

INSTITUTIONAL ETHICS COMMITTEE (IEC)
ALL INDIA INSTITUTE OF MEDICAL SCIENCES,
MANGALAGIRI, ANDHRA PRADESH

General Guidelines/Policies

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Policy on the Recruitment of Research Subjects

Specific recruitment guidelines

1. In addition to its review for scientific merit and protection of subjects from unnecessary research risks, the IEC will evaluate all protocols for subject recruitment especially with respect to women with childbearing potential, children and normal volunteers as controls. Exclusion of women of child bearing age or children will be recommended or approved when inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

2. Patients may be identified as potential research subjects through direct contact of the PI with the patients, collaboration with physicians of other medical specialties, contact with individual attending physicians, posted written notices, radio announcements, or other IEC approved methods.

a. **Inpatients** - May be recruited by the investigator or other member of the research team only after consultation with the patient's attending physician.

b. Outpatients:

1. For minimal risk research which does not bear directly upon a specific continuing therapeutic relationship between the individual and a AIIMS, Mangalagiri, physician, outpatients may be recruited without prior notification of their personal physicians. However, when possible, subject's personal physician should be notified of the study and informed that the patient has been entered into a clinical study

c. **Community studies:** Epidemiology is defined as the study of the distribution and determinants of health related states or events in specified populations and the application of this study to control health problems. Epidemiological studies are of primary importance in a large developing country like ours where the natural history, incidence, prevalence and impact on morbidity and mortality of a variety of diseases are not known. Such studies are on large scale and assist in improving the public health, which includes both patients and healthy people and communities.

In most epidemiological research it would be necessary to have the consent of the community, which can be done through the Village Leaders, the Panchayat head, the tribal leaders etc. who are considered to be gate keepers of the society/ community. Particularly in a country like India, with the level of poverty that is prevalent it is easy to use inducements, especially financial inducements, to get individuals and communities to consent. Such inducements are not permissible. However, it is necessary to provide for adequate compensation for loss of wages and travel / other expenses incurred for participating in the study.

Benefits:

When epidemiological studies (like those on mortality and morbidity as a result of exposure to an agent) lead to long associations with the community, the results if released in timely manner could give improved health care facilities or educate the community to reduce the impact of adverse environment on health and tackle the problem at their end in time. A community can be defined as a group of people sharing the same location, beliefs, culture, ideals, goals, age, gender, profession, lifestyle, common interests, geographical locations or settings or disease. When research participants are drawn from a specific community, members of that community can be involved to discuss any concerns it may have regarding the research. In different ways such a dialogue can be facilitated.

If an ethics committee does not have a member from the community, it may ask a local community representative to be the voice for all participants. On the other hand, community representatives can formally join together to form a group termed as Community Advisory Board, Community Working Group, or Community Advisory Group, which takes part in the research at all stages of the study. In international studies, particularly on issues involving communities, representation from this body ensures that the community's health needs and expectations are addressed, informed consent is appropriate, and access to research benefits is provided through research that is designed and implemented in the best interests of science and community

Community representation should be involved before, during and after the study. Before the study is initiated the community is informed to see if it agrees that the research addresses a need or problem relevant to that community and to confirm that the design is culture specific and

brings some benefits to research participants or the community. Since some risk may be associated the community representation is needed to assist in developing appropriate ways to protect the participants. During the study, the association with community representatives continues to educate others about the research and to alert the researcher to ethical issues related to the research. After the study is completed, community representatives can help in making the results known to the entire community. However, application of research findings may take a long time, which the community representatives should be made to understand. The benefits may be participants' and community's access to intervention. Whose responsibility and conditions under which this would be done, duration of availability of intervention, methods of improving the quality of health care in the community and any expected desirable behavioral change in the community should be clearly explained to community by the Ethics Committee or community representatives.

