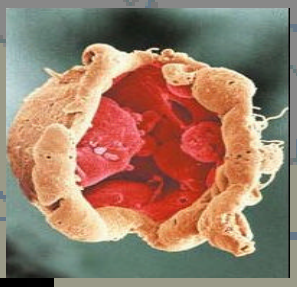
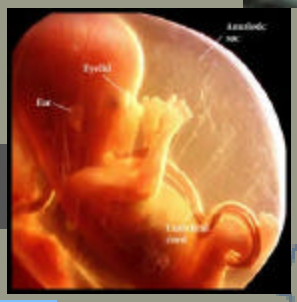
ICMR -DBT Guidelines For Stem Cell Research And Therapy





2006

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Guidelines for Stem Cell Research and Therapy

1.0 Introduction

The stem cell research holds great promise of improving human health by control of degenerative diseases and restoration of damage to organs by various injuries; but at the same time it also raises several ethical and social issues such as destruction of human embryos to create human embryonic stem (hES) cell lines, potential for introducing commodification in human tissues and organs with inherent barriers of access to socio-economically deprived and possible use of technology for germ-line engineering and reproductive cloning. The research in this field, therefore, needs to be regulated to strike a balance.

Of utmost importance is assurance of safety and rights of those donating gametes/ blastocysts/ somatic cells for derivation of stem cells; ÒR fetal tissues/umbilical cord cells/ adult tissue (or cells) for use as stem cells. Safeguards have also to be in place to protect research participants receiving stem cell transplants, and patients at large from unproven therapies/remedies. With success of growing human embryonic stem cells without feeder layer, derivation of histocompatible hES from embryo created by Somatic Cell Nuclear Transfer (SCNT) and tissue specific differentiation of umbilical cord/bone marrow derived mesenchymal stem cells, there is a need to generate public confidence in potential benefit of stem cell research to human health and disease. As stem cell therapy is poised to bring about clinical success in future there is an urgent need to evolve guidelines for Stem cell Research and Therapy (SCRT).

Milestones in Stem Cell Research

1960s: Research begins on stem cells taken from adult tissue
1981: First mouse embryonic stem cell line established
1998: First isolation of human embryonic stem cell lines at University of Wisconsin by James Thomson.
1998: First isolation of pluripotent stem cells from germ cells established by Gearheart.
2001: NIH registry of human embryonic stem cell lines established, 15 Institutions and 78 cell lines were registered and eligible for US federal funding including 10 from India from two institutes.
2003: Britain became first country to issue research license for human embryonic cloning to create stem cells.
2004: South Korean scientists clone 30 human embryos and develop them over several days;
2004: UK open stem cell bank
2005: Dr Hwang and team from Korea develop stem cells tailored to match individual patients but shrouded with controversy;
2005: Wisconsin scientists grow two new human embryonic stem cell lines in animal cell free culture.

2.0 Aims and Scope

2.1 To lay down general principles for stem cell research and therapy keeping in view the ethical issues.

2.2 To formulate specific guidelines for derivation, propagation, differentiation, characterization, banking, and use of human stem cells for research and therapy.

These guidelines provide a mechanism to ensure that a research with human stem cells is conducted in a responsible and ethically sensitive manner and complies with all regulatory requirements pertaining to biomedical research in general and stem cell research in particular.

3.0 General Principles

Any research on human beings, including human embryos, as subjects of medical or scientific research or experimentation, shall adhere to the general principles outlined in the "Ethical guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research (ICMR) in October, 2000 (www.icmr.nic.in/bioethics). The same in brief are enumerated below:

3.1 Essentiality of research with potential health benefits.
3.2 Respect for human dignity, human rights and fundamental freedoms.
3.3 Individual autonomy with respect to informed consent, privacy and confidentiality in harmony with the individual's cultural sensitivity and environment.
3.4 Justice with equitable distribution of burden and benefits.
3.5 Beneficence with regard to improvement of health of individuals and society.
3.6 Non-malificence with the aim of minimization of risk and maximization of benefit.
3.7 Freedom of conducting research with due respect to the above within the regulatory framework**.**

4.0 Separate Mechanism of Review and Monitoring

The area of stem cell research being new; 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 of Review and Monitoring is proposed 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)**.

