NATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL AND HEALTH RESEARCH INVOLVING HUMAN PARTICIPANTS

INDIAN COUNCIL OF MEDICAL RESEARCH
2017

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Relevant Extract on
Human Genetics Testing and Research and Genome Editing

taken from

National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

Full document (PDF) available at:

1. **http://www.icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf**
2. **http://www.ncdirindia.org/Ethics/Download/ICMR_Ethical_Guidelines_2017.pdf**

HUMAN GENETICS TESTING AND RESEARCH

10.0 In no other area of biomedical and health research has there been a greater concern for ethical issues than in the field of human genetics. In recent years this concern has grown even further because of direct to consumer testing and the possibilities of embryo manipulations. While the recent DNA technology has provided one of the most powerful tools in the hands of mankind to unravel the mysteries of the human genome and its manipulation, it has also led to a great deal of concern about scientists' ability to handle such information. There is also a very narrow gap between routine genetic testing and research raising several ethical, legal and social issues (ELSI), which warrant continuous and prompt monitoring and judicious response to the emerging ethical issues.

10.1 General issues

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

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

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

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

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

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

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

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

10.1.9 Genetic testing and research often require dealing with persons who are unable to protect their rights and safety and may be vulnerable, such as children, individuals

with mental illness, cognitively impaired individuals, people with rare diseases and others. See section 6 for further details.

10.2 Genetic Counselling

10.2.1 Pre- and post-test non-directive counselling should be given by persons who are qualified and experienced in communicating the meaning of genetic information as some conditions may require termination of pregnancy or selection of embryos to avert birth of a genetically abnormal child/foetus. While disclosing the result, appropriate options should be provided to the family to enable them to come to a decision.

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

10.3 Privacy and confidentiality

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

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

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

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

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

10.3.5. The researcher cannot reveal the genetic information to family members without the participant's permission. If family members are recruited/tested

then their information should be kept confidential from each other by the physician/researcher.

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

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

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

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

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

10.3.11. Newer genomic techniques for research like whole exome sequencing (WES) and whole genome sequencing (WGS) may create uncertain evidence at the present level of knowledge. Therefore, the confidentiality of data, and pre- and post-test counselling need to be revisited with an entirely new perspective.

10.4. Informed consent

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

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

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

10.4.3. It needs to be emphasized that consent for screening or a subsequent confirmatory test does not imply consent to any specific treatment or termination of the pregnancy or for research.

10.4.4. If the research or testing involves a child, appropriate age-specific assent (verbal/oral/written) should be obtained along with parental consent. See section 6 for further details.

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

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

10.4.6. Group consent/community consent

- In case of population or community based studies, it may be noted that the genetic research may generate information applicable to the community/populations from which the participants were drawn, and therefore, group consent must be taken from the community head and/or the culturally appropriate authority.
- Even if group consent is taken, it will not be a replacement for individual consent as individual consent is important. See section 5 for further details.
- Researchers should be aware of potential stigmatization of the entire group and must explain ways to avoid the same during the conduct of research and publication of research results.

10.5 Culturally sensitive issues

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

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

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

10.6 Storage of samples for future genetic research

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

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

10.7 Results of genetic testing

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

10.7.2 The researcher should work with the local EC to decide on the validity of the research finding and the severity of the potential disease in order to return the results which should be avoided if the logical outcome of the research is expected to be inconclusive and the participants were informed of this in the ICD.

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

10.8 Publication aspects

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

10.8.2 Features on the face should be masked to prevent identification. If these features have to be revealed for scientific reasons, this fact should be stated clearly in the consent form and fresh consent must be obtained, if not taken earlier.

10.9 Commercialization and COI

10.9.1 Direct to consumer testing (DTC) in laboratories offering a battery of genetic tests is rapidly growing. While this ensures a patient's autonomy to undergo testing, it is important that the sensitivity and specificity of these investigations and the ability of the laboratory personnel to interpret the result in consultation with treating physician/ clinical geneticist is ensured before arriving at a diagnosis.

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

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

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

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

10.10 Role of the team in genetic testing and research

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

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

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

10.11 Quality standards of the laboratory

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

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

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

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

10.12 Misuse of genetic technology

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

10.12.1 Prenatal sex selection is not allowed and to prevent misuse of genetic tests, particularly pre-selection of sex, GOI has enacted the Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition of Sex Selection) Act, 1994, amended in 2003.[i] All researchers in this area shall follow the provisions of this Act. Prenatal sex determination is prohibited by law for sex selection of the foetus.

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

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

10.13 Genetic diagnosis/testing and screening

10.13.1 History and pedigree studies: These involve obtaining history of other members of the family of the proband under investigation. It may reveal information about the likelihood of individual members of the family being either carriers of genetic defects or being affected by the disease. Privacy and confidentiality issues involved in this process are given in section 10.2.

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

10.13.3 Genetic screening: Genetic screening implies searching a population for those individuals who have, or are susceptible to a serious genetic disease; or who, though

not at risk themselves, are carriers and thus at risk for having children with a particular genetic disease.