Policy on Research Costs to Subjects

If a research participant has to bear any costs, all potential subjects must be fully informed of the nature and estimated extent of these costs when obtaining consent. Examples of additional research costs include:

1. Prolongation of treatment or hospitalization.
2. Extra diagnostic tests necessary for the research.
3. Extra clinical or laboratory assessments to evaluate research treatment outcome.
4. A research treatment (whether randomly assigned or not) which may be more costly than a standard treatment.
5. Other substantial costs associated with extra visits to AIIMS, Mangalagiri.

Guidelines on Compensation for Research Subjects

Compensation for participation (ICMR guidelines 2006) Subjects may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. However, payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgment (inducement). All payments, reimbursement and medical services to be provided to research subjects should be approved by the IEC.

Care should be taken:

1. When a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;
2. When a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation;
3. When a subject withdraws for any other reasons he/she should be compensated in proportion to the amount of participation.

Compensation for accidental injury:

Research subjects who suffer physical injury as a result of their participation in the Clinical Trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from IEC In case of death; their dependents are entitled to material compensation.

- a. Obligation of the sponsor to pay : The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any serious physical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible.

Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. During the initial review of a research protocol, the IEC is required to review both the

amount of compensation proposed and the method and timing of disbursement to assure that neither are coercive or present undue influence. The following are some additional guidelines:

1. Any compensation should not be contingent upon the subject completing the study, but should accrue as the study progresses
2. Unless it creates undue inconvenience or a coercive practice, compensation to subjects who withdraw from the study should be made at the time they would have completed the study, had they not withdrawn.
3. Compensation given as a “bonus” or incentive for completing the study is acceptable, providing that the amount is not coercive. The IEC is responsible for determining if the incentive amount is not so large as to be coercive or represent undue influence.
4. The amount of compensation should be clearly set forth in the informed consent document.

Policy on the Use of Third Party / Surrogate Consent in Research at AIIMS, Mangalagiri

Applicability When an AIIMS investigator proposes to conduct a research project utilizing adult subjects who by virtue of age, physical impairment, mental impairment, language barrier or any other reason may not be able to personally execute legally effective informed consent, the IEC shall review the project on the basis of ‘risk’ and ‘benefit’ and shall determine that each project be assigned to one of the categories below. This policy does not mean to imply that the requirement for written documentation of consent is waived. Rather, it applies to those studies in which third party/surrogate consent is obtained from a legally authorized representative. Investigators must complete and submit an IEC Form for review and approval of inclusion of subjects who are decisional impaired.

Category I - Risks to subjects are minimal, direct benefits may or will accrue to subjects.

Category II - Risks to subjects are minimal, direct benefits will not, or are unlikely, to accrue to subjects but potential societal benefits are inherent in research.

Category III - Risks to subjects are greater than minimal, direct benefits may or may not accrue to subjects.

Category IV - Risks to subjects are greater than minimal, direct benefits will not, or are unlikely, to accrue to subjects but potential societal benefits are inherent in the research.

IEC recommendations to the administration When categorization has been accomplished, the IEC will recommend to the AIIMS, Mangalagiri, Administration to consider implementation or non-implementation of the project based upon the level of benefit to be gained by the individual or society from this project as compared to the level of risk involved. IEC will recommend normally Category I projects to be initiated. IEC will not recommend normally initiation of any Category IV projects. IEC recommendation on Category II and III projects will depend on case to case assessment of risk/benefit ratio to subject and community.

Guidelines on Blood Withdrawal for Research Purposes

Applicability For many studies where the only research intervention is the collection of blood for analysis, the IEC categorizes the following procedures for obtaining blood from children and adults as having minimal risk:

A. General Requirements

1. There are no special health reasons (e.g., anemia) to contraindicate blood withdrawal.
2. In patients from whom blood is already being drawn for clinical purposes, there are no other health reasons to preclude additional blood collection provided the amount is limited as mentioned in B and C.
3. In subjects from whom blood is not already being drawn for clinical purposes, the withdrawal method is by cutaneous pricks (e.g., heel or finger) or by standard venipuncture in a reasonably accessible peripheral vein, and the frequency of punctures should not exceed two per week except in pharmacokinetic study.
4. The volume of blood drawn from lactating or known pregnant subjects does not exceed 20 ml per week. 5. All blood withdrawals and collections should be carried out by experienced professional or technical personnel.

