duplication of effort in the parallel review by the involved ECs, wastage of time and also those related to communication between the committees. Therefore, in multicentric studies using a common protocol the considerations mentioned in sections 4.10.1 and 4.10.2 may be made.

4.10.1 Separate review by ECs of all participating site

- The ECs/Secretariats of all participating sites should establish communication with one another.

- If any EC does not grant approval for a study at a site the reasons must be shared with other ECs and deliberated upon.
- The EC can suggest site-specific protocols and informed consent modifications as per local needs.
- Separate review may be requested for studies with a higher degree of risk, clinical trials or intervention studies where conduct may vary depending on the site or any other reason which requires closer review and attention.

4.10.2 Common review for all participating sites in multicentric research

- In order to save time, prevent duplication of effort and streamline the review process, the ECs can decide to have one designated main EC, the decisions of which may be acceptable to other ECs. This is especially important for research involving low or minimal risk, survey or multicentric studies using anonymized samples or data or those that are public health research studies determined to have low or minimal risk.
- The meeting of the designated main EC can be attended by nominated members of ECs of the participating centres to discuss their concerns, if any, about ethics or human rights and to seek solutions and communicate the decision of the main EC to their respective ECs.
- This EC should be located in India and registered with the relevant authority (if applicable).
- Meetings should be organized at the initial and, if required, intermediary stages of the study to ensure uniform procedures at all centres.
- The site ECs, however, retain their rights to review any additional site specific requirements, ensure need-based protection of participants or make changes in the informed consent document (ICD), translations and monitoring research as per local requirements.
- The protocol may be modified to suit local requirements and should be followed after it is duly approved by the EC of the host institutes/decision of main EC is accepted.
- Adherence to protocols, including measures to terminate the participation of the erring local centres, if required should be monitored.
- The common review is applicable only for ECs in India. In case of international collaboration for research and approval by a foreign institution, etc., the local

participating sites would be required to obtain local ethical approval. See section 3.8.3 for further details.

- Sponsor/funding agencies should be informed about any site-specific changes being made, and the modified version should only be used by the concerned site.
- Plans for manuscript publication and a common final report with contributors from the participating sites should be decided upon before initiation of the study.
- Site-specific data may be published only after the appropriate authorities accept the combined report and appropriate permissions are obtained.

4.11 Continuing review

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

4.11.2 The EC should continually evaluate progress of ongoing proposals, review SAE reports from all sites along with protocol deviations/violations and non-compliance, any new information pertaining to the research and assess final reports of all research activities.

4.11.3 Clinical trials under the purview of a licensing authority must comply with all regulations applicable to SAEs. The EC should also ensure compliance by the researcher. For academic and other trials, an institutional policy should be established.

4.11.4 The EC should examine the measures taken for 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 the control arm.

4.11.5 Compensation must be given for research-related injuries if applicable, as determined by the EC and as per regulatory requirement (if applicable).

4.11.6 For protocol deviations/violations the EC should examine the corrective actions. If the violations are serious the EC may halt the study. The EC may report to the institutional head/government authorities where there is continuing non-compliance to ethical standards.

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

4.12 Site monitoring

4.12.1 It is recommended that ECs should follow mechanisms described in a SOP to monitor the approved study site until completion of the research to check for compliance or improve the function.

4.12.2 Monitoring can be routine or "for cause" and must be decided at a full committee meeting. For research that involves higher risk or vulnerable participants or if there is any other reason for concern, the EC at the time of initial review or continuing review can suggest that routine monitoring may be conducted at more frequent intervals. Some causes for monitoring are given in Box 4.6.

Box 4.6 Examples of "for cause" monitoring

The following situations may justify "for cause" monitoring:

- high number of protocol violations/ deviations;
- large number of proposals carried out at the study site or by the same researcher;
- large number of SAE reports;
- high recruitment rate;
- complaints received from participants;
- any adverse media report;
- adverse information received from any other source;
- non-compliance with EC directions;
- misconduct by the researcher; and
- any other cause as decided by the EC.

4.13 Record keeping and archiving

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

4.13.2 Confidentiality should be maintained during access and retrieval procedures by designated persons.

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

4.13.4 Records can be maintained in hard copies as well as soft copies.

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

4.13.6 Documents related to regulatory clinical trials must be archived for 5 years after the completion/termination of the study or as per regulations.

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

4.13.8 EC should describe archival and retrieval mechanisms in SOPs.

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

4.13.10 ECs may adopt methods for electronic storage of records wherever feasible.

Table 4.4 gives examples of records that can be maintained.

Table 4.4 Documents to be maintained by EC for record

Type of document	Document specifics
Administrative documents	• Constitution and composition of the EC • Appointment letters • Signed and dated copies of the most recent curriculum vitae of all EC members • Signed confidentiality agreements • COI declarations of members • Training records of EC members • Financial records of EC • Registration/accreditation documents, as required • A copy of national and international guidelines and applicable regulations • Regulatory notifications • Meeting-related documents • Agenda and minutes • All communications received or made by the EC • SOPs
Proposal-related documents	• One hard copy and a soft copy of the initial research proposal and all related documents • Decision letters • Any amendments submitted for review and approval • Regulatory approvals • SAE, AE reports • Protocol deviations/violations • Progress reports, continuing review activities, site monitoring reports • All correspondence between the EC and researchers • Record of notification issued for premature termination of a study with a summary of the reasons • Final report of the study • Publications, if any

4.14 Administration and management

4.14.1 Every institution should have an office for the EC.

4.14.2 The institution should provide space, infrastructure and staff to the EC for maintaining

a full-time secretariat, safe archival of records and conduct of meeting.

4.14.3 Every institution should allocate reasonable funds for smooth functioning of the EC.

4.14.4 A reasonable fee for review may also be charged by the EC to cover the expenses related to optimal functioning in accordance to Institutional policies.

4.15 Registration and accreditation of ECs

4.15.1 ECs must ensure that processes are in place to safeguard the quality of ethical review as well as compliance with national/international and applicable regulations.

4.15.2 ECs should register with the relevant authority as per the regulatory requirements.

4.15.3 Efforts should be made to seek recognition/certification/accreditation from recognized national/international bodies such as Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Association for the Accreditation of Human Research Protection Programmes (AAHRPP), CDSCO and Quality Council of India through National Accreditation Board for Hospitals and Healthcare Providers (NABH) or any other. Such certification/accreditation should be kept updated on a continuing basis.

4.15.4 Certification/accreditation are voluntary exercises and help in quality assurance and quality improvement to ensure that ECs follow best practices in protecting the dignity, rights, safety, and well-being of their participants.

INFORMED CONSENT PROCESS

5.0 The researcher must obtain voluntary written informed consent from the prospective participant for any biomedical and health research involving human participants. This requirement is based on the principle that competent individuals are entitled to choose freely whether or not to participate or continue to participate in the research. Informed consent is a continuous process involving three main components – providing relevant information to potential participants, ensuring competence of the individual, ensuring the information is easily comprehended by the participants and assuring voluntariness of participation. Informed voluntary consent protects the individual's freedom of choice and respects the individual's autonomy.

5.1 Requisites

5.1.1 The participant must have the capacity to understand the proposed research, be able to make an informed decision on whether or not to be enrolled and convey her/his decision to the researcher in order to give consent.

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

5.1.3 In the case of an individual who is not capable of giving voluntary informed consent, the consent of LAR must be obtained. See section 6 for further details.

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

5.1.5 It is necessary to maintain privacy and confidentiality of participants at all stages.

5.2 Essential information for prospective research participants

5.2.1 Before requesting an individual's consent to participate in research, the researcher must provide the individual with detailed information and discuss her/his queries about the research in the language she/he is able to understand. The language should not only be scientifically accurate and simple, but should also be sensitive to the social and cultural context of the participant.

5.2.2 The ICD has two parts – patient/participant information sheet (PIS) and the informed consent form (ICF). Information on known facts about the research, which has relevance

Box 5.1 Essential and additional elements of an informed consent document

An informed consent form must include the following:

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 to the participant, community or others that might reasonably be expected as an outcome of research
5. Any foreseeable risks, discomfort or inconvenience to the participant resulting from participation in the study
6. Extent to which confidentiality of records could be maintained, such as the limits to which the researcher would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality
7. Payment/reimbursement for participation and incidental expenses depending on the type of study
8. Free treatment and/or compensation of participants for research-related injury and/or harm
9. Freedom of the individual to participate and/or withdraw from research at any time without penalty or loss of benefits to which the participant would otherwise be entitled
10. The identity of the research team and contact persons with addresses and phone numbers (for example, 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
2. If there is a possibility that the research could lead to any stigmatizing condition, for example HIV and genetic disorders, 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. Other specifics are as follows:
   - i period of storage of the sample/data and probability of the material being used for secondary purposes.
   - ii whether material is to be shared with others, this should be clearly mentioned.
   - iii right to prevent use of her/his biological sample, such as DNA, cell-line, etc., and related data at any time during or after the conduct of the research.
   - iv risk of discovery of biologically sensitive information and provisions to safeguard confidentiality.
   - v post research plan/benefit sharing, if research on biological material and/or data leads to commercialization.
   - vi Publication plan, if any, including photographs and pedigree charts.

   See section 11 for further details.

to participation, is included in the PIS. This is followed by the ICF in which the participant acknowledges that she/he has understood the information given in the PIS and is volunteering to be included in that research.

5.2.3 Adequate time should be given to the participant to read the consent form, if necessary discuss it with family and friends, and seek clarification of her/his doubts from the researchers/research team before deciding to enroll in the research.

5.2.4 Essential elements of an informed consent document are given in Box 5.1.

5.3 Responsibility of researchers

5.3.1 The researcher should only use the EC approved version of the consent form, including its local translations.

5.3.2 Adequate information necessary for informed consent should be communicated in a language and manner easily understood by prospective participants.

5.3.3 In case of differently abled participants, such as individuals with physical, neurological or mental disabilities, appropriate methods should be used to enhance the participants' understanding, for example, braille for the visually impaired.

5.3.4 There should be no restriction on the participant's right to ask questions related to the study or to discuss with family and friends or take time before coming to a decision.

5.3.5 The researcher should not give any unjustifiable assurances or influence or intimidate a prospective participant to enroll in the study.

5.3.6 The researcher must ensure that the participant is competent and has understood all aspects of the study and that the consent is given voluntarily. Where the participant and/or the LAR are illiterate, an impartial literate person, not connected to the research, should be present throughout the consent process as witness.

5.3.7 The researcher should administer a test of understanding whenever possible for sensitive studies. If need be, the test may be repeated until the participant has really understood the contents.

5.3.8 When a participant is willing to participate but not willing to sign or give a thumb impression or cannot do so, then verbal/oral consent may be taken on approval by the EC, in the presence of an impartial witness who should sign and date the consent document. This process can be documented through audio or video recording of the participant, the PI and the impartial witness, all of whom should be seen in the frame. However, verbal/oral consent should only be taken in exceptional circumstances and for specific, justifiable reasons with the approval of the EC. It should not to be practiced routinely.

5.3.9 Reconsent or fresh informed consent of each participant must be taken under circumstances described in section 5.8.

5.3.10 The researcher must assure prospective participants that their decision whether or not to participate in the research will not affect their rights, the patient–clinician relationship or any other benefits to which they are entitled.

5.3.11 Reimbursement may be given for travel and incidental expenses/participation in research after approval by the EC.

5.3.12 The researcher should ensure free treatment for research related injury (disability, chronic life-threatening disease and congenital anomaly or birth defect) and if required, payment of compensation over and above medical management by the investigator and/institution and sponsor(s), as the case may be.

5.3.13 The researcher should ensure that the participant can continue to access routine care even in the event of withdrawal of the participant.

5.4 Documentation of informed consent process

Documentation of the informed consent process is an essential part of this exercise.

5.4.1 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.

5.4.2 In case the participant is incompetent (medically or legally) to give consent, the LAR's consent must be documented.

5.4.3 The process of consent for an illiterate participant/LAR should be witnessed by an impartial literate witness who is not a relative of the participant and is in no way connected to the conduct of research, such as other patients in the ward who are not in the study, staff from the social service department and counsellors. The witness should be a literate person who can read the participant information sheet and consent form and understand the language of the participant.

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

5.4.5 The researcher who administers the consent must also sign and date the consent form.

5.4.6 In the case of institutionalized individuals, in addition to individual/LAR consent, permission for conducting the research should be obtained from the head of that institution.

5.4.7 In some types of research, the partner/spouse may be required to give additional consent.

5.4.8 In genetic research, other member of a family may become involved as secondary

participants if their details are recorded as a part of the family history. If information about the secondary participants is identifiable then their informed consent will also be required.

5.4.9 Online consent may be obtained, for example, in research involving sensitive data such as unsafe sex, high risk behaviour, use of contraceptives (condoms, oral pills), or emergency contraceptive pills among unmarried females in India etc. Investigators must ensure that privacy of the participant and confidentiality of related data is maintained.

5.5 Electronic consent

Electronic media can be used to provide information as in the written informed consent document, which can be administered and documented using electronic informed consent systems. These are electronic processes that use various, and possibly multiple, electronic formats such as text, graphics, audio, video, podcasts or interactive websites to explain information related to a study and to document informed assent/consent from a participant or LAR.

5.5.1 The process, electronic materials, method of documentation (including electronic/digital signatures), methods used to maintain privacy of participants, confidentiality, and security of the information as well as data use policies at the research site must be reviewed and approved by the EC a priori.

5.5.2 The electronic consent must contain all elements of informed consent in a language understandable by the participant. See Box 5.1 for further details.

5.5.3 The PI or her/his designee must supervise the process.

5.5.4 In addition to electronic consent, if required a paper/soft copy of the document is needed for archiving and a paper/soft copy is also given to the participant.

5.5.5 Interactive formats, if used, should be simple to navigate.

5.5.6 Electronic methods should not be used if participants, for any reason, indicate a lack of comfort with electronic media.

5.5.7 Such tools may be reviewed and approved by EC before implementation.

5.6 Specific issues in Clinical trials

There may be additional requirements for informed consent for clinical trials as specified by CDSCO. See section 7 for further details.

5.7 Waiver of consent

The researcher can apply to the EC for a waiver of consent if the research involves less than minimal risk to participants and the waiver will not adversely affect the rights and welfare of the participants Box 5.2.

Box 5.2 Conditions for granting waiver of consent

The EC may grant consent waiver in the following situations:

- research cannot practically be carried out without the waiver and the waiver is scientifically justified;
- retrospective studies, where the participants are de-identified or cannot be contacted;
- research on anonymized biological samples/data;
- certain types of public health studies/surveillance programmes/programme evaluation studies;
- research on data available in the public domain; or
- research during humanitarian emergencies and disasters, when the participant may not be in a position to give consent. Attempt should be made to obtain the participant's consent at the earliest.

5.8 Re-consent or fresh consent

Re-consent is required in the following situations when:

- new information pertaining to the study becomes available which has implications for participant or which changes the benefit and risk ratio;
- a research participant who is unconscious regains consciousness or who had suffered loss of insight regains mental competence and is able to understand the implications of the research;
- a child becomes an adult during the course of the study;
- research requires a long-term follow-up or requires extension;
- there is a change in treatment modality, procedures, site visits, data collection methods or tenure of participation which may impact the participant's decision to continue in the research; and
- there is possibility of disclosure of identity through data presentation or photographs (this should be camouflaged adequately) in an upcoming publication.
- the partner/spouse may also be required to give additional re-consent in some of the above cases.

5.9 Procedures after the consent process

5.9.1 After consent is obtained, the participant should be given a copy of the PIS and signed ICF unless the participant is unwilling to take these documents. Such reluctance should be recorded.

5.9.2 The researcher has an obligation to convey details of how confidentiality will be maintained to the participant.

5.9.3 The original PIS and ICF should be archived as per the requirements given in the guidelines and regulations.

5.10 Special situations

5.10.1 Gatekeepers

Permission of the gatekeepers, that is, the head/leader of the group or culturally appropriate authorities, may be obtained in writing or audio/video recorded on behalf of the group and should be witnessed.

5.10.2 Community consent

In certain populations, the community plays an important role in the consent process. Some participants may not participate 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 (see section 8 for further details). In such situations community consent is required. When permission is obtained from an organization that represents the community, the quorum required for such a committee must be met. For example, in a village panchayat the number of members ordinarily required to conduct a meeting must be present while giving consent. Individual consent is important and required even if the community gives permission.

5.10.3 Consent from vulnerable groups

Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests and providing valid informed consent. The list of vulnerable populations/communities is given in Box 6.2.

5.11 Consent for studies using deception

Some types of research studies require deception due to nature of research design. A true informed consent may lead to modification and may defeat the purpose of research. Such research may be carefully reviewed by the EC before implementation.

5.11.1 True informed consent in studies involving deception is difficult due to the nature of research. A two-step procedure may be required comprising an initial consent and a debriefing after participation.

5.11.2 The possibility of unjustified deception, undue influence and intimidation should be avoided at all costs. Although deception is not permissible, approval may be taken from the EC in circumstances where some information requires to be withheld for validation until the completion of the research.

5.11.3 In such instances, an attempt should be made to debrief the participants/communities after completion of the research.

VULNERABILITY

6.0 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; social injustice; lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so. These vulnerable persons have some common characteristics which are listed in Box 6.1.

Box 6.1 Characteristics of vulnerable individuals/populations/group

Individuals may be considered to be vulnerable if they are:

- socially, economically or politically disadvantaged and therefore susceptible to being exploited;
- incapable of making a voluntary informed decision for themselves or whose autonomy is compromised temporarily or permanently, for example people who are unconscious, differently abled;
- able to give consent, but whose voluntariness or understanding is compromised due to their situational conditions; or
- unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent.

The key principle to be followed when research is planned on vulnerable persons is that others will be responsible for protecting their interests because they cannot do so or are in a compromised position to protect their interests on their own. The populations or communities mentioned in Box 6.2 may be vulnerable at some or all times. Please note that this is not an exhaustive list.