- It is essential for screening to be purposive. Besides validation of screening tests, it should also be ensured that a suitable intervention and counselling are available.
- Those being screened are entitled to receive sufficient information about what is proposed to be done, reliability of the screening test, and what will be done with the collected samples.
- Although screening may be permissible to allay anxiety, the response of different individuals might vary, which should be borne in mind by the health-care provider.
- Confidentiality should be maintained in handling of results with emphasis on responsibility of individuals with an abnormal result to inform partners and family members. In case of refusal, the duty of confidentiality shall weigh higher than the duty for beneficence to family members unless sharing of information is vital to prevent serious harm to the beneficiary in the family. In such case, appropriate precautions may be taken to ensure that only the genetic information needed for diagnosis/treatment is shared.
- Screening tests should be sensitive enough to identify a significant proportion of affected persons (the detection rate) with minimal misidentification of unaffected persons (the false positive rate). Screening tests do not aim to make a diagnosis, but rather rationalize the use of more accurate confirmatory tests.

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

- Population screening should not be undertaken without prior education of the population to be screened and counselling should be integrated with the programme.
- Screening tests should be robust with acceptable sensitivity and specificity.
- Wherever applicable, community permission/group consent should be taken in addition to individual informed consent.
- Researchers may conduct coded or reversible anonymized testing on general population in order to establish prevalence of genetic traits/diseases. See Table 11.1 for further details. Blood spots collected for screening newborns for treatable disorders could also be used for this purpose. In case information derived from

stored specimens might be useful to an individual, the code may be broken with the approval of the EC.

10.13.5 Prenatal screening: Prenatal screening is aimed to screen mothers and foetuses that are at high risk of having functional or structural defects including chromosomal and single gene disorders. There are many screening tests which are recommended in routine practice.

- **Biochemical and ultrasound screening:** Various combinations of serum screening and ultrasound screening tests are done either during first (dual marker) or second trimester (triple or quadruple screening) for aneuploidy screening. It is important to discuss detection rates, false positive and negative results with participants.
- **Invasive testing for prenatal diagnosis:** Preliminary genetic counselling of women for invasive prenatal diagnosis should include the following:
  - risk of the fetus being affected;
  - natural course and prognosis of the specific disorder;
  - risks and limitations of the invasive procedures to be used;
  - time required before a report can be issued;
  - possible need for a repeat procedure in the event of a failed attempt; and
  - limitation of a test due to laboratory error.
- **Non-invasive prenatal screening/testing (NIPS/NIPT):** Recent advances in genomic technologies have resulted in the shift of antenatal aneuploidy screening towards the development of NIPS methods by using cell-free foetal (CFF) DNA sequences isolated from a maternal blood sample. This test prevents the risk of an invasive procedure which would also be beneficial for high risk mothers. However, there are several limitations of these techniques which should be clearly explained.

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

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

In this technique, in vitro screening is done on early embryos for a panel of common genetic disorders, such as aneuploides, and specific disorders (if there is a family history or proven carrier status in parent(s) to implant unaffected embryos. This

obviates the need for invasive testing for associated risks and also termination of the affected foetus, which is traumatic for the family.

- Advanced techniques like chromosomal micro array (CMA) are being used for PGS and NGS for screening which might theoretically raise ethical issues regarding eugenics and designer babies based on selection of embryos.
- This also raises ethical concerns regarding selection of sex.

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

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

10.13.8 Screening of children

- Children should not be screened for carrier status or disease merely at the request of their parents.
- Testing of children should be deferred until they are able to comprehend and are able to participate in the decision-making process, unless early intervention based on results of the test is likely to be of direct therapeutic benefit to them.

- Screening for late onset diseases should not be done in children unless there is any suitable intervention available for treating during the childhood stage.

10.13.9 Screening for carrier status

- **Single gene:** If there is a family history of a single gene disorder (autosomal recessive, X linked), the individual should be tested after administering informed consent when she/he is able to comprehend the benefits and risks of screening. Stigmatization for carrier status is common and therefore, the information should be kept confidential.
- **Chromosomal:** If there is a family history of balanced translocation in any individual, then immediate relatives may be at risk. The same principles as for carrier testing should be followed.

10.14 Gene therapy

All gene therapies are considered as research and all protections for human research participants should be in place. See section 4 for further details.

10.14.1 Somatic cell gene therapy is permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option. It should be restricted to alleviation of life threatening or seriously disabling genetic disease in individual patients and should not be permitted to change normal human traits.

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

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

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

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

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

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

10.14.8 Eugenic genetic engineering for changing/selecting/altering genetic characteristics and creating so called designer babies is prohibited. These should not be attempted, as we possess insufficient information at present to understand the effects of attempts to alter/enhance the genetic machinery of humans. It would be unethical to use genetic engineering for improvement of intelligence, memory, formation of

body organs, fertility, physical, mental and emotional characteristics, etc. even if specific gene/genes are identified in future.

10.15 Use of newer technologies

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

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

10.15.2 Whole exome sequencing and whole genome sequencing

These high throughput next generation sequencing techniques are used for sequencing all the exons (WES) or the whole genome including introns (WGS). These techniques are increasingly being used in clinical practice, particularly WES, and have raised a new challenge for counsellors as well as patients.

- These genomic techniques identify pathogenic mutations or variations of unknown significance in many other genes, hidden genetic disorders or cancers which may manifest later. The individual should be informed and asked whether she/he will like to know about unrelated genetic mutations. The results should always be interpreted keeping in mind the coverage of genes of interest.
- Families/individuals opting for the test should be counselled regarding grey areas in these upcoming technologies prior to testing. They should be aware that WES/WGS may not give conclusive results.