B. Additional Requirements for Adults (Subjects over 18 years of age)

1. If less than 50 ml is being collected, there are no additional restrictions with regard to hemoglobin or hematocrit.
2. If a volume greater than 50 but less than 200 ml is being collected for “no-benefit” studies, hemoglobin levels should be >11.0 g/dl for males and >9.5 g/dl for females with MCVs >85 fl (These restrictions would not apply if iron deficiency anemia or other forms of anemia were critical for inclusion in the study).
3. The cumulative volume withdrawn or collected may not exceed 450 ml per twelve-week period (this maximum includes blood being drawn for clinical purposes) from patients 18 years of age or older in good health and not pregnant.

C. Additional Requirements for Children (Subjects under 18 years of age)

1. No more than three (3) skin punctures are to be made in any single attempt to draw blood, and the frequency of punctures does not exceed twice per week.
2. The volume of blood withdrawn, including blood for clinical purposes, does not exceed the limit of 50 ml or 3 ml/kg in an eight week period and collection may not occur more frequently than 2 times per week.
3. The cumulative volume of clinical and research blood withdrawn per eight-week period does not exceed six per cent (6.0%) of the child's total blood volume.
4. In patients from whom blood is already being drawn for clinical purposes and when the research is directly related to the child's condition, there is no maximum number of extra volume specimens which can be collected as long as the preceding requirements are met.
5. In subjects from whom blood is not already being drawn for clinical purposes, the maximum number of allowable separate specimens (again, within the limits of the preceding restrictions) depends upon the child's age and whether the research is directly related to the child's condition.

D. Cord Blood Cord blood from newborns can be used without restrictions when blood is extracted from the placental side of the cord, after it has been clamped and severed. X per cent (6.0%) of the child's total blood volume.

Guidelines Participant Information Document and (PID) and Consent Form (CF)

A. General Requirements Except as described below, investigators may not enroll human subjects in research unless they have obtained the legally effective, written, informed consent of the subject or the subject's legally authorized representative, prior to enrollment of the subject in the research. Investigators are responsible for ensuring that subjects, or their representatives, are given sufficient opportunity to consider whether or not to participate and must seek to avoid coercion or undue influence. Information given to potential subjects or their representatives must be in language that is understandable to the subject or representative. No process of obtaining consent may include language through which the subject waives any of their legal rights or releases or appears to release the investigator, sponsor, or institution or its agents from liability for negligence.

B. Elements of Participant Information Document and Consent Form

The sample consent form contains all the required elements of consent. The IEC requires that all consent forms be written in the first person, e.g., "I understand that...". The following are the basic required elements of Participant Information Document

1. A statement that the study involves research, an explanation of the purpose of the proposed research, the duration of the subject's participation, a description of the procedures, and which procedures are experimental;
2. The number of subjects that will be involved with the study, totally and at AIIMS, Mangalagiri;
3. A description of reasonably foreseeable risks or discomforts that the subjects may encounter, and, if appropriate, a statement that some risks are currently unforeseeable;
4. A description of possible benefits, if any, to the subject and others which may be reasonably expected. It should be stated that since it is an experimental treatment or procedure, no benefits can be guaranteed;
5. A discussion of possible alternative procedures or treatments, if any, which are available to the subject. One alternative might be to choose not to participate in the research and this will not affect the usual standard of care;
6. A discussion of how confidentiality of records associated with the subject will be maintained;
7. A description of any compensation or reimbursement for time, inconvenience, travel, parking, and other similar costs to the subject;
8. A description of any provisions for treatment of or compensation for research related injury;
9. A statement of whom to contact for answers about the research and in the event there is a research related injury. (This is generally the PI or another staff member closely associated with the study.) A separate contact must be named for questions concerning the subject's rights;
10. A statement that the subjects' participation is voluntary, that refusal to participate will not involve penalty or loss of benefits to which the subject is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits;
11. If appropriate, any circumstances under which the subjects participation may be terminated, with or without the subjects consent; and
12. A description of additional costs for which the subject will be responsible, those are likely to result from participation in the research study.
13. Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;

14. Risk of discovery of biologically sensitive information;
15. Publication, if any, including photographs and pedigree charts.

