INSTITUTIONAL ETHICS COMMITTEE

JAWAHARLAL NEHRU INSTITUTE OF MEDICAL SCIENCES

POROMPAT, IMPHAL 795005

Standard Operating Procedures
For
Institutional Ethics Committee

Revised October 2021

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Jawaharlal Nehru Institute of Medical Sciences
Standard Operating Procedures (SOP) for Institutional Ethics Committee for Biomedical and Health Research involving Human Participants

1. Introduction

Research is needed to help towards the increase of knowledge about the human condition and to address the burden of disease. In accordance with the Declaration of Helsinki, other similar international guidelines and ICMR for biomedical research, it is necessary for all research proposals involving human subjects to be cleared by an appropriately constituted Ethics Committee (EC) to safeguard the welfare and rights of participants. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects, but also have a continuing responsibility to regularly monitor compliance with all ethical requirements, till the completion of the study. The Indian Council for Medical Research has issued the revised **National Ethical Guidelines for Biomedical and Heath Research involving Human Subject 2017** to be followed in the country to ensure ethical conduct of research studies involving human subjects. Further the **New drugs and Clinical trials rules 2019** was introduced on 19th March 2019 vide GSR 227 (E) by Ministry of Health and Family Welfare (MoHFW), Government of India. This new rules have set specific requirements for ethics committee (EC) and aims to promote clinical research in the country. The Institutional Ethics Committee, Jawaharlal Nehru Institute of Medical Sciences (hereinafter referred as **IEC JNIMS**) will follow these guidelines in all such studies to be conducted in the Institute. But in areas where the said guidelines are silent, or inadequate, it would be open to the Ethics committee of the Institute to resort to other standard national or international guidelines.

2. Objective

The objective of this SOP is to contribute to the effective functioning of the Institutional Ethics Committee (IEC) of JNIMS so that a quality and consistent ethical review mechanism for health and biomedical research is put in place for

all proposals dealt by the IEC JNIMS based on the National Ethical Guidelines for Biomedical and Heath Research involving Human Subject 2017 of the Indian Council of Medical Research, the New Drugs and Clinical Trials Rule 2019, and relevant National and International guidelines.

3. Roles of the IEC JNIMS

i. The IEC JNIMS will review and approve *all types* of research proposals involving human participants with a view to safeguard the dignity, rights, safety and well being of all actual and potential research participants. The goals of research, however important, should never be permitted to override the health and well being of the research participants.

ii. The IEC JNIMS will take care that all the cardinal principles of research ethics viz. *Autonomy, Beneficence, Non - malfeasance and Justice* are taken care of in planning, conducting and reporting of the proposed research. It will look into the aspects of informed consent process, risk benefit ratio, distribution of burden and benefit and provision of compensation wherever required.

iii. It will review the proposals before start of the study as well as monitor the research throughout the study until and after completion of the study through appropriate well documented procedures for example interim reports, final reports and site visits.

iv. The IEC JNIMS shall take up the dual responsibilities of reviewing both the scientific content and ethical aspects of the proposal.

v. The IEC JNIMS will also examine compliance with all regulatory requirements, applicable guidelines and laws of the country and/or other countries/ organizations wherever applicable / feasible.

vi. The IEC JNIMS will ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.

vii. The IEC JNIMS will assist in the development and the education of a research community responsive to local health care requirements.

viii. A separate ethics sub-committee shall be formed from time to time to review research proposals from the students (both undergraduate and

postgraduate including PhD work). Members of the sub-committee, will be from amongst the IEC, JNIMS members which will include the legal expert or lay person member, along with members from clinical and pre-para clinical specialities. The Member Secretary of IEC JNIMS shall chair the sub-committee.

4. Composition, affiliations, qualifications of IEC JNIMS

The IEC JNIMS should be multidisciplinary and multisectoral in composition with adequate representation of age and gender. Independence and competence are the two hallmarks of an IEC. Preferably 50% of the members should be non-affiliated or from outside the institution. The number of persons in IEC JNIMS should preferably be 7 - 12 members including the chairperson and member secretary and a minimum of five members should be present to meet the quorum requirements.

The composition shall be as close as follows:-

A. Chairman
B. One - two persons, (preferably one woman member) from basic medical science area (preferably one from Pharmacology and another from Public Health/Community Medicine)
C. One - two clinicians (preferably one woman member and one from medical and another from surgical specialty).
D. One legal expert or retired judge
E. One social scientist/ representative of non-governmental voluntary agency
F. One philosopher/ ethicist/ theologian
G. One lay person from the community
H. Member Secretary

Table 4.1 Composition, affiliations, qualifications

Sl.no	Member of EC	Criteria
1.	Chairperson	Non-affiliated Qualifications - A well-respected person from any background with prior experience of having served/ serving in an EC
2.	Member Secretary	Affiliated Qualifications - Should be a staff member of the institution - Should have knowledge and experience in clinical research and ethics, be motivated and have good communication skills -Should be able to devote adequate time to this activity which should be protected by the institution
3.	Basic Medical Scientist(s)	Affiliated/ non-affiliated Qualifications - Non-medical or medical person with qualifications in basic medical sciences - In case of EC reviewing clinical trials with drugs, the basic medical scientist should preferably be a pharmacologist
4,	Clinician(s)	Affiliated/ non-affiliated Qualifications - Should be individual/s with recognized medical qualification, expertise and training
5.	Legal expert/s	Affiliated/ non-affiliated Qualifications - Should have a basic degree in Law from a recognized university, with experience Desirable: Training in medical law.
6.	Social scientist/ philosopher/ ethicist/theologian	Affiliated/ non-affiliated Qualifications - Should be an individual with social/ behavioural science/ philosophy/ religious qualification and training and/or expertise and be sensitive to local cultural and moral values. Can

		be from an NGO involved in health-related activities
7.	Lay person(s)	Non-affiliated Qualifications - Literate person from the public or community -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

Box 4.1 Requirements of the IEC JNIMS members

A. The members of the IEC must provide a recent signed CV and training certificates on human research protection and good clinical practice (GCP) guidelines
B. The members of the IEC shall follow the provisions of these rules, Good Clinical Practices Guidelines and other regulatory requirements to safeguard the rights, safety and well-being of trial subjects.
C. Every member of the IEC shall be required to undergo such training and development programmes as may be specified by the Central Licensing Authority from time to time.
D. No member of the IEC, having a conflict of interest, shall be involved in the oversight of the clinical trial or bioavailability or bioequivalence study protocol being reviewed by it and all members shall sign a declaration to the effect that there is no conflict of interest.
E. While considering an application which involves a conflict of interest of any member of the IEC, such member should voluntarily withdraw from the IEC review meeting, by expressing the same in writing, to the Chairperson. The details in respect of the conflict of interest of the member shall be duly recorded in the minutes of the meetings of the IEC.

F. The members of the IEC must be willing to place her/his full name, profession and affiliation to the EC in the public domain; and
G. Must be committed and understanding to the need for research and for imparting protection to research participants in research

5. Power and Functions of the IEC JNIMS members

5.1.1. Chairperson

i. The Chairperson of the IEC JNIMS will be from outside the Institution to maintain the independence of the committee.
ii. The Chairperson shall chair all meetings of the IEC JNIMS be accountable for independent and efficient functioning of the committee. The Chairperson is also empowered to convene emergency meetings of the full IEC JNIMS or a sub-group/committee as per requirement.
iii. Ensure active participation of all members (particularly non-affiliated, non-medical/ non- technical) in all discussions and deliberations
iv. Ratify minutes of the previous meetings
v. In case of anticipated absence of 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.
vi. Seek Conflict of Interest declaration from members and ensure quorum and fair decision making.
vii. Handle complaints against researchers, IEC members, conflict of interest issues and requests for use of IEC data, etc.