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

This is a powerful technology which efficiently edits DNA with immense value for accurate and precise genome editing to alter human genes to cure and eliminate certain genetic based diseases. Experiments done so far have shown that the

technique can be used to rapidly, easily and efficiently modify genes in a wide variety of cell types and in organisms. Somatic cell genome editing has an immediate clinical translational potential and can be used in a variety of areas such as drug development, gene surgery, understanding genetic variation, and it also has implications for biomaterial, fuels, food etc. CRISPR works as a pair of DNA scissors, and Cas9 is the protein in the system that unzips DNA and finds the target by matching the DNA sequence against a snippet of its guide RNA. When Cas9 finds its target and snips it, there are concerns about associated risks, which blur the excitement about its usefulness. Similar concerns are there for the use of other genome editing technologies such as zinc finger nucleases (ZFN) and transcription activator-like effector nuclease (TALEN). Today therapeutic applications are possible for a wide range of indications, in preclinical models or in clinical settings through clinical trials in humans. There are some considerations related to the use of this technology.

- The risks are irreversible changes in germline, risks of inaccurate genome editing, implications for future generations, interactions with other genetic variations and environment, and the fear that once the genetic change is introduced it may be permanent which would have long-term effects.
- Despite the promise of the technique, there is a possibility of encountering error in genetic engineering which has unforeseen implications. Cas9 will sometimes identify a wrong target even when up to five of the guide RNAs do not match the DNA – hence the off-target mutations may cause disease or alter germline or DNA of future generations of humans.
- It could be used to change harmless genes, as for eye colour, leading to designer possibilities. There are also possibilities of creating interspecies organogenesis or chimerism. There are possibilities of making gene correction in zygotes using CRISPR-Cas9 which has ethical implications.
- The application of this technology in plants and animals can lead to possible lateral transfer and emergence of irreversible damage to biodiversity and environment which can be a risk to not only human and animal life but also the environment due to its long-term consequences. It could also possibly be used for bioterrorism.
- CRISPR-Cas9 needs to be judged for the good of future generations. This needs time and thus, at present, there is a ban on germline manipulations.

- There is a need to consider the possibility of commercialization, patenting or rightful access, therefore, a vigorous benefit-risk evaluation is required to address the expectations and concerns of the public. There is need for an initial cautious approach before this technology can be widely used for various applications.
- An open and transparent discussion, advocacy and public engagement should be encouraged with various stakeholders to understand, build trust and be involved in decision making. Capacity building is required not only of researchers but also regulators and policy makers to carefully consider social and ethical aspects and put systems in place to ensure safety.
- At the moment, there is a need for initiatives to increase knowledge base, infrastructure, funding, guidelines, inter agency communications and interactions, engagement with public and other stakeholders, and establish science communication. In addition, attempts should be made to foster research to assess the feasibility, efficacy and safety of CRISPR technology.

10.15.4 Genome-wide association study (GWAS)

Genetic epidemiology, also known as whole genome-wide association study, involves an examination of many common genetic variants in different individuals to see if any variant is associated with a trait. A GWAS typically focuses on associations between single-nucleotide polymorphisms (SNPS) and traits like major diseases, particularly multifactorial disorders.

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

10.16 Research on human embryos

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

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

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10.17 Foetal autopsy

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

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

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

Biological materials, biobanking and datasets

11.0 Biological materials or biospecimens or samples include biological fluids, such as blood, dried blood spots, body fluids, urine, tissues, organs, cord blood, oocytes, sperm, semen or embryos. These may be stored or prospectively collected.

A repository or biobank is an organized collection of resources that can be accessed to retrieve human biological material and data for research purposes. The bio resources would therefore be protocol-based prospective collection of biospecimens, left-over samples after clinical investigations or research proposals, biopsy materials, surgical or autopsy specimens/tissues, embryos or foetuses, cell lines, or waste materials like abandoned organs/tissues. Repository activities involve three components: collection of biospecimens and/or data; storage of biospecimens and data including its management; and retrieval and disbursement to researchers.

A dataset is an organized collection of data and information maintained in physical and/or electronic/digital form that can be used for biomedical and health research. Besides data related to biospecimens as in biobanks, there are other repositories like disease registries, health surveys, disease surveillance, census data and even personal health records in health-care institutions which may have huge potential for subsequent research. The data may be based from small numbers to whole population or major parts of it.

Examples of biobanks and datasets are Iceland's deCODE biobank, National Institute of Mental Health and Neuro-Sciences (NIMHANS) Brain Bank, Tumour Tissue Bank at Tata Memorial Hospital (TMH), Census data, NFHS data, Cancer Registry of India, CTRI, etc.

11.1 Biobanking

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

facilities with central coordination which provide medical, genetic and life-style related data. Thus biobank may be very large with public or private funding, for commercial or non commercial use and on other hand may be small limited to a researcher who stores samples in the laboratory or at institutional level where common facility is available for storing samples. Biobanks can also store non-human materials, such as plant, animal, microbes and parasites, but for the purpose of these guidelines this section will only pertain to human biomaterials and/or related data.