C. Waiver of informed consent

The IEC may waive the requirements for obtaining informed consent or approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent listed above, provided that:

1. The research involves no more than minimal risk to the subjects
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after par

D. Documentation of informed consent

Consent must be documented by the use of a written consent form reviewed and approved by the IEC and signed by the subject or subject's legally authorized representative in the presence of a witness. A copy must be given to the subject or person signing the form. For AIIMS, Mangalagiri patients, a copy of the signed consent form should also be placed in the subject's medical record. It is assumed that the consent form is only part of the total consent process in which the investigator, perhaps using the written consent form as an outline, describes all facets of the study and answers the subject's questions. The investigator is responsible for ensuring that research subjects understand the research procedures and risks. Failure of the subjects to ask questions should not be construed as understanding on the part of subject.

E. Record retention requirements for subject consent forms

1. The PI or project director shall maintain, in a designated location, all executed subject consents. These consent forms are to be available for inspection by authorized officials of the IEC, DSMSC, regulatory agencies and sponsors. For DCGI/RA regulated test article studies, all signed subject consent forms shall be retained by the principal investigator for the appropriate period(s) specified below.

Drugs: Two (2) years following the date a marketing application is approved or the study is discontinued

Devices: Two (2) years after a study is terminated or completed and the records are needed to support DCGI/ RA approval.

Policy for obtaining Informed Consent

A. Informed consent process

1. Informed Consent of Subject: For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject or in the case of an individual who is not capable of giving informed consent, the consent of a legal guardian. Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not. Informed consent protects the individual's freedom of choice and respect for individual's autonomy. When research design involves not more than minimal risk (for example, where the research involves only collecting data from subject's records) the IEC may waive off some of the elements of informed consent. Waiver of informed consent could also be considered during conditions of emergency. However, this would be permissible only if IEC has already approved the study or use of drug. However, the patient or the legal guardian should be informed after she/he regains consciousness or is able to understand the study.

2. Obligations of investigators regarding informed consent: The investigator has the duty to –

i. Communicate to prospective subjects all the information necessary for informed consent. There should not be any restriction on subject's right to ask any questions related to the study as any restriction on this undermines the validity of informed consent.

ii. Exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the subject is not permissible. However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.

iii. Seek consent only after the subject is adequately informed. Investigator should not give any unjustifiable assurances to subject, which may influence the subject's decision to participate in the study.

iv. As a general rule obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial and in case of incompetence to do so, a legal guardian or other duly authorized representative.

v. Renew the informed consent of each subject, if there are material changes in the conditions or procedures of the research or new information becomes available during the ongoing trial.

vi. Use of intimidation in any form invalidates informed consent. The investigator must assure prospective subjects that their decision to participate or not will not affect the patient - clinician relationship or any other benefits to which they are entitled. The quality of the consent

of certain social groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

This is accomplished as part of the total consent process by using a consent form that has been reviewed and approved by the IEC. Confusion sometimes arises as to who can obtain consent and who can be designated to sign the consent form. The following are the acceptable methods for documentation of informed consent of human research subjects at AIIMS:

1. The IEC must be made aware of the person (s) who will be conducting the consent interviews. These faculty/staff members should be the only personnel allowed to obtain consent unless indicated otherwise. The IEC requires that the person obtaining consent is medically trained.

2. Each subject (or their legally authorized representative) must be provided adequate time to read and review the consent form, in addition to being advised of the procedures, risks, potential benefit, alternatives to participation, etc. This is frequently accomplished using the consent form as an outline for the interview process.

3. After completing the consent interview and assuring that the subject (or their representative) has no further questions and agrees to participate in the research activity, the interviewer should instruct the subject to sign and date the consent form in the appropriate spaces.

4. A witness must sign and date in the appropriate spaces. The witness cannot be the person conducting the consent interview, but is not further restricted.