4.1 All institutions and investigators carrying out research on human stem cells should be registered with the NAC-SCRT through IC-SCRT.
4.2 All research studies using human stem cells shall have prior approval of IC-SCRT for permissive research as given in these guidelines, and of the NAC-SCRT for restricted research also defined in these guidelines
4.3 All new stem cell lines shall be created, only when necessary and for the purposes defined in these guidelines, with prior approval of IC-SCRT/NAC-SCRT as given in these guidelines.
4.4 All established cell lines from any source, imported or created in India, should be registered with IC-SCRT and NAC-SCRT.
Permission for import/procurement from other Indian lab shall be obtained from IC-SCRT. The investigator shall ensure that the cell line has been established in accordance with existing guidelines of the country. An appropriate MTA shall be adopted for the purpose.
4.5 All clinical trials with any stem cells shall have prior approval of IC-SCRT, IEC and DCGI; and shall be registered with the NAC-SCRT; except that International

Collaboration shall **also** have prior approval of NAC-SCRT and respective funding agency as per its procedure/Health Ministry's screening committee (HMSC).

The composition and functions of NAC-SCRT and IC-SCRT are given in Annexure I.

5.0 Classification of Human Stem Cells

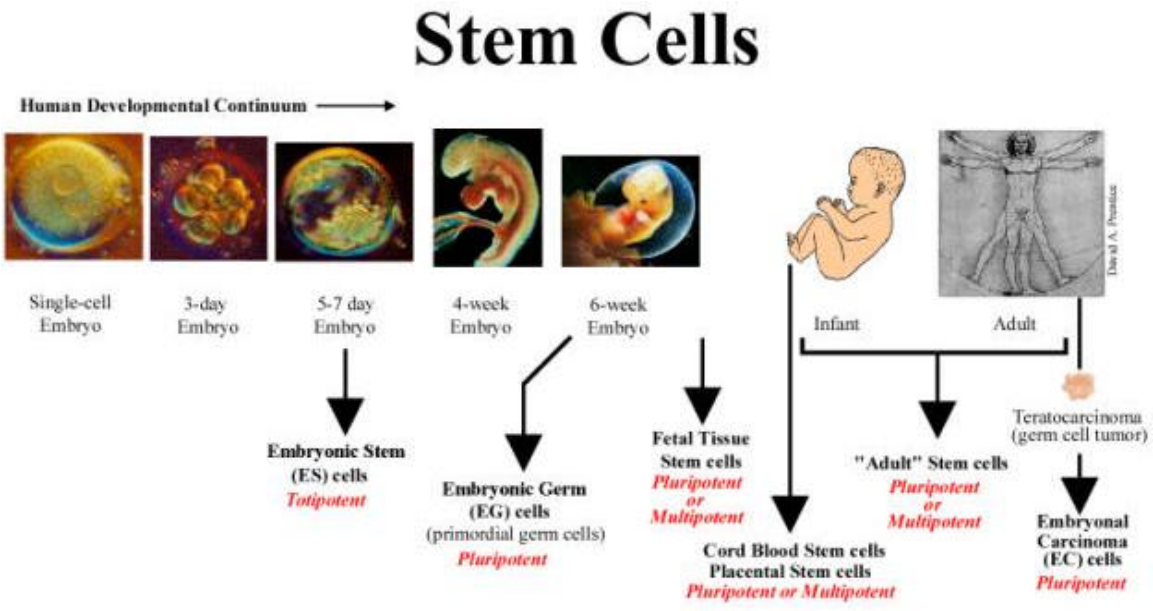
On the basis of their origin three groups of stem cells are recognized:

5.1 ***Human embryonic stem (hES) cells***, derived from the blastocysts:

5.1.1 Blastocysts derived from surplus embryos from IVF clinics.
5.1.2 Blastocysts derived specifically for research using IVF.
5.1.3 Blastocysts derived by technique like SCNT etc.

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

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



Source: www.robby.nstemp.com/photo6.html

6.0 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

6.1 Permissible Areas of Research

6.1.1 In-vitro studies on established cell lines from any type of stem cell viz. hES, hEG, hSS or fetal/adult stem cells may be carried out with notification to IC-SCRT, provided the cell line is registered with the IC-SCRT/NAC-SCRT and GLP is followed.

