Institutional Ethics Committee
Sanjay Gandhi Postgraduate Institute of Medical Sciences
(IEC, SGPGI)

Appendices

AP1/V1

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. SGPGI patients - 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 SGPGI 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.

AP2/V1

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 SGPGI.

AP3/V1

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.

AP4/V1

Policy on the Use of Third Party / Surrogate Consent in Research at SGPGI

Applicability

When a SGPGI 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 SGPGI 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.

AP5/V1

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.

AP6/V1

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 (AN8-V1/SGSOP 03/V1 and AN10-V1/SGSOP 03/V1) 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 (AN7-V1/SGSOP 03/V1 and AN9-V1/SGSOP 03/V1):

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 SGPGI;
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 participation.

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 SGPGI 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.

AP7/V1

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 with held 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 SGPGI:

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.

AP8/V1

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 of 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.

AP9/V1

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.

iii. 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.

iv. 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.

v. 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.

vi. The length of time the genetic material will be maintained must be indicated in the consent form.

C. 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.

AP10/V1

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. ICMRs 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, adenoassociated 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, re-injection 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?

G. Information to subjects

- Have prospective participants been adequately informed of the following:

1. What is being studied and why, giving details about study procedures, known or potential risks, discomforts and benefits, and alternatives to participation;
2. Their rights: (a) to information on an ongoing basis, confidentiality with regard to their participation and handling of their data, and the right to consult with others before making a decision whether to participate; and (b) to withdraw from the study without penalty or loss of benefits, as well as of any health consequences of withdrawal for themselves or their immediate contacts, or limitations on withdrawal, if any;
3. Any special issues related to this gene therapy trial, such as uncertainty associated with short and long term risks and benefits or the possibility of media attention; and
4. Any commercial or financial interests in the research.

- Have prospective participants been provided this information in simple language, using translation where necessary, with answers to their questions, referral to other sources of information, and adequate time to make up their minds whether to participate?
- If there is no individual benefit from participation in the research, has this been appropriately disclosed?
- Will the general study results be made available to subjects?
- Do all of the elements of the consent process combine to allow subjects a full opportunity to make an informed choice?

Reference: Ethical Guidelines for Biomedical Research on Human Subjects ICMR 2006

AP11/V1

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

Preamble

In view of the tremendous growth of interest on the human genome, resulting from various conceptual and technological breakthroughs, genetic research and services have been growing at an accelerated pace. Such research and services impinge on human society, both at individual and group levels, resulting in various ethical concerns. In 1997, the UNESCO issued the Universal Declaration on the Human Genome and Human Rights. To consider whether any amendments are required in this Universal Declaration, to liaison with the International Bioethics Committee of UNESCO, as also to develop national policies for human genetic research and services, a National Bioethics Committee was constituted with the approval of the Minister of Science & Technology, Government of India, in November 1999. This Committee deliberated on various issues concerning the human genome. The policies provided in this document resulted from these deliberations. These policies have been so formulated that they are harmonized with the Ethical Guidelines for Biomedical Research on Human Subjects developed by the Indian Council of Medical Research in 2000.

Membership of the national bioethics committee

The committee has experts (Scientific and Legal) covering the areas of basic research, genetics, genomics, education and legal aspects. (Please see Appendix)

Introduction:

Genetic research involving humans has already provided benefits to humankind in the form of drugs, vaccines, diagnostics and other knowledge for better management of health and disease. With the availability of biotechnological tools and techniques, new vistas in molecular medicine have opened up for human welfare. Such research involves the collection and analyses of information (e.g., clinical, demographic) and biological samples (such as blood and other tissues) from individuals or groups of individuals. Sometimes, genetic research involves the administration of foreign material to individuals and analysis of resultant effects. There are potential risks involved in the collection of information and samples. The results of genetic research and services also have the potential of creating adverse effects, physical and/or mental, on individuals or groups of individuals. It is important to recognize that the results may have impact not only on those who are the principal focus of the research but also on others. It is, therefore, necessary to conduct genetic research involving humans and to provide genetic services following certain ethical principles and procedures so as to minimize harm, and to

maximize benefits, to those human beings who may participate in such research. Results of genetic research often lead to the creation of intellectual property rights that are of national commercial interest. It is, therefore, important to harness and to share these commercial benefits appropriately. Such research is often conducted collaboratively by scientists belonging to multiple institutions. In particular, when such collaborations involve foreign institutions and/or private companies, it is crucial to safeguard national interests.

The purpose of this document is to outline the national ethical policies for the human genome, genetic research and services. It is intended that this document will provide guidance for researchers, service providers, ethics committees, institutions, organizations and the public on how such research and services should be designed and conducted so as to conform to recognized ethical principles and values. Since it is not possible to foresee all potential problems or harm that can arise from genetic research and services, these policies may need revision from time to time. The principles and policies indicated in this document offer guidance for ethically sound research and practice.

This Report has drawn on internationally accepted ethical principles. Accordingly, this Policy document is recommended for use by any individual, institution or organization conducting genetic research or providing genetic services.

Principles

One of the essential requirements for research is that of the integrity of researchers. This includes the commitment to research questions that are designed to contribute to knowledge, a commitment to the pursuit and protection of truth, a commitment to reliance on research methods appropriate to the discipline and honesty.

Ethical considerations are as germane to good research as are scientific considerations. Ethical inadequacies in a research proposal are as significant as scientific inadequacies. It is, however, important to recognize that scientific inadequacies also have ethical implications.

Consistent with Declaration of Helsinki (adopted by the World Medical Assembly in 1964, and amended in October 2000) and the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), the basic ethical principles that should be followed in genetic research and services are :

1. Autonomy: Choice of participation is autonomous, voluntary and based on informed consent; persons or groups with diminished autonomy should be given protection.
2. Privacy: Identifiable information (clinical, genetic, etc.) of individuals or groups is confidential and should be protected.
3. Justice: There should be no discrimination against individuals (born or unborn including embryo) or groups. No harm should be done and benefits should be maximized.
4. Equity: There should be equitable access to information, tests and procedures.

Policies

Integrity, Respect and Beneficence

• All researchers should be guided by the principle of integrity, which is expressed in a commitment to the search for knowledge, to recognized scientific procedures of research conduct and in the honest and ethical conduct of research and dissemination and communication of results. Human Genome and Genetic research must be conducted by professionally qualified investigators. The experimental and other procedures used in research should be quality and safety assured prior to their implementation.

• When conducting genome and genetic research involving humans, the guiding ethical principle for researchers is respect for persons which is expressed as regard for the welfare, rights, beliefs, perceptions, customs and cultural heritage, both individual and collective, of persons involved in research. The culture and traditions of the group to which the participant belongs must be respected. It is desirable that a group be consulted prior to undertaking research on the group with the purpose of understanding whether implementation of the proposed research protocols may cause disrespect or harm to them in any way.

• In human genome and genetic research no participant or group must be exposed to more than a minimum acceptable risk. If it is anticipated that research exposes a participant or a group to a specific risk, this should be disclosed. Each participant must have the right to demand compensation from the investigator for any injury or harm arising from his/her participation. Appropriate liability agreements should be drawn between the researcher and the participating individual and/or group before commencement of the research.

• Each research protocol must be designed to ensure that respect for human rights, dignity and well-being of the participants and of the group to which the participants belong takes precedence over the expected gains to knowledge.

Justice

1. The ethical value of justice requires that, within a population, there is a fair distribution of the benefits and burdens of participation in research and, for any research participant, a balance of burdens and benefits.

