STANDARD OPERATING PROCEDURES

for

INSTITUTIONAL HUMAN ETHICS COMMITTEE

Chettinad
Dental College & Research Institute

CHETTINAD DENTAL COLLEGE AND RESEARCH INSTITUTE - 2020

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INTRODUCTION

Chettinad Dental College and Research Institute (NAAC Accredited "A" grade institution) is a global centre of excellence in learning, teaching, research, health care and service to the community. It offers both Postgraduate and Undergraduate Dental Surgery Course being affiliated to The TN Dr. MGR medical university, Chennai and recognized by the Dental council of India.

Chettinad Dental College and Research Institute aspires to impart global standard education with great values, thereby transforming our students to be competent professionals on par with future needs. It offers inter and multidisciplinary high-quality innovative programmes in the broad fields of Dental Sciences and related technologies and promotes clinical and ethical dental research in areas of national and local health problems.

The need for Institutional Human Ethics Committee in medical/dental and research establishments resulted from the realization that affirms human rights as an essential right to all members of society. This involves a number of ethical issues which needs to be addressed. The Institutional Human Ethics Committee (IHEC) plays the vital role of guiding researchers in the ethical issues associated with their research. The guidelines heretofore mentioned in this document are prepared based on the National Ethical Guidelines for Biomedical and Health Research involving Human Participants, published by the Director-General of Indian Council of Medical Research in the year 2017*.

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The code of conduct for physicians was well laid out in traditional Indian systems of medicine and 'do no harm' were 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. 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, followed by the revised Ethical Guidelines for Biomedical Research on Human Participants in 2006. In the meantime, the Central Drugs Standard Control Organization (CDSCO) also released the Indian Good Clinical Practice Guidelines (2001) for clinical trials and revised Schedule Y of the Drugs and Cosmetics Act, 1940, in the year 2005 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.

The Nuremberg Code of 1947 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.

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. 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). The International Conference on Harmonization (ICH) brought out the Good Clinical Practice Guidelines E6 (R1) in 199611 revised as E6 (R2) in 2016. The National Bioethics Advisory Commission, USA (2001), the Council for International Organizations of Medical Sciences (CIOMS), Geneva (2002 revised in 2016), 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) 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, dental, social and behavioural science research for health conducted in the institution 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.

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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. 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, dental, 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.

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/dental terminology in simple terms and be in a language that the participant understands.

Table 2.1 Types 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, dental IOPA, obtaining body fluids without invasive intervention, such as hair, saliva gingival crevicular fluid 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 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.

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 barrier 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.

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.

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. Wherever possible they should also seek opportunities 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, 200318 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)

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 nonfinancial) 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.

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. 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 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

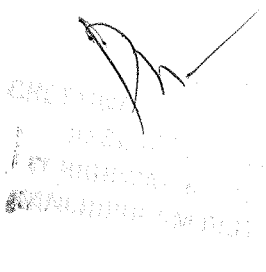
Scientific disclosure and progress has been dependent largely on peers evaluating research and judging the quality and utility of conducting and publishing research.

• 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 confidential until the enquiry is complete.

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). The institution uses the web based system, 'Urkund' (available at

https://secure.urkund.com/account/account/create) for checking the plagiarism of student's research write-up. The students has to log-in with username and password, and can upload their research write-up to check for the percentage of similarity in content with external sources.

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.

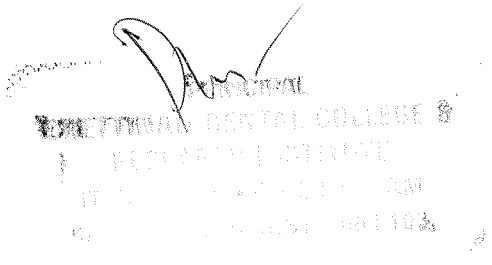
3.8.2 Responsibilities of ethics committees, researchers and institutions

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, 198620, the Biological Diversity Act, 200221, 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.

• 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 Act should 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.

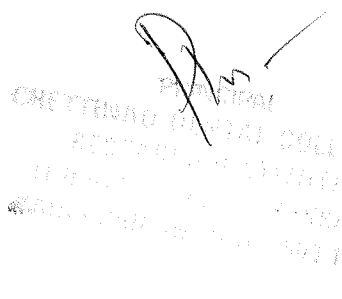
4.2.2 An institution that does not have its own EC (user institution) may utilize the services of the EC of another institution (host institution) preferably in the adjoining/nearby area. Relevant requirements must be fulfilled before they do so. See Box 4.1 for further details

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 well-being 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
	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
	Member Secretary/ **Alternate Member Secretary** (optional) Affiliated	• 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

	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 • Should be able to devote adequate time to this activity which should be protected by the institution	• 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. • 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.
	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.
	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 care, management and compensation.

		• Thorough review of protocol, investigators brochure (if applicable) and all other protocol details and submitted documents.
	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
	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.
	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	• 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.

	• 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	

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, Dental, non-medical/non-dental 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/Dental 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 1. 8. Investigator's brochure (as applicable for drug/biologicals/device trials) 9. Details of funding agency/sponsor and fund allocation (if applicable)	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) 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)

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	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 include 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	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

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;	confidentiality of personal information/ identity. 18. ethical considerations and safeguards for protection of participants.

Table 4.2 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)
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 predefined study assessment form and for factors as described in Table 4.3.

Table 4.3 Ethical issues related to reviewing a protocol

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.
Scientific design and conduct of the study	• Valid scientific methods are essential to make the research ethically viable as poor science can expose research participants or communities to risks without any possibility of benefit. • Although ECs may obtain documentation from a prior scientific review, they should also determine that the research methods are scientifically

	sound, and should examine the ethical implications of the chosen research design or strategy. • 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.
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)
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.
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. • 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.
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.
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.
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.
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.
Plans for medical management and compensation for	• The proposed plan for tackling any medical injuries or emergencies should be reviewed.

study related injury	• Source and means for compensation for study related injury should be ascertained.
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; • 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 minute 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.

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

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 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 enrol in the research.

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

Box 5.1 Essential and additional elements of an informed consent document

An informed consent form must include the following:	**In addition, the following elements may also be required, depending on the type of study:**
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	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 pretest- and post-test counselling 3. Insurance coverage if any, for research-related or other adverse events

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)	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.

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 enrol 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.

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.

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 wellbeing 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

6.4 Women in special situations

Women have equal rights to participate in research and should not be deprivedarbitrarily 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". 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 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 6.4 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.

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 involved).

• 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: m an explanation about the study and how it will help the child; m 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).

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 201627 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).

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

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, 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.

Box 7.2 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.

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.

Table 7.1 Classification of medical/dental Instruments

Class	Level of risk	Instrument examples
A	Low	Mouth mirrors/tongue depressors/impression plates/Tweezer/Cheek retractor
B	Low-moderate	Suction apparatus/Needle holder/Orthodontic braces/bands/
C	Moderate-high	Periodontal probes/explorers/Suture material
D	High	Dental implants/Curettes/surgical instruments/

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 interdependence 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

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.

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.

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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