

Guidelines for Stem Cell Research (Draft)



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Abbreviations

NAC-SCR	-	National Apex Committee for Stem Cell Research
IC-SCR	-	Institutional Committee for Stem Cell Research
IEC	-	Institutional Ethics Committee
IAEC	-	Institutional Animal Ethics Committee
IVF	-	In-vitro Fertilization
SCNT	-	Somatic Cell Nuclear Transfer
DCGI	-	Drugs Controller General of India
ICMR	-	Indian Council of Medical Research
DBT	-	Department of Biotechnology
DST	-	Department of Science and Technology
HMSC	-	Health Minister's Screening Committee
hES Cells	-	Human Embryonic Stem Cells
hEG Cells	-	Human Embryonic Germ Cells
hSS	-	Human Somatic Cells
GLP	-	Good Laboratory Practices
GTP	-	Good Tissue Practices
GMP	-	Good Manufacturing Practices
GCP	-	Good Clinical Practices
SOP	-	Standard Operative Procedures
BMT	-	Bone Marrow Transplantation
GOI	-	Government of India
MOU	-	Memorandum of Understanding
SCID	-	Severe Combined Immunodeficiency Disease
HLA	-	Human Leukocyte Antigens
iPSc	-	Induced Pluripotent Stem Cells
NBE	-	New Biological Entity
IND	-	Investigational New Drug
MTA	-	Material Transfer Agreement
CTRI	-	Clinical trial Registry India
siRNA	-	Small interfering Ribonucleic Acid
DNA	-	Deoxy Ribonucleic Acid
ASC	-	Adult Stem Cell
PSC	-	Pluripotent Stem Cell
HSC	-	Hematopoietic Stem Cell
MSCs	-	Mesenchymal Stem Cells
NSCs	-	Neural Stem cells
ICM	-	Inner Cell Mass

Guidelines for Stem Cell Research

1.0 Preamble

Stem cell research holds great promise for improving human health by restoring cellular and organ function damaged by degeneration and various injuries. At the same time it also raises several scientific, ethical and social issues in the development of such applications. Apart from challenges of using the right kind of stem cells in the most appropriate way for a particular disease, there are also issues related to the use of human embryos to create human embryonic stem (hES) cell lines, potential for commoditization of human tissues and cells with inherent danger of exploitation of underprivileged people, and challenges related to prevention of human germ-line engineering and reproductive cloning. There are also potential dangers of tumorigenicity with use of these cells keeping in view their potential for unlimited proliferation and possible introduction of genomic changes during in-vitro manipulations also limitations related to immunological tissue incompatibility between individuals. Research in this field, therefore, needs to be regulated with special attention to these issues.

Of utmost importance is assurance of safety and rights of those donating embryonic, fetal or adult stem cells for basic and clinical research. Safeguards have to be in place to protect research participants receiving stem cell transplants, and patients at large from receiving unproven stem cell therapies. In recent years societal concern regarding compensation for research related injury has also gained considerable momentum. This revised version of the guidelines has incorporated these issues. It also takes note of the fact that pluripotent stem cells of different kinds are at the threshold of entering clinical trials and appropriate guidance is needed with regard to their use.

2.0 Aim and scope

These guidelines apply to all stakeholders' viz. individual researchers, organizations, sponsors, oversight committees and others, associated with research on human stem cells and for their derivatives, both basic and clinical. This includes all types of stem cells from humans - autologous or allogenic, embryonic or fetal or adult, with or without manipulation; but excludes research with animal stem cells - restricted to animal to animal studies.

- 2.1 These guidelines reiterate that general principles as applicable to all biomedical research involving human participants shall also be applicable to all human stem cell research,
- 2.2 They also lay down specific guidelines unique for stem cells taking into consideration their potential for unlimited proliferation, differentiation to tissues and cells of all three germ layers and their involvement in pre-implantation stages of human development. These include guidelines for:
 - 2.2.1 Procurement of gametes, embryos and somatic cells for derivation and propagation of Pluripotent stem cell lines, their banking and distribution,
 - 2.2.2 Regulated differentiation into desired progenitor cells and their characterization, and
 - 2.2.3 Use of human stem cells and progenitors derived from them, or their products for pre-clinical and clinical research.

These guidelines have been laid down to ensure that 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. It is important to recognize that this is a rapidly evolving field and that recommendations may change with time. It is the responsibility of the researcher to understand the principles of these guidelines and keep abreast of the relevant rules and guidelines that are current in the country at any point in time.