Accordingly, a researcher must

(a) design research so that the selection, recruitment, exclusion and inclusion of research participants is fair;

(b) make appropriate arrangements to provide liberty to every participant to withdraw from the research, and demand destruction of data or samples collected from him/her, at any time, without being penalized in any way for withdrawal;

(c) not impose any unfair burden of participation in research on any individual or group, and, therefore, no inordinate inducements, monetary or otherwise, should be offered to individuals

or groups for participation;
(d) establish agreements for sharing of benefits arising out of the research (such as, intellectual property rights, access to products or procedures, capacity building) before commencement of a research study;
(e) not discriminate in the selection and recruitment of actual and future participants by including or excluding them on the grounds of race, age, gender, disability, vulnerability or religious or spiritual beliefs except where the exclusion or inclusion of particular groups is essential to the purpose of the research;
(f) provide protection to participants with reduced autonomy (e.g., children, disabled or vulnerable individuals) during the conduct of research;
(g) Not undertake research that may place the embryo and fetus of a pregnant woman at an undue risk of any kind.
Consent
1. Before recruitment of any individual/group in human genome and genetic research, consent of the participants must be obtained.
The ethical and legal requirements of consent have two aspects: the provision of information and the capacity to make a voluntary choice. So as to conform with ethical and legal requirements, obtaining consent should involve :
(a) provision to participants, at their level of comprehension and in a language or method understandable to them, of information about the purpose, methods, demands, risks, inconveniences, discomforts, and possible outcomes of the research; and
(b) The exercise of a voluntary choice to participate.
Where a participant lacks competence to consent, a person with lawful authority to decide for that participant must be provided with that information and exercise that choice.
It is, therefore, recommended that :
(i) A researcher must explain the purpose of the research, the foreseeable risks and benefits of participation and alternative procedures, if any.
(ii) Consent obtained from each participant, and the participating group (where applicable), must be documented.
(iii) Consent is valid only for the research for which it is given by the participant (primary use). If the information or samples for primary use are to be used for other purposes or for sharing with other investigators (secondary use), clear mention of such secondary uses must be made during the process of obtaining informed consent. New consent must be taken for any use for which consent was not explicitly obtained. However this will not be required if the sample is used as an 'Unidentified' or 'Unlinked' sample.
(iv) Consent from a potential participant who is a minor or is so handicapped that she/he is

Incapable of providing informed consent (e.g., persons who are legally incompetent, physically or mentally challenged) may be taken from a close biological relative, such as parents, sibling, or from a legally authorized representative. For a mentally ill person, a psychiatrist should certify his/her capability of providing voluntary informed consent.

(v) If information pertaining to a deceased individual is required, this information may be obtained from a close biological relative or from a legally authorized representative.

(vi) Data pertinent to research may be collected on relatives of a participant, provided that no information revealing the identity of the relative is collected.

(vii) When research pertains to a specific community (e.g., an ethnic group, an organization of patients), it is desirable to obtain group consent before obtaining individual consent. Group consent must also be documented.

(viii) Consent of parents must be taken for collection and use of biological material from a dead fetus for the purpose of research.

(ix) For research based on information in databases or samples in repositories,

(a) no consent of the donor/ participant will be required if the information/ samples are unidentified,

(b) individual informed consent of the donor/ participant will be required if the information/ samples are identified,

(c) Individual informed consent of the donor/ participant will be required if the information/ samples are coded, unless the owner(s) of the database or repository and the research investigator mutually agree not to provide/ receive the research findings based on the information/ samples.

(x) For research based on human biological materials collected during and as part of a clinical procedure or medical care, an informed consent for research use of the samples should be obtained separately from that obtained for the clinical procedure.

(xi) A person may refuse to participate in a research project or withdraw from a research project without giving any reason or justification.

Dissemination of Research Results

Researchers should be encouraged to disclose their findings, after these have been scientifically validated. The results of research (whether publicly or privately funded) and the methods used should normally be published, with appropriate IPR protection wherever relevant, in ways which permit scrutiny and contribute to public knowledge. Disclosure of findings with significant implications for the health of a participant must be carefully done to the participant after obtaining her/his consent, and only when an appropriate ameliorative course of action (such as a medical treatment or life-style change) is readily available. In such cases, appropriate medical advice, referral or counseling should be provided to the participant by a

trained professional. Disclosure of research information should not be done if it can have adverse societal implications, national or international.

Gene Therapy & Human Cloning

• Somatic cell gene therapy research and service may be done with appropriate safety measures. Gene therapy may be undertaken when it is the only therapeutic option or it is indisputably considered superior to other existing options. Appropriate protocols as developed by Department of Biotechnology, Govt. of India must be followed.

• Considering the present state of knowledge, germ line therapy in humans shall be proscribed. However, research on embryonic stem cell biology may be undertaken with adequate safety measures.

• As a principle, human cloning shall not be permitted.

Genetic Testing and Counseling

• Individuals, laboratories or institutions providing genetic testing services should be licensed or registered by the appropriate Governmental authority. Such service providers should operate in accordance with nationally accepted standards for scientific accuracy, confidentiality of information and bioethics. No disclosure of results of genetic testing should be made to the patient in the absence of genetic counseling.

• When genetic testing of an individual reveals that he/she has a predisposition to suffer disease or disability in the future, then the tested individual shall have the right exercised by freedom of choice whether to be informed of the results of such testing.

• Interventions based on results of genetic testing should be carried out under appropriate medical advice.

Genetic Privacy and Discrimination

• Discrimination of any kind on the basis of genetic characteristics or information shall be prohibited.

• Immediate and effective measures, particularly in the fields of teaching, education, culture and information, shall be implemented with a view to removing prejudices based on genetic characteristics and variability.

Intellectual Property Rights and Benefit Sharing

1. The human genome, part of human body or any human material in its natural state cannot become the subject of a direct financial gain.

2. International Law allows for the identification of ownership of sovereign rights over human genetic material (like any other biodiversity plants, animals and microbes) which shall be implemented.

3. Intellectual property based on the human genome may be patented or otherwise recognized in accordance with national laws and international treaties.

4. All patents filed in India or abroad utilizing such biological material must disclose the source of the material and associated information so as to protect the economic interests of the original source/ nation.
5. It will be obligatory for national/international profit making entities to dedicate a percentage (e.g., 1% - 3%) of their annual net profit arising out of the knowledge derived by use of the human genetic material, for the benefits of the community.
6. Protection of Intellectual Property Rights (IPR) must be ensured and adequate safeguards taken for sharing of benefits arising from clinical trials based on pharmacogenomic studies in a given population.