5.1.2 Member Secretary

i. The Member Secretary is responsible for organizing and convening all meetings in consultation with the chairperson, maintaining the records and communicating with all concerned including a copy to the Director, JNIMS.
ii. The member secretary is in Charge of the Secretariat of the IEC JNIMS and reports to the Chairperson on all matter related to the IEC JNIMS, monitoring of the research proposals reviewed by IEC JNIMS.
iii. Organize documentation, communication and archiving of all IEC documents
iv. Ensure training of IEC secretariat and IEC members
v. Ensure SOPs are updated as and when required
vi. Ensure adherence of EC functioning to the SOPs
vii. Prepare for and respond to audits and inspections
viii. Ensure completeness of documentation at the time of receipt and timely inclusion in agenda for EC review.
ix. Assess the need for expedited review/ exemption from review or full review.
x. Assess the need to obtain prior scientific review,
xi. Invite independent consultant, patient or community representatives.
xii. Ensure quorum during the meeting and record discussions and decisions

5.1.3 Basic Medical Scientist(s)

i. 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
ii. For clinical trials, pharmacologist to review the drug safety and pharmacodynamics.

5.1.4 Clinician(s)

i. Scientific review of protocols including review of the intervention, benefit-risk analysis, research design, methodology, sample size, site of study and statistics

ii. Ongoing review of the protocol (SAE, protocol deviation or violation, progress and completion report)
iii. Review medical care, facility and appropriateness of the principal investigator, provision for medical car, management and compensation.
iv. Thorough review of protocol, investigators brochure (if applicable) and all other protocol details and submitted documents.

5.1.5 Legal expert/s

i. Ethical review of the proposal, Informed Consent Document (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.
ii. Interpret and inform EC members about new regulations if any

5.1.6 Social scientist/ philosopher/ ethicist/theologian

i. Ethical review of the proposal, ICD along with the translations.
ii. Assess impact on community involvement, socio–cultural context, religious or philosophical context, if any
iii. Serve as a patient/participant/ societal / community representative and bring in ethical and societal concerns

5.1.6 Lay person(s)

i. Ethical review of the proposal, ICD along with translation(s).
ii. Evaluate benefits and risks from the participant's perspective and opine whether benefits justify the risks.
iii. Serve as a patient/participant/ community representative and bring in ethical and societal concerns.
iv. Assess on societal aspects if any.

5.2 Criteria for selection of members of IEC JNIMS

i. 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 IEC. See Table 4.1and section 5.1.1 to 5.1.7 for further details.

ii. Members are appointed to the IEC 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.

Box 6.1 **Quorum requirements for EC meetings**

1. A minimum of five members present in the meeting room.
2. The quorum should include both medical, non medical or technical or/and non-technical members.
3. Minimum one non-affiliated member should be part of the quorum.
4. Preferably the lay person should be part of the quorum.
5. The quorum for reviewing regulatory clinical trials should be in accordance with current CDSCO requirements: In case of clinical trial or bioavailability or bioequivalence protocol and related documents will not be reviewed by the IEC unless at least five of its members are present namely, ((i) medical scientist (preferably a pharmacologist); (ii) clinician; (iii) legal expert; (iv) social scientist or philosopher or ethicist or theologian or a similar person; (v) lay person are present.
6. No decision is valid without fulfilment of the quorum.

6.1 Terms of Reference

i. The Director, Jawaharlal Nehru Institute of Medical Sciences constitutes the IEC JNIMS. It would be preferable to appoint persons trained in bioethics or persons conversant with ethical guidelines and laws of the country.

ii. The duration of appointment is initially for a period of 2 years. At the end of 2 years, as the case may be, the committee is reconstituted, and up to 50% of

the members may be replaced by a procedure that includes nominations by the chairperson of the IEC, JNIMS and head of the institute.

iii. A member can be replaced by a substitute nominated member in the event of death or long-term non-availability **(absence in 3 consecutive meetings)** or for any action not commensurate with the responsibilities laid down in the guidelines deemed unfit for a member.

iv. A member can tender her/his resignation to the chairperson of the IEC, JNIMS with reasons and the committee will take the decision.

v. All members should maintain absolute confidentiality of all discussions during the meeting and sign a confidentiality (undertaking form) form.

vi. Conflict of interest should be declared by members of the IEC JNIMS.

vii. The JNIMS authority is responsible for providing logistical support, such as infrastructure, staff, space, funds, adequate support and protected time for the Member Secretary to run the IEC JNIMS functions.

viii. Normally, the IEC JNIMS will meet in the months of **March, June, September and December every year at 1 PM on the 1st of the month.** If it falls on holiday, the meeting will be held on the next working day. However, extraordinary meetings can be called with the consent of the chairperson for discussion of urgent matters.

ix. Any change in the membership or the constitution of the registered IEC will be intimated in writing to the Central Licensing Authority within thirty working days.

x. A minimum of five members is required to form the quorum without which a decision regarding the research should not be taken. The quorum should be as specified in Box 6.1.

xi. Processing fee if any should be remitted along with the application.

xii. Honorarium for attending the review meeting for the non-affiliated members in the IEC JNIMS including invited experts shall be fixed at Rs2000/-(Rupees two thousand only) per sitting and Rs 1000/-(Rupees One thousand only) for affiliated members, which will be subjected to changes from time to time.

xiii. The SOP IEC JNIMS shall be updated periodically based on the changing requirements.

6.2 **Training**

i. Members should be trained in human research protection, IEC functions and SOPs, and should be conversant with ethical guidelines, GCP guidelines (if applicable) and relevant regulations of the country.
ii. EC members should undergo initial and continuing training in human research protection, applicable IEC SOPs and related regulatory requirements. All trainings should be documented.
iii. Any change in the relevant guidelines or regulatory requirements should be brought to the attention of all EC members.
iv. EC members should be aware of local, social and cultural norms and emerging ethical issues.

7. Application Procedures

i. All proposals should be submitted in the prescribed application form duly signed by the Principal investigator and Co-investigators/collaborators should be forwarded by the Head of the Departments/Institution to the Ethics committee. Details of which is given in Appendix I
ii. Thirteen (seven in case of the students/scholars) copies of the proposal should be submitted along with the application form. List is given in Box 7.1.
iii. All relevant documents should be enclosed with the application form.
iv. The date of meeting will be intimated to the researcher, to be present, if necessary to offer clarifications.
v. Processing fee should be remitted along with the application wherever applicable.
vi. The IEC JNIMS secretariat shall screen **all** proposals for their completeness and depending on the risk involved and categorise them into three types, namely, exemption from review, expedited review and full review.
vii. Generally, research proposals should be submitted at least 3 weeks before the scheduled meetings.
viii. The decision of the IEC JNIMS will be communicated in writing.

Box 7.1 List of documents required for submission for ethical approval from IEC, JNIMS

1. Covering letter to the Member Secretary
2. Type of review requested
3. **Thirteen (13) copies** of duly filled in application form along with
    a. Inform consent document in English and Manipuri (plus assent form wherever applicable)
    b. Case record form/questionnaire
    c. Recruitment procedures: advertisement/notices (wherever applicable)
    d. Brief CV of all investigators
    e. Details of funding agency/sponsor and fund allocation (if applicable)
    f. Budgetary break-up (for funded projects)
    g. Insurance documents for study participants (wherever applicable)
    h. A statement on Conflict of interest (wherever applicable)
    i. GCP training certificate of investigators (for clinical trials)
    j. List of ongoing research undertaken by Principal Investigator
4. **One (01)** Copy of full research protocol
5. Undertaking for payment of processing fee after fund release (for funded projects only)
6. Regulatory permissions (wherever applicable)
7. Relevant administrative approvals (such as HMSC approval for International trials)
8. Clinical trial agreement between the sponsors, investigator and the head of the institution(s) (if applicable)
9. Documentation of clinical trial registration (preferable)
10. Copy of approval letters from ICMR or other collaborating sites (for multi-centric studies)
11. MoU in case of studies involving collaboration with other institutions (if applicable)

- All sections and subsections in the IEC, JNIMS application form to

be duly filled in with information related to JNIMS specific site in case of Multi-centric studies.