6.1.2 In-vivo studies with established cell lines from any type of stem cells viz., hES, hEG, hSS, including differentiated derivatives of these cells, *on **adult** animals other than primates* with prior approval of IC-SCRT, provided such animals are not allowed to breed. This includes pre-clinical evaluation of efficacy and safety of human stem cell lines.

6.1.3 In-vivo studies on experimental animals (other than primates) using *fetal/adult somatic stem cells* from Bone marrow, peripheral blood, umbilical cord blood, skin, limbal cells, dental cells, bone cells, cartilage cells or any other organ (including placenta), with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.

6.1.4 Establishment of new hES cell lines from spare, supernumerary embryos with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines given below. Once the cell line is established it shall be registered with the IC-SCRT and NAC-SCRT.

6.1.5 Establishment of fetal/adult hSS cell lines with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.

6.1.6 Establishment of Umbilical Cord stem cell bank with prior approval of the IC-SCRT and IEC provided guidelines given in this document for collection, processing, and storage etc of the umbilical cord blood are followed. Appropriate SOPs shall be approved by the IC-SCRT and IEC.

6.1.7 Clinical trial with clinical grade stem cells, following ICMR Guidelines for Biomedical Research and GCP guidelines of the GOI, may be carried out with prior approval of IC-SCRT, IEC and DCGI. Clinical grade stem cells are required to be produced under international GMP/GTP conditions. The cells should be well characterized about their stemness and safety as per guidelines given in Annexure II. The headings under which the clinical trial protocols should be written are given in Annexure III. All clinical trials on stem cells shall be registered with NAC-SCRT through IC-SCRT.

6.2 Restricted Areas of Research

6.2.1 Creation of a zygote by IVF, SCNT or any other method with the specific aim of deriving a hES cell line for any purpose.

- Specific justification would be required to consider the request for approval by the NAC-SCRT through IEC and IC-SCRT.
- It would be required to establish that creation of zygote is critical and essential for the proposed research, and no other alternative will serve the purpose.
- Informed consent procedure for donation of ova, sperm, somatic cell or other as detailed in these guidelines would need to be followed.

6.2.2 Clinical trials sponsored by multinationals, involving stem cell products imported from abroad. Such collaboration shall require prior approval of the NAC-SCRT through IC-SCRT, IEC,DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC)

6.2.3 Research involving introduction of hES/hEG/hSS cells into animals, including primates, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into non-human animal tissues.

- If there is a possibility that human cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be strong. ***The animals derived from these experiments shall not be allowed to breed***.
- Such proposals would need approval of the NAC-SCRT through Animal IEC and IC-SCRT.

6.2.4 Studies on chimeras where stem cells from two or more species are mixed and introduced into animals, including primates, at any stage of development viz., embryonic, fetal or postnatal, for studies on pattern of development and differentiation.

6.2.5 Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

6.3 Prohibited Areas of Research

6.3.1 Any research related to germ line genetic engineering or reproductive cloning.

6.3.2 Any in-vitro culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier

6.3.3 Transfer of human blastocysts generated by SCNT or parthenogenetic or androgenetic techniques into a human or non-human uterus.

6.3.4 Any research involving implantation of human embryo into uterus after in-vitro manipulation, at any stage of development, in humans or primates.

6.3.5 Animals in which any of human stem cells have been introduced at any stage of development should not be allowed to breed.

6.3.6 Research involving directed non-autologous donation of any stem cells to a particular individual is also prohibited.

7.0 Research Using Umbilical Cord Blood Stem Cells

Cord blood stem cell banking is permissible. All Cord blood banks have to be registered with the Drug Controller General of India (DCGI) as per the guidelines of blood banks. Purpose of banking should be clearly explained to couples interested in storing cord blood. 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 advertising involved in getting and collecting samples, conflict of interest, utility of samples, accessibility and affordability should also be carefully looked into.