6.1 Principles of research among vulnerable populations

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

6.1.2 If any vulnerable group is to be solely recruited then the research should answer the health needs of the group.

6.1.3 Participants must be empowered, to the maximum extent possible, to enable them to

Box 6.2 Vulnerable populations or groups

Following are some examples of vulnerable populations or groups:

- economically and socially disadvantaged (unemployed individuals, orphans, abandoned individuals, persons below the poverty line, ethnic minorities, sexual minorities – lesbian/gay/bisexual and transgender (LGBT), etc.);
- unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent;
- children (up to 18 years);
- women in special situations (pregnant or lactating women, or those who have poor decision-making powers/poor access to healthcare);
- tribals and marginalized communities;
- refugees, migrants, homeless, persons or populations in conflict zones, riot areas or disaster situations;
- afflicted with mental illness and cognitively impaired individuals, differently abled – mentally and physically disabled;
- terminally ill or are in search of new interventions having exhausted all therapies;
- suffering from stigmatizing or rare diseases; or
- have diminished autonomy due to dependency or being under a hierarchical system (students, employees, subordinates, defence services personnel, healthcare workers, institutionalized individuals, under trials and prisoners).

decide by themselves whether or not to give assent/consent for participation.

6.1.4 In vulnerable populations, when potential participants lack the ability to consent, a LAR should be involved in decision making.

6.1.5 Special care must be taken to ensure participant's privacy and confidentiality, especially because breach of confidentiality may lead to enhancement of vulnerability.

6.1.6 If vulnerable populations are to be included in research, all stakeholders must ensure that additional protections are in place to safeguard the dignity, rights, safety and well-being of these individuals.

6.2 Additional safeguards/protection mechanisms

When vulnerable individuals are to be recruited as research participants additional precaution should be taken to avoid exploitation/retaliation/reward/credits, etc., as 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 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 dependant's participation, the feeling of being pressed to participate may be irresistible which will undermine the potential voluntariness of the consent to participate.

6.2.1 Researchers must justify the inclusion of a vulnerable population in the research.

6.2.2 ECs must satisfy themselves with the justification provided and record the same in the proceedings of the EC meeting.

6.2.3 Additional safety measures should be strictly reviewed and approved by the ECs.

6.2.4 The informed consent process should be well documented. Additional measures such as recording of assent and reconsent, when applicable, should be ensured.

6.2.5 ECs should also carefully determine the benefits and risks of the study and examine the risk minimization strategies.

6.2.6 As potential participants are dependent on others, there should be no coercion, force, duress, undue influence, threat or misrepresentation or incentives for participation during the entire research period.

6.2.7 Vulnerable persons may require repeated education/information about the research, benefits, risks and alternatives, if any.

6.2.8 Research on sensitive issues such as mental health, sexual practices/preferences, HIV/AIDS, substance abuse, etc. may present special risks to research participants.

6.2.9 Researchers should be cognisant of the possibility of conflicting interests between the prospective participant and LAR and should be more careful.

6.2.10 Participants may be prone to stigma or discrimination, specifically when the participant is enrolled as a normal control or is recruited from the general population in certain types of research.

6.2.11 Efforts should be made to set up support systems to deal with associated medical and social problems.

6.2.12 Protection of their privacy, confidentiality and rights is required at all times – during conduct of research and even after its completion.

6.2.13 Whenever possible, ancillary care may be provided such as setting up of a facility, school for unattended children of the participants or a hospital, or counselling centre.

6.3 Obligations/duties of stakeholders

All stakeholders have different responsibilities to protect vulnerable participants. See Table 6.1 for further details.

Table 6.1 Obligations/duties of stakeholders

Stakeholders	Obligations / duties
Researchers	• Recognize the vulnerability of the participant and ensure additional safeguards are in place for their protection. • Justify inclusion/exclusion of vulnerable populations in the study. • COI issues must be addressed. • Have well defined procedures (SOPs) to ensure a balanced benefit-risk ratio. • Ensure that prospective participants are competent to give informed consent. • Take consent of the LAR when a prospective participant lacks the capacity to consent. • Respect dissent from the participant. • Seek permission of the appropriate authorities where relevant, such as for institutionalized individuals, tribal communities, etc. • Research should be conducted within the purview of existing relevant guidelines/regulations.
Ethics Committees	• During review, determine whether the prospective participants for a particular research are vulnerable. • Examine whether inclusion/exclusion of the vulnerable population is justified. • Ensure that COI do not increase harm or lessen benefits to the participants. • Carefully determine the benefits and risks to the participants and advise risk minimization strategies wherever possible. • Suggest additional safeguards, such as more frequent review and monitoring, including site visits. • Only the full committee should do initial and continuing review of such proposals. It is desirable to have empowered representatives from the specific populations during deliberations. • ECs have special responsibilities when research is conducted on participants who are suffering from mental illness and/or cognitive impairment. They should exercise caution and require researchers to justify cases for exceptions to the usual requirements of participation or essentiality of departure from the guidelines governing research. ECs should ensure that these exceptions are as minimal as possible and are clearly spelt out in the ICD. • ECs should have SOPs for handling proposals involving vulnerable populations.

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Sponsors	• The sponsor, whether a government, an institution or a pharmaceutical company, should justify the inclusion of vulnerable groups in the protocol and make provisions for protecting their safety. • The sponsor must enable monitoring and ensure that procedures are in place for quality assurance (QA) and quality control (QC). • The sponsor should ensure protection of the participants and research team if the research is on sensitive topics.

6.4 Women in special situations

Women have equal rights to participate in research and should not be deprived arbitrarily of the opportunity to benefit from research. Informed consent process for some women can be challenging because of cultural reasons. Hence, the women may consider consulting their husbands or family members, if necessary. Although autonomy of the woman is important, the researcher must follow the requirements of local cultural practices so as not to disturb the harmony in the household/family/community.

6.4.1 Participation of a woman in clinical trials or intervention studies that may expose her to risk is elaborated in Box 6.3. See section 7.18 for more details.

Box 6.3 Risks for women participants in clinical trials/intervention studies

1. Researchers must provide the EC with proper justification for inclusion of pregnant and nursing women in clinical trials designed to address the health needs of such women or their foetuses or nursing infants. Some examples of justifiable inclusion are trials designed to test the safety and efficacy of a drug for reducing perinatal transmission of HIV infection from mother to child, trial of a device for detecting foetal abnormalities or trials of therapies for conditions associated with or aggravated by pregnancy, such as nausea, vomiting, hypertension or diabetes.
2. If women in the reproductive age are to be recruited, they should be informed of the potential risk to the foetus if they become pregnant. They should be asked to use an effective contraceptive method and be told about the options available in case of failure of contraception.
3. A woman who becomes pregnant must not automatically be removed from the study when there is no evidence showing potential harm to the foetus. The matter should be carefully reviewed and 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 for as long as necessary.

6.4.2 Prenatal diagnostic studies – research related to prenatal diagnostic techniques in pregnant women should be limited to detecting 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.

6.4.3 Research on sensitive topics – when research is planned on sensitive topics, for instance, domestic violence, genetic disorders, rape, etc., confidentiality should be strictly maintained and privacy protected. In risk mitigation strategies, appropriate support systems such as counselling centres, police protection, etc. should be established. 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.

6.5 Children

Children are individuals who have not attained the legal age of consent (up to 18 years). At younger ages, children are considered vulnerable 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. At older ages, although they may attain the cognitive ability to understand the research, they still lack legal capacity to consent. Therefore, the decision regarding participation and withdrawal of a child in research must be taken by the parents/LAR in the best interests of their child/ward. More details are available in ICMR "National Ethical Guidelines for Bio-Medical Research involving Children, 2017".[24]

Research on children can be carried out in a situation, condition, disorder or diseases as described in Box 6.4.

6.5.1 The EC should do the benefit–risk assessment to determine whether there is a need to put into place additional safeguards/protections for the conduct of research in children. For example, research should be conducted in child-friendly settings, in the presence of parent(s) and where child participants can obtain adequate medical and psychological support.

6.5.2 The EC should 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 to society as a whole.

6.5.3 Consent of the parent/LAR is required when research involves children. See Box 6.5 for further details.

6.5.4 Assent

In addition to consent from parents/LARs, verbal/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 are able to understand and respond. Respecting the child's reaction, the child is made a party to the consent process by the researcher, who

Box 6.4 Conditions for research on children

Children can be included in research if the situation, condition, disorder or disease fulfils one of the following conditions:

1. It is exclusively seen in childhood.
2. Both adults as well as children are involved, but the issues involved are likely to be significantly different in both these populations.
3. Both adults as well as children are involved in a similar manner and are of similar nature in terms of morbidity, severity and/or mortality, wherever relevant, and studies in adults have demonstrated the required degree of safety and efficacy.
4. Test interventions are likely to be at least as advantageous to the individual child participant as any available alternative intervention.
5. Risk of test interventions that is not intended to benefit the individual child participant is low as compared to the importance of the knowledge expected to be gained (minor increase over minimal risk).
6. Research is generally permitted in children if safety has been established in the adult population or if the information likely to be generated cannot be obtained by other means.
7. The physiology of children is different from that of adults, and the pharmacokinetics of many drugs is age-dependent based on the maturation of the drug metabolism pathways. For example, children metabolize many drugs much more rapidly as compared to adults, hence the dose of the drug per kg of body weight that needs to be given, is much higher in children as compared to adults. The absorption of drugs also varies with age. Pharmacokinetics and toxicity profile varies with growth and maturation from infancy to adulthood.
8. The adverse effects of many drugs may also be different in children as compared to adults. For instance, tetracyclines cause teeth discoloration in young children, aspirin use is associated with Reye's syndrome in children.
9. Age appropriate delivery vehicles and formulations (e.g. syrups) are needed for accurate, safe, and palatable administration of medicines to infants and children.
10. The pathophysiology of many disorders is dependent on a child's growth, development and adaptive plasticity. Examples include adaptive changes in the motor system following a perinatal stroke.

explains the proposed research in a very simple manner, in a language that ensures, that the child understands the request to participate in the research. A child's agreement to participate in research is called assent. If the child objects, this wish has to be respected. At the same time, mere failure to object should not be construed as assent. However, if the test intervention is likely to be lifesaving and is available only if the child participates

in the study, the dissent by the child may be disregarded provided parental consent and prior approval from the EC is obtained. Requirements of assent are given in Box 6.6.

Box 6.5 Consent of parent/LAR

1. The 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 and/or that offers direct benefit to the child. Consent from both parents may have to be obtained when the research involves more than minimal risk and/or offers no benefit to the child.
3. Only one parent's consent is acceptable if the other parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, irrespective of the risk involved.
4. Whenever relevant, the protocol should include a parent/LAR information sheet that contains information about specific aspects relevant to the child such as effects on growth and development, psychological well-being and school attendance, in addition to all components described in the participant information sheet.
5. When the research involves sensitive issues related to neglect and abuse of a child, the EC may waive the requirement of obtaining parental/LAR consent and prescribe an appropriate mechanism to safeguard the interests of the child.
6. 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. The potential benefits and risks must be carefully explained to parents so as to make them understand the proposed research.
7. Research involving institutionalized children would require assent of the child, consent of parents/LAR, permission of the relevant institutional authorities (for example, for research in a school setting: the child, parents, teacher, principal or management may be inviolved).

- Content of the assent form has to be in accordance with the developmental level and maturity of the children to be enrolled and explained while considering the differences in individual understanding. 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:
  - ❍ an explanation about the study and how it will help the child;
  - ❍ an explanation of what will be done in the study, including a description

of any discomfort that the child is likely to feel;

- ❍ the contact information of the person whom the child can approach if she/he needs an explanation; and
- ❍ a paragraph emphasizing that the child can refuse to participate in the study and if she/he chooses to do so, the treatment at the centre will not be compromised.

The above list is not exhaustive and may be dealt with on a case to case basis.

- Waiver of assent: All the conditions that are applicable to waiver of informed consent in adults also apply for waiver of assent in children. See section 5.7 for further details. If the available intervention is anticipated to definitely benefit the child but would be available only if the child participates in the study, waiver of assent could be allowed. However, this situation should be accepted only in exceptional cases where all forms of assent/consent have failed. In such cases, approval of the EC should be obtained.

Box 6.6 Considerations for assent

- There is no need to document assent for children below 7 years of age.
- For children between 7 and 12 years, verbal/oral assent must be obtained in the presence of the parents/LAR and should be recorded.
- For children between 12 and 18 years, written assent must be obtained. This assent form also has to be signed by the parents/LAR.
- 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 parents/LAR should 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, for example, in behavioural studies in IV drug users where parental consent may not be possible.

6.6 Research involving sexual minorities and sex workers

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

6.6.1 Protection of their dignity and provision of quality healthcare under these circumstances should be well addressed in the research proposal, preferably in consultation with the community before the proposal is finalized.

6.6.2 It would be advisable to have a representative of the sexual minority group/ lesbian/ gay/bisexual and transgender (LGBT) community as a special invitee/member to participate in the meeting of the EC if there is a research proposal involving these participants.

6.6.3 The EC can suggest setting up of a community advisory board to act as an interface between the researcher(s) and the community.

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

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

6.7 Research among tribal population

6.7.1 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.

6.7.2 Due approval from competent administrative authorities, like the tribal welfare commissioner or district collector, should be taken before entering tribal areas.

6.7.3 Whenever possible, it is desirable to seek help of government functionaries/local bodies or registered NGOs who work closely with the tribal groups and have their confidence.

6.7.4 Where a panchayat system does not exist, the tribal leader, other culturally appropriate authority or the person socially acceptable to the community may serve as the gatekeeper from whom permission to enter and interact should be sought.

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

6.7.6 Even with permission of the gatekeeper, consent from the individual participant must be sought.

6.7.7 Additional precautions should be taken to avoid inclusion of children, pregnant women and elderly people belonging to particularly vulnerable tribal groups (PVTG).[25]

6.7.8 Benefit sharing with the tribal group should be ensured for any research done using tribal knowledge that may have potential for commercialization.

6.8 Research involving individuals with mental illness or cognitively impaired/affected individuals

Mental illness: 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. According to the Mental Healthcare Act, 2017,[26] "mental illness" means a substantial disorder of thinking, mood, perception, orientation or memory that grossly impairs judgment, behaviour, capacity to recognize reality or ability to meet the ordinary demands of life, mental conditions associated with the abuse of alcohol and drugs, but does not include mental retardation which is a condition of arrested or incomplete development of the mind of a person, specially characterized by subnormality of intelligence. Presence of a mental disorder is not synonymous with incapacity of understanding or inability to provide informed consent.

Cognitively affected or impaired: Conscious mental activities such as thinking, understanding, learning and remembering are defined as cognition. Those in whom these activities are not fully functional are regarded as cognitively impaired. Such individuals or groups include people who are without full intellectual potential (intellectually disabled, previously called mentally retarded), unconscious, 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).

6.8.1 There are some psychiatric conditions that may lead people to cause risk or harm to themselves or others.

- During the informed consent process, prospective participants must be informed about how the researcher will address a participant's suicidal ideation or other risks of harm to themselves or others.
- 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 harm to self or others.
- While some interventions, like hospitalization and treatment for suicidality/ homicidal ideas, may be primarily for the participants' own benefit, they themselves may not perceive these as such and may want to refuse to participate

in a study if any such interventions are required.

- Interventions should be of short duration, as least restrictive as possible and invoked only when necessary, in accordance with relevant laws.
- Some research designs may reduce or violate human participant protections/rights or specific requirements of informed consent by resorting to deception in order to achieve the objectives of the research for public good. Types of deception that can be used in a research plan are described in Box 9.5. All such studies should be reviewed by the EC very carefully before approval.

6.9 Individuals who have diminished autonomy due to dependency or being under a hierarchical system

While reviewing protocols that include students, employees, subordinates, defence services personnel, healthcare workers, institutionalized individuals, under trials, prisoners, and others the EC must ensure the following:

6.9.1 Enrolling participants as described above is specifically pertinent to the research questions and is not merely a matter of convenience.

6.9.2 Individuals in a hierarchical position may not be in a position to disagree to participate for fear of authority and therefore extra efforts are required to respect their autonomy.

6.9.3 It is possible for the participant to deny consent and/or later withdraw from the study without any negative repercussions on her/his care.

6.9.4 Mechanisms to avoid coercion due to being part of an institution or hierarchy should be described in the protocol.

See Section 5 for informed consent issues.

6.10 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 give them a ray of hope. 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.

6.10.1 Since therapeutic misconception is high there should be appropriate consent procedures and the EC should carefully review such protocols and recruitment procedures.

6.10.2 Additional monitoring should be done to detect any adverse event at the earliest.

6.10.3 Benefit-risk assessment should be performed considering perception of benefits and risks by the potential participant.

6.10.4 The EC should carefully review post-trial access to the medication, especially if it is beneficial to the participant.

6.11 Other vulnerable groups

Other vulnerable groups include the economically and socially disadvantaged, homeless, refugees, migrants, persons or populations in conflict zones, riot areas or disaster situations. Additional precautions should be taken to avoid exploitation/retaliation/reward/credits and other inducements when such individuals are to be recruited as research participants.

6.11.1 Autonomy of such individuals is already compromised and researchers have to justify their inclusion.

6.11.2 ECs have to satisfy themselves with the justification provided to include these participants and record the same in the proceedings of the EC meeting.

6.11.3 Additional safety measures suggested earlier in the guidelines should be strictly followed by the ECs.

6.11.4 The informed consent process should be well documented. There should not be any undue coercion or incentive for participation. A person's refusal to participate should be respected and there should be no penalization.

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

CLINICAL TRIALS OF DRUGS AND OTHER INTERVENTIONS

7.0 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-behavioural interventions, technologies, devices, surgical techniques or interventions involving traditional systems of medicine, etc.

Clinical trials are usually well-controlled studies. They use a design that allows 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, such as spontaneous change, placebo effect, concomitant treatment/intervention or observer expectations.

As per the amended Schedule Y (2005) of the Drugs and Cosmetics Rules, 1945, a clinical trial refers to a systematic study of new drugs on human subjects to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effect with the objectives determining safety and/or efficacy of a new drug. The academic clinical trial as per GSR 313 (E) dated 16 March 2016[27] is a clinical trial intended for academic purposes in respect of approved drug formulations for any new indication or new route of administration or new dose or new dosage form. An EC has to approve such studies after due consideration of benefits and risks and all other ethical aspects and the licensing authority has to be informed as per the prescribed procedures.