- All documents for ethical approval to IEC JNIMS to be submitted through proper channel.

Any other requirements may be communicated to the principal investigator of the project after scrutiny of submitted documents.

Box 7.2 Details of documents to be included in the protocol

The protocol should including the following:

1. the face page carrying the title of the proposal with signatures of the investigators;
2. brief summary/ lay summary;
3. background with rationale of why a human study is needed to answer the research question;
4. justification of inclusion/exclusion of vulnerable populations;
5. clear research objectives and end points (if applicable);
6. eligibility criteria and participant recruitment procedures;
7. detailed description of the methodology of the proposed research, including sample size (with justification), type of study design (observational, experimental, pilot, randomized, blinded, etc.), types of data collection, intended intervention, dosages of drugs, route of administration, duration of treatment and details of invasive procedures, if any; duration of the study
8. justification for placebo, benefit–risk assessment, plans to withdraw. If standard therapies are to be withheld, justification for the same
9. 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
10. plan for statistical analysis of the study
11. plan to maintain the privacy and confidentiality of the study

participants; for research involving more than minimal risk, an account of management of risk or injury

12. proposed compensation, reimbursement of incidental expenses and management of research related injury/illness during and after research period
13. provision of ancillary care for unrelated illness during the duration of research
14. an account of storage and maintenance of all data collected during the trial; and plans for publication of results – positive or negative – while maintaining confidentiality of personal information/ identity
15. ethical considerations and safeguards for protection of participants.

8. Review Process

8.1. Element of review

i. Essentiality of the study
ii. Scientific design and conduct of the study
iii. Examination of predictable risks/harms
iv. Examination of potential benefits
v. Procedure for selection of participants, including inclusion/ exclusion of participants and other issues like advertisement details
vi. Management of research related injuries, adverse events
vii. Compensation provisions
viii. Justification for placebo in control arm, if any
ix. Availability of products after the study, if applicable
x. Patient information sheet and informed consent form in local language or the language in which it is going to be administered.
xi. Protection of privacy and confidentiality.
xii. Involvement of the community, wherever necessary.
xiii. Plans for data analysis and reporting
xiv. Adherence to all regulatory requirements and applicable guidelines
xv. Competence of investigators, research and supporting staff
xvi. Facilities and infrastructure of study sites

xvii. Criteria for withdrawal of participants, suspending or terminating the study

xviii. Account of storage and maintenance of all data collected during the trial/research

xix. Plans for publication of results – positive or negative- while maintaining the privacy and confidentiality of the study participants

xx. Details of foreign collaborators and documents for review of Health Ministry's Screening Committee (HMSC) or appropriate Committees/ agencies/authority like Drug Controller General of India (DCGI) for international collaborative studies

xxi. Memorandum of Understanding (MoU) for exchange of biological material in national/international collaborative study

8.2. Types of review

8.2.1. Exemption from review

Proposals with less than minimal risk where there are no linked identifiers, like:

i. Research conducted in established or commonly accepted educational settings, involving normal educational practices such as :
   a. research on regular and special educational instruction strategies, or
   b. research on the effectiveness of or the comparison among instruction techniques, curricula, or classroom management methods, etc.

ii. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behaviour unless:
   a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

iii. Research conducted on data available in the public domain for systematic reviews or meta-analysis

iv. Research involving 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).

v. While normally the research in the above categories will be considered for exemption, it may not be considered for exemption if it is involving children and other vulnerable groups as participants.

8.2.2. Expedited review

i. The proposals presenting no more than minimal risk to research participants may be subjected to expedited review.

a. research involving non-identifiable specimen and human tissue from sources like blood banks, tissue banks and left-over clinical samples;
b. research involving clinical documentation materials that are non-identifiable (data, documents, records);
c. modification or amendment to an approved protocol including administrative changes or correction of typographical errors and change in researcher(s);
d. revised proposals previously approved through expedited review, full review or continuing review of approved proposals;
e. minor deviations from originally approved research causing no risk or minimal risk;
f. 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

g. 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
h. research during emergencies and disasters

ii. The Chair and/or IEC member(s) designated by the Chair or a sub-committee of the IEC constituted by it will undertake the expedited review

iii. If the PI believes that her/his proposal qualifies for the expedited review, she/he should make a request for the same while submitting application for review to the IEC.

iv. The person(s) undertaking expedited review may take any action that the full committee may take except disapproval of the research proposal. Thus, in the expedited review the reviewer(s) may approve or request modification(s) in the proposal/protocol and/or consent form and other study materials or defer action pending additional information, but if disapproval is the decision, then the proposal must be referred to the full committee for review at its next convened meeting.

v. A list of all research proposals approved using expedited review procedures is provided to the IEC at its next convened meeting. When a research proposal is reviewed pursuant to the expedited review process, IEC records of the review must include documentation of the determination of minimal risk and the permissible category of research justifying the expedited review.

vi. Genetic studies should not be considered for expedited review. Appendix-II provides the categories of research that will be considered for the expedited review as per ICMR guidelines.

8.2.3. Full review

i. All research proposals presenting more than minimal risk that are not covered under exempt or expedited review should be subjected to full committee review,
   a. research with minor increase over minimal risk
   b. studies involving deception of participants

c. 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;

d. amendments of proposals/related documents (including but not limited to informed consent documents, investigator's brochure, advertisements, recruitment methods, etc.) involving an altered risk;

e. major deviations and violations in the protocol;

f. 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;

g. 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;

h. prior approval of research on predictable emergencies or disasters before the actual crisis occurs for implementation later when the actual emergency or disaster occurs.

ii. Proposals that involve vulnerable population and special groups shall be subjected to full review by all the members.

8.3. Submission and review procedures

i. Researchers should submit research proposals as soft or hard copies to the Office of IEC JNIMS through proper channel for review in the prescribed format and required documents as per IEC SOPs. The EC should prepare a checklist for the required documents as given in Box 7.1 and 7.2

ii. 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 11.1 for risk categorization and section 8.2 for further details regarding types of review.

iii. 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 IEC JNIMS. The decision on the type of review required rests with the IEC JNIMS and will be decided on a case-to-case basis. Researchers can approach the IEC with appropriate justification for the proposal to be considered as exempt, expedited or if waiver of consent is requested.

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

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

8.4. Review meeting

i. The mandate of the IEC JNIMS will be to review all research proposals involving human subjects to be conducted at the Institute or outside the institute involving personnel of JNIMS, irrespective of the funding agency. If outside laboratories are involved while carrying out such works, they should be recognized by the Institute. For the review of multicentric research is given in Box 8.4.1.

ii. 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.

iii. The review shall be done by all reviewers (members of IEC JNIMS).

iv. 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.

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

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

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

viii. The IEC JNIMS should not keep a decision pending normally for more than 3 months after its first discussion.

ix. All the proposals received in time shall be reviewed in the ensuing IEC JNIMS meeting. The meeting can be extended to another day(s) to complete the review process.

x. Researcher will be invited to offer clarifications if need be. Independent consultants/experts will be invited to offer their opinion on specific research proposals if needed but they will not take part in the final decision making.

xi. Decision will be taken by consensus after discussion.

xii. All decisions will be taken in meetings and not by circulation of project proposals.

xiii. All proposals submitted at least 3 weeks before the schedule meetings should be put up for review.

xiv. An interim review can be resorted to by a sub-committee, to be constituted by the chairperson, instead of waiting for the scheduled time of the meeting like re-examination of a proposal already examined by the IEC or any other matter which should be brought to the attention of the IEC. However, decisions taken should be brought to the notice of the main committee.

xv. Modified proposals may be reviewed by an expedited review through identified members.

xvi. In the case of urgency/emergency, after reviewing the nature of urgency/emergency, the chairperson is empowered to call a meeting of the IEC, JNIMS or form an interim review committee to review the proposal. In case of decisions taken by the interim review committee, it shall be brought up in the next IEC, JNIMS meeting for discussion and ratification.

xvii. If required, subject experts could be invited to offer their views. These experts/consultants may be specialists in ethical or legal aspects, specific diseases or methodologies, or represent specific communities; patient groups or special interest groups (e.g. cancer patients, HIV/AIDS positive persons or ethnic minorities).

xviii. 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.

xix. 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.