The following points should be considered while collecting umbilical cord blood as specified in "Ethical Guidelines for Biomedical Research in human Subjects" 2000 of ICMR:

7.1 No harm should occur to the fetus or the neonate.
7.2 Exact timing of the clamping of the umbilical cord should be defined in the clamping protocol.
7.3 Parents should be informed regarding risks and benefits involved.
7.4 Free informed consent from parents' should be obtained. If there is disagreement between the parents, the mother's wish shall prevail.
7.5 ID card should be issued for voluntary donation to enable access/benefit in future in case required for self/relative.
7.6 Standard Operative Procedures for collection, transportation, processing, storage, preservation and clinical use should be laid down with approval of the IC-SCRT and IEC.
7.7 Detailed protocol for isolation and characterization of stem cells should be approved by IC-SCRT and IEC.
7.8 Period of preservation for self-use later in life should be prescribed.
7.9 Detailed protocol for clinical use of stem cells should be in place.
7.10 Follow up plans for assessing safety and efficacy of cord blood stem cell therapy should be incorporated.

8.0 Research Using Fetal Stem Cells/Placenta

. All proposals involving fetuses or fetal tissue, for research or therapy are permissible. 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. 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 women shall not have the option to specify the use for a particular person or in a particular way.
e. The identity of the donor and the recipient should be kept confidential

9.0 Approval for Derivation of a New hES Cell Line Whether from Spare Embryos or Embryos Created for the Purpose Shall Consider:

9.1 That the goal of research cannot be achieved in any other way including research on adult stem cells.
9.2 There is no existing stem cell line that would be suitable for the purpose.

9.3 Will increase knowledge about embryo development and causes of miscarriages and birth defects.
9.4 Can develop methods to detect abnormalities in embryos before implantation.
9.5 Advance knowledge, which can be used for infertility treatment or improving contraception techniques.
9.6 Increasing knowledge about serious diseases and using this knowledge to develop treatments including tissue therapies.
9.7 Developing methods of therapy for diseased or damaged tissue or organs.
9.8 Justification for the minimum number of embryos/blastocysts required must be clearly defined.
9.9 Research teams involved should have appropriate expertise and training in derivation and culture of human/non-human ES cells.

10.0 Responsibility of Investigators and Institutions

10.1 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.

10.2 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.

10.3 Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for it's functioning.

11.0 Procurement of Gametes, Blastocysts OR Somatic Cells for Generation of hES Cell Lines

11.1 Both the IEC and the IC-SCRT, should review the process of procurement of gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines, including procurement of blastocysts in excess of clinical need from infertility clinics. Blastocysts made through IVF specifically for research purposes, and oocytes, sperm, and somatic cells donated for development of hES cell lines derived through SCNT or by parthenogenesis or androgenesis should also have approval of NAC-SCRT.

11.2 Consent for donation of supernumerary embryos should be obtained from each donor at the time of donation itself. Even people who have given prior indication of their intent to donate blastocysts that remain unutilized after clinical care should give fresh informed consent at the time of donation of the embryo for establishment of hES cell line. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

11.3 There should be no commodification of human egg, 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/ NAC-SCRT). Similarly, no payments should be made for donation of somatic cells for use in SCNT except for reimbursement for attending the clinic.

11.4 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/NAC-SCRT.

11.5 The attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells preferably should not be the same person. To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research.

11.6 In the context of donation of gametes or blastocysts for hES cell research, the informed consent process, should, at a minimum, provide the following information.

a. A statement that the blastocysts or gametes will be used to derive hES cells/cell lines for research purposes.
b. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of cells derived from it.
c. Identity of the donor and recipient would be kept confidential.
d. An assurance that investigators in research projects will follow applicable best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, will be kept secured to ensure confidentiality)
e. Investigators must document how they will maintain the confidentiality of any coded or identifiable information associated with the lines.
f. A statement that derived stem cells or cell lines and the information related to it may be archived for 15 years or more.
g. Disclosure of the possibility that results of study on the hES cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from future commercial development. However, a proportionate benefit, if any will be passed on to the community that has directly or indirectly contributed to the product.
h. A statement that research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous transplantation.

i. A statement that embryos will be fully utilized in the process of deriving hES cells.
j. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of present or future medical care provided to potential donors.
k. A statement of the risks involved to the oocyte donor and acceptance of the responsibility to provide appropriate health care in case any complication arises during the procedure.

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

12.0 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. For this purpose it is necessary to ensure that:

a. they were obtained ethically and with informed consent of donors,
b. they are well characterized and screened for safety, (see Annexure II)
c. the conditions under which they are maintained and stored meet the highest scientific standards of GLP/GTP/GMP with appropriate SOPs.