3.0 General Principles

Any research on human subjects, including human embryos and fetuses shall ensure safeguarding of human dignity, human rights and fundamental freedoms. This includes processes related to obtaining human tissues and cells for research, diagnosis and therapy as well. The fundamental tenets of beneficence, non-maleficence, justice and autonomy should be adhered to in all research involving human subjects. To achieve these objectives, all research involving use of stem cells should be guided by the general principles that have been laid down in the Ethical Guidelines for Biomedical Research on Human Subjects by the ICMR in addition to the specific principles related to stem cells as laid down in these guidelines:

3.1 Principle of essentiality

- 3.2 Principles of voluntariness, informed consent and community agreement
- 3.3 Principle of non-exploitation
- 3.4 Principle of privacy and confidentiality
- 3.5 Principle of precaution and risk minimization
- 3.6 Principle of professional competence
- 3.7 Principle of accountability and transparency
- 3.8 Principle of maximization of public interest and distributive justice
- 3.9 Principle of institutional arrangements
- 3.10 Principle of public domain
- 3.11 Principle of totality of responsibility
- 3.12 Principle of compliance

The details of the above may be seen in the parent document.

4.0 Specific Principles Related to Stem Cell Research

Stem cells are unique. It is, therefore natural that stem cell research raises several special scientific and ethical issues eg.

- 4.1 The source of cells is limited to human subjects. In case of allogenic donation there is no direct benefit to the donor per se source of the cell procurement process such as ovum donation or bone marrow donation are invasive and may carry risk to the donor. Extra care has to be taken in providing appropriate information while taking consent for donation. The donor may need to be investigated for potentially transmittable infections and also some genetic diseases, results of which, the donor may or may not like to know. The donor also needs to be informed that cell lines may be derived from the donated tissue, which may be banked and shared with others. They may also undergo genetic manipulation, and have potential for development of commercial products. In the later case, the intellectual property rights will not be of the donor. Also while confidentiality and privacy are sacrosanct; a provision needs to be kept for traceability in a contingency situation. The donor might need to be contacted in future as well.

- 4.2 The stem cells are essentially rare. Some degree of processing, viz. enrichment or in vitro expansion etc. is generally required to obtain them in enough numbers. Also, various manipulations may need to be employed to enhance their utility. In case of embryonic stem cells or iPS cells targeted differentiation may be required to generate the appropriate cells of interest. Being a biological product special care is needed in choosing appropriate reagents/ media etc; and also developing quality assurance scheme for 'in-process-acceptance' and 'final release' of the product to assure safety while maintaining their potency and efficacy. Stringent characterization requirements with reference to their type, purity and genomic stability status etc. are essential for any research in this field.
- 4.3 The two basic characteristics of stem cells viz. potential for unlimited proliferation and ability to differentiate into a variety of cells of all three germ layers, which has made them the darling of regenerative medicine, incidentally are also their biggest distracters. For eg. one of the signatures of the stem cells is their ability to produce teratoma, which is totally unacceptable in terms of safety of any therapeutic product. Also, once introduced into body, they may survive indefinitely and what type of cells they may produce could be unpredictable.
- 4.4 It is, therefore essential that besides general principles, specific principles be evolved to regulate stem cell research, particularly the translational one. This document is an effort in this direction, to ensure that progress in the field for potential benefit to mankind does not get stymied. the two corner stone's that have been proposed to achieve this purpose are:
- 4.4.1 An extra layer of oversight by those who are knowledgeable about these special issues, and
- 4.4.2 Categorizing of the stem cell research into three areas viz. permissible, restricted and prohibited; according to the risk expected from each. These are expanded in the clauses below.

5.0 Responsibility for Conduct of Stem Cell Research: Investigators, Institutions and Sponsors

- 5.1 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. Sponsors shall also take note of their responsibilities and liabilities under various statutes and regulations governing research and development in the area in-force in the country.