Box 8.4.1 Review of multicentric research

• The IEC of JNIMS will communicate with other participating sites. If IEC, JNIMS does not grant approval for a study at a site, the reasons will be shared with other ECs and deliberated upon. • The IEC, JNIMS can suggest site-specific protocols and informed consent modifications as per local needs. • Separate review may be requested by the IEC, JNIMS 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. •Sponsor/funding agencies should be informed about any site-specific changes being made to the IEC. •The site ECs in this case IEC, JNIMS, retain the 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 IEC, JNIMS. • Adherence to protocols, including measures to terminate the participation of the erring local centres, if required will also be monitored by the IEC, JNIMS.

8.5. Decision-making

i. Members will discuss the various issues before arriving at a consensus decision.

ii. Member should withdraw from the meeting during the decision procedure concerning an application where a conflict of interest arises and this should be indicated to the chairperson prior to the review of the application and recorded in the minutes.

iii. Decisions will be made only in meetings where quorum is complete.

iv. Only members can make the decision. The experts/ consultants will only offer their opinions and shall not take part in decision making.

v. Decision may be 'to approve', 'to reject' or 'to revise the proposals'. Specific suggestions for modifications and reasons for rejection should be given. The decisions may be as shown in Box 8.5.1.

vi. In cases of conditional decisions, clear suggestions for revision and the procedure for having the application re-reviewed should be specified.

vii. In case of an appeal against the decision of the IEC, JNIMS, an application should be submitted to the chairperson by the principal investigator within two weeks of communication of that decision.

Box 8.5.1 Types of decisions by IEC, JNIMS

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

8.6. Communicating the decision

i. Decision will be communicated by the Member Secretary in writing.

ii. Suggestions for modifications, if any, should be communicated to the PI.

iii. Reasons for rejection should be informed to the researchers.

iv. If revision is to be made, seven (07) copies of the revised document should be submitted within a stipulated period of time as specified in the communication.

v. The schedule / plan of ongoing review by the IEC should be communicated to the PI.

9. Processing Fee

i. **For externally funded projects, 10% of the fringe benefit (overhead charge) should be charged as processing fee by IEC, JNIMS**. If funds are not available while submitting the protocol (e.g. when IEC approval is a necessary step for applying to an external funding agency like the DST or the ICMR, etc), then the covering letter must contain an undertaking that the requisite fee will be deposited before starting the work.

ii. In case of rejection of proposal, a processing fee of Rs. 2000 (two thousand) will be levied.

iii. In case of withdrawal before the meeting, a processing fee of Rs. 1000 will be charged.

iv. Student's project works, postgraduate student's theses, internally funded projects that are non-commercial in nature, projects without sponsors (commercial or otherwise), revised submissions and self financed projects are exempted from paying the processing fee.

10. Monitoring

Once IEC JNIMS gives a certificate of approval it is the duty of the IEC JNIMS to monitor the approved studies. Actual site visits can be made especially in the event of reporting of adverse events or violations of human rights. Additionally, periodic status reports must be asked for at appropriate intervals based on the safety concerns. SAE reports from the site as well as other sites are reviewed by members of the IEC, JNIMS to be constituted by the chairperson from time to time. In case the IEC desires so, reports of monitoring done by the sponsor and the recommendations of the DSMB may also be sought.

i. **Periodic review** The ongoing research may be reviewed at regular intervals of six months if the study period is more than 6 months.

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

iii. **Monitoring / Follow up procedures**

a. Brief reports should be submitted at 6 months intervals for review.

b. Final report should be submitted at the end of study.

c. All Serious Adverse Effects and the interventions undertaken should be intimated. The IEC will also examine the measures taken for medical management of SAEs and 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.

d. Protocol deviation, if any, should be informed with adequate justifications.

e. Any amendment to the protocol should be resubmitted for renewed approval.

f. Any new information related to the study should be communicated.

g. Premature termination of study should be notified with reasons along with summary of the data obtained so far.

h. Prior permission of any change of the investigator(s)/site(s) should be taken from the IEC, JNIMS.

iv. Site monitoring

a. The IEC will follow mechanisms described in the SOP to monitor the approved study site until completion of the research to check for compliance or improve the function.

b. For research that involves higher risk or vulnerable participants or if there is any other reason for concern, the IEC, JNIMS at the time of initial review or continuing review can suggest that routine monitoring may be conducted at more frequent intervals.

11. Benefit-risk assessment

The IEC, JNIMS will assess the inherent benefits and risks, to ensure a favourable balance of benefits and risks, and evaluate plans for minimizing the risk and discomfort and decide on the merit of the research before approving it.

Table 11.1.Categories of Risk

Type of risk	Definition/description
Less than minimal risk	Probability of harm or discomfort anticipated 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 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 is unlikely. Examples history taking, physical examination, chest X-ray, obtaining body fluids without invasive intervention, e.g hair, saliva or urine samples, etc.
Minor increase over minimal risk or Low risk	Probability of harm or discomfort is only a little more than the minimal risk threshold. Examples: research on children, adolescents, persons incapable of giving consent, delaying or withholding a proven intervention or standard of care in a control group during RCT, drawing a small blood sample, trying a new diagnostic technique in pregnant and breastfeeding women, etc.
More than minimal risk or High risk	Probability of harm or discomfort anticipated is invasive and greater than minimal risk. Examples -using a drug, device or invasive procedure such as lumbar puncture, lung/liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

12. Reporting of Adverse Events (AE)/Serious Field Incidents (SFI)

i. All research proposals need to define the anticipated adverse events and the criteria for assessing their seriousness

ii. Adverse events must be reported to the IEC JNIMS within 24 hours of their occurrence. The IEC, JNIMS will decide the course of action.

iii. In the multi-site/centric research, serious adverse events from the site(s) of the study must be reported to the DSMB/IEC JNIMS within 24 hours. In SAE like death, study should be stopped till further directive comes from the

IEC JNIMS. Normally, decision for continuing the study shall be taken by IEC, JNIMS within 48 hr of the receipt of the SAE report.

iv. In all other cases, all serious adverse events/field incidents must be reported to the IEC JNIMS/DSMB within 24 hours of their occurrence.

v. While reporting adverse events/SFI to the IEC/DSMB, the PI must provide her/his views on whether: (a) the event(s) is/are related to the study, (b) it/they warrant any change in the protocol and/or informed consent form, (c) it/they warrant any change in the care or management of the participants

vi. All reports of the adverse events, opinions of the DSMB/Monitor and the action taken will be placed before the IEC JNIMS at its next meeting.

13. Compensation for research-related harm

i. The IEC, JNIMS will ensure that 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.

ii. The IEC, JNIMS will ensure that for an injury occurs to any subject during clinical trial or bioavailability and bioequivalence study of a new drug or an investigational new drug, the sponsor, shall provide free medical management to such subject as long as required as per the opinion of investigator or till such time it is established that the injury is not related to the clinical trial or bioavailability or bioequivalence study, as the case may be, whichever is earlier.

iii. The IEC, JNIMS will also ensure that the research proposal should have an in-built provision for mitigating research related harm.