12.1 Institutions that are banking or plan to bank hES cell lines should establish uniform guidelines to ensure that donors of material give informed consent through a process approved by an IC-SCRT and meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and guidelines for distribution of cells should be established as per accepted standard procedures.

12.2 Any facility engaged in obtaining and storing hES cell lines should consider the following:

12.2.1. Creation of clear and standardized protocols for banking and withdrawals.

12.2.2 Documentation requirements for investigators and sites that deposit cell lines, including.
a. A copy of the donor consent.
b. Proof of IC-SCRT approval of the procurement process.
c. Available medical information on donors, along with infectious-disease screening details.
d. Available clinical, observational, or diagnostic information about the donor(s).

e. Critical information about culture conditions (such as media, cell passage, and safety information).
f. Available cell line characterization (such as karyotype and genetic markers).

12.2.3 A repository has the right of refusal if prior culture conditions or other items do not meet its standards.

12.3 A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to

a. A plans for maintaining confidentiality (such as a coding system).
b. A secure system for inventory track from primary cell lines to those submitted to the repository.
c. A policy governing whether and how to deliver clinically significant information back to donors.

12.4 The following Standard Operating Procedures (SOPs)/ Standard of practices should be defined and maintained:

a. Assignment of a unique identifier to each sample.
b. Procedure for derivation of hES lines
c. A process for characterizing cell lines.
d. A process for expanding, maintaining, and storing cell lines.
e. A system for quality assurance and control.
f. A Website that contains scientific descriptions and data related to the available cell lines. Central Registry to set up by the NAC-SCRT.
g. A procedure for reviewing request applications for cell lines.
h. A process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
i. A system for auditing compliance.
j. A schedule of charges.
k. A statement of intellectual property policies.
l.. When appropriate, creation of a clear Material Transfer Agreement or user agreement.
m. A liability statement.
n. A system for disposal of material.
o. Clear criteria for distribution of cell lines

13.0 Use of Stem Cells for Therapeutic Purposes

13.1 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 IEC, IC-SCRT and DCGI. All such trials shall be registered with the NAC-SCRT.

13.2 Only clinical grade stem cells/cell lines shall be used for stem cell clinical trials. These should meet the standards of GTP/GMP adopted by international tissue banks. As far as possible the use of animal products such as calf serum/feeder layer etc. for derivation and maintenance of cell lines shall be avoided.

13.3 The injectible product should meet pharmacopial specifications for parenteral preparations. As far as possible the cells used for therapy shall be free from animal products and microbial contamination.

13.4 The centers carrying out stem cell clinical trials, and the source providing clinical grade stem cells/cell lines for the trial' shall be registered/accredited with the NAC-SCRT through IC-SCRT. In case of International Collaboration the NAC-SCRT shall ensure that the certification provided by the collaborating country fulfills the requirements laid down in these guidelines.

13.5 The cell/cell lines used in the trial shall be characterized as suggested in Annexure II.

13.6 The headings under which clinical trial protocol for stem cell therapy shall be prepared is given in Annexure III.

14.0 International Collaboration

14.1 National guidelines of respective countries should be followed.

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

14.3 Export of cell lines will be covered under GOI guidelines for Transfer of Biological materials.

14.4 If there is a conflict between scientific and ethical perspectives of the International collaborator and the domestic side then Indian Ethical guidelines or law will prevail.

15.0 Commercialization and Patent Issues

Research on stem cells/ lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on merits of each case. If the IPR is commercially exploited, a proportion of benefits shall be ploughed in to the community, which has directly or indirectly contributed to the IPR. Community includes all potential beneficiaries such as patient group, research group etc.

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ICMR Ethical Guidelines for Biomedical Research in Human Subjects 2000

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ANNEXURES

Annexure - I

Monitoring Mechanism:

Establishment of National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and Institutional Committees for Stem Cell Research and Therapy (IC-SCRT)

A national body should be established to assess periodically the adequacy of the guidelines proposed in this document and to provide a forum for continuing discussion of issues involved in hES research in light of ever growing changes in the science. The committee will also review and approve specific research protocols falling under restricted category. Such a body should also address to new unforeseen issues of public interest from time to time. The body should be independent and should be respected by both the lay and scientific communities. This would be called the NAC-SCRT. An IC-SCRT shall function at the institutional level and have appropriate expertise as suggested to support this effort.