DNA and Cell-line Banking

1. The sample collector must obtain explicit informed consent of the donor for DNA banking or for cell-line transformation and banking. The process of seeking informed consent for purposes of banking must clearly state, in addition to possible risks and benefits, the conditions under which samples from the Repository will be provided to other researchers, how long the samples will be preserved in the Repository and what may be the costs to individual researchers to obtain samples from the Repository. The sample collector must also explicitly inform every donor that he/she reserves the right to order destruction of his/ her sample from the Repository at any time. If any commercial use is made of the samples in the Repository, appropriate written benefit-sharing agreements, consistent with the policies stated earlier, must be jointly signed by the donor, sample collector and Repository Director. It is also desirable that community consultations are held prior to collection of samples to be stored in a Repository, and group consent be obtained.
2. Any DNA/ Cell-line Repository must have its own Ethical Review Committee.
3. Before any sample is placed in the Repository, the Ethical Review Committee must ensure that the sample was collected as per national ethical policies and guidelines.
4. Any researcher who intends to use samples from a Repository must submit a Statement of Research Intent, which must be approved by the Ethical Review Committee of the Repository. The Repository's Ethical Review Committee will be responsible for determining whether the intended research is consistent with the informed consent provided by the donor, and, where applicable, of the group.
5. Unless scientifically essential, the Repository must not provide to an individual researcher any information linked to the samples. When linked information is to be provided, only the minimal information as required for the intended research must be provided.
6. The identity of the Repository from which samples were obtained must be revealed in all reports/ patents/ copyrights arising out of these samples.
7. No samples placed in the repositories or obtained from the repositories can be shared with

any scientist/ organizations within and beyond the boundaries of India, without approval of 'National Bioethics Committee' / or Department of Biotechnology, Government of India.

International Collaboration

1. To encourage human genetic research, to promote international dissemination of scientific knowledge concerning the human genome and to foster scientific and cultural cooperation, collaborative research with other countries may be undertaken, with appropriate protection of intellectual property rights.
2. To safeguard national interests, all human genetic research involving international collaboration must be undertaken after formal clearance of the national government. This will also apply to private sector research.
3. In international collaborative research, when genetic material from India forms the primary basis of such research, intellectual property rights should be protected with a majority share of the patent, if any, being held by the collaborating Indian institution/organization. At least 10% of the benefit accruing from such a patent should be used by the individual institutions to develop better services for the population(s) that provided genetic materials. A minimum of 10% of intellectual property rights should be held by Indian institution/organization in any international collaborative research.

Implementation of ethical policies

National or an Institutional Ethical Review Committee must clear all genomic/ stem cell research involving humans to be undertaken in India. The Ethical Review Committee will ensure that national ethical policies and recommendations are followed.

When a research study involves the administration of a new chemical/ biological entity, the advice/approval of the Drugs Controller General of India should be taken.

All Ethical Review Committees involved in reviewing international collaborative research must ensure that the research complies with the Indian national ethical policies and guidelines and also those of the sponsoring/ funding country. Appropriate ethical clearances must be obtained from India and other relevant countries, including the sponsoring/ funding country, involved in the research. If some ethical rules of any of the relevant countries cannot be implemented in any of the host countries, then the Ethical Review Committees of all the countries must be informed and appropriate waivers obtained.

In all publications/ patents applications, the source of the genetic material is to be clearly stated, without compromising the privacy of the participants.

Research results/ inventions involving genetic material obtained from the jurisdiction of a foreign nation should be accepted for publication/ patenting only after the appropriate ethical guidelines have been followed.

Categories of Human Biological Materials

Repository Collections

Unidentified specimens: For these specimens, identifiable personal information was collected or, if collected, was not maintained and cannot be retrieved by the repository.

Identified specimens : These specimens are linked to personal information in such a way that the persons from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e. his or her relationship to a family member whose identity is known.).

Research Samples

Unidentified samples: Sometimes termed 'anonymous,' these samples are supplied by repositories to investigators from the collection of unidentified human biological specimens.

Unlinked samples: Sometimes termed 'anonymized,' these samples lack identifiers or codes that can linked a particular sample to an identified specimen or a particular human being.

Coded samples: Sometimes termed 'linked,' or 'identifiable,' these samples are supplied by repositories to investigators from identified specimens with a code rather than personally identifying information, such as a name or a Social Security number.

Identified Samples: These samples are supplied by the repositories from identified specimens with a personal identifier (such as a name or a patient number) that would allow the researcher to link the biological information derived from their search directly to the individual from whom the material was obtained.

Definitions

Research is defined as a systematic scientific activity designed to develop or contribute to knowledge that can be generalized. The present Report considers only research that is biomedical in nature, involving human participants. Such research includes, but is not limited to, investigations for testing biological or medical hypotheses, evaluating a diagnostic procedure or a drug, determining the mode of inheritance of a disease or trait, mapping disease genes, etc.

Biomedical research is distinct from medical practice which solely caters to the needs of an individual, and generally pertains to interventions (usually in the form of diagnosis or therapy) with the goal of enhancing or maintaining the well-being of an individual.

A participant in biomedical research is a living human being who provides identifiable private information or tissue samples to the research investigator through direct interaction or allows him/her to be subjected to interventions required by the research protocol. For the purpose of this report, 'identifiable' implies that the identity of the participant can be readily ascertained from the private information (that is, information not in the public domain prior to the participant providing the information to the investigator in question) provided to the investigator.

Often genome research is conducted on information or samples collected earlier, possibly by other investigators (detailed in Annexure I). Such information or samples may be: (a) unidentified - that is, without any identifiable private information, (b) identified - that is, with identifiable private information to which the identity of the donor/participant can be linked. Sometimes, data or tissue sample repositories send coded information or samples to research investigators. Coded information or samples do not permit the research investigator to link the information or samples to the donors/participants, but the repository can link the research findings to the donors/participants.

Depending on the objectives and protocols, a biomedical research study often pertains to a group or a community. A group or a community may be defined as a collection of individuals sharing some common characteristics, such as ethnicity, geographical proximity of habitat, a common disease, etc. The working definition of a group or community may vary from one study to another, and may need to be identified during the study.

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Recommended Terms for Use in Consent Forms

To facilitate understanding of consent forms by the subject, it is recommended that the language used is at a reading level of a 12 year old. The following lay terms, definitions and suggestions are recommended to help investigators in this process.

For	**Use**
adjuvant	helpful; assisting; aiding
ambulate (-action –ory)	walk; able to walk; ability to walk
ameliorate	make smaller or less, reduce
analgesia	pain relief
anaphylactic reaction	a severe and sometimes dangerous reaction which may cause problems breathing, fainting, itching and skin rash
anorexia	lack of appetite
arrhythmia	abnormal heartbeat
aspiration	removal by using a sucking machine; fluid entering the lungs
asymptomatic	without symptoms; having no symptoms
barrier method	diaphragm and condom (with spermicide), cervical cap, or sponge
benign	not malignant; usually without serious consequences
bolus	an amount given all at once
bradycardia	slow heartbeat
carcinogenic	capable of causing cancer
cardiac	heart
cerebral	the brain; of the brain
CHD	coronary heart disease; heart disease
controlled trial	study in which the experimental treatment is compared to a standard treatment
conventional therapy	standard treatment
coronary	pertaining to the blood vessels that supply the heart
CT (CAT)	scan computerized series of x-rays
cutaneous	relating to the skin
DCGI	Drug Controller General of India
diastolic	the lower number in a blood pressure reading
disseminated	widely-spread, all through the body
distal	toward the end; away from the center of the body
diuretic	drug that causes an increase in urine secretion
double-blind	neither the subject nor physician can know what is being given
dysfunction	improper function
dysplasia	abnormal cells
echocardiogram	sound wave test of the heart
edema	fluid in the tissues; puffiness; swelling
emesis	vomiting
endoscopic	examination of the inside of the body with a lighted tube
epidural	outside the spinal cord