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

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

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

Table 11.1 Types of samples

<table>
<tr><td>Anonymous or unidentified</td><td colspan="2">No identifiers are present from the start or if collected, are not maintained. Such samples are received by biobanks without any identifiers and supplied to researchers.</td></tr>
<tr><td>Anonymized</td><td colspan="2">This involves systematic de-identification, reversible or irreversible: link of samples/data to personal identity is reversibly or irreversibly cut.</td></tr>
<tr><td></td><td>Coded or reversibly anonymized:
There is an indirect link of sample/data to the participant’s identity with restricted access. This link could be re-linked if required; therefore, it may also be termed reversible anonymization.</td><td>Irreversibly anonymized:
Link to the participant’s identity is removed and cannot be re-linked.</td></tr>
<tr><td>Identifiable</td><td colspan="2">A direct link of sample/data to the participant’s identity exists.</td></tr>
</table>

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

This pertains to both personal identifiers and the related data of the participant. Some key points for maintaining privacy and confidentiality related to donors are listed in Box 11.1.

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

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

1. The procedure of anonymization minimizes the connection between the identifiers and the stored sample or medical data by delinking the person from her/his biological material.
2. Maintaining confidentiality of data and respecting ethnic identity is of prime importance, especially in population based genetic studies.
3. More precautions should be sought when the research pertains to stigmatizing diseases.
4. When data pertains to epidemiological and public health practice or research, it may be dealt with in the manner described in section 8.

11.2 Storage of biospecimens and data with personal identifiers

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

11.2.2 Under certain circumstances, some degree of identifiability may have to be retained for reasons related to the research. For example, anonymized data or specimens will not allow later withdrawal of consent by an individual, while in the coded category, this will be possible. In the latter scenario, the custodians of the respective biorepository or biobank have a greater responsibility to take adequate measures to safeguard the codes and the data so as to respect the privacy and confidentiality of individual research participants.

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

11.3 Ethical issues related to donors

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

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

collaborations and potential commercialization. These raise issues of access and benefit sharing.

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

The following is an example of multiple options in a multi-layered consent:
Please pick one of the choices below:

a. I agree to allow my biospecimen to be stored for future use for any biomedical research.
b. I agree to allow my biospecimen to be stored for future use for specific disease such as cancer research.
c. I agree to allow my biospecimen to be stored for future use for other pre-specified health problems, such as diabetes, heart disease.
d. I do not wish to allow my biospecimen to be used in future research which is beyond the scope I have already consented for, unless researchers re-contact me to seek my permission.
e. I do not wish to allow my biospecimen to be used in future research. I do not want researchers to contact me about future studies.
f. I wish to be informed/not to be informed about the results of my investigation.

Examples of different types of consent processes and their implications are given in Box 11.3.

Box 11. 3 Types of consent processes and their implications

1. **Blanket or broad consent:** This is an open consent given only once to collect the sample, store it and use it for any research at any time in future without the need to revert to the individual for a re-consent. A consent model that allows for current and future access and use of samples or data for research without necessarily specifying what the focus of such studies might be.
2. **Tiered consent:** This model of consent offers several options from which participants can choose. It includes an opt-in option for future use specifying general permission, or use only related to some aspects of research, sharing of biospecimens/data benefit sharing, etc. It also takes into consideration return of results for which options are also provided for consent. See section 11.4.4, for further details.
3. **Specific consent:** Consent is obtained for a specific research purpose. Participants are re-contacted for every new use of their stored samples/data if the scope of research is outside that for which they had originally given consent.
4. **Delayed consent: I**t may be administered in the post-medical procedure period when biospecimen or data may be collected for appropriate research from critically ill patients who may not have given prior consent for research. Consent may be taken from the participant or LAR when it is practical.
5. **Dynamic consent:** This consent is different from one of static, paper-based consent and involves an ongoing engagement and interactions over time with participants to re-contact in response to changing circumstances using technology based platforms. It incorporates a flexible, configurable, technology-based design accommodating both participant and researcher needs. Modern longitudinal biobanks equipped with advanced technology strive for this type of consent.

6. **Withdrawal of consent or destruction of sample:** The donor has the right to ask for destruction of her/his collected sample(s) and discontinuation/withdrawal from participation in the research. In longitudinal studies, a participant may withdraw from one component of the study, like continued follow-up/data collection when withdrawal may be referred to as partial.
7. **Waiver of consent:** While using anonymized (de-identified) samples/data, researchers should seek the approval of the EC of the institution or the repository for waiver of consent from donors.
8. **Re-consent** • **Secondary or extended uses of stored samples/dataset:** In such an instance, one of the preliminary considerations for ECs must be to identify the circumstances under which the research requires re-use of collected identifiable biological material to generate the data or utilize the pre-existing identifiable dataset. This must also include review of the informed consent obtained originally to see if re-consent is warranted. There may be situations where consent would be impossible or impracticable to obtain for such research, in which case the research may be done only after independent evaluation by an EC (Declaration of Helsinki, October 2013). • **Paediatric donors:** In longitudinal studies once the child donor attains the legal age of consent a re-consent should be sought for the storage and use of her/his tissue or sample. In paediatric biobanks or biobanks with paediatric samples it is important to address the issue of children reaching legal age of consent. Sometimes re-contact may lead to withdrawal, resulting in limited data analysis. This may lead to bias or it could evoke emotional distress about past research. On the other hand, re-consent may give the participant the power to agree. A biobank should decide the policy it would like to adopt for re-contact.

11.4 Ethical issues related to research

Biobanks can use the stored material/data for doing research themselves or they can outsource or supply such material/data to other researchers or institutions on a non-profit basis.