1. NAC-SCRT:
This is a multidisciplinary multi-agency body with a secretariat

1.1 **Scope:**

1.1.1. The Committee will have the responsibility to examine the scientific, technical, ethical, legal and social issues in the area of hESc based research and therapy.
1.1.2. All institutions involved in any type of stem cell research and therapy will be registered with the NAC_SCRT.
1.1.3. IC-SCRT has to submit six monthly reports to NAC-SCRT - A regular monitoring will be done by the NAC-SCRT by obtaining periodic report from all centers and site visits as and when required to ensure adherence to standards.
1.1.4. NAC-SCRT shall approve monitor and oversee hESc research in the country.
1.1.5. Every scientific proposal using embryonic stem cell has to be cleared through IC-SCRT and IEC before referring to NAC-SCRT.
1.1.6. NAC-SCRT member could be nominated to IC-SCRT.
1.1.7. Use of chimeric tissue for research shall be approved only by NAC-SCRT after clearance from IEC and IC-SCRT.
1.1.8. NAC-SCRT shall revise and update guidelines periodically, considering scientific developments at the national or international level.
1.1.9. *NAC-SCRT will set up standards for*: Safety and quality, Quality Control, Procedures for collection and its schedule, processing or preparation, expansion, differentiation, preservation for storage, removal from storage to assure quality and/or sterility of human tissue, prevention of

infectious contamination or cross contamination during processing, Carcinogenicity, xenotransplantation.

1.2 **Membership (12-15):**

Chairman, Deputy Chairman, Member Secretary, nominees from DBT, DST, CSIR, ICMR, DCGI, DAE, and biomedical experts drawn from various disciplines like Pharmacology, Immunology, Cell Biology, Hematology, Genetics, Developmental biology, Clinical medicine and Nursing. Other members would be legal expert, social scientist, and Women's representative.

In addition Consultants/experts could be consulted for specific topics and advice.

1.3 **Frequency of meetings:**

Quarterly, but can be more frequent, if necessary.

1.4 **Processing fees:**

This may be levied for proposals on therapeutic trials with NBEs (New Biological Entities).

2 IC-SCRT:

This would be a multidisciplinary body at the institutional level undertaking Stem Cell Research and Therapy.

2.1. **Scope**:

2.1.1 all research institutions conducting stem cell research are expected to set up a special review body to oversee this emerging field of research.

2.1.2 be registered with the NAC-SCRT.

2.1.3 Provide overview to all issues related to stem cell research and therapy.

2.1.4 Review and approve the scientific merit of research protocols.

2.1.5 Review compliance with all relevant regulations and guidelines.

2.1.6 Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.

2.1.7 Facilitate education of investigators involved in stem cell research.

2.1.8 Submit six-monthly report to NAC-SCRT.

2.2. **Membership (7-9)**:

The committee should include representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction technology, and ethical and legal issues in stem cell research. It should have the resources to coordinate reviews of various protocols.

ANNEXURE – II

SAFEGUARD FOR HUMAN EMBRYONIC STEM CELLS

Documentation of complete history of the cells, and their characterization, for use in therapy is essential to safeguard against potential risks of biological therapy. This is particularly important when human Embryonic/somatic Stem Cells are used for this purpose.

Therefor, following safeguard may be implemented before releasing human embryonic stem cell lines for clinical applications;

Safeguards	Tests/Methods
Screening Donors	HIV, HBV, HCV, CMV, HTLV, VDRL
Derivation and culture	Use control and standardized practices and procedures for establishment of human embryonic stem cell lines. GMP clean room is must if ES cells are to be used for clinical application.
Animal source	Develop alternatives to culturing ES cells on animal derived feeder cells and serum.
Characterization	Perform detail characterization of stem cell lines **Cellular markers**: SSEA-1, SSEA-3, SSEA-4, OCT-4, TRA-1-60, TRA-1-81, Alkaline phosphatase, ABCG2, **Molecular markers:** OCT-4, SOX2, NANOG, REX1, TERT, UTF-1, DPPA5, FGF4, FOXD3, TDGF1, BCRP1, ABCG2, GCTM2, Genesis, GDF3, GCNF
Karyotyping	Traditional karyotyping or FISH including sex chromosome
HLA Typing	A, B, DR
Microarray	Growth factors, cytokines and ECM molecules
Immunophenotyping	**CD markers**, CD4, CD8, CD14, CD24, CD31, CD34, CD45, CD90, CD73, CD105, CD133
Analysis of differentiation properties	Minimum 3 markers for Ectoderm, Endoderm and Mesoderm should be checked. Each cell line should be checked for differentiation potential.
Teratoma Formation	Required SCID mouse
Comprehensive toxicity	Endotoxin, mycoplasma, aerobic, anaerobic cultures for sterility; and acute, sub-acute, and chronic toxicity testing