erythrocyte	red blood cell
fibrillation	irregular heartbeat
fibrous	like scar tissue
granulocyte	white blood cell
hematocrit	concentration of red blood cells
holter monitor	portable machine for recording heartbeats
hypoxia	low oxygen level in the blood
immunosuppressive	a drug or therapy that reduces the body's ability to fight infection; helps prevent rejection of a transplanted organ
infarct	death of tissue due to loss of blood flow
intubate	the placement of a tube into the airway
ischemia	decrease in oxygen in a tissue, usually because of decreased blood flow
laparotomy	a procedure where an incision is made in the abdominal wall to enable a physician to look at the organs
lumen	cavity of an organ; inside a blood vessel
lymphocyte	a type of white blood cell important for defense against infections
marrow suppression	decreased growth of the bone marrow
metastasis	spread of cancer cells from one part of the body to another
monoclonal antibody	very specific, purified antibody
morbidity	sickness/illness
MRI	pictures of the body created using magnetic rather than x-ray energy
murine	obtained from mice
myalgia	muscle aches
myocardial	infarction heart attack
nasogastric	tube a tube from the nose to the stomach
necrosis	death of tissue
neoplasia	a tumor that may be cancerous or non-cancerous
neural	brain or nerves
neutropenia	decrease in white blood cells
occult blood test	testing a stool sample for invisible amounts of blood
oncology	the study of tumors or cancer
pancytopenia	low number of blood cells
Percutaneous	through the skin
phlebitis	irritation or inflammation of a vein
placebo	inactive medication; dummy pill; sugar tablet; containing no medication
platelets	blood cells that help the blood clot normally
prenatal	before birth
prognosis	outlook, probably outcomes
prophylaxis	a drug given to prevent disease or infection
prosthesis	artificial body parts, such as arms, legs, hips
proximal	closer to the center of the body, away from the end
psychosis	major psychiatric problem
pulmonary	pertaining to the lungs

radiotherapy	treatment with radiation
randomly assigned	similar to the toss of a coin; assignment to a treatment group by chance
refractory	not responding to treatment
regimen	pattern of giving treatment
renal	kidney
resect	remove or cut out surgically
somnolence	sleepiness
staging	a determination of the extent of the disease
stenosis	narrowing of a duct, tube, or blood vessel
stratify	arrange in groups by age, sex, etc., for analysis
subcutaneous	under the skin
supine	lying on the back
syndrome	a condition with a certain set of symptoms
systolic	the top number in blood pressure
tachycardia	fast heart beat
taper	decrease; reduce
thrombosis	to get or have a blood clot in a blood vessel
titration	gradual alteration of a drug dose to get the desired effect
topical	applied to the skin
transdermal	through the skin
uremia	kidney failure
varices	enlarged veins
vasodilation	widening of the blood vessels
vasospasm	narrowing of blood vessels due to a spasm of the vessel walls
venipuncture	taking blood from the vein

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From Essential documents for the Conduct of a Clinical Trial Good Clinical Practices for Clinical Research in India by Central Drugs Standard Control Organization, Directorate General of Health Services, New Delhi, 2001 (page 125-132)

Essential Documents are those documents which individually and collectively allow the evaluation of the conduct of a study and the quality of the data generated. These documents demonstrate the compliance (or otherwise) of the Investigator, Sponsor and Monitor with the Good Clinical Practice and with other applicable regulatory requirements. Essential Documents are needed for Sponsor's independent audit function and inspection by the Regulatory Authority.

The various Essential Documents needed for different stages of the study are classified under three groups:

1. Before the clinical phase of the study commences,
2. During the clinical conduct of the study, and
3. After completion or termination of the study.

The documents may be combined but their individual elements should be readily identifiable.

Master files containing all documents pertaining to the study should be created at the beginning of the study, at the Investigator / Institution site, Sponsor's office, the Bioethics cell and the CRO's office.

Legend :
I - Investigator / Institute, S - Sponsor, C - CRO,
E - IEC, • - Yes, × - Not applicable

Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
Before the Clinical Phase of the Trial Commences During this planning stage the following documents should be generated and should be on file before the trial formally starts.						
1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	•	•	•	•
2	Signed protocol and amendments, if any, and sample case report form(CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	•	•	•	•
3	Information given to trial subject- informed consent form (including all applicable translations)	To document the informed consent	•	•	•	•
4	Any other written information	To document that subjects will be given appropriate information (content and wording) to support their ability to give fully informed consent	•	•	•	•

5	Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	•	•	•	•
6	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	•	•	•	•
7	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	•	•	•	•
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
8	Dated, documented approval / favourable opinion of independent ethics committee (IEC) of the following: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - Subject compensation (if any) -any other documents given approval / favourable opinion	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s)	•	•	•	•
9	Independent ethics committee composition	To document that the IEC is constituted in agreement with GCP	•	•	•	•
10	Regulatory authority(ies) authorisation / approval / notification of protocol (where required)	To document appropriate authorisation / approval / notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	•	•	•	•
11	Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator(s) & Co-Investigator (s)/Sub-Investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	•	•	•	•
12	Normal value(s) / range(s) for medical/ laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	•	•	•	×
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	•	•	•	×
14	Instructions for handling of investigational product(s) and	To document instructions needed to ensure proper storage, packaging,	•	•	•	×

	trial-related materials (if not included in protocol or Investigator's Brochure)	dispensing and disposition of investigational products and trial-related materials				
15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	•	•	•	×
16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial	×	•	•	×
	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subject's treatment	•	•	•	×
17	Master randomisation list	To document method for randomisation of trial population	×	•	•	×
18	Pre-trial monitoring report	To document that the site is suitable for trial (may be combined with Trial initiation monitoring report)	×	•	•	×
19	Trial initiation monitoring report	To document that the trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with Pre-trial monitoring report)	•	•	•	×
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
During the Clinical Conduct of the Trial In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available						
20	Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	•	•	•	•
21	Any revision to: - protocol amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment(if used)	To document revisions of these trial related documents that take effect during trial	•	•	•	•
22	Dated, documented approval / favourable opinion of Independent ethics committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - informed consent for - any other written information	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s).	•	•	•	•

	provided to subject - advertisement for subject recruitment(if used) - any other documents given approval / favourable opinion -continuing review of trial (where required)					
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
23	Regulatory authority(ies) authorisations / approvals / notifications where required for: protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	•	•	•	•
24	Curriculum vitae for new investigator(s) and / or sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	•	•	•	•
25	Updates to normal value(s) / range(s) for medical/laboratory/technical procedure(s) / test(s) included in the protocol	To document normal values and ranges that are revised during the trial	•	•	•	×
26	Medical/laboratory/technical procedures /tests - certification or - accreditation or - established quality control and / or external quality assessment or other validation (where required)	To document that tests remain adequate throughout the trial period	•	•	•	×
27	Documentation of investigational product(s) and trial-related material shipment	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	•	•	•	×
28	Certificate(s) of analysis for new batches of investigational products	To document identity, purity, and strength of investigational product(s) to be used in the trial	×	•	•	×
29	Monitoring visit reports	To document site visits by, and findings of, the monitor	×	•	•	°
30	Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	•	×	•	×
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
31	Signed informed consent forms	To document that consent is obtained in accordance with GCP	•	•	•	×

		and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	Original	Copy	Copy	
32	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trials, to medical treatment, and history of subject	• Original	• Copy	• Copy	×
33	Signed, dated and completed case report forms (CRF)	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	• Copy	• Copy	• Copy	×
34	Documentation of CRF corrections	To document all changes / additions or corrections made to CRF after initial data were recorded	• Original	• Copy	• Copy	×
35	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports	•	•	•	•
36	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IEC(s) of unexpected serious adverse drug reactions and of other safety information	•	•	•	•
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
37	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	•	•	•	•
38	Interim or annual reports to IEC and authority(ies)	Interim or annual reports provided to IEC and to authority(ies)	•	•	•	•
39	Subject screening log	To document identification of subjects who entered pre-trial screening	•	• Where required	• Where required	×
40	Subject identification code list	To document that investigator / Institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ Institution to reveal identity of any subject	•	•	•	×
41	Subject enrolment log	To document chronological enrolment of subjects by trial	•	•	•	×