14. Record keeping and Archiving

All documentation and communication are to be dated, filed and preserved. Confidentiality is to be maintained during access and retrieval procedures. The following records should be maintained:

i. The Constitution and composition of the IEC JNIMS
ii. Signed and dated copies of the latest curriculum vitae of all IEC members;
iii. Standard operating procedures of the IEC JNIMS
iv. Relevant National and International guidelines
v. Copies of protocols submitted for review, progress reports, and SAEs
vi. All correspondence with IEC JNIMS members and investigators and other regulatory bodies regarding application decision and follow up
vii. Agenda of all IEC JNIMS meetings
viii. Minutes of all IEC JNIMS meetings with signature of the Chairperson
ix. Copies of decisions communicated to the applicants
x. Record of all notification issued for premature termination of a study with a summary of the reasons
xi. Final report of the study including microfilms, CDs and Video recordings.
xii. All records must be safely maintained for a *period of 5 years* after the completion/termination/publication of the study, whichever occurred later. *The Member-Secretary must hand over full custody of such records to her/his successor and the handing over must be documented.*

Box 14.1 Documents to be maintained by EC for record

Type of document	Document specifics
Administrative documents	• Constitution and composition of the EC • Appointment letters • Signed and dated copies of the most recent curriculum vitae of all EC members • Signed confidentiality agreements • COI declarations of members • Training records of EC members • Financial records of EC •Registration/accreditation documents, as required •A copy of national and international guidelines and applicable regulations • Regulatory notifications

	• Meeting-related documents • Agenda and minutes • All communications received or made by the EC • SOPs
Proposal-related documents	• One hard copy and a soft copy of the initial research proposal and all related documents • Decision letters • Any amendments submitted for review and approval • Regulatory approvals •SAE, AE reports • Protocol deviations/violations • Progress reports, continuing review activities, site monitoring reports • All correspondence between the EC and researchers • Record of notification issued for premature termination of a study with a summary of the reasons •Final report of the study • Publications, if any

15. Administration and management

i. The IEC, JNIMS have a separate office for the EC with infrastructure and staff to the EC for maintaining a full-time secretariat, safe archival of records and conduct of meeting.

ii. The institution allocates reasonable funds for smooth functioning of the IEC.

iii. A reasonable fee for review (funded projects only) is also charged by the IEC to cover the expenses related to optimal functioning in accordance to Institutional policies.

16. Registration and accreditation

i. The IEC, JNIMS will ensure that processes are in place to safeguard the quality of ethical review as well as compliance with national/international and applicable regulations.

ii. The IEC, JNIMS will register with the relevant authority as per the regulatory requirements.

iii. 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.

17. Education on Ethics

i. The IEC JNIMS members should be encouraged to keep abreast of all national and international developments in ethics through orientation courses on related topics by the IEC members or regular training organized by bodies.

ii. All relevant new guidelines should be brought to the attention of the members.

iii. Members should be encouraged to attend national and international training programs in research ethics for maintaining quality in ethical review and be aware of the latest developments in this area.

iv. Any change in the regulatory requirements should be brought to their attention and they should be aware of local, social and cultural norms, as this is the most important social control mechanism.

v. The IEC JNIMS will also conduct CME on research ethics for the Institute or other organizations whenever feasible.

18. Conflict of interest issues

i. The IEC, JNIMS will evaluate each study submitted for review in light of any disclosed COI and ensure appropriate action is taken to mitigate the COI.
ii. The researchers must ensure that documents submitted to the IEC, JNIMS include disclosure of COI (financial or nonfinancial) that may affect their research
iii. If a member of IEC, JNIMS has declared a COI for a proposal then he/she have to submit in writing to the Chairperson before beginning the meeting and it has to be recorded in the minutes.
iv. The member who has declared COI will have to withdraw from the IEC meeting (leave the room) while the specific research proposal is being discussed upon. This should be minuted and the quorum rechecked.

19. Ethical considerations in collaborative research

i. The IEC, JNIMS will review the protocols in the local, social and cultural context and ensure respect for sensitivities and values of participants and communities at collaborative sites are considered.
ii. The IEC, JNIMS will communicate between the ECs of different participating centres if necessary. In case of any conflict, the decision of the IEC, JNIMS based on relevant facts/guidelines/law of the land will be final.
iii. The IEC, JNIMS will examine whether the researcher has the required expertise and training in the area of collaboration.
iv. The IEC, JNIMS will protect the interests and rights of the collaborating researcher(s) and ensure that they are not treated as mere collectors of samples or data.

20. Informed Consent Process

20.1. 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.

i. The ICD has two parts – patient/participant information sheet (PIS) and the informed consent form (ICF).

ii. The researcher must obtain voluntary written informed consent from the prospective participant for any biomedical and health research involving human participants. . It is mandatory to administer consent before initiating any study related procedures involving the participant.

iii. In all trials, both the patient information sheet as well as the informed consent form should have to be approved by the IEC and furnished to the Central Licensing Authority. Any changes in the informed consent documents have to be approved again by the IEC and submitted to the Central Licensing Authority before such changes are implemented.

iv. In the case of an individual who is not capable of giving voluntary informed consent, the consent of LAR must be obtained. Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form and considerations for assent is given in box 20.1.1.

Box 20.1.1. 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.

v. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent or legal guardian, the welfare of a paediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental or legal guardian consent should be sufficient to allow participation in the study.

vi. **An audio-video recording** of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record:

vii. However, **in case of clinical trial of anti-HIV and anti-leprosy drugs, only audio recording** of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.

viii. 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.

ix. Essential elements of an informed consent document are given in Box 20.1.2.

Box 20.1.2 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	i. 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
2. Purpose and methods of the research in simple language	
3. Expected duration of the participation	

and frequency of contact with estimated number of participants to be enrolled, types of data collection and methods 4. Benefits to the participant, community or others that might reasonably be expected as an outcome of research 5. Any foreseeable risks, discomfort or inconvenience to the participant resulting from participation in the study 6. Extent to which confidentiality of records could be maintained, such as the limits to which the researcher would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality 7. Payment/reimbursement for participation and incidental expenses depending on the type of study 8. Free treatment and/or compensation of participants for research-related injury and/ or harm 9. Freedom of the individual to participate and/or withdraw from research at any time without penalty or loss of benefits to which the participant would otherwise be entitled 10. The identity of the research team and contact persons with addresses and phone numbers (for example, PI/Co PI for queries related to the research and Chairperson/Member Secretary/ or helpline for appeal against violations of ethical principles and human rights)	subjected ii. 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 iii. Insurance coverage if any, for research-related or other adverse events iv. 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.

20.2. Responsibility of researchers

1. The researcher should only use the IEC approved version of the consent form, including its local translations.
2. Adequate information necessary for informed consent should be communicated in a language and manner easily understood by prospective participants.
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.
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. The researcher should not give any unjustifiable assurances or influence or intimidate a prospective participant to enrol in the study.
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.
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.
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.
9. Re-consent or fresh informed consent of each participant must be taken under circumstances described in box 20.2.1.
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.

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

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.

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

Box 20.2.1. Conditions for re-consent/fresh consent

- 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.

20.3. Documentation of informed consent process

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

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.

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

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.
4. If the participant cannot sign then a thumb impression must be obtained.
5. The researcher who administers the consent must also sign and date the consent form.
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.
7. In some types of research, the partner/spouse may be required to give additional consent.
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.
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.

20.4. 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.
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 IEC a priori.

2. The electronic consent must contain all elements of informed consent in a language understandable by the participant.

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

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

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

7. Such tools may be reviewed and approved by the IEC before implementation.

8. There may be additional requirements for informed consent for clinical trials as specified by CDSCO.

20.5. Waiver of consent/assent

The researcher can apply to the IEC for a waiver of consent/assent if the research involves less than minimal risk to participants and the waiver will not adversely affect the rights and welfare of the participants as given in Box 20.5.1

Box 20.5.1 Conditions for granting waiver of consent/assent

The IEC 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.

• 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.

20.6. Procedures after the consent process

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.
2. The researcher has an obligation to convey details of how confidentiality will be maintained to the participant.
3.The original PIS and ICF should be archived as per the requirements given in the guidelines and regulations.