7.1 General guidelines

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

7.1.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit (direct or indirect) for the individual trial participant and/or society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

7.1.3 All clinical trials must be conducted in accordance with the Indian GCP guidelines, the Declaration of Helsinki (2013 or later versions as applicable), National Guidelines for Biomedical and Health Research Involving Human Participants (2017), the Drugs and Cosmetics Act (1940), and Rules (1945), and applicable amendments (including Schedule Y), and other relevant regulations and guidelines, wherever applicable.

7.1.4 A participant's right to agree or decline consent to take part in a clinical trial must be respected and her/his refusal should not affect routine care.

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

7.1.6 Therapeutic misconception in potential participants must be avoided (for example, by having a co-investigator who is not the primary treating physician administer the consent).

7.1.7 At least one member of the research team must have the qualifications and adequate research experience in the subject on which the trial is planned.

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

7.1.9 Applicable regulatory approvals must be taken (if required).

7.1.10 All clinical trials must be registered with the Clinical Trial Registry -India (CTRI).[28]

7.1.11 Written informed consent must be obtained from each participant before any research related procedure is performed.

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

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

7.1.14 SAEs must be reported for all trials and if applicable timelines as specified by regulators to be followed (within 24 hours to the sponsor, EC and regulator, if applicable, followed by a due analysis report in 14 days).

7.1.15 Free medical management of AEs and SAEs, irrespective of relatedness to the clinical trial, should be given for as long as required or till such time as it is established that the injury is not related to the clinical trial, whichever is earlier.

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

7.1.17 Ancillary care may be provided to clinical trial participants for non-study/trial related illnesses arising during the period of the trial. This could be in the form of medical care or reference to facilities, as may be appropriate.

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

7.2 Clinical drug/vaccine development

7.2.1 The broad aim of the process of clinical development of a new drug or vaccine, (referred to as an 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. Phases of drug development are given in Box 7.1.

Box 7.1 Phases of drug development

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 preclinical data and in lower doses than is required for a conventional Phase I study. This is invariably part of a regulatory study.

Phase I

Phase I starts with the initial administration of an investigational new drug/vaccine into humans. These studies usually have non-therapeutic objectives. Phase I studies are conducted on healthy participants or patients, in the case of drugs with significant potential toxicity, such as 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); or early measurement of drug activity (including immunogenicity in case of vaccines).

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 on a group of patients or participants who are selected according to 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.

(Contd.)

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). Such studies are:

a) designed to confirm the evidence from Phase II studies about the safety and efficacy of a drug or 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) conducted to explore new uses of an already marketed drug for a new indication, dosage form, dosage regimen, or route of administration. If such studies are intended for ultimate commercial use of the drug, they require regulatory approval. Research on off label use comes under this category. See section 7.16.4 for further details; and

d) planned as bridging trials and pivotal trials.

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 optimizing the use of the product. They may include:

a) post-marketing surveillance – the practice of monitoring the safety of a product after it has been released in the market;

b) Phase IV clinical trials – a study conducted to assess safety, tolerability and effectiveness of a marketed product when prescribed in the usual manner in accordance with the terms of the marketing authorization, such as the efficacy and safety in special populations.

c) outcomes research – which aim to study the effectiveness and efficiency of the intervention after its introduction for human use; and

d) registries – which propose to maintain data about patients with certain shared characteristics and who have received a particular intervention (for example a stent) that collects ongoing and supporting data over time on well-defined outcomes of interest.

7.2.2 Ethical considerations

All clinical trials should be scientifically and ethically sound. The sponsor of the study, the researcher, institution, EC, and regulatory authority (if applicable) are responsible for ethical conduct of a study. Before any clinical trial is initiated, adequate data from preclinical 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.

The investigator should make an assessment to determine if a clinical trial is under the regulatory ambit and if so, to ensure that all requirements as specified by CDSCO must

also be followed. If required, the EC may provide relevant guidance to the members in deciding the same.

- Phase I (for drugs and vaccines) studies
  - ❍ All Phase I trials require EC approval and applicable regulatory approvals.
  - ❍ A Phase I study is a non-therapeutic trial in which there is no anticipated direct clinical benefit to the participant. In general, therefore, it should be conducted in participants who can give voluntary informed consent themselves and who can sign and date the written informed consent forms themselves, unless the therapy under investigation is for diseases specific to those who cannot give consent, such as children, in which case consent of the LAR may be taken.
  - ❍ As Phase I studies are most often conducted in healthy volunteers, all safeguards to protect the participants must be established, especially recruitment methods, payment for participation, evidence of non-coercion and consent procedures.
  - ❍ When a Phase I study is conducted in participants with a disease such as cancer, due consideration should be given to the seriousness of the medical condition and the study procedures planned.
  - ❍ The study protocol should describe measures to minimize the risks of a Phase I clinical trial in healthy volunteers and patients. These include, but are not limited to, the measures given in Box 7.2.

Box 7.2 Risks of Phase I clinical trials

The measures to be taken to minimize risks in a Phase I clinical trial include:

- exclusion of participants who may be at increased risk from the study;
- careful review of investigational procedures posing high risk of physical harm or serious discomfort;
- evaluation of available data to decide if the IP or procedures proposed in the protocol have been associated with SAEs and steps taken to prevent or minimize such risks; and
- careful monitoring of the condition of participants and intervention to manage adverse events.

  - ❍ A Phase I study unit must have robust resources and tested procedures for immediate resuscitation and maintenance of life support and onward transfer to an intensive care unit, if necessary.

- ❍ A Phase I study with a high-risk IP, such as first-in-human, biologic should be carried out in a hospital where experienced personnel and facilities are immediately available to manage medical emergencies.
- ❍ Medical pharmacologist/physicians trained in clinical pharmacology should be involved in Phase I studies.

- Phase II, III and IV studies
  - ❍ All Phase II and III studies require EC approval and applicable regulatory approvals.
  - ❍ In the case of Phase IV studies, the following are some examples of studies that require EC approval:
    - (i) Phase IV clinical trials
    - (ii) Outcome research
    - (iii) Registries
    - (iv) Data that is used to answer any research question
    - (v) New use/route/dose/dosage form/combination/regimen of a marketed drug for non-commercial purpose such as academic research
  - ❍ In addition to EC approval, a Phase IV clinical trial on drugs with a market authorization of less than 4 years requires regulatory approval (CDSCO).
  - ❍ Routine post-marketing surveillance (PMS) may not require EC approval. See Box 7.1 for further details.

- Vaccine studies

  Vaccines can be prophylactic and/or therapeutic in nature. The guidelines for conducting clinical trials on investigational vaccines are similar to those governing a drug trial. However, the phases of these trials differ from drug trials as given below:

  - ❍ Phase I is for the study of dose and route of administration for determining its safety and biological effects, including immunogenicity, and should involve low risk.
  - ❍ Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulations when there is a 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.

- 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.
- Vaccines administered simultaneously with 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. Types of vaccines are listed in Box 7.3.

Box 7.3 Types of vaccines

- Live and attenuated vaccines (measles, mumps, rubella and chickenpox)
- Inactivated vaccine (flu vaccine)
- Toxoid vaccines (diphtheria and tetanus vaccines)
- DNA vaccines
- Recombinant vector vaccines

- 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 this.
- The participants in control groups, or when subjected to ineffective vaccines, run a risk of contracting the disease. In such an event, provisions be made to provide free treatment for the disease.
- For recombinant DNA vaccines and products, applicable governmental guidelines and regulations should be followed.
- Post-trial, the control group should receive the complete dose of an effective vaccine (either one that is already available or the investigational vaccine).

7.3 Bioavailability/bioequivalence study

Bioavailability (BA) 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 (BE) is a term used in pharmacokinetics when there are two or more

medicinal products (proprietary preparations of a drug), containing the same active substance that need to be compared in vivo for biological equivalence. These comparative studies are used to assess if 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.

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

7.3.1 Ethical issues

- All BA/BE studies should be scientifically sound and conducted in compliance with principles of ethical conduct described earlier for a Phase I study.
- Ethical conduct of BA/BE study requires evaluation of the benefit–risk profile of:
  a. the reference (comparator) and investigational (generic) product; and
  b. the study procedures such as indoor stay, fasting, screening, blood sampling.
- BA/BE studies are usually conducted in healthy volunteers. Hence, they have no direct benefit to the participant but may pose risks due to the adverse effects of the drug. Therefore, all safeguards to protect participants must be in place.
- The EC must carefully review the recruitment methods, payment for participation and consent procedures. Volunteers often regularly participate in such studies 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. Care must be taken to maintain confidentiality of biometric data.
- The amount of blood drawn for a BA/BE study should be within physiological limits irrespective of study design and the EC should take specific note on the amount of blood drawn depending on whether the individual is a healthy adult or a child or a patient.

7.4 Ethical implications of study designs

Clinical trials have a wide range of methodological approaches. ECs need to look into the details of the ethical concerns involved.

7.4.1 If a SAE occurs in a blinded study, and it is imperative, in the interest of managing the event to know what the patient was receiving, unblinding mechanisms should be available to the researcher.

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

7.4.3 Placebo may be used as a comparator under the conditions given in Box 7.4.

Box 7.4 Conditions where a placebo may be used

A placebo may be used when:

- there is no established effective therapy available;
- withholding an established effective therapy would not expose participants to serious harm, but may cause temporary discomfort or delay in relief of symptoms;
- if the disease is self-limited; or
- 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 additional risk of serious or irreversible harm to the participants.

7.4.4 If a placebo must be used for scientific reasons, then certain precautions must be exercised. These should be reviewed and approved by the EC. See Box 7.5 for further details.

Box 7.5 Precautions to be taken when a placebo is used

1. The protocol must have added safeguards to protect participants from harm, such as but not restricted to having clear-cut withdrawal criteria, intensive monitoring and rescue medications.
2. Use an add-on trial design where the IP or placebo are added to standard of care.
3. Expose fewer patients to placebo groups, for example 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, for example, 2:2:1 (IP: active comparator: placebo).
5. Ensure transition to standard of care/active medicine for study participants after research is completed, including post-trial arrangements for implementing any positive trial results.

7.5 Multicentric trials

Multicentric trials are carried out with a primary aim of providing a sound basis for the subsequent generalization of its results.

7.5.1 ECs of all sites should follow all applicable regulatory guidelines, including registration with regulating bodies.

7.5.2 The ethical review procedure for common review of multicentric research is given in section 4.10. Not applicable for clinical trials under Drugs and Cosmetic Act.

7.6 Phytopharmaceutical drugs

The Drugs and Cosmetics Rules, 8th Amendment, 2015,[29] defines a new class of drugs called phytopharmaceutical drug as "purified and standardized 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 details described in 7.2 also apply to this group of drugs.

7.7 Device trials

7.7.1 A medical device is defined as a medical tool which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means but which may be assisted in its intended function by such means. It may be an instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including a software or an accessory, intended by its manufacturer to be used specially for human beings or animals for one or more of the specific purposes of:

(i) detection, diagnosis, prevention, monitoring;

(ii) treatment or alleviation of any physiological condition or state of health, or illness;

(iii) replacement or modification or support of the anatomy or congenital deformity;

(iv) supporting or sustaining life;

(v) disinfection of medical devices; or

(vi) control of conception.

- Clinical trials should be conducted in accordance with the ethical principles described in these guidelines, Indian GCP as well as applicable regulations for medical and medicated devices, that is, GSR 78 (E) dated 31.1.2017 or as per amendments/modifications issued from time-to-time.
- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered in the same way as for a new drug under the Drugs and Cosmetics Rules, 1945.
- Apart from safety considerations of the device, the procedures to introduce the

medical device in the patient should also be evaluated for safety.

- Devices should be provided free of cost or, if expensive, at feasible reduced rates.
- Avoid therapeutic misconceptions.
- Any AE/SAE should be reported within timelines as per the schedule for a new drug. Here user error could also be the cause of AE/SAE.
- 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 in the trial without prejudice to her/his ongoing treatment.
- If feasible, post-trial obligations should be emphasized with the sponsor.
- The duration of follow-up should be long enough to detect late onset adverse reactions, especially when the device is implanted within the body.

7.7.2 Devices could be used internally or externally for diagnosis, treatment, mitigation or prevention of disease or disorder. Depending upon risks involved, devices (other than in vitro diagnostic devices) are classified as given in Table 7.1:

Table 7.1 Classification of medical devices

Class	Level of risk	Device examples
A	Low	Thermometers/ bandages /tongue depressors
B	Low–moderate	Hypodermic needles /suction equipment
C	Moderate–high	Lung ventilator /bone fixation plate
D	High	Heart valves/implantable defibrillator

7.7.3 Devices used for in vitro diagnosis could be a reagent, calibrator, control material, kit, instrument, apparatus, equipment, system, or specimen receptacle, whether used alone or in combination with any other such devices, that is intended by its manufacturer to be used in vitro for examination of any specimen, including any blood or tissue donation derived from the human body solely or principally for the purpose of providing information. The information could be related to:

(i) a physiological or pathological state;

(ii) congenital deformity;

(iii) determining the safety and compatibility of any blood or tissue donation with a potential recipient thereof; or

(iv) monitoring of therapeutic measures.

- Diagnostics devices can be notified and non-notified. Notified are in vitro diagnostic devices for testing HIV, HBsAg, HCV and blood grouping. Non-notified are those for testing malaria, TB, dengue, chikungunya, typhoid, syphilis, cancer markers, etc.

7.8 Biologicals and biosimilars

Biologics (biopharmaceutical drug) can be composed of sugars, proteins, 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 7.1 are also applicable to biologics.

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

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

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

7.8.4 All applicable and current regulations must be followed.

7.9 Clinical trials with stem cells

In recent years, stem cell research has undergone rapid developments promising new leads in the treatment of several incurable diseases. According to the source and degree of expected risk to human participants, stem cell research is categorized into permissible (adult and cord blood), restricted (embryonic) and prohibited (reproductive cloning) areas of research. In India, only permissible and restricted areas of research are permitted with appropriate approvals. It is necessary to ensure that donors are not exploited and commodified.

To address issues related to stem cell research, ICMR and DBT published Guidelines for Stem Cell Research and Therapy in 2007, 2013 and revised as National Guidelines for Stem Cell Research in 2017. [6]

7.9.1 Except haemopoietic stem cell transplantation for haematological disorders, any other uses of stem cells are categorized as research and must be conducted as clinical trials, needing the approval of the EC, IC-SCR (permissible research), National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) (restricted research) and CDSCO (IND products and drugs) as the case may be.[29] Use of stem cells outside the domain of a clinical trial for any purpose is considered unethical and hence not permissible.

7.9.2 Clinical trials must be carried out with clinical grade cells processed as per applicable national Good Laboratory Practices (GLP)[30], Good Manufacturing Practices (GMP)[31], and GCP guidelines.[12]

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

7.9.4 All clinical trials must be approved by IC-SCR, which in turn should be registered with NAC-SCRT. All such studies should also be registered with CTRI. The EC should give final approval before initiation of the clinical trial.

7.10 Surgical interventions

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

7.10.1 In any protocol where an established surgical intervention is to be studied, the researcher must provide references for the procedure and describe the most likely complications in the protocol for the EC to review and perform benefit-risk assessment. The frequency of each complication should also be mentioned.

7.10.2 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.

7.10.3 In trials where an entirely new surgical intervention is being tested, the EC may insist on some animal data/modeling data which establishes the efficacy and safety of the technique or case reports/case series that indicate benefits and describe risks.

7.10.4 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.

7.10.5 Provision of free treatment and compensation for any study-related injury must be ensured for the trial participant. The EC must determine the compensation amount after the investigator has described the relatedness.

7.10.6 Due to inherent ethical issues, sham surgery should not be included in the design of clinical trials, except in cases where there are strong scientific reasons. Under such circumstances, certain conditions must be met. See Box 7.6 for further details.

Box 7.6 Conditions for sham surgery

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

7.11 Community trials (public health interventions)

Community trials are 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. The 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 (see section 8 for further details).

7.12 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. Social stigma, culturally embedded myths about HIV, marginalization, lack of legal status or criminalization of some communities that are susceptible to HIV or the disparity in standards of care in different parts of the world are examples of special issues.

7.12.1 Global studies in HIV/AIDS in specific communities should receive approval from the relevant national authority and any other relevant authority, such as the HMSC, where applicable, in addition to approval from the EC.

7.12.2 When testing for HIV is done, consent and pre-test- and post-test counselling should be done as per National AIDS Control Organization (NACO) guidelines.

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

7.12.4 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 privacy of the HIV positive individual.

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

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

7.12.7 When a trial with a preventive HIV vaccine is conducted, it can result in 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 result.

7.12.8 Research that involves sexual minorities or IV drug users should have community engagement (community leaders) throughout the life of the project, until completion and dissemination of results.

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

7.12.10 Where possible, for example, if the drug is found useful, standard of care is not available or regulatory permissions are in place, the EC should ensure post-trial access of the IP for the participants.

7.12.11 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 HIV positive participants about any other research being done on them, such as research on hepatitis B.

7.13 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 has recognized Ayurveda, Siddha, Unani, Yoga, Naturopathy and Homeopathy as traditional Indian systems of medicine. In 2012, Sowa Rigpa (Amchi or Tibetan medicine) was also added to the list. Ministry of AYUSH (Ayurveda, Unani, Siddha and Homeopathy) governs and regulates these systems. Drugs under these systems come under the Drugs and Cosmetics Act, 1940, as ASU and H drugs. Drugs/formulations under these systems of medicine are classified into two groups. See Box 7.7 for further details:

7.13.1 Research on AYUSH and ASU interventions of traditional medicines (TM) including external medicines/therapeutic procedures, 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[32], as well as other applicable regulations of the country.

Box 7.7 Classification of drugs/formulation under AYUSH

1. Classical preparations/formulations are those that are to be clinically evaluated for the same indication for which it is being used or as has been described in 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 Yoga, Naturopathy, Unani, Siddha, Homoeopathy, SOWA–RIGPA systems, as the case may be), 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.

7.13.2 If IPs/comparators of more than one traditional system of medicine are to be investigated, then investigator(s) from the respective systems should be included in the study as co-investigator(s).