		number				
42	Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol	•	•	•	×
43	Signature sheet	To document signatures and initials of all persons authorised to make entries and / or corrections on CRFs	•	•	•	×
44	Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	•	•	•	×
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
After Completion or Termination of the Trial After completion or termination of the trial, all of the documents identified should be in the file together with the following						
45	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, return by the subjects, and returned to sponsors	•	•	•	×
46	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site	• dest roye d at site	•	•	×
47	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	•	•	•	°
48	Audit certificate (if available)	To document that audit was performed	×	•	•	×
49	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	×	•	•	×
50	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	×	•	•	×
Title of the document		**Purpose**	**Located in files of**			
			I	**S**	**C**	**E**
51	Final report by investigator to IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	•	•	•	•
52	Clinical study report	To document results and interpretation of trial	•	•	•	•

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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, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

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, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
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 exercised 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.
Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

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 reports. 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 in the publication. 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 who serve as research subjects.

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, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

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 study 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.

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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 _____

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Clinical Trial Registry – India

The Clinical Trials Registry- India (CTRI), hosted at the ICMR's National Institute of Medical Statistics (NIMS), is a free and online public record system for registration of clinical trials being conducted in India that was launched on 20th July 2007 (www.ctri.nic.in). Initiated as a voluntary measure, since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General (India) (DCGI) (www.cdsco.nic.in). Moreover, Editors of Biomedical Journals of 11 major journals of India declared that only registered trials would be considered for publication.

Today, any researcher who plans to conduct a trial involving human participants, of any intervention such as drugs, surgical procedures, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies as well as trials being conducted in the purview of the Department of AYUSH (http://indianmedicine.nic.in/) is expected to register the trial in the CTRI before enrollment of the first participant. Trial registration involves public declaration and identification of trial investigators, sponsors, interventions, patient population etc before the enrollment of the first patient. Submission of Ethics approval and DCGI approval (if applicable) is essential for trial registration in the CTRI. Multi-country trials, where India is a participating country, which have been registered in an international registry, are also expected to be registered in the CTRI. In the CTRI, details of Indian investigators, trial sites, Indian target sample size and date of enrollment are captured. After a trial is registered, trial lists are expected to regularly update the trial status or other aspects as the case may be. After a trial is registered, all updates and changes will be recorded and available for public display.
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).

CTRI Dataset and Description

CTRI Field	**Description**
Public title of study	Title intended for the lay public in easily understood language. **Example:** A clinical trial to study the effects of two drugs, ramipril and candesartan in patients with high blood pressure and type 2 diabetes mellitus.

Scientific title of study Acronym, if any	Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available. **Example:** A randomized double-blind placebo controlled crossover clinical trial to compare the safety and efficacy of ramipril and candesartan in hypertensive patients with type 2 diabetes mellitus. **Acronym** RACE
Secondary IDs, if any	Secondary ID is any number that is associated with a clinical trial, such as Protocol Number or any other Trial Registry Number, if registered in another Registry, such as ClinicalTrials.gov, ACTR, ISRCTN etc. There is no limit on the number of Secondary ID numbers that can be provided. In case of a multi-country trial, the trial may have already been registered in another registry such as the www.ClinicalTrials.gov. However, the trial, if also being conducted in India needs to be registered in the CTRI as well. In this case, the ClinicalTrials.gov identifying number would be this trial's Secondary ID number. **Universal Trial Number** UTN (earlier known as UTRN) may be obtained from http://apps.who.int/trialsearch/utn.aspx Please quote the obtained UTN number under SECONDARY ID. Currently obtaining the UTN is not mandatory **If there are no secondary IDs** select NIL from the drop down list and type in NIL in the corresponding box.
Principal Investigator's name and address	Details should include name, official address, affiliation and designation, contact telephone and fax numbers and email ID. For a multi-center study, enter the contact information for the lead Principal Investigator (PI) or overall Trial Coordinator. Designated person must be from India (for trials being conducted in India). This is not a mandatory field.
Contact person (Scientific Query)	Details should include name, official address, affiliation and designation, email address, telephone number, Fax No and postal address, and affiliation of the local person (in case of multi-country trial) to contact for scientific queries about the trial (local principal investigator, medical contact of sponsor). May or may not be the same as the PI.
Contact person (Public Query)	Details should include name, official address, affiliation and designation, email address, telephone number, Fax No and postal address of the contact who will respond to general queries, including information about current recruitment status. This may or may not be the same as the contact person for scientific queries.
Source/s of monetary or material support	Major source/s of monetary or material or infrastructural support for the trial (e.g., funding agency, foundation, company, hospital, university, etc).
Primary sponsor	Name and address of the individual, organization, group or other legal person taking responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the study design meets appropriate standards and to ensure appropriate conduct and reporting). The Primary Sponsor is responsible for ensuring that the trial is properly registered. The Primary Sponsor may or may not be the main source of funding. In commercial trials, the primary sponsor is normally the main applicant for regulatory authorization to begin the study. It may or may not be the main source of funding. In investigator initiated trials, the principal investigator is the primary sponsor, though the affiliated institution may be the main source of funding, and acknowledged under "Source/s of Monetary or Material Support".

Secondary Sponsor	Name and address of additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship. A secondary sponsor may have – • Agreed to take on all the responsibilities of sponsorship jointly with the primary sponsor; • To form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; • To act as the sponsor's legal representative in relation to some or all of the trial sites; or to take responsibility for the accuracy of trial registration information submitted.
Countries of recruitment	Select from drop down list, countries from which participants are intended to be, or have been recruited. E.g.: India - for trials conducted only in India; India, USA, France - for multi-country trials (as the case may be)
Site/s of study	List all site/s within India including the site address as well as the complete address, email, telephone number and Fax No of responsible contact person at each site (This individual should be a medically qualified person and to whom the EC approval is addressed, i.e. the PI; in case a separate person is mentioned, the PI should also be mentioned in any of the other contact person details ("PI or Overall trial coordinator, Contact Person (Scientific query or Public query). **For PMS trials** with hundreds of trial sites, site details may be 'copy-pasted' in the Brief summary, specifying the few initiated sites under "Site/s of study"
Name of Ethics Committee and approval status	Provide name of Ethics Committee (EC) from whom approval has been sought; for multi-centre trials, add names of all ECs from whom approval has been sought; also provide approval status, i.e. submitted for approval or approved with date. Please indicate whether an EC is an Independent Ethics Committee or not. Mention EC approval status of each site separately even if it is "under review" and/or from the same IEC (please mention the city from which the IEC functions). **For PMS trials "Not applicable" or "No objection certificate obtained" as appropriate.**
Regulatory clearance obtained from DCGI	Mention whether approval has been taken from Drugs Controller General (India) [DCGI] or not. If DCGI has been notified, the same should be selected. **It is the responsibility of the Sponsor to ascertain whether or not DCGI approval is required for a particular trial**.
Health condition/problem studied	State the primary health condition(s) or problem(s) studied. If the study is conducted in healthy human volunteers belonging to the target population of the intervention (e.g., preventative or screening interventions), enter the particular health condition(s) or problem(s) being prevented or screened **Exemple:** Type 2 Diabètes Mellitus; Hypertension
Study type	Please indicate if trial part of post-graduation thesis Please select whether the trial is an Interventional trial, Observational trial or Post marketing surveillance **Interventional Trial:** An interventional trial is one that prospectively assigns human participants or groups of humans to one or more health-related intervention to evaluate the effect on outcomes.