5. The person conducting the consent interview must then sign and date the consent form in the appropriate spaces (PI or designee). It is assumed that in most cases, all persons signing the consent form will do so at the conclusion of the consent interview.

6. Each subject (or their representative) must be given a copy of the signed consent form. The original consent form and PID should be filed in such a manner as to insure immediate retrieval when required by auditing entities, IEC, or sponsor monitors.

7. A written documentation informed consent is required. Therefore, obtaining consent from an authorized third party via the telephone is not acceptable unless agreed upon by IEC.

8. The regulations also include provisions for approval of a waiver or alteration of part or all of the consent process. The IEC will consider written requests for waiver or alteration of the process when accompanied by sufficient justification.

9. Obtaining informed consent from subjects must be accomplished prior to performing the research activity and using only an IEC approved consent form. Written requests for amendments to an existing consent form must be approved by the IEC prior to implementation.

10. Copies of old versions should be destroyed upon receipt of an IEC approved revised consent form, to prevent inadvertent use. Copies of the most recently approved consent form should be used.

Health Record Research

The following is the IEC policy concerning research involving the study of medical records or other forms of health information. Research projects may involve the study of Patient case files with the stipulations described below. Such studies raise issues of confidentiality that must be carefully addressed by the investigator and the official custodian of the records. If it is anticipated that if an individual's records or specimens are likely be used for research purposes, the potential subject should be informed of the potential use of such materials upon entry into the institution or program in which the materials will be developed or collected and be given an opportunity to either provide or refuse consent to such research. Patient case files may be used or disclosed for research purposes if it has been de-identified and linkage back to a specific patient would not be possible. To use or disclose identifiable Patient case files without authorization of the research participant, the investigator must accomplish one of the following:

1. Complete and submit an IEC Form to request waiver of the requirements for obtaining informed consent;
2. Provide written documentation that the use or disclosure of patient case files is solely used to design a research protocol or to assess feasibility of conducting a study, or;
3. Document that the use or disclosure is solely for research on the patient case files of decedents.

Investigators must maintain in their files a letter from the IEC identifying the date on which the waiver or alteration of the requirements to obtain informed consent was approved by the IEC, and a statement that the IEC has determined that the waiver or alteration satisfies the following criteria:

1. The use or disclosure of patient case files involves no more than minimal risk to the research participants;
2. The alteration or waiver will not adversely affect the privacy rights and welfare of the subjects;
3. The research cannot practicably be conducted without the alteration or waiver;
4. The research could not practicably be conducted without access to or the use of the patient case files;

5. The privacy risks to individuals whose case files is to be used or disclosed are reasonable in relation to the anticipated benefits, if any, to the individuals, and the importance of the knowledge that may reasonable be expected to result from the research;

6. There is an adequate plan to protect the identifiers from improper use and disclosure;

7. There is an adequate plan to destroy the identifiers at the earliest possible opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers, and;

8. There are adequate written assurances that the Patient case files will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of Patient case files would be permitted by this policy.

The IEC letter should also contain a brief description of the Patient case files for which use or access has been determined by the IEC to be necessary, a statement that the waiver or alteration was approved by Expedited Review or at a convened meeting, and the letter should be signed by the IEC Chair or the Member Secretary.

Research use or disclosure of identifiable Patient case files with authorization of the research participant is permitted providing that use or disclosure is for only the Patient case files that were originally authorized. In order to use or disclose additional information, the investigator would either have to obtain consent or request a waiver of the requirements to obtain consent.

Guidelines for Research Protocols which require Collection and Storage of Genetic Materials

For the purpose of these guidelines, “Genetic Materials” are defined as human tissue samples (blood, serum, tumor, etc.) on which genetic related research, such as biochemical studies of inherited human traits or identification of DNA mutations may be performed.

A. Previously acquired samples

- i. Previously acquired genetic material may be used if identifiers are stripped irrevocably from samples.
- ii. If identifiers are present, experiments not described in present protocols must be submitted for fresh IEC review.