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

7.13.4 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 IPRs and patents for the product.

7.13.5 While conducting trials using intervention(s) of traditional medicine, the investigator must ensure the quality of the interventional product.

7.14 Trials of diagnostic agents

A diagnostic agent refers to any pharmaceutical product used as part of a diagnostic test, 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.

7.14.1 Benefit-risk assessment involving diagnostic agents additionally includes the assessment of benefits, such as technical performance, diagnostic performance, impact on diagnostic thinking and impact on patient management/outcome, and the risks related to the agent itself, such as immunogenicity, allergic reactions, but also risks related to incorrect handling of test procedures or incorrect diagnosis induced by its use.

7.14.2 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 the human body (in vivo use). Special expertise may be co-opted in the EC for review of such products.

7.14.3 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.

7.14.4 A placebo may be used as comparator when the response to a diagnostic test is being assessed using subjective evaluation criteria, for example, 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.

7.14.5 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.

7.14.6 Long-term safety (when appropriate) should be assessed especially for agents accumulating in the body, such as deposits of gadolinium in bones and skin.

7.15 Radioactive 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 previous sections will apply. However, if it is to be evaluated as a diagnostic agent then section 7.15 applies. 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. Additionally, the following considerations must be applied:

7.15.1 The investigating site should have a license from the competent authority to store, handle and dispense the radioactive substance.

7.15.2 The investigator and clinical trial team must be competent and should have received appropriate training in handling radioactive substances and X-rays.

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

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

7.15.5 When a trial involving radioactive substances is planned in healthy participants, they should preferably have completed their family and receive radiation in a dose as low as permitted.

7.15.6 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.

7.15.7 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 ensure that relatives or close co-habitants are not exposed to radiation.

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

7.16 Investigator initiated clinical trials

Academic institutions routinely carry out investigator initiated clinical trials.

7.16.1 In such trials, the investigator has the dual responsibility of being an investigator as well as the sponsor.

7.16.2 Financial arrangements must be made by the institution/investigator for the conduct of the study as well as to pay for free management of research-related injury and compensation, if applicable. Funds should be made available or appropriate mechanisms be established.

7.16.3 The institution must have or introduce policies that establish mechanisms to ensure quality of the data generated and safety of the intervention, such as monitoring,

auditing, DSMB, etc.

7.16.4 When academic clinical trials are planned for "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 such clinical trials designed by researchers/academicians may not currently require regulatory approval. However, an EC has to approve such studies after due consideration of benefits and risks and all other ethical aspects and the licensing authority has to be informed as per GSR 313(e) dated 16.3.2016 issued by CDSCO.

7.16.5 The trials must be registered in CTRI and there should be mechanism for appropriate methods for informed consent, conduct of trial and proper follow-up of patients.

7.16.6 For student conducting clinical trials as part of their academic thesis, the guide and the academic institution should take up the responsibilities of the sponsor.

7.17 Clinical trials on contraceptives

Several methods of contraception are available including, barrier methods, hormonal methods, emergency contraception, intra-uterine and surgical methods. Since these studies are conducted in healthy participants, all efforts to minimize 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 whether they be drugs, devices or surgeries:

7.17.1 All procedures for clinical trials will be applicable.

7.17.2 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.

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

7.17.4 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.

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

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

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

7.17.8 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 (MTP).

7.17.9 A compensation policy must be established at the beginning of the trial to provide a cover for this contingency or issues related to trial.

7.18 Pregnancy and clinical trials

Any clinical trial conducted in women of childbearing age raises 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.

7.18.1 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 ICD and it should be ensured that these methods are understood and followed by the woman participant.

7.18.2 In clinical trials that include women of reproductive age, there may be occasional inadvertent pregnancy. In such an instance the 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 foetus must be stated in the protocol and ICD.

7.18.3 EC to review the need if, during research participation, the female sexual partner of a male participant gets pregnant, the protocol and ICD must state a plan to document this and both pregnant partner and foetus must be followed for outcome and reported.

7.18.4 Pregnant women have the right to participate in clinical research relevant to their healthcare needs such as gestational diabetes, pregnancy induced hypertension and HIV.

7.18.5 Benefit–risk assessment must be done at all stages for both the mother and the foetus.

7.18.6 Research involving pregnant women and foetuses must only take place when the object of the research is to obtain new knowledge directly relevant to the foetus, the pregnancy or lactation. The criteria described in Box 7.8 must be fulfilled.

7.18.7 Women should not be encouraged to discontinue nursing for the sake of participation in research except in those studies where breast-feeding is harmful to the infant. In case a woman decides to cease breastfeeding, harm of cessation to the nursing child

Box 7.8 Criteria for research involving pregnant women and foetuses

1. Appropriate studies on animals and non-pregnant individuals should have been completed (if applicable).
2. The risk to the foetus must be 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 foetus, or the risk to the foetus is minimal.
3. Researchers should not participate in decision making regarding any termination of a pregnancy.
4. No procedural changes, which will cause greater than minimal risk to the woman or foetus, will be introduced into the procedure for terminating the pregnancy solely in the interest of the trial.

should be properly assessed. Supplementary food, such as milk formula should be considered in such instances.

7.18.8 For the conduct of research related to termination of pregnancy only pregnant women who undergo MTP as per the Medical Termination of Pregnancy Act, 1971 can be included.

7.19 Clinical trials in oncology

There are several ethical issues when research is conducted in terminally ill patients for whom this may be a last hope for cure, or a way to get free treatment for their disease which may be otherwise beyond their reach. These need to be addressed during planning, conduct, oversight and publication of such trials. Three primary factors motivate participation in oncology clinical trials: hope for a cure; altruism that even if the patient does 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 7.1 and stated in drug trials, biologics and radioactive substances, apply to oncology clinical trials. In addition, while reviewing oncology studies, the following should be kept in mind:

7.19.1 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.

7.19.2 The patient population may be vulnerable as they are often terminally ill. Economically

disadvantaged populations may participate in the research to gain 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.

7.19.3 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.

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

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

7.19.6 Undue inducement must be avoided.

7.19.7 Patients should not be charged for any intervention including standard of care in the control arm. If the trial is an add-on design, the background standard of care may not be given free. The EC should review this carefully.

7.19.8 A post-trial access plan must be in place for patients who show benefit from 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.

7.20 Clinical trials of products using any new technology

If any product using new technologies (such as nanotechnology) is developed for human use and is to be evaluated in human beings, the following ethical issues have to be taken into consideration in addition to all the general ethical guidelines for clinical trials as elaborated in the guidelines.

7.20.1 Compliance with GLP, GMP, and GCP norms should be observed in research using new technology products.

7.20.2 Before the use of a new technology product in a human being, preclinical studies should be carried out and all applicable regulatory requirements fulfilled.

7.20.3 The new technology-based products should be contained and released into the environment in a step-wise manner after clearance from the appropriate authority regarding environmental safety.

7.20.4 Differing process based technologies can result in similarly functioning biological products which can give rise to IPR issues.

7.20.5 The research on new technologies should have a well-established mechanism or system for assessing the risk, both in terms of severity and temporality. The unpredictable

metabolic behaviour in a human system during clinical trial cannot exclude long-term side effects which may manifest later, leading to compensation issues.

7.20.6 Training of all stakeholders should address issues regarding safe research, handling of products, environmental safety and community misconceptions.

7.21 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".[33] The ethical, legal and social issues pertain to the impact of this science on society, biosafety, biosecurity, IPRs, 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 the biotechnology industry which includes genetically modified organisms, stem cells, cloning, artificial life forms like biofuels, bioweapons, vaccines, diagnostics, etc. Software and bioinformatics as design tools, along with 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 the environment.

7.21.1 Special considerations

- Precautionary principle: This applies to the prevention of harm to humans, environment and ecosystem because development of a new technology may emit hazardous elements like X-ray radiation, electro-magnetic currents and non-ionizing magnetic waves in the environment, which may manifest only later. Safety measures should be followed as per the Environmental Protection Act, 1986, Atomic Energy Act[34], Biomedical Waste Management Rules[35], and other relevant laws.
- Biosecurity: Sometimes, the product can have dual use, that is, one beneficial use for a particular purpose and the other for harmful use which could be unintentional or intentional, for example, 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 maintaining vigilance to prevent misuse. There should be effective partnership between researchers and policy makers to create a secure system.
- GLP, GMP and GCP should be observed when conducting clinical trials.
- Products should be contained and released into the environment in a step-wise manner after clearance from the appropriate authority regarding its safety.

- Training should be given for safe handling of the product and conduct of research and should address community misconceptions.
- Testing of biomaterials and biocompatibility should be as per relevant Indian regulatory standards or American Society for Testing and Materials (ASTM)[36] international standards until Indian standards for biomaterials are in place. The testing of such standards shall be done in a laboratory certified by the National Accreditation Board for Testing and Calibration Laboratories (NABL).
- Appropriate training for safety of healthcare workers should be given and they should be provided periodic health check-ups due to exposure to occupational risks.

PUBLIC HEALTH RESEARCH

8.0 Public health raises a complex relationship between the state, its policies and society involving individuals and organizations with a precautionary approach. Ethics in public health apply to both practice and research, both of which utilize epidemiology and methods of other disciplines to ensure better societal conditions for healthier lives. Therefore, public health protects both the individual and the population at large, since the benefits and risks are not limited to an individual, but influence communities, populations and the environment. It is important to realize that public health interventions have the potential to expose and perhaps exploit the vulnerabilities of communities and segments of the population. Public health research investigations and interventions should therefore be conducted through a process of ethical reflection, together with establishment of appropriate protections, oversight procedures and governance mechanisms.

Defining boundaries between public health practice and research remains a challenge in public health ethics as the purpose or intent of the investigation may overlap. Public health practice involves data collection through surveillance, vital statistics, disease reporting and registries; investigation of outbreaks including contact tracing, use of preventive interventions and health promotion; monitoring and programme evaluation; and enforcing of mandatory requirements, such as screening, treatment, immunization, notifying diseases and, sometimes, quarantine depending upon the situation. By using epidemiological designs, sampling techniques and analysis, some of these activities could create generalizable knowledge, which is the primary intent of research. Considering these difficulties in clear delineation of boundaries between practice and research, both requiring ethical oversight and governance of public health information, an EC may have to differentiate this to determine its role with more clarity. This section however, highlights the specific ethical issues pertaining to research on public health. The EC will determine if a particular protocol pertains to public health practice or research.

8.1 Principles of public health research ethics

- **Principle of respect for autonomy, rights and dignity** – In public health research, the principle of autonomy is relational, since the interests of an individual as part of

a community are relational in nature. Therefore, sometimes individual autonomy may not be appropriate as a stand-alone for application at the community level. While respect for the rights and dignity of all participants need to be considered and ensured, the same should be observed about the community. This can be facilitated by engaging the community in discussion. The conventional method of informed consent from an individual may be replaced with alternative methods after approval by the EC on a case-by-case basis. See section 8.4.2 for further details.

- **Principle of beneficence** – Public health research aims at achieving public good through societal benefit to the maximum possible level as against individual benefit.
- **Principle of non-maleficence** – Maximum efforts should be made to minimize harm done to individuals and others, such as the community, especially while collecting data and its subsequent disclosure. Harm could be in the form of stigma, poverty, and discrimination that affect persons living with diseases like HIV, STD, TB, mental illnesses, etc. Safeguards to maintain confidentiality should be established as there could also be indirect harm to the individual/community/ relationships and loss of benefit.

  The following principles may overlap with public health service and research.

  (i) **Harm principle** – If liberty of an individual or group is rightfully restricted against the person's will to prevent harm to others, the decision to do so should be backed by strong ethical justification, for example in disease outbreaks.

  (ii) **Principle of least infringement** – As far as possible the least restrictive means should be adopted when liberty is curtailed.

  (iii) **Principle of proportionality** – This principle requires public health authorities to minimize risks and promote well-being of the public. Breach of autonomy and privacy of individuals should be balanced against probable public benefits and the necessity of such an intervention. It should justify burdens suffered by participants/communities.
- **Principle of social justice** – The benefits and burden of public health research, should be equitably distributed across all study groups. When vulnerable or disadvantaged populations are involved, research that retains or enhances existing inequities should be avoided. Implied as a positive obligation to improve health

of the least advantaged, this principle supports research into the upstream factors among the social determinants of health that influence health equity.

- **Principle of reciprocity** – This principle requires that individuals or communities, who have borne a disproportionate share of burden or risks for the benefit of others be given some form of benefit. The benefit should be context specific such as protection from further exposure, access to food, healthcare, clothing and shelter, communication or compensation for lost income.
- **Principle of solidarity** – Public health research should respect the intra- and inter-dependence among members of communities leading to solidarity for collective welfare or the common good.
- **Principle of accountability and transparency** – The conduct of research must be fair, honest and transparent. The results should be made available in the public domain.

In order to undertake a review of public health research, an EC must carefully consider the points given in Box 8.1.

Box 8.1 Public health research proposal review

When reviewing public health research proposals, ECs should consider the followings aspects:

1. Are the objectives of the study scientifically sound and linked to the achievement of public health goals?
2. Is individual written informed consent required?
   - If not, is gatekeeper consent/permission sufficient? Who is a gatekeeper and how is this decided?
   - Is it a two-stage process – initially a gatekeeper consent/permission followed by individual consent?
3. If applicable, is respect for the community applied through community engagement? If so, is the methodology appropriate?
4. Which segments of the population are likely beneficiaries and what are the expected benefits?
5. Is individual harm overriding the potentially larger societal benefit?
   - If so, is it justified?
   - What are the different types of potential harm?
   - Who would be harmed?
   - What, if any, measures can be taken to mitigate/minimize this?
   - Is the harm fairly distributed?
   - How do societal benefits outweigh individual harm?
6. Is social justice considered while designing, implementing and assessing outcomes of the study?

8.2 Ethical issues of epidemiological and public health research study designs

8.2.1 Epidemiological and public health research studies

These involve use of different study methods and tools on a large number of research participants in single or multiple settings. These include observational studies (such as cross-sectional studies), case control studies, cohort studies, case reports, case series and other descriptive studies and experimental studies (such as field trials and cluster randomized controlled trials, stepped-wedge and quasi-experimental study designs involving groups, geographic areas, institutions or systems collectively rather than individually).

- Specific ethical issues emerge from the scientific merit and design of the research and its implementation and should be considered by EC.

8.2.2 Surveillance, programme monitoring data and programme 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 researchers for generating new evidence to improve programme performance, and for more generalizable application at other sites and contexts. Programme evaluation refers to the systematic application of scientific and statistical procedures for measuring programme conceptualization, design, implementation and utility; the comparison of these measurements; and the use of the resulting information to optimize programme outcomes. Evaluation research may or may not involve human participants such as health personnel, patients, community members and other stakeholders. It will also involve screening the documents and observations of various activities at different levels.

- These studies may be placed under the exempt from review category in specific situations where the sole purpose of the exercise is refinement and improvement of the programme or where an unspecified but large number of stakeholders are to be interviewed who are spread across large geographic areas.
- Proper ethical review must be carried out for programme evaluation research activities if it is clearly for generalizable knowledge, to ensure scientific soundness, examine the 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 those mentioned in section 8.3.

8.2.3 Demographic surveillance sites and registries

A demographic surveillance site is a geographically defined population with continuous demographic monitoring and regular production of data and reports on all births, deaths and migrations. This monitoring system should provide a platform for assessing a wide range of health-systems and 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 programme effectiveness. The aim of a surveillance site is to provide an evidence base for improving the lives of people living in developing countries by informing and influencing existing as well as future health-related policy and practice. They can also help define a relevant research and development agenda.

- Prior approval from competent state/national authorities and from the community leadership is required to set-up the demographic surveillance sites, with or without the use of geographic information system (GIS) facilities. Setting-up such sites need not be subject to prior review and approval by an EC.
- Strategies for research studies to be undertaken at these sites including data-set collection and its storage, with plans to maintain confidentiality, will have to undergo appropriate EC review. To safeguard the confidentiality of personally identifiable records, the collected data at demographic sites must be stored in an encrypted format with primary identifiers accessible only to restricted designated individuals who are bound by a confidentiality agreement.
- Spatial epidemiology, including use of GIS technology, in health is an evolving area and the related ethical issues that may emerge need to be addressed as experience grows.
- Registries are a systematic collection of data concerning a particular diseases and/or health conditions at one or more places. For registries that are established as part of research projects or if the data emerging from these registries is proposed to be used for research, prior approval of the EC is required.
- On the other hand, registries that are set-up as part of public health programmes by a national authority may be exempted from the ethical review process if the data is de-identified, but are subject to governance processes and a certificate

from an EC for exemption for ethics review and if required for waiver of informed consent.

- The ethical concerns for EC approval are similar to those mentioned in section 8.3.

8.2.4 Implementation research

At local, national and global levels, a persistent challenge is to effectively implement and scale-up policies, programmes and interventions that can save lives and improve health. A new approach to achieving these goals is through implementation research (IR), which facilitates informed decisions about health policies, programmes and clinical practices. 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. For research to be relevant to public health it is co-designed and co-implemented with implementers and end users to understand and encourage uptake of a piloted or completed research or programme. This requires a long-term mutually advantageous relationship between researchers, other stakeholders and the community from the inception stage of the research project involving issues such as framing of questions, research design and delivery of strategy for influencing implementation and wider dissemination as part of its design. IR may involve simple methods or more sophisticated research designs and often uses mixed, quantitative and qualitative, methods. Analyses is done with the intention to reach, rather than the intention to treat, for equitable population health impact. Specialized analyses may also be used to explain how and why a policy works, how best to scale an intervention, or how to introduce and expand an innovation. To account for the changing contexts and interventions during the period concerned, a detailed pre-specification of interventions and outcome measures may not be feasible in many projects. IR is essentially adaptive in nature and is different from protocols that require precise pre-definition of interventions, mode of delivery, outcome measurement and the role of study participants.

- ECs should, therefore, understand this requirement of flexibility or resilience while reviewing IR projects.
- The IR process attempts to distribute roles and responsibilities between researchers and other stakeholders including those researched, at least to a certain extent.
- ECs should acknowledge these aspects of good participatory practice in IR and delivery sciences – both formally (by undergoing training) and informally (by

encouraging discussion and debate).