	Choose the intervention that is best suited for the trial, more than one option may be selected according to the intervention/s being used; e.g. Drug & Ayurveda **Observational Trial** An observational trial is one where no experimental intervention or treatment is given to human participants. In this type of trial, the investigator only observes the effect of a risk factor, diagnostic test, or treatment on a particular outcome. Choose the intervention that is best suited for the trial. PMS: Post marketing surveillance study Choose a Study Design from the list provided **Examples:** Single arm trial Non-randomized, placebo controlled trial Non-randomized, active controlled trial Non-randomized, multiple arm trial Randomized parallel group trial Randomized, parallel group, placebo controlled trial Randomized, parallel group, active controlled trial Randomized, parallel group, multiple arm trial Randomized, crossover trial Cluster randomized trial Randomized factorial trial
Intervention and comparator agent	Enter the specific name of the intervention/s and the comparator/control/s being studied. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise"). The control intervention/s is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name/s of that intervention, or enter "placebo" or "no treatment" as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc). **Example:** Ramipril 2.5 mg OD for 12 months Candesartan 16 mg OD for 12 months For observational trials, NIL may be mentioned with trial details mentioned in the Brief Summary.

Inclusion/ Exclusion criteria	Inclusion and exclusion criteria for participant selection, including age and sex. Age and sex to be mentioned in specific boxes. **Example:** Inclusion criteria Adult males or females with a diagnosis of type 2 diabetes mellitus and hypertension Hypertension defined as systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg Diabetes defined as those patients with fasting glucose levels of $\geq$ 126 mg/dl or random blood glucose > or = 200 mg/dl, HbA1c > or = 6.5%, 2 h blood glucose on 75 g oral glucose tolerance test (OGTT) > or = 200 mg/dl, or current treatment with hypoglycemic therapy). **Exclusion Criteria:** A history of coronary heart disease or stroke, serum creatinine $\geq$1.5 mg/dl, albuminuria $\geq$40 µg/min, and use of lipid-lowering drugs, aspirin, or other antihypertensive agents. **Please separate each criteria by using the "Enter" button**
Method of generating randomization sequence	The method used to generate the random allocation sequence. The main purpose of randomization is to eliminate selection bias and balance known or unknown confounding factors in order to create a control group that is as similar as possible to the treatment group. Methods for randomly assigning participants to groups, which limits bias, include the use of a table of random numbers and a computer program that generates random numbers. Methods of assignment that are prone to bias include alternating assignment or assignment by date of birth or hospital admission number. **Example:** Coin toss, lottery, toss of dice, shuffling cards etc Random number table Computer generated randomization Permuted block randomization, fixed Permuted block randomization, variable Stratified randomization Stratified block randomization Adaptive randomization, such as minimization Other, describe
Method of allocation concealment	Concealment of the randomization sequence is critical to prevent selection bias. Adequate allocation concealment is a pre-requisite for adequate blinding. Adequate allocation concealment methods include: • centralized (e.g. allocation by a central office unaware of subject characteristics) • pharmacy-controlled randomization • pre-numbered or coded identical containers which are administered serially to participants

	• on-site computer system combined with allocations kept in a locked unreadable computer file • sequentially numbered, sealed, opaque envelopes Allocation concealment that is prone to bias include • alternation • case record numbers • dates of birth or day of the week • an open list of random numbers and • any procedure that is entirely transparent before allocation
Blinding/masking	Blinding refers to methods used to prevent participants and investigators from knowing what interventions are being used to reduce bias. Open trials do not use blinding. Masking refers to the methods used to camouflage interventions to achieve blinding. Examples: • Open label • Participant blinded • Investigator blinded • Outcome assessor blinded • Double blind double dummy • Participant and Investigator blinded • Participant and outcome assessor blinded • Participant, investigator and outcome assessor blinded • Participant, investigator, outcome assessor and data-entry operator/statistician blinded
Primary outcome/s	Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention. The primary outcome could be the outcome used in sample size calculations, or the main outcome/s used to determine the effects of the intervention/s. Enter the names of all primary outcomes in the trial as well as the pre-specified time point/s of primary interest. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10 "rather than just "depression"). **Examples** Outcome Name: all-cause mortality, Time-points: 5 years; or Outcome Name: Mean Beck Depression Score, Time-point: 18 weeks.
Secondary outcome/s	Secondary outcomes are events, variables, or experiences that are of secondary interest or that are measured at time-points of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at time-points

	other than those of primary interest (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: all-cause mortality at 1 year, 3 years), or may involve a different event, variable, or experience altogether (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: hospitalization rate at 5 years). Enter the name and time-point(s) for all secondary outcomes of clinical and/or scientific importance.
Target sample size	Total number of participants that the trial plans to enroll. **For global/multi-country trials**, enter both Total sample size and Target sample size from India. This is a numbers only field. **Example** Target sample size **120** India **500** Total **For trials being conducted only in India**, target sample should be same under both columns Target sample size **120** India **120** Total
Phase of trial	Phases of investigation, usually applied to a drug trial Phase 1: includes initial study to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing does, and to gain early evidence of effectiveness; may include healthy participants and/or patients (such as those testing anticancer or anti-HIV drugs) . Trials are often dose ranging trials which are done to determine the maximum dose of a new medication that can be safely given to a patient. Phase 1 / Phase 2: for trials that are at a combined stage of phases 1 and 2 Phase 2: includes controlled clinical study conducted to evaluate/test the effectiveness of a new drug/medication or intervention for a particular indication or indications in patients with the disease or condition being studied and to determine the common short-term side effects and risks Phase 2 / Phase 3: for trials that are at a combined stage of phases 2 and 3 Phase 3: includes expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of a new drug/medication or intervention, including possible adverse reactions. It is also to provide an adequate basis for physician labeling Phase 3 /Phase 4: For trials that are at a combined stage of phases 3 and 4 Phase 4: Studies (other than routine surveillance) performed after drug is marketed and is related to the approved indication. Trials are done to monitor the toxicity, risks, utility, benefits and optimal use after the efficacy of the drug/medication or intervention has been proven. Not applicable: This selection is for a non-drug trial Post marketing surveillance: Routine surveillance trials after marketing approval **Example** Phase 3
Date of first enrollment	Select anticipated or actual date of enrollment of the first participant from the calendar. **For global/multi-country trials**, both global trial start date as well as start date in India

	should be mentioned. **Example** **date of first enrollment** 02/05/2009 **India** 15/06/2010 **Global**
Estimated duration of trial	Specify the expected time duration of trial, starting from enrollment of first patient to final submission of report.
Recruitment status of trial	Indicate status of trial. **For global/multi-country trials** enter status of global arm as well as Indian arm o **Pending**: Yet to initiate patient enrolment o **Recruiting**: Participants are currently being recruited and enrolled o **Temporary halt or suspended**: There is a temporary halt in recruitment and enrolment but potentially will resume o **Completed**: Closed to recruitment of participants and data analysis complete o **Other:** • **Closed to recruitment of participants**: Follow- up continuing • **Terminated**: Recruiting or enrolling participants has halted and will not resume
Brief Summary	Short description of the primary purpose of the protocol, including a brief statement of the study hypothesis. Include publication/s details (link/reference), if any. **Example:** This study is a randomized, double blind, parallel group, multi-centre trail comparing the safety and efficacy of Ramipril 2.5 mg daily and Candesartan 16 mg daily for 12 months in 500 patients with diabetes and hypertension that will be conducted in five centers in India, three in France and five in USA. The primary outcome measures will be all-cause mortality at five years and Mean Beck Depression Score at 18 weeks. The secondary outcomes will be all-cause mortality at 6 months and 1 year; and Mean glycosylated hemoglobin A1C at 4 and 8 weeks.