11.4.1 Ownership of the biological samples and data: The participant owns the biological sample and data collected from her/him and therefore, could withdraw both the biological material donated to the biobank and the related data unless the latter is required for outcome measurement and is so mentioned in the initial informed consent document. Complete anonymization would practically make the original donor lose the right of ownership. Biobanks/institutes are the custodians or trustees of the samples and data through their ECs as their present and future use would be done under supervision of the respective ECs. Researchers have no claim for either ownership or custodianship.

11.4.2 Transfer of biospecimens: An MTA should be executed if the biospecimens are likely to be shipped from the host institution to collaborating institutions within the country or abroad. The EC should oversee the process of the in-country and international material transfer. Mandatory regulatory clearances with appropriate MoU are required

if biospecimens are to be sent overseas. See section 3.3.3 for further details. Directorate General of Foreign Trade (DGFT) has issued a notification related to transfer of human biological material for commercial purposes.

11.4.3 Secondary or extended uses of stored samples/re-consent: The EC will examine circumstances under which the biological material or the data were originally collected and informed consent obtained. The decision about anonymization/informed consent waiver or re-consent will be made on a case-by-case basis as provided in Box 11.3.

Box 11.3 Use of stored samples

The following must be considered when stored samples are to be used:

1. whether the proposed use is aligned with the original consent given for the earlier research and scrutinize the validity of the objectives of the new research;
2. whether provisions for ensuring anonymity of the samples for secondary use are stated;
3. whether the permission of LAR is obtained for post-mortem uses of samples;
4. whether the consent form mentions retention and various possible future uses of tissues in the form of a tiered consent; and
5. Whether provisions have been made for allowance of waiver of consent if the donor is not traceable or the sample/data is anonymized or it is impractical to conduct the research.

11.4.4 Return of research results to individual/groups

There are several possibilities which may be appropriate for a particular research and, according to the suitability, could be included in the participant information sheet/informed consent document for biobanking.

- Results of the study should be communicated back to the providers of samples/data.
- If the findings are in an aggregate form, the participant will not be able to receive any feedback on individual data.
- Wherever applicable, research findings in aggregate form (which does not reveal individual results) must be discussed with the community, especially when research involves populations who are more vulnerable, such as tribal populations, ethnic groups and people living with certain diseases.
- In the absence of an appropriate mechanism to deal with informational harm that can occur if participants are provided feedback when they are not prepared to face it or if it is not actionable or when such information is unrelated, a lot of distress could be caused to participants concerned.
- At the time of sample collection, it may be a good approach to offer donors the choice of receiving the results of the research whether they are beneficial or not. Participants may also choose not to be contacted about their results. Another alternative is to give

participants the option of receiving an aggregate report of all the results of the study which could become a shared benefit for the community. The aforementioned options may be incorporated in a tiered consent.

11.4.5 Benefit sharing

Biological materials and/or data have potential commercial value but the participants' contribution and their share in this benefit is very often not known to them. The informed consent document should emphasize this aspect with necessary clauses for clarity about benefit sharing. See Box 11.4 for further details.

Box 11.4 Considerations for benefit sharing

1. The document should describe whether donors, their families, or communities would receive any financial or non-financial benefits by having access to the products, tests, or discoveries resulting from the research.
2. The benefits accrued, if any, should be returned to the communities from where the donors were drawn in community-based studies.
3. To the maximum extent possible, benefits should be indirect or in kind.

11.4.6 **Role of the EC**

ECs play a key role in oversight and use of the bio- and data repositories for research, scientific and public health programmes. Research proposals, which require biorepository services including material transfer and available data sets, should be reviewed by the EC, either an institutional one or that of the biorepository.

11.5 Biological material/data in forensic departments of laboratories

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

11.5.1 Informed consent: If there is no written consent by the deceased person permitting use of organs or tissues, the family can be approached for consent for use of left-over organs or tissues.

11.5.2 No consent would be required if sample or data is anonymized.

11.5.3 If the deceased has no claimant then forensic officials will be authorized to give permission for use of material/data from its sources and be responsible for use of unclaimed cadavers.

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

11.5.5 The information in the informed consent document should state what tissue/organ will be retained, who will be the custodian, duration of storage of sample, what type of research would be conducted and method for disposal of the remains.

11.5.6 Genetic research or revelation of any other stigmatizing factors like HIV, etc. in the deceased may have implications for family members. In such instances, all ethical requirements as in the case of live participants should be followed.

11.5.7 The role of the EC is to review and approve the type of consent – broad, tiered with or without option to opt-out or specific and to assess from whom it would be taken – the family, closest relative or friend – or whether sample anonymization should be done.

11.6 Governance of biobank/biorepository

Institutions where data are collected and archived must have an established governance structure with the following requirements for regulation.

11.6.1 Each biorepository should have its own technical authorization committee with representation of both science and ethics and external members. This committee should function in tandem with the EC.

11.6.2 A technical authorization committee, indigenous to the biorepository, should govern collection of specimens, disbursement of biospecimens and data to researchers. The same committee should also oversee regulatory aspects like execution of MTA or data transfer agreement (DTA) for transfer of biospecimens and/or data to other institutions.

11.6.3 Stand-alone huge repositories should have separate technical authorization committees and ECs to undertake the above-mentioned tasks.