- 5.2 The regulatory bodies shall appreciate that stem cell research is a nascent field. While there have been tremendous advances in understanding the biology of stem cells, these are several elements of unpredictability in the translation of research in this area. It is of utmost importance that review of research in this field ensures highest degree of scientific rigor and resolution of ethical concerns. The members of the regulatory committee shall remain in constant touch with advances in this field.
- 5.3 Each institution should maintain a registry of its investigators who are conducting stem cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of these cells. It shall also be the responsibility of the institution to ensure that most current standards are applied.
- 5.4 Each institution shall constitute an IC-SCR as provided in these guidelines and provide adequate support for its functioning in early years when work load is limited and expertise in the field of stem cell research is limited locally, the IEC supplemented with additional expertise may handle the proposals related to research on stem cells. Alternatively, another IC-SCR in the local area may accept the responsibility. The IC-SCR shall discharge all its function as envisaged under these guidelines (Annexure I)
- 5.5 All records pertaining to adult stem cell research must be maintained for at least 5 years and those for hES/iPS cell research for 10 years.
- 5.6 A NAC-SCR has been constituted to provide an oversight to all the IC-SCRs for achieving a uniform standard across the country. In addition, it will have the major role of reviewing, approving and monitoring of research categorized as restricted, after initial review and recommendation by the IC-SCR. A close cooperation and compliance by all the statutory bodies essential to achieve the desired goals. The responsibilities and functions of the NAC-SCR are outlined in (Annexure I).
- 5.7 The physician/scientist engaged in stem cell research and therapy shall ensure that no hype or unrealistic expectations is created in the minds of subjects or public at large regarding stem cell therapy. They must inform the parent and the family. The bare facts both what is known and what is not known about the status of stem cell research for the

given indication and the alternatives available for the same. Their responsibility is to generate robust scientific evidence through controlled trials which may be applied for the benefit of the patients.

- 5.8 The institutions carrying out such research shall also establish suitable mechanisms for creating awareness and communicating scientific evidences to the public.
- 5.9 The basic scientists engaged in stem cell research from human sources shall be vigilant to safeguard human rights and human dignity of those from where samples have been obtained. The biological material should be treated with utmost respect and care in all experiments. The use of human embryos shall be restricted as much as possible, and shall be resorted to where there are no other alternatives. Also, special care should be taken in introducing human cells in animals, particularly in early developmental stages, which may lead to development of chimeras or incorporation into brain/gonads.
- 5.10 It shall be understood that while no bar is placed in carrying out experiments which may lead to benefit to humanity, but this should not take them down on the slippery road to prohibited areas of research.

6.0 Mechanism for review and regulatory oversight of stem cell research

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 in the field of human stem cells, one at the National level called as National Apex Committee for Stem Cell Research (NAC-SCR) and the other at the institutional level called Institutional Committee for Stem Cell Research (IC-SCR) with necessary expertise in field of stem cell biology and its translation. The composition, functions and responsibilities of NAC-SCR and IC-SCR are given in Annexure I. These Regulatory bodies shall ensure that review, approval and monitoring of all research projects in the field of stem cell research is done rigorously and effectively taking into account various scientific & ethical issues related to stem cell research.

- 6.1 In early stages, say 5 years, when expertise in this field is limited, IC-SCR committees of one institution may assist neighboring institutions under a formal arrangement. The institutions may also carry out regulatory oversight of stem cell projects through IEC's with induction of extra expertise in the field of stem cells as co-opted members with full-voting rights.

- 6.2 All institutions and investigators, both public and private, carrying out research on human stem cells should be registered with the NAC-SCR through IC-SCR.
- 6.3 All research studies using human stem cells shall have prior approval of IC-SCR for permissible research as given in these guidelines, and of the NAC-SCR for restricted research, also defined in these guidelines.
- 6.4 All new human pluripotent stem cell lines, irrespective of the source and methodology used, shall be created, with prior approval of IC-SCR/NAC-SCR. The requirements for taking decisions regarding creation of embryos for the purpose of establishment of stem cell line are elaborated in these guidelines,
- 6.5 All established human stem cell lines from any source, imported or created in India, should be registered with IC-SCR and NAC-SCR. Import shall also follow Import/ Export policy of the GOI for biological materials. Permission for import or procurement from other Indian laboratories shall be obtained from IC-SCR. The investigator shall ensure that imported cell line has been established in accordance with the ethical guidelines of the country of origin which are comparable to those of our country. An appropriate MTA shall be adopted for the purpose.
- 6.6 All clinical trials with any stem cells shall have prior approval of IC-SCR and Institutional Ethics Committee (IEC). Prior approval of Drug Controller General of India (DCGI) will also be required for stem cell based IND products & new drug applications (cells for therapy are deemed as drugs). All clinical trials shall be registered with the NAC-SCR through IC-SCR. International Collaborations shall have prior approval of respective funding agency as per its procedure or Health Ministry's screening committee (HMSC).