B. Prospectively acquired samples

1. Anonymous samples (further identification made impossible)
 - i. Ownership of genetic material will generally remain with the institution. This must be stated in the consent form.
 - ii. The general scope of the investigations must be explained in the consent form, but new avenues of investigation in the future are permissible if this possibility is explained in the consent form

- and agreed upon by the participant.
- iii. Whether the genetic material will be shared by other investigators should be explicit in the consent form.
 - iv. The consent form should make clear that no specific information relative to the individual donor will be forthcoming; however, information that accrues from the study that is valuable to society may be shared with the individual.

2. Identified samples

- i. If genetic material is linked to the donor by specific identifiers, ownership of the material will generally remain with the institution. If a commercial use is anticipated for the genetic material, the individual must be notified. The general policy of ownership should be stated in the consent form using the following wording:
“I understand that additional or “leftover” (blood, serum, tumor, etc.) tissue may be used for future research which may result in financial gain for SGPGI and the researchers. I also understand that my donated tissue will be one of many that are used in the research and it will be virtually impossible to attribute findings to any one sample. I understand, however, that I am not otherwise waiving any of my legal rights by participating in this study.”
- ii. If identifiers are present, new experiments must be reviewed by the IEC and new consent obtained from the research participant regardless of the details of ownership.

The investigator may include a provision in the consent form for new experiments not requiring new consent if identifiers are irrevocably removed from the samples. If the investigator anticipates future experiments without identifiers, this possibility should be present in the original consent form. The methods for removal of identifiers must be approved by the EC. Removal of identifiers must not be employed as a method of avoiding ownership issues.

- iii. A satisfactory method for sharing or withholding information gained by the research must be in the research protocol and clearly indicated in the consent form.
- iv. Details for sharing or not sharing the genetic material with other investigators must be present in the protocol and clearly indicated in the consent form.
- v. The length of time the genetic material will be maintained must be indicated in the consent form.
- vi. The length of time the genetic material will be maintained must be indicated in the consent form.

Donation of genetic material as a requirement for participation in a research protocol.

- i. Donation of genetic material may be required for participation in a protocol only if the presence of the genetic material is necessary to satisfy the central question of the research.
- ii. The investigator will be required to make a clear case in the research protocol for the necessity of the genetic material, if donation of genetic material is mandatory.
- iii. This policy applies to genetic material with or without identifiers.

Guidelines for Submission and IEC review of Gene Therapy/Gene Transfer Protocols

Available at:

http://ncdirindia.org/Ethics/Download/ICMR_Ethical_Guidelines_2017.pdf (pg 122)

Ethical Policies on the Human Genome, Genetic Research and services, Department of Biotechnology, Ministry of Science and Technology, Govt. of India, 2002

Available at: <https://www.india.gov.in/ethical-policies-human-genome-genetic-research-and-services-department-biotechnology>

National Guidelines for Stem Cell Research (ICMR, 2017).

Available at: www.dbtindia.nic.in/wp-content/uploads/National_Guidelines_StemCellResearch-2017.pdf;
<http://www.dbtindia.nic.in/guidelines/>

Guidelines for Submission and IEC review of Gene Therapy/Gene Transfer Protocols

As of October 10, 2000 the ICMR formulated Ethical Guidelines for Biomedical Research on Human Subjects. ICMR's goal is to insure that no research participant is enrolled in a human gene therapy/gene transfer research protocol before the local IEC have the benefit of the broad perspective and experience in protocol review and risk assessment. In January 2002, the Department of Biotechnology also published the Ethical Policies on the Human Genome, Genetic Research and Services. Guidelines are available at the Office of Biotechnology Activities Internet site <http://dbtindia.nic.in/ethical.html> and as AP11/V1 as in the present document. The following items are required to be addressed in the protocol to provide the necessary information for IEC review:

A. Background and justification

i. Why is this disease a good candidate for gene transfer or gene therapy? ii. What previous work has been done, including studies of animals and cultured cell models? Does the work demonstrate effective gene delivery? How does the proposed study relate to previous work? iii. Is the disease course sufficiently predictable to allow for meaningful assessment of the results of the treatment proposed? iv. What level of gene expression is presumed to be required to achieve the desired effect? v. Given responses to the above questions, is there a sufficient justification for the investigator to proceed at this point to a clinical trial?