20.7. Special situations

1. Gatekeepers

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

2. Community consent

In certain populations, the community plays an important role in the consent process. Some participants may not participate in the research unless the community's consent is available. There may be situations when individual consent cannot be obtained as it will change the behaviour of the individual. In such situations community consent is required. When permission is obtained from an organization that represents the community, the quorum required for such a committee must be met. For example, in a village panchayat the number of members ordinarily required to conduct a meeting must be present while giving consent. Individual consent is important and required even if the community gives permission.

3. Consent from vulnerable groups

Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests and providing valid informed consent.

20.8. Consent for studies using deception

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

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

2. The possibility of unjustified deception, undue influence and intimidation should be avoided at all costs. Although deception is not permissible, approval may be taken from the IEC in circumstances where some

information requires to be withheld for validation until the completion of the research.

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

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

Research involving any kind of deception should:

- pose no more than minimal risk;
- not adversely affect the welfare and safety of the participants;
- be conducted only when the research cannot be carried out without deception;
- have an adequate plan for debriefing the participants after completion of the study, if appropriate;
- disseminate results of research to the participants, if applicable; and
- be carefully reviewed by the EC and different types of deception is given in box 20.8.1.

Box 20.8.1 Types of deception

1. Active deception: Selective withholding of the information/hypothesis of the study in the consent form along with giving incorrect information for achieving public good without influencing the outcome of the study, for example, psychology, neuro-behavioural, behaviour intervention study.

2. Incomplete disclosure: If research involves incomplete disclosure but no deception.

3. Authorized deception: Unlike in active deception, participants are informed that they would be deceived prior to the research but the nature of the deception will not be disclosed or research will not be described accurately or some procedures will be deceptive. Such revelation provides the participants an opportunity to decide whether or not to participate on these terms.

20.9. Informed consent in social and behavioural sciences research on health

The different types of informed consent processes in social and behavioural sciences research are provided in Box 2.9.1

Box 20.9.1 Types of Informed consent in social and behavioural sciences research on health

1. Community consent/gatekeeper consent/individual consent: Individual informed consent has to be taken after obtaining the permission of gatekeepers, such as community heads or leaders/ culturally appropriate local authorities/healthcare providers/institutions or organizations responsible for community welfare or their appointed advocates. Consent procedures must respect local cultural customs, however, community traditions do not substitute for individual consent unless a waiver has been granted.
2. Participant consent: Researchers must develop culturally appropriate ways to communicate information necessary for adherence to the standard required in the informed consent process.
3. Selective withholding of study information: The IEC may permit selective withholding of information/hypothesis of the study in the consent form for achieving overall social and public good, without influencing the outcome of the study. On completion of the research, the participants should be de-briefed, if applicable.
4. Participant refusal: Often the power differences between participants and researchers in India make it difficult for people to explicitly refuse to participate. Researchers should be alert to cultural symbols of refusal, such as body language, silence, monosyllabic replies, or restlessness that communicate discomfort. They must not persist with the research under these circumstances.
5. Relational autonomy: Individuals are socially embedded wherein the person's identity is shaped by social determinants, such as caste, class, ethnicity and gender. Therefore, the participant may not be autonomous in decision making. Right to autonomy must be understood in relation to substantive equality of opportunity, sufficient social support and conditions for self-respect. Accordingly, concerns about social justice must be central to

any adequate conception of individual autonomy. The IEC may take into account this context with due diligence regarding the vulnerable status of prospective participants during review, for example, a woman asking her husband or family before giving consent.

6. Waiver of informed consent: If the research has important social and public health value and poses no more than minimal risks to participants, the IEC may waive the requirement for individual informed consent if it is convinced that the research would not be feasible or practicable to carry out without a waiver, for example, research on harmful practices.

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

Box 20.10.1 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 theI EC have to decide on the complex issues of feasibility and type of consent to be obtained from the participants.

21. Special Considerations

There are certain specific concerns pertaining to specialised areas of research which require additional safe guards / protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable subjects and those with diminished autonomy, besides issues pertaining to commercialisation of research and international collaboration.

22. VULNERABILITY

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 22.1.

Box 22.1 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

22.1. Principles of research among vulnerable populations

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

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

3. Participants must be empowered, to the maximum extent possible, to enable them to decide by themselves whether or not to give assent/consent for participation.

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

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. 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 individual

22.2. Additional safeguards/protection mechanisms

1. 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.

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

3. The IEC member must satisfy themselves with the justification provided and record the same in the proceedings of the IEC meeting.

4. Additional safety measures should be strictly reviewed and approved by the IEC.

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

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

7. 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.

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

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

10. Researchers should be cognisant of the possibility of conflicting interests between the prospective participant and LAR and should be more careful.
11. 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.
12. Efforts should be made to set up support systems to deal with associated medical and social problems.
13. Protection of their privacy, confidentiality and rights is required at all times – during conduct of research and even after its completion.
14. 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

22.3. Obligations/duties of stakeholders

All stakeholders have different responsibilities to protect vulnerable participants. See Table 22.1 for further details.

Table 22.1: Obligations/duties of stakeholders

Stakeholders	Obligations / duties
Researchers	• Recognize the vulnerability of the participant and ensure additional safeguards are in place for their protection. • Justify inclusion/exclusion of vulnerable populations in the study. • COI issues must be addressed. • Have well defined procedures (SOPs) to ensure a balanced benefit-risk ratio. • Ensure that prospective participants are competent to give informed consent. • Take consent of the LAR when a prospective participant lacks the capacity to consent. • Respect dissent from the participant. • Seek permission of the appropriate authorities

	where relevant, such as for institutionalized individuals, tribal communities, etc. • Research should be conducted within the purview of existing relevant guidelines/regulations.
Ethics Committees	• During review, determine whether the prospective participants for a particular research are vulnerable. •Examine whether inclusion/exclusion of the vulnerable population is justified. • Ensure that COI do not increase harm or lessen benefits to the participants. • Carefully determine the benefits and risks to the participants and advise risk minimization strategies wherever possible. • Suggest additional safeguards, such as more frequent review and monitoring, including site visits. • Only the full committee should do initial and continuing review of such proposals. It is desirable to have empowered representatives from the specific populations during deliberations. • ECs have special responsibilities when research is conducted on participants who are suffering from mental illness and/or cognitive impairment. They should exercise caution and require researchers to justify cases for exceptions to the usual requirements of participation or essentiality of departure from the guidelines governing research. ECs should ensure that these exceptions are as minimal as possible and are clearly spelt out in the ICD.

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

22.4.Review of research proposal involving vulnerable population,

i. Only the IEC, JNIMS full committee will do initial and continuing review of such proposals.
ii. The IEC, JNIMS will examine whether inclusion/exclusion of the vulnerable population is justified.
iii. The IEC, JNIMS will ensure that COI do not increase harm or lessen benefits to the participants.
iv. The benefits-risks assessment to the participants will be determine and will advise for risk minimization strategies wherever possible by the IEC, JNIMS.
v. The IEC, JNIMS will ask for consent of the parent/LAR whenever research involves children.
vi. The IEC, JNIMS will ensure that special care must be taken by the researcher to safeguard the participant's privacy and confidentiality.
vii. The IEC, JNIMS will take necessary precautions to avoid exploitation /retaliation /Rewards/credits, etc., by the researchers.

22.5. Women in special situations

1. Women have equal rights to participate in research and should not be deprived arbitrarily of the opportunity to benefit from research. Informed consent process for some women can be challenging because of cultural reasons. Hence, the women may consider consulting their husbands or family members, if necessary. Although autonomy of the woman is important, the researcher must follow the requirements of local cultural practices so as not to disturb the harmony in the household/family/community. Participation of a woman in clinical trials or intervention studies that may expose her to risk is elaborated in Box 22.2.

Box 22.2. Risks for women participants in clinical trials/intervention studies

1. Researchers must provide the IEC 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.

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.

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 IEC should be especially vigilant regarding these sensitive issues.