- The theoretical core of a complex intervention must be kept constant while allowing and accepting the unique flexibility and resilience of the study design. The ethics of IR is an emerging area and will keep growing as more experience accumulates.
- There is a critical role of governance and accountability of all stakeholders due to the asymmetry of knowledge and power relationships which should be considered.

8.2.5 Demonstration projects

A demonstration project tests the effects of a new policy approach on the health system in a real-world situation. By their very nature, such projects change the status quo of existing public programmes, affecting communities, users/beneficiaries, providers, and expenditures. They help policymakers to learn about the potential impact and operational challenges of a new policy/programme or modification of the existing policy to a public health system, but in a more controlled environment and on a limited basis. Demonstration projects affect a large population – a district or cluster of districts or a state, thus involving hundreds of thousands of people (users and health providers) with substantial resource investment.

- A number of key issues must be considered in designing, implementing and evaluating demonstration projects. This most often requires some level of research for cultural and geographical appropriateness (formative research) to support their development and evaluation to report to the policy makers on recommendations regarding the proposed approach.
- All demonstration projects should be subject to ethical scrutiny.

Some of the key questions that the EC should raise are:

- Why is the demonstration project being undertaken?
- How is this designed/being initiated/implemented?
- What impact is the project likely to have on broader health systems?
- Will there be issues involving equity and vulnerable populations?
- What is the range of design and implementation situations on the ground?
- Should a decision on the exemption from review and consent waiver be taken on a case- by-case basis?

8.2.6 Community Trials

These are trials carried out at the community level or on groups and the treatment or intervention is allocated to communities rather than individuals. These could both be interventional or observational studies. Such studies may be carried out for conditions that are influenced due to social reasons and the interventions may be directed at group behaviour as well. These studies target the community as a whole and the randomization is also at community level and usually the method is useful in order to study public health interventions or disease prevention models.

- The studies require review and monitoring by EC as for other research.
- Informed consent issues are complex and details in section 8.4 may be seen.

8.3 Use of administrative and other data sources for research

Administrative data refer to systematically collected or compiled information designed to assist in programmatic and organizational operations. There is a shift in use of these data sets, from primarily managing and monitoring programmes 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 and time- and cost-effectiveness. Data files are often population based, providing information on large numbers of persons and permitting longitudinal analysis over multiple years.

- While such data can provide quick and easy access to information for secondary analysis, there are possibilities of misinterpretation of the data, violations of terms and conditions for which data was allowed access thus compromising data security, confidentiality of information, disclosure permissions, unauthorized and inappropriate use of the data, and unethical publication.
- Partnership between the researcher(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.
- ECs should ensure that research using administrative data does not violate any principles of public health research ethics.

8.4 Informed consent

8.4.1 Obtaining informed consent – Several public health research studies, such as cluster

randomized field trials or IR, have participants who cannot avoid interventions. This implies that participant's 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 in such types of research protocols should therefore be differently reviewed by an EC than in individually randomized trials because of methodological consequences.

8.4.2 The hierarchical structure of such trials imply consideration of two levels of consent. The first level is the gatekeeper(s) who could be the guardian or local authority normally responsible for participants' well-being; who give permission for participation and randomization of individual participation. The other level is individual participants, consent from whom can cover different aspects:

- consent that routinely held data on individuals be collected;
- consent regarding the collection of supplementary data;
- consent for active participation;
- Field trials which involve new pharmaceutical agents require individual consent for both intervention and collection of data.

8.4.3 Types of consent

Written voluntary informed consent is the norm for research. However, for specific research the following types of consent may be considered by the EC.

Box 8.2 Types of Consent

- Verbal/oral consent: For research on sensitive topics, verbal/oral consent or pseudonyms may be suitable with appropriate approval of the EC and with proper documentation.
- Broad consent: Providing an individual opt-out option, consultation may be held with only a small representative group of the population of interest.
- Group consent: Cluster randomized trials (CRT), IR, and demonstration projects are examples where ECs have to decide on the complex issues of feasibility and type of consent to be obtained from the participants.

The process of obtaining such forms of consent and the associated documentation should be approved by the EC.

8.4.4 Waiver of consent – Most epidemiological and public health research would follow standard informed consent guidelines. However, the EC can consider consent waiver in the following conditions, as given in Box 8.3.

Box 8.3 Waiver of consent in public health research

Consent in public health research may be waived:

- on routinely collected data under programme conditions, including research involving linkage to large anonymous databases of information that has been routinely collected such as administrative data and through surveillance activities. However, at the time of collection people concerned may have been told that the data would be used for other purposes, including research;
- in circumstances where obtaining consent is impractical, such as for stored anonymous data/ biological samples, surveillance and administrative data or personal non-identifiable data/ material available from public health programmes;
- for studies performed within the scope of regulatory and public health authorities, such as process and impact evaluations of national policies and programmes, including neonatal screening programmes or diabetes screening as part of national programme activities may be exempt from the requirement for informed consent;
- when the primary purpose is refinement and improvement of the public health programmes;
- for studies using health-related registries that are authorized under national regulations; or
- when it is not practical or meaningful to obtain consent in large geographical clusters in cluster randomization trials and several IRs.

8.4.5 **Re-consenting in longitudinal studies:** There is need for re-consenting when there is a change in protocol, new information is sought, a new intervention is introduced, or new information is available which has likely influence on the safety of participants. If there is no change in the study protocol there is no need for re-consent. Other guidelines for re-consent, as described in section 5, should be followed.

8.5 Role of the EC

8.5.1 ECs should ensure that the researcher has taken adequate measures for data security, confidentiality of information, disclosure permissions, and stated appropriate use of the accessed data.

8.5.2 EC members need to give appropriate importance to the social benefit, public good and public health impact these studies may be addressing. The ECs must take decisions regarding consent on a case- by-case basis.

8.5.3 EC membership should include experts in public health or the EC should get comments from, or invite experts for, the relevant meeting.

8.5.4 ECs should consider the following while assessing a public health research:

- standards of care in public health;

- ancillary care in public health;
- stakeholder engagement – identifying and defining stakeholders' roles especially in IR, health systems and policy research; and
- responsibility of the researcher to scale-up, advocate, promote uptake, or sustain the public health intervention.

8.6 Protecting participants and communities

8.6.1 Special provisions should be provided in the design and execution of public health studies that are likely to have the potential to exploit research participants, especially socioeconomically deprived ones.

8.6.2 People who have limited access to healthcare may misunderstand the research as an opportunity to receive medical care and other benefits, besides financial incentives.

8.6.3 ECs have to consider these issues proactively and mindfully. Specific measures should also be established to protect the welfare of related community members who have not participated.

8.7 Stakeholders in public health research

8.7.1 It is important for ethical conduct of research to engage with all stakeholders, such as researchers, public health providers/professionals, sponsors, government agencies, participants, ECs, institutions, NGOs, and others who are involved in public health research in any manner.

8.7.2 The involved stakeholders must make every effort to provide post-research public health interventions, post-research use of the findings, or sustainability of the public health action.

SOCIAL AND BEHAVIOURAL SCIENCES RESEARCH FOR HEALTH

9.0 The context of health research using methods from the social and behavioural sciences is often different from clinical, biomedical and public health research. Social and behavioural sciences include, but are not limited to, anthropology, sociology, psychology, philosophy, political science, economics, history, communications and education. Many of these research initiatives are relevant in the mid to long term for knowledge production, science and society. Such research efforts will also have scholarship value besides relevance for policy and programme development, providing a deeper understanding of explanatory factors. Moreover, social science research informs policy-making activities about the various facets that can be considered to ensure that social equity and intersectionality of populations are accounted for. Sometimes such studies are done as a precursor to the execution of major IR and programme evaluation projects. Similarly, community behavioural studies or formative research on cultural and geographical contexts 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 development and refinement of programmes and policies. To be judicious and ethical in understanding and assessing human behaviour, the details of symbolic communication of culture, which includes a group's skills, knowledge, attitudes, values and motives, have to first be understood as they influence a participant's response to research. Ethical relativism applies to moral diversity among different cultures and societies. In the Indian context, this is evident due to multi-religious, caste, class, endogamic, gender and geo-ethnic variations which are important characteristics of society that need to be considered in socio-behavioural research proposals. In view of the above, ECs should be aware of the challenges that may be encountered in the process of conducting such studies.

9.1 Some key features

9.1.1. Conventional social science research on health underscores the importance of bringing contemporary contexts to biomedical and health research.

9.1.2. It has now emerged as a cross-cutting area of enquiry relevant to almost every type of

medical, biomedical, clinical and health research such as clinical trials, epidemiological research, programme evaluations, implementation research, genetics, research on disaster and conflict contexts.

9.1.3. The principles of social science research ethics, with rights and responsibilities of the different stakeholders including participants, researchers, reviewers, publishers, etc., are similar to those for biomedical and public health research.

9.1.4. There are, however, specific ethical issues involved in social and behavioural sciences studies as given in Box 9.1.

Box 9.1 Ethical issues in social and behaviour sciences studies

1. Risks are non-measurable and dynamic in nature and therefore might be misconstrued as no/minimum risk research.
2. PI's obligations related to data sharing, incidental findings and post-research benefits to the study population would need to be reviewed by the EC on a case-by-case basis, and prior approval from the EC should be obtained for any exemptions.
3. What would constitute ancillary care during such research needs to be carefully considered on a case-by-case basis by the EC.
4. As part of the research protocols, socially, legally, medically and technically unacceptable practices and behaviour may be discovered, documented, or observed. While researchers are not required to interrupt such behaviours to determine the truth, they must document these in the research findings and appropriately disseminate the findings for the larger social good.
5. While maintaining the privacy and confidentiality of the respondent's identity, researchers have an obligation to report the extent or the patterns of behaviour, such as suicidal tendency or infanticide, to the concerned authorities.

9.1.5 Ethical challenges are more pronounced in collaborative research (national or international) due to possible inequity of expertise and knowledge access between partnering institutions and researchers, and funding relationships. See section 3.8.3 for further details.

9.1.6 Appropriate experts/expertise of EC members in the social and behavioural sciences domain are an essential aspect to address the above challenges.

9.2 Addressing the ethical challenges

9.2.1 Design and conduct of the study is important for a meaningful outcome in social and behavioural research. See Box 9.2 for further details.

Box 9.2 Consideration for appropriate design and conduct of study

1. Like any other research, the researchers must ensure that the proposed studies are scientifically sound, built on an adequate prior knowledge base, and are likely to generate valuable information.
2. In socially stratified groups and communities, researchers must spend time to become conversant with cultural norms and practices in order to develop strategies to build trust and negotiate power in ways that do not put research participants at risk.
3. In some types of research within communities, appropriate interpreters would be required. They need to be carefully selected, keeping in mind the hierarchies existing in the context. A local person from the same village in which the research is to be conducted should not be used as an interpreter. Instead, an interpreter should be chosen from some other nearby village so that her/his vulnerability and perceived threat from other participants can be mitigated. Institutions should develop or have SOPs for handling deteriorating situations, including a pre-tested communication plan.
4. The information about these norms/practices should be collected from reliable and multiple sources including multiple persons/groups, which should be mentioned in detail. This knowledge should be considered while deciding the group of participants and style of interview/investigation. However, the final decision about recruiting the participant should be based on the participant's and her/his family's opinion about norms/practices. These issues become particularly pertinent in cases of research that involve patriarchal or restrictive communities.
5. Field work challenges for research team – Research team members may sometimes be subjected to unforeseen situations which may involve trauma, humiliation and threats of violence. Training should be given to the research team to meet such challenges.

9.2.2 Ethical review

There are some unique features of social and behavioural sciences research which need to be considered by the EC on a case-by-case basis. See Box 9.3 for further details.

Box 9.3 Considerations by the EC for ethical review

1. Social and behavioural sciences research approaches are not always positivist and, therefore, articulation of a hypothesis may not be possible at the beginning of the research. Instruments/documents are developed during the course of the research; are reflective; and may keep changing as the research progresses. The EC must be kept informed about these changes and appropriate re-consent taken from participants.
2. The researcher must take prior permission from the EC with justifiable reasons for audio/video recording of participants' interviews.

9.2.3 Risk assessment

Participants of research in behavioural and social science face the potential of being exposed to significant and unique harm which may not be limited to physical harm. The researchers, research team and EC must recognize the cultural context and associated harm related to dignity as well as social and informational harm. This will avoid hurting or transgressing rights of the participants/community.

- **Harm to dignity** 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 of respect. This is also sometimes classified as another form of negligence. It may result in individuals feeling hurt, humiliated, excluded, dismissed or unfairly treated.
- **Psychological and emotional harm** may result from participating in a study where memories of traumatic experiences such as disasters (natural or otherwise), violence, conflict, abuse, assault and other such conditions need to be revisited by the participants. This may also affect and compound the vulnerabilities of participants already experiencing post-traumatic stress disorder (PTSD).
- **Social harm** is a non-medical adverse consequence of study participation, including difficulties in personal relationships and stigma or discrimination from family or community. Social harm can be related to personal relationships, travel, employment, education, health, housing, institutions (government/non-government) and others.
- **Informational risk** is the potential for harm from disclosure of information about an identified research participant to others. For much of social and behavioural research, informational risk is one of the primary risks.

9.2.4 Risk mitigation

Measures should be employed to minimize potential risks and their negative impact, such as short- and long-term adverse impacts on participants of studies on abortion, sexual abuse and other sensitive subjects. These measures should be incorporated into research methods, with special reference to hierarchies that exist in the social context where the research is undertaken.

9.2.5 Community engagement

While devising methods and interpreting observations, researchers 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 dissemination of its results.

9.2.6 Informed consent

Human participants in a proposed research study must be informed about the nature of the research project, and researchers/research teams must obtain their voluntary consent prior to their participation in the study. The different types of informed consent processes in social and behavioural sciences research are provided in Box 9.4.

Box 9.4 Informed consent in social and behavioural sciences research on health

1. **Community consent/gatekeeper consent/individual consent:** Individual informed consent has to be taken after obtaining the permission of gatekeepers, such as community heads or leaders/ culturally appropriate local authorities/healthcare providers/institutions or organizations responsible for community welfare or their appointed advocates. Consent procedures must respect local cultural customs, however, community traditions do not substitute for individual consent unless a waiver has been granted.
2. **Participant consent:** Researchers must develop culturally appropriate ways to communicate information necessary for adherence to the standard required in the informed consent process.
3. **Selective withholding of study information:** ECs may permit selective withholding of information/hypothesis of the study in the consent form for achieving overall 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 as described in section 5.11 is also applicable here.
4. **Participant refusal:** Often the power differences between participants and researchers in India make it difficult for people to explicitly refuse to participate. Researchers should be alert to cultural symbols of refusal, such as body language, silence, monosyllabic replies, or restlessness that communicate discomfort. They must not persist with the research under these circumstances.
5. **Relational autonomy:** Individuals are socially embedded wherein the person's identity is shaped by social determinants, such as caste, class, ethnicity and gender. Therefore, the participant may not be autonomous in decision making. Right to autonomy must be understood in relation to substantive equality of opportunity, sufficient social support and conditions for self-respect. Accordingly, concerns about social justice must be central to any adequate conception of individual autonomy. The EC may take into account this context with due diligence regarding the vulnerable status of prospective participants during review, for example, a woman asking her husband or family before giving consent.
6. **Waiver of 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 the requirement for individual informed consent if it is convinced that the research would not be feasible or practicable to carry out without a waiver, for example, research on harmful practices. See section 5.7 for further details.

9.2.7 Privacy and confidentiality

Privacy and confidentiality of research participants should be considered while selecting sites for data collection, choosing sensitive research areas, specific contexts and settings. In some circumstances participants become more vulnerable in research because of heightened psychological, social, physical or legal risks. Breach of confidentiality in these types of research may cause serious harm to vulnerable participants. It is important to protect study participants from potential future risks and harm by establishing culturally sensitive and context specific safeguards.

9.2.8 Duty to disclose sensitive information

As mentioned in Box 9.1, researcher(s) may come across certain facts detrimental to a participant's self or others, such as suicidal tendency/ideation, notifiable diseases. In such a situation, researchers have a responsibility to disclose this information to relevant persons/authorities to save life or prevent damage contemplated by the participant. Measures to be taken in such instances are given below:

- If there is a high likelihood of getting sensitive incidental findings during the research process, then the ways to handle these at individual, family and community levels should be discussed and mentioned in the protocol.
- Researchers and the EC should have a basic understanding of the legal provisions in the related area. Persons with the necessary domain knowledge and experience can be special invitees to EC meetings.

9.2.9 Studies Using Deception

Deception occurs when researchers provide false or incomplete information to participants for the purpose of misleading them so as to achieve the study objectives and for larger public good. Research employing any type of deception should undergo full committee review.

Research involving any kind of deception should:

- pose no more than minimal risk;
- not adversely affect the welfare and safety of the participants;
- be conducted only when the research cannot be carried out without deception;
- have an adequate plan for debriefing the participants after completion of the study, if appropriate;
- disseminate results of research to the participants, if applicable; and
- be carefully reviewed by the EC.

Box 9.5 Types of deception

1. **Active deception:** Selective withholding of the information/hypothesis of the study in the consent form along with giving incorrect information for achieving public good without influencing the outcome of the study, for example, psychology, neuro-behavioural, behaviour intervention study.
2. **Incomplete disclosure:** If research involves incomplete disclosure but no deception.
3. **Authorized deception:** Unlike in active deception, participants are informed that they would be deceived prior to the research but the nature of the deception will not be disclosed or research will not be described accurately or some procedures will be deceptive. Such revelation provides the participants an opportunity to decide whether or not to participate on these terms.

9.2.10 Safety of participants

Support systems, such as access to counselling centres, rehabilitation centres, police protection, etc., should be in place when research is on a sensitive issue, such as mental health, gender based violence and social exclusion and discrimination.

9.2.11 Safety of research teams in the field

The safety of the research team is the responsibility of the institution, sponsors and local authorities, particularly in research on sensitive topics or in sensitive research settings since there would be a possibility of the researcher or research team being subjected to disturbing instances while conducting the research. Besides providing safety, including insurance coverage, and giving training to the researcher or research team to meet such challenges, setting up community advisory boards could be helpful to ease the situation.