B. Research design

- i. What are the objectives of the proposed study (e.g., establishing feasibility or relative safety of the gene transfer, determining therapeutic effectiveness, establishing a safe dose range, demonstrating proof of principle, etc.)?
- ii. Is the goal of the study to ameliorate or cure disease or to enhance healthy individuals?
- iii. What is the target tissue for gene transfer (e.g., bone marrow cells, skeletal muscle cells, respiratory epithelial cells, central nervous system tissue, etc.)?
- iv. What method(s) (e.g., direct injection, inhalation, ex vivo genetic modification with injection of modified cells) and reagent(s) (e.g., vectors based on retroviruses, adenoviruses, adeno associated viruses, herpes viruses) will be employed for gene delivery? What is the rationale for their use? Are other methods or reagents known that are more appropriate with regard to efficacy, safety, and stability?
- v. How will the investigator determine the proportion of cells that acquires and expresses the added DNA? vi. How will the investigator determine if the product is biologically active?
- vii. Is the planned statistical treatment appropriate: i.e., is it likely to provide valid answers to the study question? viii. Is it reasonable to expect that the research design proposed will meet the investigator's objectives?

C. Procedures

- i. What research-specific procedures and research-specific investigations are required by the study over and above those that would be required for patients receiving standard clinical care (e.g., physical examinations, venous or arterial blood tests, collection of target cells, imaging procedures, irradiation, chemotherapy, direct injection of vector, reinjection of genetically modified cells, organ or tissue transplantation, surgery, tissue/tumor donation, questionnaires, interviews)?
- ii. Is long term follow-up appropriate or essential for this protocol? If long term follow-up is proposed, is there justification for the number of visits and the length of time required? Is such follow-up feasible in the case of this protocol (e.g., have provisions been made for subjects who move? Is adequate funding available for such follow-up?)?
- iii. What are the procedures for obtaining or maintaining information in a data/DNA bank (e.g., use of identifiers, limitation on access, need for consent, sharing with other investigators, duration of storage, future subject contact)?
- iv. Are all of the research-specific procedures necessary? In combination with data collected in the course of clinical care, is it reasonable to expect that the information produced by this study will be sufficient to answer the research question?

D. Confidentiality

i. Are the practical steps for maintaining confidentiality of data/records/database information clearly specified and adequate (e.g., encryption, use of unique identifiers, sequestering of records, security measures)?

E. Subject selection

i. How has the study population been defined?

ii. Has an adequate rationale been provided for each eligibility criterion (e.g., safety considerations, definition of disease, avoidance of additional concurrent therapies, administrative considerations)? Do they strike a defensible balance between scientific validity and generalizability (i.e., is the study population sufficiently, but not unduly, restricted so as to yield interpretable results)?

iii. How will subjects be recruited? If a cohort of eligible patients exists, how will selection be made amongst them? If several trials exist for which the same patients are eligible, how will this be presented to prospective subjects?

iv. Does the definition of the research population reflect appropriate scientific, clinical, and ethical norms? In recruiting and negotiating with potential subjects, have the norms of nondiscrimination been respected?

F. Risks, discomforts, and benefits

i. What risks and discomforts are associated with the research-specific procedures and investigations (e.g., surgery, chemotherapy, radiation, bone marrow transplantation)? Have they been minimized?

ii. If a virus-mediated gene transfer is proposed, what is the potential for the presence of a replication-competent or pathological virus or other form of contaminants? How sensitive are the tests to detect such viruses or contaminants? What level of viral presence or other form of contamination would be tolerable in this protocol?

iii. Has the possibility of vertical transmission (i.e., gene insertion into germ cells or a fetus) or horizontal transmission (e.g., to family members or health care staff) been considered? What measures have been taken to minimize the risks of transmission? Are other measures possible? If transmission were to occur, what would be the consequences?

iv. What are the risks for the vector to activate an oncogene or inactivate a tumor suppressor gene leading to vector-related malignancy?

v. Are the risks and discomforts of the study justified given the potential benefit to subjects and the scientific importance of the research?