22.6. 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. Research on children can be carried out in a situation, condition, disorder or diseases as described in Box 22.3.

Box 22.3 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.

22.6.1. The IEC 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.

22.6.2. The IEC 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.

22.6.3. Consent of the parent/LAR is required when research involves children.

Box 22.4 Consent of parent/LAR

1. The IEC 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 IEC may waive the requirement of obtaining parental/LAR consent and prescribe an appropriate mechanism to safeguard the interests of the child.
6. Cognitively impaired children or children with developmental disorders form one of the most vulnerable populations. In fact, their parents are also vulnerable and there is a high likelihood of therapeutic misconception. The potential benefits and risks must be carefully explained to parents so as to make them understand the proposed research.
7. Research involving institutionalized children would require assent of the child, consent of parents/LAR, permission of the relevant institutional authorities (for example, for research in a school setting: the child, parents, teacher, principal or management may be inviolved).

22.6.4. Assent

1. 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 IEC is obtained.

2. 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.

3. Points to be included in the assent form are as given below:

i. an explanation about the study and how it will help the child;

ii. an explanation of what will be done in the study, including a description of any discomfort that the child is likely to feel;

iii.the contact information of the person whom the child can approach if she/ he needs an explanation; and

v. 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.

22.6.5. Waiver of assent: All the conditions that are applicable to waiver of informed consent in adults also apply for waiver of assent in children. 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 IEC should be obtained.

Box 22.5 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

22.7. 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.

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.
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 IEC if there is a research proposal involving these participants.
3. The IEC can suggest setting up of a community advisory board to act as an interface between the researcher(s) and the community.
4. Among the LGBT community there are inhibitions between the different groups, so details of the research should be explained to each group separately.
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.

22.8. Research among tribal population

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.
2. Due approval from competent administrative authorities, like the tribal welfare commissioner or district collector, should be taken before entering tribal areas.
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.
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.
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. Even with permission of the gatekeeper, consent from the individual participant must be sought.
7. Additional precautions should be taken to avoid inclusion of children, pregnant women and elderly people belonging to particularly vulnerable tribal groups (PVTG).
8. Benefit sharing with the tribal group should be ensured for any research done using tribal knowledge that may have potential for commercialization.

22.9. Research involving individuals with mental illness or cognitively impaired/affected individuals

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 sub normality 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). 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. All such studies should be reviewed by the EC very carefully before approval.

22.10. 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:

1. Enrolling participants as described above is specifically pertinent to the research questions and is not merely a matter of convenience.
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.
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.
4. Mechanisms to avoid coercion due to being part of an institution or hierarchy should be described in the protocol.

22.11. 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.

1. Since therapeutic misconception is high there should be appropriate consent procedures and the IEC should carefully review such protocols and recruitment procedures.
2. Additional monitoring should be done to detect any adverse event at the earliest.
3. Benefit-risk assessment should be performed considering perception of benefits and risks by the potential participant
4. The IEC should carefully review post-trial access to the medication, especially if it is beneficial to the participant.

23. Clinical Trials of Drugs and other Interventions

23.1. Bioavailability/bioequivalence study

Bioavailability (BA) is the measurement of the proportion of the total administered dose of a therapeutically active drug that reaches the systemic circulation and is therefore available at the site of action. Bioequivalence (BE) is a term used in pharmacokinetics when there are two or more medicinal products (proprietary preparations of a drug), containing the same active substance that need to be compared in vivo for biological equivalence. These comparative studies are used to assess if the new version (generic) produces the same concentration in the systemic circulation when given to human participants. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same. BE studies are used as surrogates for clinical effectiveness data for generic drugs where no clinical difference is anticipated between the two products.

23.1.1. Ethical issues

1. Bioavailability or bioequivalence study at each site shall be initiated after approval of bioavailability or bioequivalence study protocol, as the case may be, and other related documents by the Ethics Committee of that site, registered under rule 8 of the New Drugs and Clinical Trials Rules, 2019.

2. In case the Ethics Committee of a bioavailability or bioequivalence study centre rejects the approval of the protocol, the details of the same should be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the bioavailability or bioequivalence study at the same site.

3. The Central Licencing Authority shall be informed about the approval granted by the registered Ethics Committee within a period of 15 working days of the grant of such approval.

4.The study of new drug or investigational new drug shall be conducted only in the bioavailability or bioequivalence study centre registered with the Central Licencing Authority under rule 47 of the New Drugs and Clinical Trials Rules, 2019;

5. The study of investigational new drug shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the study;

6. The study shall be conducted in accordance with the approved bioavailability or bioequivalence study protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and provisions of these rules;

7. In case of termination of any bioavailability or bioequivalence study, the detailed reasons for such termination shall be communicated to the Central Licencing Authority within thirty working days of such termination;

8. Any report of serious adverse event occurring during bioavailability or bioequivalence study to a subject of such study, shall, after due analysis, be forwarded to the Central Licencing Authority, the chairperson of the Ethics Committee and the institute or the centre where the bioavailability or bioequivalence study, as the case may be, has been conducted within fourteen days of its occurrence.

9. In case of an injury during bioavailability or bioequivalence study to the subject of such study, complete medical management and compensation shall be provided in accordance with the provisions of Chapter VI of the New Drugs and Clinical Trials Rules, 2019 and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of the receipt of order issued in accordance with the provisions of said Chapter;

10. In case of bioavailability or bioequivalence study related death or permanent disability of any subject of such study during the study, compensation shall be provided in accordance with Chapter VI of the New Drugs and Clinical Trials Rules, 2019 and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order issued in accordance with the provisions of said Chapter;

11. The premises of the sponsor including his representatives and bioavailability and bioequivalence study centre shall be open for inspection by officers of the Central Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by

the Central Licencing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to bioavailability or bioequivalence study, as the case may be, and furnish reply to the queries raised by the said officer in relation to bioavailability or bioequivalence study;

12. The study shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the Central Licencing Authority shall be required

13. Ethical conduct of BA/BE study requires evaluation of the benefit–risk profile of: a. the reference (comparator) and investigational (generic) product; and b. the study procedures such as indoor stay, fasting, screening, blood sampling.

14. The IEC must carefully review the recruitment methods, payment for participation and consent procedures. Volunteers often regularly participate in such studies at the cost of their health and care should be taken that taking part in multiple trials is avoided by maintaining volunteer registries, biometry, follow up, etc. Care must be taken to maintain confidentiality of biometric data.

15. The amount of blood drawn for a BA/BE study should be within physiological limits irrespective of study design and the EC should take specific note on the amount of blood drawn depending on whether the individual is a healthy adult or a child or a patient.

23.1.2. Ethical implications of study designs

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

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

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

3. Placebo may be used as a comparator under the conditions given in Box 23.1.

Box 23.1. Conditions where a placebo may be use

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.

5. If a placebo must be used for scientific reasons, then certain precautions must be exercised. These should be reviewed and approved by the IEC. See Box 23.2. for further details.

Box 23.2. 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

23.2. Device trials

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

(i) detection, diagnosis, prevention, monitoring;

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

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

(iv) supporting or sustaining life;

(v) disinfection of medical devices; or

(vi) control of conception.

• Clinical trials should be conducted in accordance with the ethical principles described in these guidelines, Indian GCP as well as applicable regulations for medical and medicated devices, that is, GSR 78 (E) dated 31.1.2017 or as per amendments/modifications issued from time-to-time.

• Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered in the same way as for a new drug under the Drugs and Cosmetics Rules, 1945.

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

• Devices should be provided free of cost or, if expensive, at feasible reduced rates.

• Avoid therapeutic misconceptions.

• Any AE/SAE should be reported within timelines as per the schedule for a new drug. Here user error could also be the cause of AE/SAE.

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

• If feasible, post-trial obligations should be emphasized with the sponsor.