9.2.12 Qualitative research

The knowledge gathered through qualitative research is interpretative based on the observation and its analysis by the researcher or research team which is socially constructed at individual and socio-cultural levels.

- Informed consent is very often dynamic in nature and negotiable. When written consent may not be possible, other means could be used and documented.
- The EC may look at issues that pertain to the design involving researcher–participant relationships, informed consent process and conduct of the research.
- Preliminary activity of observation for preparing notes, before actually initiating research based on the observation, need not be submitted for EC's review.

However, any ethical issues arising even during that preliminary phase, before actual collection of data, should be included in the research proposal for review by the EC.

- On some occasions/in some observational research the EC may approve waiver of consent, provided mechanisms for maintaining privacy and confidentiality are justified.
- In collaborative research, it is desirable to establish a rapport with the community to be engaged in research through the gatekeepers or community advisory boards.
- Sharing raw data and notes with repositories, researchers, peer community, institutions, and funders is increasingly becoming a requirement for transparency in research.
- Sharing raw data including audio-visual material should protect confidentiality of the individual and research setting by sufficiently processing data to mask identifiers before sharing.
- Researchers have a duty of disclosure to share research findings in aggregated form and relevant information in a user-friendly format with community leaders, gatekeepers and communities without disclosing individual identities. They must also share these findings and relevant information with the participants.

HUMAN GENETICS TESTING AND RESEARCH

10.0 In no other area of biomedical and health 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 its manipulation, it has also led to a great deal of concern about scientists' ability to handle such information. There is also a very narrow gap between routine genetic testing and research raising several ethical, legal and social issues (ELSI), which warrant continuous and prompt monitoring and judicious response to the emerging ethical issues.

10.1 General issues

10.1.1 The harm/risks associated with genetic testing may be psychosocial rather than physical in the form of anxiety, depression or disrupted family relationships.

10.1.2 Potential benefits and risks should be discussed thoroughly with prospective participants. Appropriate communication skills are required for genetic counselling which is akin to therapy.

10.1.3 There is a likelihood of social stigmatization and discrimination in schooling, employment, health and general insurance, which requires greater care in recruiting participants in research.

10.1.4 Maintaining confidentiality is very important in genetic testing as results have social implications.

10.1.5 There is often an overlap between genetic research and services for the physician as well as the patient and therefore, adequate safeguards against therapeutic misconception are needed.

10.1.6 Genetic manipulations may have known or unknown consequences for the future and therefore, greater caution against potential dangers is necessary.

10.1.7 Emerging genetic/genomic technologies cause emergence of newer ethical concerns and issues. Therefore, there is a need for professionals to keep abreast of such advancements

and understand their implications.

10.1.8 The EC reviewing genetic research should have necessary expertise to understand the ethical implications and provide safeguards for research participants.

10.1.9 There is a need to have a team of clinicians, geneticists, genetic counsellors and laboratory personnel to work together.

10.1.10 Genetic testing and research often require dealing with persons who are unable to protect their rights and safety and may be vulnerable, such as children, individuals with mental illness, cognitively impaired individuals, people with rare diseases and others. See section 6 for further details.

10.2 Genetic Counselling

10.2.1 Pre- and post-test non-directive counselling should be given by 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/foetus. While disclosing the result, appropriate options should be provided to the family to enable them to come to a decision.

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

10.3 Privacy and confidentiality

The researcher should explain the specific nature of the confidentiality of data generated through genetic testing/research to the patient/participant. Disclosure may cause psychosocial harm and needs careful handling.

10.3.1 Participants should be told of the limits of the researcher's ability to safeguard confidentiality in certain circumstances and the anticipated consequences of breach of confidentiality.

10.3.2 The researcher can delink data to maintain confidentiality and safeguard the information for basic research. However, If the result of the research is of benefit to the health of the participant then, with approval of the EC, data could be re-linked for communication of the result. See Table 11.1 for further details.

10.3.3 Genetic research requires collection of family history and details about other members of the family, thus involving them as secondary participants. If identifiable information is being collected about the secondary participants, their informed consent will be required.

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

10.3.5 The researcher cannot reveal the genetic information to family members without the participant's permission. If family members are recruited/tested then their information should be kept confidential from each other by the physician/researcher.

10.3.6 If disclosure is absolutely warranted to provide treatment or counselling, the physician must first obtain informed consent from the family member concerned. If that family member does not consent, then the physician should balance the risks of non-disclosure against breach of confidentiality and take an appropriate decision.

10.3.7 Storage of samples collected as part of routine care with potential for future genetic research should be done with appropriate consent from individuals.

10.3.8 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.

10.3.9 Handling IPRs related to gene patenting and development of newer technologies for commercial gains should follow the applicable national policy/regulations.

10.3.10 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- and post-test counselling need to be revisited with an entirely new perspective.

10.4 Informed consent

Stringent norms and caution should be followed in the consent process when done for research purposes.

10.4.1 For routine genetic diagnostic testing, written consent may or may not be needed as per institutional policies; however, for any research it is required.

10.4.2 Informed written consent is essential for procedures such as pre-symptomatic testing,next generation sequencing (NGS), prenatal testing, genomic studies, carrier status etc.

10.4.3 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 or for research.

10.4.4 If the research or testing involves a child, appropriate age-specific assent (verbal/

oral/written) should be obtained along with parental consent. See section 6 for further details.

10.4.5 In addition to the general contents specified in section 5, the consent form for genetic testing for research may have explanations/details on the following elements:

- the nature and complexity of information that would be generated;
- the nature and consequences of return of results and choice offered to the participant whether to receive that information or not and incidental findings, if any;
- direct/indirect benefits and their implications including if there are no direct benefits to the participants;
- how the data/samples will be stored, for how long, and procedures involved in anonymisation, sharing , etc. See section 11 for further details;
- choice to opt out of testing/withdraw from research at any time;
- whether the affected individual or the proband would like to share her/his genetic information with family members who may benefit from it; and
- issues related to ownership rights, IPR concerns, commercialization aspects, benefit sharing,. See section 11 for further details.

10.4.6 Group consent/community consent

- In case of population or community based studies, it may be noted that the genetic research may 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.
- Even if group consent is taken, it will not be a replacement for individual consent as individual consent is important. See section 5 for further details.
- Researchers should be aware of potential stigmatization of the entire group and must explain ways to avoid the same during the conduct of research and publication of research results.

10.5 Culturally sensitive issues

10.5.1 Transmission of a genetic abnormality from parents, especially the mother to the foetus, could be a very sensitive cultural issue. Such possibility arises when during routine testing or prenatal diagnosis it is revealed that the wife is a carrier of X-linked or recessive disease affecting the foetus or making it a carrier of fatal or late onset disease conditions, such as haemophilia, huntington's disease, non-syndromic deafness

and mitochondrial conditions where a female foetus could transmit the abnormality to the next progeny, etc. If information is revealed to the husband or other members of the family, it may cause marital discord despite the fact that the husband himself is a carrier of the autosomal recessive disorder. Appropriate counselling should be part of the testing process.

10.5.2 Consanguineous marriages are common in some communities. If there are inherited diseases detected in the family, it is the responsibility of the health professionals/ researchers to inform participants regarding the possible implications that may arise due to consanguinity. Appropriate pedigrees need to be prepared and stored, as these can reveal a lot regarding disease inheritance in affected families.

10.6 Storage of samples for future genetic research

10.6.1 Rapid advances in science and technology have necessitated the storage of biological materials for future genetic research.

10.6.2 The samples from patients with rare genetic conditions, ethnic groups/tribes/ populations on the verge of extinction, endogamous groups and others have great cultural and geographical value and need to be preserved for future research. See section 11 for further details.

10.7 Results of genetic testing

10.7.1 Results of the tests should be informed to the participants. Return of the results depends on the research findings. If results are anticipated to be actionable, leading to potential benefits of improving health outcomes through correction of diet as therapy or prevention (such as phenylketonuria) 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 must be specified in the ICD. For this, participants' contact details should be available.

10.7.2 The researcher should work with the local EC to decide on the validity of the research finding and 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 were informed of this in the ICD.

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

10.8 Publication aspects

10.8.1 Publication of pictures, pedigrees or other identifying information about individuals, families or secondary participant(s) should be done with fresh or re-consent.

10.8.2 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 the informed consent form and fresh consent must be obtained, if not taken earlier.

10.9 Commercialization and COI

10.9.1 Direct to consumer testing (DTC) in laboratories offering a battery of genetic tests is rapidly growing. While this ensures a 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 in consultation with treating physician/ clinical geneticist is ensured before arriving at a diagnosis.

10.9.2 When research is conducted by commercial companies, steps should be taken to protect researchers and participants from possible coercion or inducement.

10.9.3 Academic or research institutions require a review to probe possible COI between scientific responsibilities of researchers and business interests (for example ownership or part-ownership of the researcher in the company developing a new product).

10.9.4 An EC should determine if the COI could damage the scientific integrity of a proposal or cause harm to research participants and should advise accordingly.

10.9.5 Institutions need self-regulatory processes to monitor, prevent and resolve such COI and assess the need of informing prospective participants.

10.10 Role of the team in genetic testing and research

10.10.1 Adequate awareness should be created by professional societies and universities/ institutions regarding genetic diseases, their prevention, screening and prenatal diagnosis amongst obstetrician, geneticists, paediatricians, neonatologists, radiologists, laboratory professionals and others.

10.10.2 Laboratory personnel, attending physician(s) and counsellors should possess formal qualifications/sufficient experience in genetics.

10.10.3 The concerned specialists dealing with genetic disorders should ideally undergo training in genetic counselling and be able to devote time to handle sensitive issues appropriately.

10.11 Quality standards of the laboratory

10.11.1 There is a paucity of quality assurance programmes in the country and therefore valid and reliable testing is a constant concern for both clinical practice and research. Any

misinterpretation of genetic results or misdiagnosis may lead to psychological harm, and unnecessary or inappropriate intervention.

10.11.2 It is important to set standards for laboratories to ensure that test results are reliable, manpower is competent and the care provider is updated on developments in genetics.

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

10.12 Misuse of genetic technology

Genetic information has potential for misuse as well as long-term implications.

10.12.1 Prenatal sex selection is not allowed and to prevent misuse of genetic tests, particularly pre-selection of sex, GOI has enacted the Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition of Sex Selection) Act, 1994, amended in 2003.[37] 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.

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

10.12.3 Research involving genetic manipulations must be carefully reviewed and protections established for participants.

10.13 Genetic diagnosis/testing and screening

10.13.1 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 section 10.3.

10.13.2 Predictive genetic testing: The results of genetic tests in diseases that are multifactorial in origin and have a polygenic basis involving multiple genes or gene–environment interaction or those that are late onset, must be communicated carefully to prevent unnecessary worry or fear in the minds of individuals.

10.13.3 Genetic screening: Genetic screening implies searching a population for those individuals who have, or are susceptible to a serious genetic disease; or who, though not at risk themselves, are carriers and thus at risk for having children with a particular

genetic disease.

- It is essential for screening to be purposive. Besides validation of screening tests, it should also be ensured that a suitable intervention and counselling are available.
- 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.
- 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.
- 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, the 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.
- 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 rationalize the use of more accurate confirmatory tests.

10.13.4 Population screening: Genetic disorders can be population specific (for example, ß-thalassemia and sickle cell disease in some population groups in India).

- Population screening should not be undertaken without prior education of the population to be screened and counselling should be integrated with the programme.
- Screening tests should be robust with acceptable sensitivity and specificity.
- Wherever applicable, community permission/group consent should be taken in addition to individual informed consent.
- Researchers may conduct coded or reversible anonymized testing on general population in order to establish prevalence of genetic traits/diseases. See Table 11.1 for further details. 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 may be broken with

the approval of the EC.

10.13.5 Prenatal screening: Prenatal screening is aimed to screen mothers and foetuses that 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.

- Biochemical and ultrasound screening: 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 detection rates, false positive and negative results with participants.
- Invasive testing for prenatal diagnosis: Preliminary genetic counselling of women for invasive prenatal diagnosis should include the following:
  - ❍ risk of the 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; and
  - ❍ limitation of a test due to laboratory error.
- 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 NIPS methods by using cell-free foetal (CFF) DNA sequences isolated from a maternal blood sample. This test prevents the risk of an invasive procedure which would also be beneficial for high risk mothers. However, there are several limitations of these techniques which should be clearly explained.

Utmost caution should be taken while reporting the foetal status after prenatal testing. HLA testing on embryos and foetuses should not be done.

10.13.6 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, such as aneuploides, and specific disorders with family history or proven carrier status in parent(s) to implant unaffected embryos. This obviates the need for invasive testing for associated risks and also termination of the affected foetus, which is traumatic for the family.

- Advanced techniques like chromosomal micro array (CMA) are being used for

PGS and NGS for screening which might theoretically raise ethical issues regarding eugenics and designer babies based on selection of embryos.

- This also raises ethical concerns regarding selection of sex and therefore adequate safeguards should be in place to prevent misuse.

10.13.7 Newborn screening (NBS): Newborn screening is a robust measure for secondary prevention of genetic diseases through early diagnosis with timely intervention and should ideally be in a programme mode and providing not only diagnosis, but also management and treatment alongwith counseling.

- Screening of newborns is recommended for treatable genetic diseases, the serious effects of which could be prevented by a suitable intervention, such as a special diet or drug. Examples of such conditions include hypothyroidism, phenylketonuria and many other inborn errors of metabolism.
- Such screening should not be generally done when there are no existing therapeutic modalities available (such as special diets) or treatment may not be affordable (such as lysosomal storage disorders). There may also be no known intervention for management.
- The family should have a choice to decide if they would like to be part of newborn screening program with appropriate consent explaining the requirements and implications of the screening with provision to "optout".
- Community education and advocacy regarding NBS should precede the initiation of the programme.
- Availability of facilities for confirmatory diagnosis and experts for management of the disorders have to be in place before initiating the programme.
- Use of advanced technologies like chromosomal micro array (CMA) and WES for NBS will generate many new dimensions for debate in this area.

10.13.8 Screening of children

- Children should not be screened for carrier status or disease merely at the request of their parents.
- 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 results of the test is likely to be of direct therapeutic benefit to them.
- Screening for late onset diseases should not be done in children unless there is any suitable intervention available for treatment during the childhood stage.

10.13.9 Screening for carrier status

- 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 benefits and risks of screening. Stigmatization for carrier status is common and therefore, the information should be kept confidential.
- 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.

10.14 Gene therapy

All gene therapies are considered as research and all protections for human research participants should be in place.

10.14.1 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.

10.14.2 Prior to obtaining approval for initiating a gene therapy trial, an approval from the local EC and DBT has to be obtained for the gene construct.

10.14.3 If the trial is for a product for commercial use or for marketing purposes, approval needs to be taken from CDSCO.

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

10.14.5 Informed consent must be taken, especially regarding uncertainties about outcome.

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

10.14.7 Germ line therapy is prohibited under the present state of knowledge.

10.14.8 Eugenic genetic engineering for changing/selecting/altering genetic characteristics and creating 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. It would be unethical to use genetic engineering for improvement of intelligence, memory, formation of body organs, fertility, physical, mental and emotional characteristics, etc. even if specific gene/genes are identified in future.

10.15 Use of newer technologies

New technologies like CMA, WES and 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 genomes. Each individual's genome is a unique and definite identity, which in spite of anonymization 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 digitized medical records of such sophisticated data, additional efforts should be made to maintain confidentiality.

10.15.1 Chromosomal micro array –Interpretation of CMA results should be done with caution since on many occasions the identified copy number variation (CNV) may be a variation of unknown significance (VOUS) which may be reported or unreported and may not explain the phenotype.

10.15.2 Whole exome sequencing and whole genome sequencing

These high throughput 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 raised a new challenge for counsellors as well as patients.

- 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.
- Families/individuals opting for the test should be counselled regarding grey areas in these upcoming technologies prior to testing. They should be aware that WES/WGS may not give conclusive results.

10.15.3 Gene editing technology – Clustered, regularly interspaced, short palindromic repeat (CRISPR)

This is a powerful technology which efficiently edits DNA with immense value for accurate and precise genome editing to alter human genes to cure and eliminate certain genetic based diseases. Experiments done so far have shown that the technique can be used to rapidly, easily and efficiently modify genes in a wide variety of cell types and in organisms. Somatic cell genome editing has an immediate clinical translational potential and can be used in a variety of areas such as drug development, gene surgery,

understanding genetic variation, and it also has implications for biomaterial, fuels, food etc. 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 associated risks, which blur the excitement about its usefulness. Similar concerns are there for the use of other genome editing technologies such as zinc finger nucleases (ZFN) and transcription activator-like effector nuclease (TALEN). Today therapeutic applications are possible for a wide range of indications, in preclinical models or in clinical settings through clinical trials in humans. There are some considerations related to the use of this technology.

- The risks are irreversible changes in germline, risks of inaccurate genome editing, implications for future generations, interactions with other genetic variations and environment, and the fear that once the genetic change is introduced it may be permanent which would have long-term effects.
- Despite the promise of the technique, there is a possibility of encountering error in genetic engineering which has unforeseen implications. 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 or alter germline or DNA of future generations of humans.
- It could be used to change harmless genes, as for eye colour, leading to designer possibilities. There are also possibilities of creating interspecies organogenesis or chimerism. There are possibilities of making gene correction in zygotes using CRISPR-Cas9 which has ethical implications.
- The application of this technology in plants and animals can lead to possible lateral transfer and emergence of irreversible damage to biodiversity and environment which can be a risk to not only human and animal life but also the environment due to its long-term consequences. It could also possibly be used for bioterrorism.
- CRISPR-Cas9 needs to be judged for the good of future generations. This needs time and thus, at present, there is a ban on germline manipulations.
- There is a need to consider the possibility of commercialization, patenting or rightful access, therefore, a vigorous benefit-risk evaluation is required to address the expectations and concerns of the public. There is need for an initial cautious approach before this technology can be widely used for various applications.
- An open and transparent discussion, advocacy and public engagement should be

encouraged with various stakeholders to understand, build trust and be involved in decision making. Capacity building is required not only of researchers but also regulators and policy makers to carefully consider social and ethical aspects and put systems in place to ensure safety.