Guidelines for Submission and IEC review of Gene Therapy/Gene Transfer Protocols

Available at:

[http://ncdirindia.org/Ethics/Download/ICMR Ethical Guidelines 2017.pdf](http://ncdirindia.org/Ethics/Download/ICMR_Ethical_Guidelines_2017.pdf) (pg 122)

Ethical Policies on the Human Genome, Genetic Research and services, Department of Biotechnology, Ministry of Science and Technology, Govt. of India, 2002

Available at: <https://www.india.gov.in/ethical-policies-human-genome-genetic-research-and-services-department-biotechnology>

National Guidelines for Stem Cell Research (ICMR, 2017).

Available at:

[www.dbtindia.nic.in/wpcontent/uploads/National_Guidelines_StemCell_Research-2017.](http://www.dbtindia.nic.in/wpcontent/uploads/National_Guidelines_StemCell_Research-2017.pdf)

pdf; <http://www.dbtindia.nic.in/guidelines/>

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

- Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 (Recent Amendment 2013)

A. Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, other participants in medical research involving human subjects should adopt these principles.

3. It is the duty of the physician/researcher to promote and safeguard the health of patients, including those who are involved in medical research.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. Principles for all medical research

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be taken in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for

treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the

study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their data. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared explicitly. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a research or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgments it offers hope of saving life, re-establishing health or alleviating suffering. Where

possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

(Investigational New Drug) IND Application Exemption Checklist

This checklist is intended to be used by the investigator as a preliminary test of whether an IND application needs to be submitted to the DCGI for studies involving DCGI/RA-approved drugs. If any question is answered “yes”, an IND application must be submitted to the DCGI. If the answers to all questions are “no”, then the study may meet the criteria for an exemption from an IND.

1. Name of Drug:

Dosage:

Route:

2. Does the study involve a different route of administration of the marketed drug than already approved? YES NO
3. Does the study involve the administration of different drug dosage levels that significantly increase risk or decrease the acceptability of risk to study subjects? YES NO
4. Does the study involve the administration of the drug to a different patient population for whom there may be increased risk or decreased acceptability of risk? YES NO
5. Does the study entail any other factor that significantly increases the risk or decreases the acceptability of risk to study subjects? YES NO
6. Are the results of the study intended to be reported to the DCGI/RA in support of any significant change in labeling or advertising for the drug (only for corporate sponsored studies)? YES NO

Principal Investigator's signature: _____

Date: _____

Clinical Trial Registry – India

The Clinical Trials Registry- India (CTRI), is free online service, established under the ICMR's National Institute of Medical Statistics (NIMS) on 20th of July 2007. As per the office order from the Drug Controller General of India (DCGI), the registration of clinical trials in CTRI became mandatory since 15th of June 2009. The website address of CTRI is <http://ctri.nic.in>. Many of the peer reviewed indexed journals had come to the consensus that, only registered clinical trials under CTRI or any other national trial registry or international platforms only be accepted for publication. All the clinical trials involving human beings as study participants with intervention like drugs, surgical procedures, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies has to be registered with the CTRI before the recruitment of first study participant. It is important to have approval of ethics committee approval and DCGI office clearance (If applicable) for the registration process in the CTRI. If India is a part of multicentre clinical trials, even if the clinical trial is registered in international registry platforms, it is obligatory to register the same in the CTRI website. The CTRI website includes array of information regarding the clinical trial including list of investigators, details of clinical trial sites, target population, sample size, date of initiation of clinical trial etc. After successful registration of clinical trial in CTRI, it needs to be updated as and when required to keep up the progress of clinical trial more transparently to the general public. Being a Primary Register of the International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/search/en/>), registered trials are freely searchable both from the WHO's search portal, the ICTRP as well as from the CTRI (www.ctri.nic.in).