ANNEXURE – III

Clinical trial protocol for Stem Cell Therapy

Study Title
Phase of the study
Institution conducting the trial
Sponsor
Principal Investigator/s

1. **Synopsis of the protocol (Summary)**
2. **Introduction**
3. **Study objectives**
4. **Study Plan**
    a. Study design
    b. Number of Patients
    c. Inclusion Criteria
    d. Exclusion Criteria
    e. Chart of Schedule of visits and activities at each visit
    f. Ethical considerations – risks and benefits
        a. Screening phase
        b. Treatment Phase
        c. Post – Treatment phase
        d. Withdrawal of Patients prior to study completion
    g. Efficacy Assessment
        a. Primary efficacy outcome
        b. Secondary efficacy outcome
        c. Efficacy measurements

6. **Safety assessment**
    Adverse Events documentation in a prescribed format
        i. Definitions
        ii. Documentation of Adverse Events
        iii. Reporting of serious Adverse events

7. **Concomitant Medications**
        i. Documentation of Medications – Name, dose, duration
        ii. Intercurrent illness
        iii. Prohibited Medications
8. **Product Information, Dose scheme and Administration Instructions**
        i. Product Information
        ii. Dose Scheme
        iii. Route of administration
        iv. Cell preparation and administration instructions
9. **Data Evaluation/Statistics**
    a. Sample size determination

b. Study population analyses
c. Efficacy Analysis/Methods
d. Safety Analysis/Methods
e. Adverse Events
f. Clinical Laboratory studies

10. Ethical and Administrative Issues

a. Patient's /Parent/Relative's Informed consent
b. Institutional Review Board Approval
c. Data and safety monitoring Board
d. Adherence to the protocol
e. Protocol Amendment Approval
f. Data Collection, source documentation and retention of patient records
g. Accountability of Investigational drug/product
h. Monitoring of the study and audit
i. Retention of Patient Records
J. IPR issues: (patent obtained/filed

11. Requirements for study initiation and completion

12. Confidentiality and publication

13. Enclosures

1. **Investigator Brochure including background, rationale, product details, pre-clinical studies results, human experiences, references and Publication reprints**
2. **Case Record Form**
3. **Manual of efficacy assessments, safety assessments, laboratory procedures etc.**
4. **Administrative approvals**
    a. **DCGI for IND/NDA**
    b. **IEC (of each center)**
    c. **Approved patient information sheet and consent form**
    d. **IC-SCRT approval**
    e. **NAC-SCRT approval wherever if required**
    f. **MOU/MTA in case of international collaboration with transfer of biological materials**
    g. **Funding of the Project/sponsor**
    h. **Conflict of Interest Declaration**
    i. **Cash rewards to investigators/patients**
    j. **Post trial benefits**
    k. **Medical insurance coverage**
    l. **Sponsor's responsibility towards cost of trial/complications**
    m. **Investigator's bio-data/acceptance**

GLOSSARY

Adult stem cell: a stem cell derived from the tissues or organs of an organism after birth (in contrast to embryonic or fetal stem cells)

Blastocyst: a hollow ball of 50-100 cells reached after about 5 days of embryonic development. It consists of a sphere made up of an outer layer of cells (the trophoectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells in the interior (the inner cell mass)

Cell line: cells of common descent continuously cultured in the laboratory is referred to as a cell line

Cell nuclear replacement (CNR): The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryo without the fusion of sperm and egg**. It is also known as Somatic Cell Nuclear Transfer (SCNT).**

Clone: a cell or organism derived from, and genetically identical to another cell or organism