- At the moment, there is a need for initiatives to increase knowledge base, infrastructure, funding, guidelines, inter agency communications and interactions, engagement with public and other stakeholders, and establish science communication. In addition, attempts should be made to foster research to assess the feasibility, efficacy and safety of CRISPR technology.

10.15.4 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. A GWAS typically focuses on associations between single-nucleotide polymorphisms (SNPs) and traits like major diseases, particularly multifactorial disorders.

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

10.16 Research on human embryos

Embryonic state is the period between 15 days and 8 weeks post-conception of a pregnancy and in the absence of more precise information (such as menstrual cycle length), conception is presumed to have taken place 2 weeks after the beginning of the woman's last menstrual period. The distinction of the 15-day stage as the beginning of the embryonic stage is because of the formation of neural crest (future nervous system symbolizing moral being or personhood) by then. At 8 weeks, the rudiments of nearly all the main structures are developed giving a general appearance of a mammal-to-be with four limbs and a head. Research on human embryos raises a number of ethical issues.

The concerns are more social, including questions about the rights of unborn babies and the roles of humans in making permanent genetic changes. If research is planned on embryos, consent of both parents should be taken.

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10.16.2 If research is planned on embryos, consent of both parents should be taken.

10.17 Foetal autopsy

10.17.2 Foetal autopsy should be done after informed consent, preferably from both parents/ LARs.

10.17.3 Relevant samples may be stored for possible future use following the guidelines of biological materials, biobanking and datasets given in section 11.

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

BIOLOGICAL MATERIALS, BIOBANKING AND DATASETS

11.0 Biological materials or biospecimens or samples include biological fluids, such as blood, dried blood spots, body fluids, urine, tissues, organs, cord blood, oocytes, sperm, semen or embryos. 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 for research purposes. The bio resources would therefore be protocol-based prospective collection of biospecimens, left-over samples after clinical investigations or research proposals, biopsy materials, surgical or autopsy specimens/tissues, embryos or foetuses, cell lines, or 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 researchers.

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 health-care institutions which may have huge potential for subsequent research. The data may be from small numbers to large numbers or whole population. Examples of biobanks and datasets are Iceland's deCODE biobank, National Institute of Mental Health and Neurosciences (NIMHANS) Brain Bank, Tumour Tissue Bank at Tata Memorial Hospital (TMH), Census data, NFHS data, Cancer Registry of India, CTRI, etc.

11.1 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 with inbuilt policies for transparency. The space occupied by organized collection of these materials and data is termed biorepository. Research on such biospecimens or samples 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 organizations, judiciary custody, pharmaceutical companies and may extend into large warehouse like facilities at a single site or a chain of facilities with central coordination which provide medical, genetic and life-style related data. Thus biobank may be very large with public or private funding, for commercial or non commercial use and on other hand may be small limited to a researcher who stores samples in the laboratory or at institutional level where common facility is available for storing samples. Biobanks can also store non-human materials, such as plant, animal, microbes and parasites, but for the purpose of these guidelines this section will only pertain to human biomaterials and/or related data.

There is a need to comply with all the safety requirements and sets of universal standards, testing of biomaterials and biocompatibility as per relevant regulatory standards. The testing of such standards could be done in a NABL certified laboratory.

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 the 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, clarity on custodianship, approval of the EC and the repository governance committee and post-research benefit sharing, wherever applicable.

11.1.1 Samples can be classified in a variety of manner. Samples classified on the basis of availability of attached identifying information are provided in Table 11.1.

11.1.2 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. Some key points for maintaining privacy and confidentiality related to donors are listed in Box 11.1.

11.2 Storage of biospecimens and data with personal identifiers

11.2.1 Informed consent, confidentiality, privacy and re-consent are largely influenced by the degree of identifiability, whether the biospecimens and data are anonymized or not. As a general principle, research must be conducted on least identifiable data.

Table 11.1 Types of samples

Anonymous or unidentified	No identifiers are present from the start or if collected, are not maintained. Such samples are received by biobanks without any identifiers and supplied to researchers.	
Anonymized	This involves systematic de-identification, reversible or irreversible: link of samples/data to personal identity is reversibly or irreversibly cut.	
	Coded or reversibly anonymized: There is an indirect link of sample/data to the participant's identity with restricted access. This link could be re-linked if required; therefore, it may also be termed reversible anonymization.	**Irreversibly anonymized:** Link to the participant's identity is removed and cannot be re-linked.
Identifiable	A direct link of sample/data to the participant's identity exists.	

Box 11.1 Confidentiality and privacy of donors related to biological materials and/or data

Some key aspects related to maintaining confidentiality and privacy of donors of biological materials and/or data:

1. The procedure of anonymization 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 precautions should be sought when the research pertains to stigmatizing diseases.
4. When data pertains to epidemiological and public health practice or research, it may be dealt with in the manner described in section 8.

11.2.2 Under certain circumstances, some degree of identifiability may have to be retained for reasons related to the research. For example, anonymized 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 a 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.

11.2.3 Permissibility of a certain research design, acceptability of benefits versus risks, and adequacy of the informed consent, will thus have to be assessed by the EC on a case-by-case basis, taking into account specific contextual and potential vulnerability factors of the participants and the sensitive nature of the proposed research.

11.3 Ethical issues related to donors

11.3.1 Informed consent for biobanking poses specific ethical issues as the aims of scientific study based on which biospecimens are collected and stored in a 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.

11.3.2 The issues involve multiple stages at which consent needs to be administered – storage, analysis of the biospecimens/samples, use of data linked to the sample, incidental findings, return of results to the participant, sharing of the sample/data with other researchers/national or international institutions, multicentre and multinational collaborations and potential commercialization. These raise issues of access and benefit sharing.

Box 11. 2 Example of multiple options in a multi-layered consent

Please pick one of the choices below:

a. I agree to allow my sample/biospecimen to be stored for future use for any biomedical research.

b. I agree to allow my sample/biospecimen to be stored for future use for specific disease such as cancer research.

c. I agree to allow my sample/biospecimen to be stored for future use for other pre-specified health problems, such as diabetes, heart disease.

d. I do not wish to allow my sample/biospecimen to be used in future research which is beyond the scope I have already consented for, unless researchers re-contact me to seek my permission.

e. I do not wish to allow my sample/biospecimen to be used in future research. I do not want researchers to contact me about future studies.

f. I wish to be informed/not to be informed about the results of my investigation.

Examples of different types of consent processes and their implications are given in Box 11.3.

Box 11. 3 Types of consent processes and their implications

1. **Blanket or broad consent:** This 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 revert 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 from which participants can choose. It includes an opt-in option for future use specifying general permission, or use only related to some aspects of research, sharing of biospecimens/data benefit sharing, etc. It also takes into consideration return of results for which options are also provided for consent. See section 11.4.4 for further details.
3. **Specific consent:** Consent is obtained for a specific research purpose. Participants are re-contacted for every new use of their stored samples/data if the scope of research is outside that for which they had originally given consent.
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.
5. **Dynamic consent:** This consent is different from one of static, paper-based consent and involves an ongoing engagement and interactions over time with participants to re-contact in response to changing circumstances using technology based platforms. It incorporates a flexible, configurable, technology-based design accommodating both participant and researcher needs. Modern longitudinal biobanks equipped with advanced technology strive for this type of consent.
6. **Withdrawal of consent or destruction of sample:** The donor has the right to ask for destruction of her/his collected sample(s) and discontinuation/withdrawal from participation in the research. In longitudinal studies, a 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 consent:** While using anonymized (de-identified) samples/data, researchers should seek the approval of the EC of the institution or the repository for waiver of consent from 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).

(Contd.)

- **Paediatric 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 paediatric biobanks or biobanks with paediatric 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. This may lead to bias or it could evoke emotional distress about past research. On the other hand, re-consent may give the participant the power to agree. A biobank should decide the policy it would like to adopt for re-contact.

11.4 Ethical issues related to research

Biobanks can use the stored material/data for doing research themselves or they can outsource or supply such material/data to other researchers or institutions on a non-profit basis.

11.4.1 Ownership of the biological samples and data: The participant owns the biological sample and data collected from her/him and therefore, could withdraw both the biological material donated to the biobank and the related data unless the latter is required for outcome measurement and is so mentioned in the initial informed consent document. Complete anonymization would practically make the original donor lose the right of ownership. Biobanks/institutes are the custodians or trustees of the samples and data through their ECs as their present and future use would be done under supervision of the respective ECs. Researchers have no claim for either ownership or custodianship.

11.4.2 Transfer of biospecimens: An MTA should be executed if the biospecimens are likely to be shipped from the host institution to collaborating institutions within the country or abroad. The 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. See section 3.8.3 for further details. Directorate General of Foreign Trade (DGFT) has issued a notification related to transfer of human biological material for commercial purposes.[38]

11.4.3 Secondary or extended uses of stored samples/re-consent: The EC will examine circumstances under which the biological material or the data were originally collected and informed consent obtained. The decision about anonymization/informed consent waiver or re-consent will be made on a case-by-case basis as provided in Box 11.4

Box 11.4 Use of stored samples

The following must be considered when stored samples are to be used:

1. whether the proposed use is aligned with the original consent given for the earlier research and scrutinize the validity of the objectives of the new research;
2. whether provisions for ensuring anonymity of the samples for secondary use are stated;
3. whether the permission of LAR is obtained for post-mortem uses of samples;
4. whether the consent form mentions retention and various possible future uses of tissues in the form of a tiered consent; and
5. Whether provisions have been made for allowance of waiver of consent if the donor is not traceable or the sample/data is anonymized or it is impractical to conduct the research.

11.4.4 Return of research results to individual/groups

There are several possibilities which may be appropriate for a particular research and, according to the suitability, could be included in the participant information sheet/ informed consent document for biobanking.

- Results of the study should be communicated back to the providers of samples/ data.
- If the findings are in an aggregate form, the participant will not be able to receive any feedback on individual data.
- Wherever applicable, research findings in aggregate form (which does not reveal individual results) must be discussed with the community, especially when research involves populations who are more vulnerable, such as tribal populations, ethnic groups and people living with certain diseases.
- In the absence of an appropriate mechanism to deal with informational harm that can occur if participants are provided feedback when they are not prepared to face it or if it is not actionable or when such information is unrelated, a lot of distress could be caused to participants concerned.
- At the time of sample collection, it may be a good approach to offer donors the choice of receiving the results of the research whether they are beneficial or not. 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 which could become a shared benefit for the community. The aforementioned options may be incorporated in a tiered consent.

11.4.5 Benefit sharing

Biological materials and/or data have potential commercial value but the participants' contribution and their share in this benefit is very often not known to them. The informed consent document should emphasize this aspect with necessary clauses for clarity about benefit sharing. See Box 11.5 for further details.

Box 11.5 Considerations for benefit sharing

1. 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.
3. To the maximum extent possible, benefits should be indirect or in kind.

11.4.6 Role of the EC

ECs play a key role in oversight and use of the bio- and data repositories for research, scientific and public health programmes. Research proposals, which require biorepository services including material transfer and available data sets, should be reviewed by the EC, either an institutional one or that of the biorepository.

11.5 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 (for example, highly decomposed bodies, disaster situations). In academic institutions, there is a demand for organs and tissues for education, training and research purposes.

11.5.1 Informed consent: If there is no written consent by the deceased person permitting use of organs or tissues, the family can be approached for consent for use of left-over organs or tissues.

11.5.2 No consent would be required if sample or data is anonymized.

11.5.3 If the deceased has no claimant then forensic officials will be authorized to give permission for use of material/data from its sources and be responsible for use of unclaimed cadavers.

11.5.4 The quantity of tissue taken should ideally be minimal, 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.

11.5.5 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 method for disposal of the remains.

11.5.6 Genetic research or revelation of any other stigmatizing factors like HIV, etc. in the deceased may have implications for family members. In such instances, all ethical requirements as in the case of live participants should be followed.

11.5.7 The role of the EC is to review and approve the type of consent – broad, tiered with or without option to opt-out or specific and to assess from whom it would be taken – the family, closest relative or friend – or whether sample anonymization should be done.

11.6 Governance of biobank/biorepository

Institutions where data are collected and archived must have an established governance structure with the following requirements for regulation.

11.6.1 Each 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 the EC.

11.6.2 A technical authorization committee, indigenous to the biorepository, should govern collection of specimens, disbursement of biospecimens and data to researchers. The same committee should also oversee regulatory aspects like execution of MTA or data transfer agreement (DTA) for transfer of biospecimens and/or data to other institutions.

11.6.3 Stand-alone huge repositories should have separate technical authorization committees and ECs to undertake the above-mentioned tasks.

11.6.4 The biobank should have well-structured SOPs and clear guidelines for collection, coding, anonymization, storage, access, retrieval and sharing of biospecimens and data.

11.6.5 The technical authorization committee/governance committee could comprise members such as clinicians, geneticists, lawyers, basic scientists, sociologists, epidemiologists, statisticians and ethicists.

11.7 Special issues related to datasets

11.7.1 With increasing ease of establishing and maintaining large repositories the primary objective of data collection and storage in some of these databases may not be research but with advances in information technology (IT) and decreasing costs, they offer a huge potential for subsequent research as well as commercialization. Whenever such repositories are used for purposes of research or for subsequent commercialization, it must follow the expected requirements of any other health-related research with due

diligence, including review by an EC.

11.7.2 There is also a proliferation of data mining and other data science tools that can be employed on existing databases for research purposes to reduce costs and health related processes. EC approval is required to establish legitimacy of the purpose for data mining, access control and about the usefulness of information for particular groups (such as rare disease group). Data privacy, data accuracy, data security, and possibility of legal liability should be ensured when the data is outsourced or sold. Auditing could be done to detect misuse.

11.7.3 Health data is increasingly being collected outside of traditional healthcare settings. Data is shared with third parties not only for research, but also for commercial gain. Big data in health research raise a wide spectrum of ethical issues, ranging from risks to individual rights, such as privacy and concerns about autonomy to individuals. There are unique aspects, such as its data sources, scale, and open access provisions. Ethical issues related to data security, sharing, rights, benefit sharing and others surrounding big data need to be closely examined.

11.7.4 Databases maintained in electronic/digital formats, linked by internet or other networks, 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 as given in Box 11.6.

Box 11.6 Measures to ensure privacy and confidentiality of individuals

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

11.8 Contingency plan

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

RESEARCH DURING HUMANITARIAN EMERGENCIES AND DISASTERS

12.0 A humanitarian emergency or disaster is an event or series of events that represents a critical threat to the health, safety, security or well-being of a community or other large group of people, usually covering a wide land area. For the purpose of these guidelines, humanitarian emergencies and disasters include both man-made and natural ones, some of which occur at periodic frequency. Emergencies, such as an earthquake, flood, mass migration, conflict and outbreak of disease, leading to substantial material damage affecting persons, communities, society and state(s), create an imbalance between capacity and resources to meet the needs of the survivors or the people whose lives are threatened during that 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. Local, national or international responses and preparedness, without interfering with measures to control the crisis or ecology, are the key to reducing morbidity and mortality in such events.

Humanitarian emergencies raise complex issues. The health system, communications, research infrastructure, and research governance frameworks may be adversely affected during such situations, which create challenges for the feasibility and oversight of conduct of research. While there may 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. A unique challenge would be the response to rapidly evolving health needs or priorities of those impacted by the humanitarian emergency when the research cannot be conducted outside the humanitarian emergency situation. Designing or adopting innovative relevant research, based on rapidly evolving scientific and ethical uncertainties, which is expected to yield scientifically valid results is another significant challenge. The other challenges are inadequate time to design a study and lack of infrastructure facilities and resources to

conduct it within a disrupted physical-socio-cultural environment. The role of ECs in such circumstances is very important in reviewing protocols prepared for such emergency situation(s). Responsiveness to the situation, supervision, training and prevention of heightened risk of violence are other factors to be considered and planned.

12.1 Pre-emptive research preparation for future humanitarian emergency

A 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.

12.1.1 Researchers and sponsors could make arrangements about research questions to be addressed in the design, collection of samples and data, and sharing mechanisms much in advance of a future humanitarian emergency.

12.1.2 Researchers could screen available and/or relevant draft research protocols to expedite the review process.

12.1.3 The EC could review proposals prior to the occurrence of the emergency and determine who could be an acceptable LAR in the absence of intended LARs (authorized/acceptable) in such situations.

12.2 Informed consent requirements

12.2.1 Obtaining valid informed consent in humanitarian emergencies is a challenge as the decisional capacity of the participants would be so low that they may not be able to differentiate between reliefs offered and research components. This should be very clearly distinguished during the informed consent process.

12.2.2 Additional safeguards are required for participants due to their vulnerability, for example, counselling, psychological help, medical advice and process of stakeholder consultation.

12.2.3 The potential research participants might be under duress and traumatized. Researchers should be sensitive to this situation and are obligated to ensure that the informed consent process is conducted in a respectful manner.

12.2.4 Researchers should strive to identify and address barriers to voluntary informed consent and not resort to inducements for research participation.

12.2.5 The different roles of researchers, caregivers and volunteer workers must always be clarified, and potential COI declared.

12.2.6 If research involves incompetent individuals (such as minors), then the 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 an individual who is not part of the research team who should be designated by the institution/agency conducting research.

12.2.7 For seeking waiver of consent, the researchers should give the rationale justifying the waiver. EC should approve such a waiver after careful discussion on the issue. See section 5 for further details.

12.2.8 When consent of the participant/LAR/assent is not possible due to the situation, informed consent must be administered to the participant/LAR at a later stage, when the situation allows. However, this should be done only with the prior approval of the EC.

12.3 Risk-minimization and equitable distribution of benefits and risks

12.3.1 Considerations for fair selection of participants are described in Box 12.1.

Box 12.1 Considerations for fair selection of participants

1. The overall effort is not to over-sample, particularly vulnerable segments of the 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 research participants are not exploited during the research project by imposing additional burdens on them.
4. It is desirable to set up a DSMB to frequently review the data to check on risk quantum.

12.3.2 Efforts should be made to see that the positive results of a specific research are applicable to future similar disaster situations.