11.6.4 The biobank should have well-structured SOPs and clear guidelines for collection, coding, anonymization, storage, access, retrieval and sharing of biospecimens and data.

11.6.5 The technical authorization committee/governance committee could comprise members such as clinicians, geneticists, lawyers, basic scientists, sociologists, epidemiologists, statisticians and ethicists.

11.7 Special issues related to datasets

11.7.1 With increasing ease of establishing and maintaining large repositories the primary objective of data collection and storage in some of these databases may not be

research but with advances in information technology (IT) and decreasing costs, they offer a huge potential for subsequent research as well as commercialization. Whenever such repositories are used for purposes of research or for subsequent commercialization, it must follow the expected requirements of any other health-related research with due diligence, including review by an EC.

11.7.2 There is also a proliferation of data mining and other data science tools that can be employed on existing databases for research purposes to reduce costs and health related processes. EC approval is required to establish legitimacy of the purpose for which the data would be mined, access control and about the usefulness of information for particular groups (such as rare disease group). Data privacy, data accuracy, data security, and possibility of legal liability should be ensured when the data is outsourced or sold. Auditing could be done to detect misuse.

11.7.3 Health data is increasingly being collected outside of traditional healthcare settings. Data is shared with third parties not only for research, but also for commercial gain. Big data in health research raise a wide spectrum of ethical issues, ranging from risks to individual rights, such as privacy and concerns about autonomy to individuals. There are unique aspects, such as its data sources, scale, and open access provisions. Ethical issues related to data security, sharing, rights, benefit sharing and others surrounding big data need to be closely examined.

11.7.4 Databases maintained in electronic/digital formats, linked by Internet or other networks, using cloud computing technologies and those associated with big data initiatives, may pose additional risks to privacy and confidentiality than what is described under biobanks or traditional paper-based data repositories. Hence, in such situations all reasonable measures must be adopted to respect and protect privacy and confidentiality of individuals as given in Box 11.5.

Box 11.5 Measures to ensure privacy and confidentiality of individuals

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

11.8 Contingency plan

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

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ABBREVIATIONS AND ACRONYMS

AAHRPP	Association for the Accreditation of Human Research Protection Programmes
AE	adverse event
ART	assisted reproductive technology
AYUSH	Ayurveda, Unani, Siddha and Homeopathy
BA/BE	bioavailability / bioequivalence
CAB/ CAG	community advisory board/ community advisory group
CDSCO	Central Drugs Standard Control Organization
COI	conflict of interest
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
CRO	contract research organization
CRT	cluster randomized trials
CTRI	Clinical Trial Registry-India
DCGI	Drug Controller General of India
DGFT	Directorate General of Foreign Trade
DGHS	Directorate General of Health Services
DSMB	Data and Safety Monitoring Board
DTA	data transfer agreement
EC	ethics committee
ELSI	ethical, legal and social issues
GCP	good clinical practice
GLP	good laboratory practices
GMP	good manufacturing practices
GOI	Government of India
HMSC	Health Ministry's Screening Committee
ICD	informed consent document
ICF	informed consent form
ICH	International Conference on Harmonization
ICJME	International Committee of Medical Journal Editors
ICMR	Indian Council of Medical Research
IC-SCR	institutional committee for stem cell research
IND	investigational new drug
Ind EC	independent ethics committee
IP	investigational product
IPR	intellectual property rights
LAR	legally acceptable/authorized representative
MoHFW	Ministry of Health and Family Welfare
MOU	memorandum of understanding
MTA	material transfer agreement
MTP	medical termination of pregnancy
NABH	National Accreditation Board for Hospitals and Healthcare Providers
NABL	National Accreditation Board for Testing and Calibration Laboratories
NACO	National AIDS Control Organization
NAC-SCRT	National Apex Committee for Stem Cell Research and Therapy
PGD/ PGS	pre-implantation genetic diagnosis / screening
PIS	participant information sheet
RCR	responsible conduct of research
SAE	serious adverse events
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SOP	standard operating procedure
TM	traditional medicines
TOR	terms of reference