For any clarifications please contact –

Clinical Trials Registry – India

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AP17/V1

Guidelines for Stem Cell Research and Therapy: (ICMR) 2000, and revised in 2006

1.0 In brief are enumerated below:

1.1 Essentiality of research with potential health benefits.

1.2 Respect for human dignity, human rights and fundamental freedoms.

1.3 Individual autonomy with respect to informed consent, privacy and confidentiality in harmony with the individual's cultural sensitivity and environment.

1.4 Justice with equitable distribution of burden and benefits.

1.5 Beneficence with regard to improvement of health of individuals and society.

1.6 Non-maleficence with the aim of minimization of risk and maximization of benefit.

1.7 Freedom of conducting research with due respect to the above within the regulatory framework.

2.0 Mechanism for review and monitoring

The area of stem cell research being new and associated with rapid scientific developments and complicated ethical, social and legal issues requires extra care and expertise in scientific and ethical evaluation of research proposals. Hence, a separate mechanism for review and monitoring is essential for research and therapy in the field of human stem cells, one at the National level called as National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and the other at the institutional level called Institutional Committee for Stem Cell Research and Therapy (IC-SCRT).

3.0 Classification of human stem cells

On the basis of their origin three groups of stem cells are recognized.

3.1 Human embryonic stem (hES) cells, derived from blastocysts.

3.1.1 Blastocysts derived from surplus embryos from IVF clinics.

31.2 Blastocysts derived specifically for research or therapy using IVF.

3.1.3 Blastocysts derived by other techniques like SCNT etc.

3.2 Human embryonic germ (hEG) cells, which are derived from primordial germ cells of the fetus.

3.3 Human somatic stem (hSS) cells, which are derived from fetal or adult tissues or organs, including umbilical cord blood / placenta.

4.0 Categorization of research on stem cells

According to the source of stem cells and nature of experiments, the research on human stem cells is categorized into following three areas:

Permissible research areas

Restricted research areas

Prohibited research areas

5.0 Clinical use of umbilical cord blood stem cells

Cord blood stem cell banking is permissible. However, all Cord blood banks should be registered with the DCGI as per guidelines applicable to the blood banks. Commercial exploitation of stored blood should be regulated strictly. No trading shall be permitted in this area as in organ donation. Special care must be taken in collection, processing and storage of umbilical cord stem cells to avoid transmission of infections. Maternal screening should be carried out for transmissible infections. Purpose of banking should be clearly explained to couples interested in storing cord blood. The ideal use of these cells at present is for allogenic hematopoetic stem cell transplantation. Expansion of umbilical cord stem cells for transplantation in adult and use for non-hematopoetic indications is still in experimental stage. Specific mention shall be made that at present the use of stored umbilical cord blood for self is practically nil. The ethical issues include concern about ownership, and risk of transmission of potential genetic disorders, besides other general issues of confidentiality, justice and beneficence. When it comes to registries and banking, the commercial aspects pose additional problems. The advertisement related to collection of samples should be carefully looked into with respect to, conflict of interest, utility of samples, accessibility and affordability.

6.0 Research using fetal stem cells/placenta

All studies involving fetal tissue for research or therapy are permissible subject to approval by IC-SCRT and IEC. However,

a. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.

b. Informed consent to have a termination of pregnancy and the donation of fetal material for purpose of research or therapy should be taken separately.

c. The medical person responsible for the care of the pregnant woman planning to undergo termination of pregnancy and the person who will be using the fetal material should not be the same.

d. The woman shall not have the option to specify the use of the donated material for a particular person or in a particular manner.

e. The identity of the donor and the recipient should be kept confidential.

7.0 Responsibility of investigators and institutions

7.1 The investigators and the institutions where the stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. In particular, scientists whose research involves hES cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for SCNT, and be sensitive to public concerns about research that involves human embryos.

7.2 Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of hES cells.

7.3 Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for its functioning or ensure that its IEC has adequate expertise to handle proposals related to research with stem cells.

7.4 All records pertaining to adult stem cell research must be maintained for at least 5 years and those for hES cell research for 10 years.

8.0 Procurement of gametes, blastocysts or somatic cells for generation of hES cell lines

8.1 There should be no commodification of human oocyte, human sperm or human embryo by way of payment or services, except for reimbursement of reasonable expenses incurred by the person (amount to be decided by IC-SCRT/ IEC. Similarly, no payments should be made for donation of somatic cells for use in SCNT except for reimbursement for attending the clinic.

8.2 Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for SCNT) may be reimbursed for direct expenses incurred as a result of the procedure, as determined by the IC-SCRT/ IEC. They should be informed about potential hazards, complications etc which are related to the hormonal induction process.

8.3 Any clinic/research personnel who have a conscientious objection to hES cell research should not be coerced to participate or impart information.

9.0 Banking and distribution of hES cell lines

There are several models for banking of human biological materials, including hES cells. All guidelines developed in this regard adhere to key ethical principles that focus on need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells.

10.0 Use of stem cells for therapeutic purposes

10.1 As of date, there is no approved indication for stem cell therapy as a part of routine medical practice, other than Bone Marrow Transplantation (BMT). Accordingly all stem cell therapy other than BMT (for accepted indications) shall be treated as experimental. It should be conducted only as clinical trial after approval of the IC- SCRT/IEC and DCGI (for marketable products). All experimental trials shall be registered with the NAC-SCRT.

10.2 Cells used in such trials must be processed under GTP/GMP standards.

10.3 The injectable product should meet pharmacopial specifications for parenteral preparations. The cells used for therapy shall be free from animal products and microbial contamination.

10.4 The centers carrying out stem cell clinical trials and the agency/ source providing such cells for the trial shall be registered with the NAC-SCRT through IC-SCRT/IEC.

11.0 International Collaboration

11.1 National guidelines of respective countries should be followed.

11.2 Exchange of biological material will be permitted as per existing procedures of funding agencies (DST, DBT, ICMR etc) or the Health Ministry's screening committee (as per GOI Guidelines), even if no funding is involved after the joint proposal with appropriate MOU is approved by NAC-SCRT.

11.3 If there is a conflict between scientific and ethical perspectives of the International collaborator and the domestic side, then the Indian ethical guidelines or law shall prevail.

For details visit: **(www.icmr.nic.in/bioethics).**

AP18/V1

Guideline for Medical Device related Studies

Medical and health care technology has undergone rapid transformation in the past two decades. Of late, a series of technological inventions have revolutionized the preventive, diagnostic, rehabilitative, therapeutic (life-supporting or life sustaining devices) capabilities of medical sciences and biomedical technology has made considerable progress in the conceptualization and designing of bio-equipment.