12.3.3 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.

12.4 Privacy and confidentiality

12.4.1 Disruption of governance, infrastructure and communication networks and inflow of visitors during emergencies can lead to a breach of privacy and confidentiality. In some situations, there can be stigmatization and discrimination which should be minimized at all stages of research.

12.4.2 Special efforts (culturally appropriate and scientifically valid) are required to maintain dignity, privacy and confidentiality of individuals and the communities.

12.4.3 Efforts should be made to protect the identifying information about individuals and communities, for example, from exploitation by the print and visual media.

12.5 Ethics review procedures

12.5.1 Research during humanitarian emergencies and disasters can be reviewed through an expedited review/scheduled/unscheduled full committee meetings and this may be decided by the Member Secretary on a case-to-case basis depending on the urgency and need. If an expedited review is done, full ethical review should follow as soon as possible.

12.5.2 Meticulous documentation and archiving are required to enable future application in similar situations.

12.5.3 Suggestions to expedite the review process are given below:

- Measures such as virtual or tele-conferences should be attempted when face-to-face meetings are not possible.
- In exceptional situations, preliminary research procedures including but not restricted to data/sample collection that are likely to rapidly deteriorate or perish may be allowed while the review process is underway.
- Available protocol templates could be reviewed to expedite the process.
- Re-review should be done if the emergency situation changes.
- In situations where members of local ECs are unavailable due to the emergency, the ethics review may be conducted by any other recognized EC within India for initiating the study, until the local EC is able to convene its meeting. ECs should develop procedures to ensure appropriate and timely review and monitoring of the approved research. On a case-by-case basis, some protocols may require re-review as the emergency situation may change with time and circumstances.

12.5.4 The EC should closely monitor the conduct and outcome of research.

12.6 Post-research benefit

Sponsors and researchers should strive to continue to provide beneficial interventions, which were part of the research initiative even after the completion of research and till the local administrative and social support system is restored to provide regular services.

12.7 Special considerations

Humanitarian emergencies lead to fragile political environments with disruption of health systems and social situations.

12.7.1 The researchers should undertake steps to maintain participant and community trust.

12.7.2 Efforts should be made to engage the community in the conduct of research in a culturally sensitive manner to ensure public trust.

- The research team should preferably describe a preliminary community mapping/ scoping exercise.
- Wherever possible, community representatives or advocates should be involved in conceptualization, review, research and dissemination of research results in such settings.

12.7.3 In case of an outbreak of infectious diseases, monitored emergency use of unregistered and experimental interventions (MEURI) may be approved with the following precautions:

- A thorough scientific review should be conducted, followed by an ethics review by a national level EC constituted for this purpose.
- Oversight by a local EC is necessary.
- Only a product complying with GMP should be used.
- Rescue medicines and supportive treatment should be accessible.
- Sharing data on safety and efficacy would be beneficial to reduce delay for other researchers.
- Consent process is important and must be carried out with care.
- Planning should be done for community engagement.
- Fair distribution should be ensured when faced with scarce supply.

12.8 Continuation of ongoing research when a humanitarian emergency occurs

12.8.1 The research may have to be suspended and the decision may be taken by researchers with information to EC.

12.8.2 The researchers can go back to the EC for guidance regarding continuation of research or not.

12.8.3 Amendments might be incorporated in the proposal(s) to align to the research needs arising from the emergency including issues related to re-consent from participants.

12.8.4 The EC may decide if more frequent monitoring is required.

12.9 International participation in research

12.9.1 Conduct of research in a humanitarian emergency situation, which involves a foreign researcher/institution, must involve local partner(s).

12.9.2 Existing guidelines on international collaboration for biological samples, data and intellectual property including publication related issues will be applicable. See section 3.8.3 for further details.

12.9.3 The local EC will monitor the progress of the research and compliance to the various clauses of the international collaboration.

12.9.4 Permission should be obtained from relevant national and local authorities, wherever applicable.

12.9.5 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.

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ABBREVIATIONS AND ACRONYMS

AAHRPP	Association for the Accreditation of Human Research Protection Programmes
AE	adverse event
ART	assisted reproductive technology
AYUSH	Ayurveda, Unani, Siddha and Homeopathy
BA/BE	bioavailability / bioequivalence
CAB/ CAG	community advisory board/ community advisory group
CDSCO	Central Drugs Standard Control Organization
COI	conflict of interest
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
CRO	contract research organization
CRT	cluster randomized trials
CTRI	Clinical Trial Registry-India
DCGI	Drug Controller General of India
DGFT	Directorate General of Foreign Trade
DGHS	Directorate General of Health Services
DSMB	Data and Safety Monitoring Board
DTA	data transfer agreement
EC	ethics committee
ELSI	ethical, legal and social issues
GCP	good clinical practice
GLP	good laboratory practices
GMP	good manufacturing practices
GOI	Government of India
HMSC	Health Ministry's Screening Committee
ICD	informed consent document
ICF	informed consent form
ICH	International Conference on Harmonization
ICJME	International Committee of Medical Journal Editors

ICMR	Indian Council of Medical Research
IC-SCR	institutional committee for stem cell research
IND	investigational new drug
Ind EC	independent ethics committee
IP	investigational product
IPR	intellectual property rights
LAR	legally acceptable/authorized representative
MoHFW	Ministry of Health and Family Welfare
MOU	memorandum of understanding
MTA	material transfer agreement
MTP	medical termination of pregnancy
NABH	National Accreditation Board for Hospitals and Healthcare Providers
NABL	National Accreditation Board for Testing and Calibration Laboratories
NACO	National AIDS Control Organization
NAC-SCRT	National Apex Committee for Stem Cell Research and Therapy
PGD/ PGS	pre-implantation genetic diagnosis/screening
PIS	participant information sheet
RCR	responsible conduct of research
SAE	serious adverse events
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SOP	standard operating procedure
TM	traditional medicines
TOR	terms of reference

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.	**Adverse event**	Any untoward medical occurrence in a patient or participant involved in a study which does not necessarily have a causal relationship with the intervention. The adverse event can therefore be any unfavourable or unintended sign or experience, whether or not related to the product under investigation.
3.	**Appellate authority**	It decides on the appeal filed against a decision of the lower authority. Its mandate is to ensure that due process of law is followed.
4.	**Assent**	To agree or approve after thoughtful consideration an idea or suggestion to participate in research by a young person below the age of 18 years who is old enough to understand the implications of any proposed research but not legally eligible to give consent. The assent has to be corroborated with informed consent of parent/ LAR.
5.	**Audit**	A systematic and independent examination of research activities and documents to determine whether the review and approval activities were conducted, data recorded and accurately reported as per applicable guidelines and regulatory requirements.
6.	**Autonomy**	The ability and capacity of a rational individual to make an independently informed decision to volunteer as a research participant.
7.	**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, GOI (including Ayurveda, Yoga, Naturopathy, Unani, Siddha, Homoeopathy, SOWA-RIGPA).

8.	**Biomedical and health research**	Research including studies on basic, applied and operational research designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioural), their detection, cause and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation including clinical research.
9.	**Beneficence**	To try to do good or an action which weighs the risks against benefits to prevent, reduce or remove harm for the welfare of the research participant(s) in any type of research.
10.	**Caregivers**	A caregiver or carer is an unpaid or paid person who helps another individual with illness or impairment with daily activities/ performance.
11.	**Case record/ report form (CRF)**	Case record form or case report form is a printed, optical or electronic document designed to record all the required information in the protocol on each study participant for reporting to the sponsor.
12.	**Clinical research**	Research that directly involves a particular person or group of people to study the effect of interventions, or uses materials/data from humans indirectly, such as their behaviour or samples of their tissue for prevention, treatment and diagnosis of a disease condition/health disorder.
13.	**Clinical trial**	As per amended Schedule Y (2005) of the Drugs and Cosmetics Rules, 1945, a clinical trial refers to a systematic study of new drugs in human subjects to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and /or adverse effect with the objectives determining safety and/or efficacy of a new drug. The academic clinical trial as per GSR 313 (e) dated 16 March 2016 is a clinical trial intended for academic purposes in respect of approved drug formulations for any new indication or new route of administration or new dose or new dosage form.
14	**Clinical trial registry**	An official platform for registering a clinical trial, such as Clinical Trial Registry-India
15	**Clinician**	A person with recognized medical qualification and expertise/ training.
16	**Cognitive impairment**	When a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life.

17	**Coercion**	An overt or implicit threat of harm to a participant which is intentional to force compliance.
18	**Collaborative research**	An umbrella term for methodologies that actively engage researchers, communities and/ or policy makers in the research process from start to finish.
19	**Compensation**	Provision of financial payment to the research participants or their legal heirs when temporary or permanent injury or death occurs due to participation in biomedical and health research.
20	**Confidentiality**	Keeping information confidential which an individual has disclosed in a relationship of trust and with the expectation that it shall not be divulged to others without permission.
21	**Confidentiality agreement**	Secrecy or non-disclosure agreements designed to protect trade secrets, information and expertise from being misused by those who have learned about them.
22	**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.
23	**Custodian**	A person who has responsibility of taking care of or protecting entrusted assets, either biological samples or data.
24	**Debriefing**	A process of providing a summary update of a condition or situation to the affected or concerned parties. It is an important ethical consideration in studies involving deception. Such post-experimental follow-up is considered beneficial even if no deception is used or there is only minimal risk to participants.
25	**Deception**	Deception occurs when investigators provide false or incomplete information to participants to misleading them to achieve the study objectives and for larger public good. Research employing any type of deception should undergo full committee review.
26	**Distributive justice**	Fair distribution of burden, resources and benefits. In research, it means fair selection of participants.
27	**Ethicist**	One whose judgement on ethics and ethical codes is based on knowledge/experience through qualification or training.
28	**Exploitation**	The action or fact of treating someone unfairly in order to benefit from their participation.

29	**Exploratory research**	Preliminary research conducted to gain insights for a problem that has not yet been clearly defined.
30	**Impartial witness**	A literate person, who is independent of the research and would not be unfairly influenced by people involved with the study, who attends the informed consent process if the participant and/or their LAR cannot read, and understand the informed consent form and any other written information supplied to the participant.
31	**Independent consultant**	An expert who gives advice, comments and suggestions to the EC and has no affiliation to the institute or researchers proposing the research protocols. This individual has no voting power for decision making.
32	**Inducement**	A motive or consideration that leads one to action or to additional or more effective actions without considering the harm that may occur.
33	**Informed consent document (ICD)**	Written signed and dated paper confirming a participant's willingness to voluntarily participate in a particular research, after having been informed of all aspects of the research that are relevant for the participant's decision to participate.
34	**Justice**	Pertains to fairness in the way people are dealt with, indicating fair selection and distribution of benefits and risks to participants who should be fully apprised about them.
35	**Lay person**	A literate person who has not pursued a medical science/health-related career in the last 5 years and is aware of the local language, cultural and moral values of the community.
36	**Legal expert**	A person with a basic degree in law from a recognized university, with experience.
37	**Legally acceptable representative (LAR)**	A person who will give consent on behalf of a prospective participant who, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the EC.
38	**Legally authorized representative (LAR)**	A person who, under applicable law or judicial authority, can give consent on behalf of a prospective participant who, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the ethics committee.

39	**Maleficence**	The act of committing harm or a harmful act.
40	**Marginalized communities**	A group of people actively separated or excluded from the rest of society.
41	**Minimal risk**	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of a healthy individual or 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.
42	**Non-therapeutic trial**	A trial 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 procedures.
43	**Ostracization**	To exclude, by general consent, from society, friendship, conversation, privileges, etc.
44	**Particularly vulnerable tribal group (PVTG)**	These are a special class of tribal groups, classified as such by the Government of India, due to their especially low development indices when compared to other local tribes. These were classified under the Dhebar Commission (1960–1961), so as to better facilitate their growth, at par with other scheduled tribes on a national scale, and help them to get included in mainstream development, while using their indigenous knowledge. They have a pre-agricultural system of existence as mainly hunters with zero or negative population growth, extremely low level of literacy and no written language.
45	**Pilot studies**	A pilot study, project or 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.

46	**Pivotal trial**	A clinical trial or study intended to provide evidence for 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.
47	**Post-marketing surveillance**	The practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market. This is an important part of the science of pharmacovigilance.
48	**Professional competence**	The broad professional knowledge, attitude and skills required in order to work in a specialized area or profession.
49	**Principal investigator**	An individual or the leader of a group of individuals who initiates and takes full responsibility for the conduct of biomedical health research; if there is more than one such individual, they may be called co-principal investigators/ co-investigators.
50	**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.
51	**Quorum**	Minimum number and/or kind of EC members required for decision making during a meeting.
52	**Research-related injury**	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 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.
53	**Risk**	Probability of harm or discomfort to research participants. Acceptable risk differs depending on the conditions inherent in the conduct of research.
54	**Serious adverse event (SAE)**	An adverse event is serious when the research outcome for the participant is death, life-threatening injury requiring hospitalization, prolongation of hospitalization, significant disability/incapacity, congenital anomaly, or requirement of intervention to prevent permanent impairment or damage.

55	**Sexual minorities**	A group whose sexual identity, orientation or practices differ from majority of the surrounding society. It refers to lesbian, gay, bisexual and transgender (LGBT), queer (including the third gender) or intersex individuals.
56	**Social scientist**	A person who is an expert on societal and social behaviour with specialization/experience in the area.
57	**Socio-behavioural research**	Refers to the socio-behavioural studies on response of individuals, groups, organizations or societies to external or internal stimuli.
58	**SOP (standard operating procedure)**	Detailed written instructions in a certain format describing all activities and actions to be undertaken by an organization to achieve uniformity in performance of a specific function.
59	**Sponsor**	An individual, institution, private company, government or non-governmental organization from within or outside the country who initiates the research and is responsible for its management and funding.
60	**Stigmatization**	Negative perceptions about an individual because of perceived differences from the population at large. It may occur on the basis of physical appearance, race or sex.
61	**Surrogate**	A substitute or deputy for another person in a specific role.
62	**Theologian**	A person who is an expert in the study of religious faith(s), including the system of spirituality, practice and experience about the nature of the divine.
63	**Test of understanding**	A simple oral or written test designed to identify if the participant has understood the details related to her/his voluntary participation in research before signing the ICD form. (Questions such as "If you decide not to take part in this research study, do you know what your options are?", "Do you know that you do not have to take part in this research study, if you do not wish to?", "Do you have any questions?", etc. will clarify the understanding of the participant.)
64	**Transparency**	It implies intentional openness, communication, and accountability operating in such a way that it is easy for others to see what actions are performed.
65	**Therapeutic misconception**	It is a misconception by participants believing that the purpose of clinical trials/research study is to administer treatment rather than to conduct research.

66	**Undue inducement**	Offer of disproportionate benefit in cash or kind that compromises judgement which may lead to acceptance of serious risks that threaten fundamental interests.
67	**Unexpected ADR**	An adverse reaction, the nature or severity of which is not described in the informed consent/information sheet or the applicable product information, such as an investigator's brochure for the unapproved IP or package insert/summary of product characteristics for an approved product.
68	**Vulnerability**	Vulnerability in research pertains to 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.

STANDARD OPERATING PROCEDURES (SOPs)

S. No.	List of SOPs
1	Writing, Reviewing, Distributing and Amending Standard Operating Procedures for ECs
2	Constituting an Ethics Committee
3	Confidentiality Agreements
4	Conflict of Interest Agreements
5	Training Personnel and EC Members
6	Selection of Independent Consultants
7	Procedures for Allowing a Guest or Observer
8	Categorization of Submitted Protocols for Ethics Review **a.** Initial Full Committee Review of New Research Protocols **b.** Expedited Review of Research Protocols **c.** Exemption from Ethics Review of Research Protocols
9	Agenda Preparation, Meeting Procedures and Minutes
10	Review of New Medical Device Studies
11	Review of Resubmitted Protocols
12	Review of Protocol Amendments
13	Continuing Review of Protocols
14	Review of Final Reports
15	Review of Serious Adverse Events (SAE) Reports
16	Review of Study Completion Reports
17	Management of Premature Termination, Suspension, Discontinuation of the Study
18	Waiver of Written or Verbal/oral Informed Consent
19	Site Monitoring Visits
20	Dealing with Participants' Requests and Complaints
21	Emergency Meetings
22	Communication Records
23	Maintenance of Active Study Files
24	Archive and Retrieval of Documents
25	Maintaining Confidentiality of EC's Documents
26	Reviewing Proposals involving Vulnerable Populations
27	Review and Inspection of the EC
28	Audio Visual Recording of the Informed Consent Process

LIST OF MEMBERS OF COMMITTEES INVOLVED IN REVISION OF GUIDELINES (2015-2017)

A. Members of Central Ethics Committee on Human Research

P. N. Tandon (Chairperson), National Brain Research Centre, Manesar

B. N. Dhawan (Late), Formerly at Central Drug Research Institute, Lucknow

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Sanjiv Datta, Former Financial Advisor, Indian Council of Medical Research, New Delhi

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Roli Mathur, Indian Council of Medical Research, National Centre for Disease Informatics and Research, Bengaluru

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Former Chair in Clinical Pharmacology & Advisor Clinical Trials Registry, ICMR, New Delhi and former Professor and Head, Dept of Pharmacology, AIIMS, New Delhi

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Scientist - G & Head, Division of BMS, Indian Council of Medical Research, New Delhi

Roli Mathur

Scientist E, Division of BMS, Indian Council of Medical Research, New Delhi (2015-2016) and presently Head, ICMR Bioethics Unit, National Centre for Disease Informatics and Research, Bengaluru

C. Members of Sub-Committees / Invited Experts

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Aditi Iyer, Public Health Foundation of India, Bengaluru

Anant Bhan, International AIDS Vaccine Initiative, New Delhi

Anura Kurpad, St John's Medical College, Bengaluru

Arun Bhatt, Indian Society for Clinical Research, Mumbai

Brogen Singh Akoijam, Regional Institute of Medical Sciences, Imphal

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The purpose of these guidelines is to safeguard the dignity, rights, safety and well-being of the human participants involved in biomedical and health research. These guidelines are required to be followed by all stakeholders including sponsors, institutions, ethics committees and researchers.