Glossary

1.	**Accountability**	**The obligation of an individual or organization to account for its activities, accept responsibility for them and to disclose the results in a transparent manner.**
2.	**Adverse event**	Any untoward medical occurrence in a patient or participant involved in a study which does not necessarily have a causal relationship with the intervention. The adverse event can therefore be any unfavourable or unintended sign or experience, whether or not related to the product under investigation.
3.	**Appellate authority**	It decides on the appeal filed against a decision of the lower authority. Its mandate is to ensure that due process of law is followed.
4.	**Assent**	To agree or approve after thoughtful consideration an idea or suggestion to participate in research by a young person below the age of 18 years who is old enough to understand the implications of any proposed research but not legally eligible to give consent. The assent has to be corroborated with informed consent of parent/LAR.
5.	**Audit**	A systematic and independent examination of research activities and documents to determine whether the review and approval activities were conducted, data recorded and accurately reported as per applicable guidelines and regulatory requirements.
6.	**Autonomy**	The ability and capacity of a rational individual to make an independently informed decision to volunteer as a research participant.
7.	**AYUSH intervention**	Includes any existing/new intervention with drug, therapeutic or surgical procedure or device in the recognized traditional systems of India as per Ministry of AYUSH, GOI (including Ayurveda, Yoga, Naturopathy, Unani, Siddha, Homoeopathy, SOWA-RIGPA).
8.	**Biomedical and health research**	Research including studies on basic, applied and operational research designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioural), their detection, cause and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation including clinical research.
9.	**Beneficence**	To try to do good or an action which weighs the risks against benefits to prevent, reduce or remove harm for the welfare of the research participant(s) in any type of research.
10.	**Caregivers**	A caregiver or carer is an unpaid or paid person who helps another individual with illness or impairment with daily activities/performance.
11.	**Case report form (CRF)**	Case record form or case report form is a printed, optical or electronic document designed to record all the required information in the protocol on each study participant for reporting to the sponsor.
12.	**Clinical research**	Research that directly involves a particular person or group of people to study the effect of interventions, or uses materials/data from humans indirectly, such as their behaviour or samples of their tissue for prevention, treatment and diagnosis of a disease condition/health disorder.
13.	**Clinical trial**	As per amended Schedule Y (2005) of the Drugs and Cosmetics Rules, 1945, a clinical trial refers to a systematic study of new drugs in human subjects to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and /or adverse effect with the objectives determining safety and/or efficacy of a new drug. The academic clinical trial as per GSR 313 (e) dated 16 March 2016 is a clinical trial intended for academic purposes in respect of approved drug formulations for any new indication or new route of administration or new dose or new dosage form.
14.	**Clinical trial registry**	An official platform for registering a clinical trial, such as Clinical Trial Registry-India
15.	**Clinician**	A person with recognized medical qualification and expertise/training.
16.	**Cognitive impairment**	When a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life.

17.	**Coercion**	An overt or implicit threat of harm to a participant which is intentional to force compliance.
18.	**Collaborative research**	An umbrella term for methodologies that actively engage researchers, communities and/ or policy makers in the research process from start to finish.
19.	**Compensation**	Provision of financial payment to the research participants or their legal heirs when temporary or permanent injury or death occurs due to participation in biomedical and health research.
20.	**Confidentiality**	Keeping information confidential which an individual has disclosed in a relationship of trust and with the expectation that it shall not be divulged to others without permission.
21.	**Confidentiality agreement**	Secrecy or non-disclosure agreements designed to protect trade secrets, information and expertise from being misused by those who have learned about them.
22.	**Contract Research Organization (CRO)**	An institution or service organization which represents a sponsor in providing research support/services on a contractual basis nationally or internationally.
23.	**Custodian**	A person who has responsibility of taking care of or protecting entrusted assets, either biological samples or data.
24.	**Debriefing**	A process of providing a summary update of a condition or situation to the affected or concerned parties. It is an important ethical consideration in studies involving deception. Such post-experimental follow-up is considered beneficial even if no deception is used or there is only minimal risk to participants.
25.	**Deception**	Deception occurs when investigators provide false or incomplete information to participants to misleading them to achieve the study objectives and for larger public good. Research employing any type of deception should undergo full committee review.
26.	**Distributive justice**	Fair distribution of burden, resources and benefits. In research, it means fair selection of participants.
27.	**Ethicist**	One whose judgement on ethics and ethical codes is based on knowledge/experience through qualification or training.
28.	**Exploitation**	The action or fact of treating someone unfairly in order to benefit from their participation.
29.	**Exploratory research**	Preliminary research conducted to gain insights for a problem that has not yet been clearly defined.
30.	**Impartial witness**	A literate person, who is independent of the research and would not be unfairly influenced by people involved with the study, who attends the informed consent process if the participant and/or their LAR cannot read, and understand the informed consent form and any other written information supplied to the participant.
31.	**Independent consultant**	An expert who gives advice, comments and suggestions to the EC and has no affiliation to the institute or researchers proposing the research protocols. This individual has no voting power for decision making.
32.	**Inducement**	A motive or consideration that leads one to action or to additional or more effective actions without considering the harm that may occur.
33.	**Informed consent document (ICD)**	Written signed and dated paper confirming a participant's willingness to voluntarily participate in a particular research, after having been informed of all aspects of the research that are relevant for the participant's decision to participate.
34.	**Justice**	Pertains to fairness in the way people are dealt with, indicating fair selection and distribution of risks and benefits to participants who should be fully apprised about them.
35.	**Lay person**	A literate person who has not pursued a medical science/health-related career in the last 5 years and is aware of the local language, cultural and moral values of the community.
36.	**Legal expert**	A person with a basic degree in law from a recognized university, with experience.
37.	**Legally acceptable representative (LAR)**	A person who will give consent on behalf of a prospective participant who, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the EC.