No regulatory mechanisms exist even with the Drug Controller General of India (DCGI) for certification, quality assurance and post market surveillance of both imported and indigenous medical devices. As the capacity of the country in this area is improving day by day the need for a regulatory mechanism / authority is increasingly obvious. The concept of regulations governing investigations involving biomedical devices is therefore relatively new in India. Earlier only needles, syringes and blood bags were covered by the Drugs and Cosmetics Act, 1940. Now sterile devices like cardiac stents, drug eluting stents, catheters, intraocular lenses, IV cannulae, bone cements, heart valves, scalp vein set, orthopedic implants, internal prosthetic replacements have been included in the list with effect from 1.3.2006.

It is proposed to set up the Indian Medical Devices Regulatory Authority (IMDRA) which is being examined by the Health Ministry. Until the guidelines are formulated and implemented by this Regulatory Authority, bodies like Indian Standard Institute, Board of Indian Standards, Drug Controller General of India, and Nuclear Medicine Board of the BARC constituted for specific purposes under an Act or Administrative authorities should approve clinical trials with biomedical devices on case-to-case basis.

During the review of medical device studies, the IEC may make some different decision than those made during the review of drug studies. The IEC must determine if the proposed investigation has Significant Risk (SR) or Non-significant Risk (NSR), and then the IEC should decide if the investigation is approved or not. In determining SR or NSR, the IEC must review all information submitted by the sponsor.

The IEC should consider the nature of the harm that may result from the use of the device. If a device being investigated might cause significant harm to any one of the participants, the study will be considered SR. In deciding if a device presents significant or non-significant risks, the IEC should consider the device's total risks, not those compared with the risks of alternative devices or procedures. If the device is used in conjunction with a procedure involving risk, the IEC should consider the risks of the procedure in conjunction with the risks of the device. The IEC may also consult with the regulatory agency to form its opinion.

The IEC may agree or disagree with the sponsor's initial NSR assessment. If the IEC agrees with the sponsor's initial NSR assessment and approves the study; the study may begin without submission of an IDE (Investigational Device Exemption, ref. AP15/V1) application to the regulatory agency. If the IEC disagrees, the sponsor must notify the regulatory

agency that an SR determination has been made. The study can be conducted as an SR investigation following regulatory approval of an IDE application.
The Bioethics cell of the IEC should follow the procedures as in SGSOP 03/V1 (Procedures for Management of protocol submission). The sponsor should inform the IEC of the Agency's assessment of the device's risk if such an assessment has been made. If the Sponsor believes the study is NSR, supporting information must be submitted.

Medical Device: Any health care product that does not achieve any of its intended purposes by chemical action or by being metabolized. Medical devices include items such as diagnostic test kits, crutches, electrodes, prescribed beds, pacemakers, arterial grafts, intra-ocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis of disease and other conditions (for example, pregnancy).

Investigational Medical Device: A medical device which is the object of clinical research to determine its safety or effectiveness.

Non-significant Risk Device (NSR): An investigational device that does not pose a significant risk. Acceptable risk differs depending on the conditions for which the product is being tested. A product for sore throat, for example, will be expected to have a low incidence of side effects. However, unpleasant side effects may be an acceptable risk when testing a promising treatment for a life threatening illness.

Significant Risk Device (SR): An investigational device that:

i. Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of the participant,
ii. Purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of the participant,
iii. For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of the participant, or
iv. Otherwise presents a potential for serious risk to the health, safety, or welfare of the participant.

Example 1. Non-Significant Risk Device Studies

- Bio-stimulation Lasers for treatment of pain
- Daily Wear Contact Lenses and Associated Cleaners and Solutions
- Dental Filling Materials, Cushions or Pads made from traditional materials and designs
- Denture Repair Kits and Re-aligners
- Externally worn Monitor for Insulin Reactions
- Magnetic Resonance Imaging (MRI) Devices within specified physical parameters
- Menstrual Pads
- Menstrual Tampons of "old" materials
- Non-implantable Male Reproductive Aids
- Ob/Gyn Diagnostic Ultrasound (within specified parameters)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain
- Wound Dressings, excluding absorbable haemostatic devices and dressings
- Caries Removal Solution
- Gynecologic Laparoscope and Accessories
- Jaundice Monitor for Infants

Example 2. Significant Risk Device Studies

Catheters:

 Cardiology – diagnostic, treatment, transluminal coronary angioplasty, intra-aortic balloon with control system

 Gastroenterology and Urology – biliary and urologic

 General Hospital – long-term percutaneous, implanted, subcutaneous and intravascular

 Neurology – cerebrovascular, occlusion balloon

 Collagen Implant Material for use in ear, nose and throat, orthopedics and plastic surgery

 Lasers for use in Ob/Gyn, cardiology, gastro-enterology, urology, pulmonary, ophthalmology and neurology

 Tissue Adhesives for use in neurology, gastro-enterology, ophthalmology, general and plastic surgery, and cardiology

Anesthesiology

 Respiratory Ventilators

 Electro-anesthesia Apparatus

 Gas Machines for Anesthesia or Analgesia

 High Frequency Jet Ventilators greater than 150 BPM

Cardiovascular

 Arterial Embolization Device

 Artificial Heart, permanent implant and short term use

 Cardiac Bypass Systems: oxygenator, cardiopulmonary blood pump, ventricular assist devices

 Cardiac Pacemaker/Pulse Generator: implantable, external transcutaneous, antitachycardia, esophageal

 Cardiovascular/Intravascular Filters

 Coronary Artery Retroperfusion System

 DC-Defibrillators

Implantable Cardioverters

 Laser Coronary Angioplasty Device

 Pacemaker Programmer

 Percutaneous Conduction Tissue Ablation Electrode

 Replacement Heart Valve

□ Vascular and Arterial Graft Prostheses Dental

□ Endosseous Implant Ear, Nose and Throat

□ Cochlear Implant

□ Total Ossicular Prosthesis Replacement

□ Gastroenterology and Urology

□ Anastomosis Device

□ Endoscope and/or Accessories

□ Extracorporeal Hyperthermia System

□ Extracorporeal Photophersis System

□ Extracorporeal Shock-Wave Lithotriptor

□ Kidney Perfusion System

□ Mechanical/Hydraulic Impotence and Incontinence Devices

□ Implantable Penile Prosthesis

□ Peritoneal Shunt

General and Plastic Surgery

□ Absorbable Hemostatic Agent

□ Artificial Skin

□ Injectable Silicone

□ Implantable Prostheses: chin, nose, cheek, ear

□ Sutures

General Hospital

□ Infusion Pumps: Implantable and closed-loop, depending on infused drug

□ Implantable Vascular Access Devices

Neurology

□ Hydrocephalus Shunts

□ Implanted Intracerebral/Subcortical Stimulator

□ Implanted Intracranial Pressure Monitor

□ Impalnted Spinal Cord and Nerve Stimulators and Electrodes

Obstetrics and Gynecology

□ Cervical Dilator

□ Chorionic Villus Sampling Catheter, phase II (pregnancy continued to term)

 Contraceptive Devices: tubal occlusion, cervical cap, diaphragm, intrauterine device (IUD) and introducer, and sponge

Ophthalmic

 Extended Wear Contacts Lens

 Intraocular Lens (investigations subject to 21 CFR 813)

 Eye Valve Implant

 Retinal Reattachment Systems: sulfur hexafluoride, silicone oil, tacks, perfluoropropane

Orthopedics

 Implantable Prostheses: ligament, tendon, hip, knee, finger

 Calcium Tri-Phosphate/Hydroxyapatite Ceramics

 Bone Growth Stimulator

 Xenografts

Radiology

 Hyperthermia Systems and Applicators

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