Clonal: Derived from a single cell

Cloning: creating an organism that is genetically identical to another organism, or a cell that is genetically identical to another cell provided that the so-called mother and daughter cells are subsequently separated (see also reproductive and therapeutic cloning)

Cloning by somatic cell nuclear transfer: involves replacing an egg's nucleus with the nucleus of the adult cell to be cloned (or from an embryo or fetus) and then activating egg's further development without fertilization. The egg genetically reprogrammes the transferred nucleus, enabling it to direct development of a whole new organism

Reproductive cloning : The embryo developed after Somatic Cell Nuclear Transfer (SCNT) is implanted into the human uterus (of the donor of the ovum or a surrogate recipient) and allowed to develop into a fetus and whole organism. The organism so developed is genetically identical to the donor of the somatic cell nucleus.

Therapeutic cloning: The development of the embryo after Somatic Cell Nuclear Transfer (SCNT) is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells could be differentiated into desired tissue using a cocktail of growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection

Consent: The voluntary consent is given by a patient (or their next of kin-legal heir) to participate in a study (which may include donating of tissue) after being informed of its purpose, method of treatment, and procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule. *The consent besides being voluntary and informed has to be without any coercion or inducement. It can be withheld, or even withdrawn at any time, without giving any reason or prejudice to present or future treatment of the individual.*

Cord blood stem cell: Stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body (hematopoietic). Cord blood is currently used to treat patients who have undergone chemotherapy to destroy their bone marrow due to cancer or other blood-related disorders.

Embryo: in humans is the developing stage from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.
Early embryo: the term "early embryo" covers stages of development up to the appearance of primitive streak i.e., until 14 days after fertilization.
Embryonic germ cell: embryonic germ cells are primordial germ cells isolated from the gonadal ridge of 5-10 weeks fetus.
Embryonic stem cell: embryonic stem cells are derived from the inner cell mass up to the stage of blastula. These cells can be cultured indefinitely under *in vitro* conditions that allow proliferation without differentiation, but have the potential of differentiating into any cell of the body including whole organism.
Feeder layer: cells used in co-culture to maintain pluripotent nature of the stem cells
Fetus: in humans, is a developing stage from eight weeks after conception to birth
Fetal stem cell: a stem cell derived from fetal tissue, including placenta. A distinction is drawn between the fetal germ cells, from which the gametes develop, and fetal somatic cells, from which rest of the organism develops.
Gamete: the male sperm or female egg
Germ cells: ova and sperm, and their precursors
Implantation: the embedding of a blastocyst in the wall of uterus. In humans implantation takes place at day 8 after fertilization.
In vitro* and *in vivo: outside and inside the body; *in vitro* (literally, in glass) generally means in the laboratory
Mesenchymal stem cells: Rare stem cells present in human bone marrow (and umbilical cord blood) that have been shown to differentiate into a variety of cell types in culture
Multipotent: Multipotent stem cells are those which are capable of giving rise to several different types of specialized cells constituting a specific tissue or organ.
Pluripotent stem cell: has the ability to give rise to various types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) Pluripotent stem cell has the potential to generate into every cell type in the body, but cannot develop into a embryo on its own.
Primitive streak: a collection of cells, which appears at about 14 days after fertilization from which the central nervous system develops
Somatic cell: cell of the body other than egg or sperm
Somatic stem cell: an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ.
Somatic cell nuclear transfer: the transfer of a cell nucleus to an egg (or another cell) from which the nucleus has been removed.
Stem cells: Cells capable of self-replication, proliferation and differentiation.
Stem cell Bank: A facility that is responsible for accessioning, processing, packaging, labeling, storage and delivery of a finished stem cell line issued under its name. It is required to characterize the cells, provide quality assurance and meet the laid down standards and procedures.
Supernumerary embryo or spare embryo: an embryo created by means of *in vitro*

fertilization (IVF) for the purpose of assisted reproduction but subsequently not used for it.

Totipotent: At two to three days after fertilization, an embryo consists of identical cells, which are **totipotent.** That is to say that each cell could give rise to an embryo on its own producing for example identical twins or quadruplets. They are totally unspecialized and have the capacity to differentiate into any of the cells, which will constitute the fetus as well as the placenta and membranes around the fetus.