38.	**Legally authorized representative (LAR)**	A person who, under applicable law or judicial authority, can give consent on behalf of a prospective participant who, for either legal or medical reasons, is unable to give consent herself/himself to participate in research or to undergo a diagnostic, therapeutic or preventive procedure as per research protocol, duly approved by the ethics committee.
39.	**Maleficence**	The act of committing harm or a harmful act.
40.	**Marginalized communities**	A group of people actively separated or excluded from the rest of society.
41.	**Minimal risk**	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of a healthy individual or general population or during the performance of routine physical or psychological examinations or tests. However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant since it would be undertaken as part of current everyday life.
42.	**Non-therapeutic trial**	A trial which is unlikely to produce any direct benefit to the participants involved. The aim of a non-therapeutic trial is to obtain knowledge which may contribute towards the future development of new forms of treatment or procedures.
43.	**Ostracization**	To exclude, by general consent, from society, friendship, conversation, privileges, etc.
44.	**Particularly vulnerable tribal group (PVTG)**	These are a special class of tribal groups, classified as such by the Government of India, due to their especially low development indices when compared to other local tribes. These were classified under the Dhebar Commission (1960–1961), so as to better facilitate their growth, at par with other scheduled tribes on a national scale, and help them to get included in mainstream development, while using their indigenous knowledge. They have a pre-agricultural system of existence as mainly hunters with zero or negative population growth, extremely low level of literacy and no written language.
45.	**Pilot studies**	A pilot study, pilot project or pilot experiment is a small-scale preliminary study conducted in order to evaluate feasibility, time, cost, adverse events and effect size (statistical variability) in an attempt to predict an appropriate sample size and improve upon the study design prior to performance of a full-scale research project.
46.	**Pivotal trial**	A clinical trial or study intended to provide evidence for drug marketing approval from the licensing authority; usually a Phase III study which presents the data that the licensing authority uses to decide whether or not to approve a drug. A pivotal study will generally be well-controlled, randomized, of adequate size, and whenever possible, double-blind.
47.	**Post-marketing surveillance**	The practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market. This is an important part of the science of pharmacovigilance.
48.	**Professional competence**	The broad professional knowledge, attitude and skills required in order to work in a specialized area or profession.
49.	**Principal investigator**	An individual or the leader of a group of individuals who initiates and takes full responsibility for the conduct of biomedical health research; if there is more than one such individual, they may be called co-principal investigators/ co-investigators.
50.	**Psychosocial harm**	Research, particularly psychology studies, can put participants in situations that may make them feel uncomfortable while learning about their reaction to a situation. The result can be psychological harm that can manifest itself through worry (warranted or unwarranted), feeling upset or depressed, embarrassed, shameful or guilty, and/or result in the loss of self-confidence.
51.	**Quorum**	Minimum number and/or kind of EC members required for decision making during a meeting.
52.	**Research-related injury**	Harm or loss that occurs to an individual as a result of participation in research, irrespective of the manner in which it has occurred, and includes both expected and unexpected adverse events and serious adverse events related to the intervention, whenever they occur, as well as any medical injury caused due to procedures.
53.	**Risk**	Probability of harm or discomfort to research participants. Acceptable risk differs depending on the conditions inherent in the conduct of research.

54.	**Serious adverse event (SAE)**	An adverse event is serious when the research outcome for the participant is death, life-threatening injury requiring hospitalization, prolongation of hospitalization, significant disability/incapacity, congenital anomaly, or requirement of intervention to prevent permanent impairment or damage.
55.	**Sexual minorities**	A group whose sexual identity, orientation or practices differ from majority of the surrounding society. It refers to lesbian, gay, bisexual and transgender (LGBT), queer (including the third gender) or intersex individuals.
56.	**Social scientist**	A person who is an expert on societal and social behaviour with specialization/experience in the area.
57.	**Socio-behavioural research**	Refers to the socio-behavioural studies on response of individuals, groups, organizations or societies to external or internal stimuli.
58.	**SOP (standard operating procedure)**	Detailed written instructions in a certain format describing all activities and actions to be undertaken by an organization to achieve uniformity in performance of a specific function.
59.	**Sponsor**	An individual, institution, private company, government or non-governmental organization from within or outside the country who initiates the research and is responsible for its management and funding.
60.	**Stigmatization**	Negative perceptions about an individual because of perceived differences from the population at large. It may occur on the basis of physical appearance, race or sex.
61.	**Surrogate**	A substitute or deputy for another person in a specific role.
62.	**Theologian**	A person who is an expert in the study of religious faith(s), including the system of spirituality, practice and experience about the nature of the divine.
63.	**Test of understanding**	A simple oral or written test designed to identify if the participant has understood the details related to her/his voluntary participation in research before signing the ICD form. (Questions such as “If you decide not to take part in this research study, do you know what your options are?”, “Do you know that you do not have to take part in this research study, if you do not wish to?”, “Do you have any questions?”, etc. will clarify the understanding of the participant.)
64.	**Transparency**	It implies intentional openness, communication, and accountability operating in such a way that it is easy for others to see what actions are performed.
65.	**Therapeutic misconception**	It is a misconception by participants believing that the purpose of clinical trials/research study is to administer treatment rather than to conduct research.
66.	**Undue inducement**	Offer of disproportionate benefit in cash or kind that compromises judgement which may lead to acceptance of serious risks that threaten fundamental interests.
67.	**Unexpected ADR**	An adverse reaction, the nature or severity of which is not described in the informed consent/information sheet or the applicable product information, such as an investigator’s brochure for the unapproved IP or package insert/summary of product characteristics for an approved product.
68.	**Vulnerability**	Vulnerability in research pertains to individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens or social injustice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so.

Annex 1. List of SOPs

STANDARD OPERATING PROCEDURES (SOPS)

S. No.	List of Standard Operating Procedures (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
	8 a. Initial Full Committee Review of New Research Protocols
	8 b. Expedited Review of Research Protocols
	8 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

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The purpose of these guidelines is to safeguard the dignity, rights, safety and well-being of the human participants involved in biomedical and health research. These guidelines are required to be followed by all stakeholders including sponsors, institutions, ethics committees and researchers.