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

2. Devices could be used internally or externally for diagnosis, treatment, mitigation or prevention of disease or disorder. Depending upon risks involved, devices (other than in vitro diagnostic devices) are classified as given in Table 23.2.1:

Table 23.2.1 Classification of medical devices

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

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

(i) a physiological or pathological state;

(ii) congenital deformity;

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

(iv) monitoring of therapeutic measures

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

23.3. Surgical interventions

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

1. In any protocol where an established surgical intervention is to be studied, the researcher must provide references for the procedure and describe the most likely complications in the protocol for the IEC to review and perform benefit-risk assessment. The frequency of each complication should also be mentioned.
2. In trials where a modification of the established surgical intervention is to be tested, the protocol and ICD must specify the need for this modification and the expected complications, if any. It is preferable that a comparative study be conducted where the conventional method is compared to the test surgical intervention.
3. In trials where an entirely new surgical intervention is being tested, the IEC may insist on some animal data/modeling data which establishes the efficacy and safety of the technique or case reports/case series that indicate benefits and describe risks.
4. During the conduct of a surgical interventional trial all adverse events must be reported to the IEC and sponsor as applicable, within the specified timelines as described for drug trials.
5. Provision of free treatment and compensation for any study-related injury must be ensured for the trial participant. The IEC must determine the compensation amount after the investigator has described the relatedness.
6. Due to inherent ethical issues, sham surgery should not be included in the design of clinical trials, except in cases where there are strong scientific reasons. Under such circumstances, certain conditions must be met.

See Box 23.3.1 for further details

Box 23.3.1 Conditions for sham surgery

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

23.4. Clinical trials of interventions in HIV/AIDS

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

1. Global studies in HIV/AIDS in specific communities should receive approval from the relevant national authority and any other relevant authority, such as the HMSC, where applicable, in addition to approval from the IEC.
2. When testing for HIV is done, consent and pre-test- and post-test counselling should be done as per National AIDS Control Organization (NACO) guidelines.
3. Issues that may arise because of discordant couples should be addressed before initiating any study in people living with HIV/AIDS.
4. As HIV is a sexually transmitted disease and is potentially life-threatening, the right to life of the sexual partner must be respected over the right to privacy of the HIV positive individual.
5. Phase I studies are permissible in patients with HIV/AIDS if the drug under study cannot be tested in healthy participants due to expected toxicity of the IP
6. A combined Phase I/II or Phase II study can be conducted in this population when other therapeutic options have been exhausted.
7. When a trial with a preventive HIV vaccine is conducted, it can result in positive serology. This does not indicate HIV infection but can create problems for travel and employment. Under such circumstances, the project investigator should issue a certificate stating that the person in question was a participant in a vaccine trial and provide clarification on the result.
8. Research that involves sexual minorities or IV drug users should have community engagement (community leaders) throughout the life of the project, until completion and dissemination of results.
9. The IEC may also consider co-opting a member from this community, if relevant for initial and continuing review of proposals.

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

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

23.5 Clinical trials on traditional systems of medicine

Although traditional systems of medicine (termed complementary and alternate systems in the west) are known for their long history of safe and effective use, validation of safety and efficacy using scientific and evidence-based methodologies is needed for the purpose of universal acceptability, gaining confidence of practitioners and satisfaction of end users in the products. Government of India has recognized Ayurveda, Siddha, Unani, Yoga, Naturopathy and Homeopathy as traditional Indian systems of medicine. In 2012, Sowa Rigpa (Amchi or Tibetan medicine) was also added to the list. Ministry of AYUSH (Ayurveda, Unani, Siddha and Homeopathy) governs and regulates these systems. Drugs under these systems come under the Drugs and Cosmetics Act, 1940, as ASU and H drugs. Drugs/formulations under these systems of medicine are classified into two groups. See Box 12.5.1 for further details:

1.Research on AYUSH and ASU interventions of traditional medicines (TM) including external medicines/therapeutic procedures, folk medicines, and patent and proprietary medicines of TM involving human participants should be conducted in accordance with all the ethical principles described in these guidelines including SAE reporting and compensation, AYUSH GCP guidelines 32, as well as other applicable regulations of the country.

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

3. The IEC must co-opt a person with relevant expertise (an expert of that traditional system of medicine) to review the proposal, especially the benefits

and risks of the intervention, eligibility criteria, doses of interventions, outcomes planned and traditional method of evaluation, if necessary.

4. When a folklore medicine/ethnomedicine is ready for commercialization after it has been scientifically found effective, benefit sharing should be ensured and the legitimate rights/share of the tribe or community from which the knowledge was gathered should be taken care of appropriately while applying for the IPRs and patents for the product.

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

Box 23.5.1 Classification of drugs/formulation under AYUSH

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

23.6 Academic clinical trial / Investigator initiated clinical trials

1. In such trials, the investigator has the dual responsibility of being an investigator as well as the sponsor. For student conducting clinical trials as part of their academic thesis, the guide and the academic institution should take up the responsibilities of the sponsor.

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

3. No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,—

(i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and

(ii) the clinical trial referred to in clause (i) has been initiated after prior approval by the Ethics Committee for clinical trial; and

(iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority;

(iv) When academic clinical trials are planned for “off-label” use of a drug (when a drug that is marketed is being used for a new indication/new dose/formulation/route) for purely academic purposes and not for commercial use, then such clinical trials designed by researchers/academicians may not currently require regulatory approval. However, an EC has to approve such studies after due consideration of benefits and risks and all other ethical aspects and the licensing authority has to be informed as per GSR 313(e) dated 16.3.2016 issued by CDSCO.

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

(vi) The observations of such clinical trial are not used for promotional purposes.

4. The approved academic clinical trial shall be conducted in accordance with the approved clinical trial protocol, ethical principles specified in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the Indian Council of Medical Research with a view to ensuring protection of rights, safety and wellbeing of trial subject during conduct of clinical trial of licensed and approved drug or drug formulation for any new indication or new route of administration or new dose or new dosage form for academic research purposes.

24. Others

While reviewing the proposals, the following situations may be carefully assessed against the existing facilities at the research site for risk/benefit analysis:

A. Collection of blood samples by finger prick, heel prick, ear prick, or venipuncture:

i. From healthy adults and non-pregnant women who weigh normal for their age and not more than 500 ml blood is drawn in an 8 week period and frequency of collection is not more than 2 times per week;

ii. From other adults and children, where the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected has been considered and not more than 50 ml or 3 ml per kg, whichever is lesser is drawn in an 8 week period and not more than 2 times per week;

iii. From neonates depending on the haemodynamics, body weight of the baby and other purposes not more than 10% of blood is drawn within 48 – 72hours. If more than this amount is to be drawn it becomes a risky condition requiring infusion/blood transfusion;

iv. Prospective collection of biological specimens for research purposes by non-invasive means. For instance:

1. Skin appendages like hair and nail clippings in a non-disfiguring manner;
2. Dental procedures - deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction of permanent teeth; supra and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth;
3. Excreta and external secretions (including sweat);
4. Non-cannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum or by applying a dilute citric solution to the tongue;
5. Placenta removed at delivery;
6. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labour;
7. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; 8. Sputum collected after saline mist nebulization and bronchial lavages.

B. Collection of data through non-invasive procedures routinely employed in clinical practice. Where medical devices are employed, they must be cleared / approved for marketing, for instance –

i. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy;

ii. Weighing or testing sensory acuity;

iii. Magnetic resonance imaging;

iv. Electrocardiography, echocardiography; electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow,

v. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

C. Research involving clinical materials (data, documents, records, or specimens) that will be collected solely for non-research (clinical) purposes.

D. Collection of data from voice, video, digital, or image recordings made for research purposes.

E. Research on individual or group characteristics or behaviour not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behaviour or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

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
CLA	Central Licensing Authority
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
ICMR	Indian Council of Medical Research
IC-SCR	institutional committee for stem cell research
IEC	Institutional ethics committee
IND	investigational new drug
IP	investigational product
JNIMS	Jawaharlal Nehru Institute of Medical sciences
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
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

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