7.0 Categories 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:

7.1 Permissible areas of research

- 7.1.1 *In-vitro* studies on established pluripotent stem cell lines viz. hES, hEG, iPS or fetal/adult stem cells, may be carried out with review and approval of IC-SCR, provided the cell line is registered with the IC-SCR/NAC-SCR and GLP are followed. For classification of stem cells refer to section 8.1. The stem cells lines should have been established following ethical guidelines as laid down in this document.

- 7.1.2** *In-vivo* studies in experimental animals (other than primates) with established cell lines from any type of pluripotent stem cells viz., hES, hEG, iPS including differentiated derivatives of these cells, with prior approval of IC-SCR and IAEC, provided such animals are not allowed to breed. This includes pre-clinical evaluation of efficacy and safety of human stem cell lines or their derivatives.
- 7.1.3** *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-SCR, IEC and IAEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.
- 7.1.4** Establishment of new hES cell lines from embryos left unutilized in IVF programme, or iPS cell lines with prior approval of the IC-SCR 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-SCR and NAC-SCR and deposited in a cell bank for use by others.
- 7.1.5** Establishment of Umbilical Cord stem cell bank with prior approval of the IC-SCR/IEC and DCGI following guidelines given in this document for collection, processing, and storage etc. Appropriate SOPs to be approved by the IC-SCR/IEC. The information sheet for consent of parents should give all pros and cons of the debate on public vs. private umbilical cord blood banking.
- 7.1.6** Clinical trials with clinical grade cells processed as per National GLP/ GTP / GMP guidelines as applicable (but without major manipulation: see section 7.1.7) may be carried out with prior approval of IC-SCR/ IEC. Prior approval of DCGI is required if the product is intended to be marketed. All clinical trials on stem cells shall be registered with NAC-SCR through IC-SCR and also with the CTRI.
- 7.1.7** Levels of manipulation (processing)

In several situations, stem cells are manipulated *in vitro* for research or for use in clinical trials. Such manipulations of stem cells are categorized as given below

- a. **Minimal manipulation:** No major alterations in cell population or function. This may include Ficoll-Hypaque separation ensuring use of clinical grade reagents, washing, centrifugation etc; all laboratory procedures not exceeding few hours, avoidance of the use of animal origin products and carried out under strict aseptic conditions.
- b. **More than minimal manipulation:** Defined as alterations in cell population (e.g. T cell depletion, cancer cell depletion, CD 34 enrichment), expansion etc. which is expected to result in alteration of function. All laboratory processes under strict aseptic conditions, and not exceeding a few days.
- c. **Major manipulation:** Long term culture of cells through multiple passages which may be accompanied with genomic instability or pathogenic genetic alterations, or induction of genetic alteration by insertion of gene/siRNA etc.

All products shall be properly labeled and fulfill the laid down acceptance and release criteria.

Clinical use of stem cells as standard of care, outside of approved clinical trials, is not permitted –

- a. Until the indications, efficacy and long term safety of the procedure is established.
- b. The origin, safety, composition, dosage, route of administration etc. of the product are adequately defined and labeled.
- c. Conditions for storage, transport and use are established in detail.

7.2 Restricted areas of research

7.2.1 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving a hES-cell line for any purpose. This requires the following:

- a. Specific justification would be required to consider the request for approval by the NAC-SCR through IEC and IC-SCR.
- b. 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.
- c. Informed consent procedure for donation of ova, sperm, somatic cell or other as detailed in these guidelines would need to be followed.

- 7.2.2. Clinical trials using cells after major manipulation or those sponsored by multinationals involving stem cell products imported from abroad shall require prior approval of the NAC-SCR through IC-SCR, IEC, DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC). The import of biological materials for research and development is regulated by GOI (F. No. L./950/53/97-H1(Pt.) dated 19th Nov 1997). Import of approved and marketed 'drugs' (therapeutic products) from abroad requires license from the DCGI as per its Act and Rules.
- 7.2.3. Research involving introduction of hES-/hEG-/iPS-/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-SCR for additional oversight and review through IAEC and IC-SCR/IEC.
- 7.2.4. 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. This would require approval of NAC-SCR through IC-SCR/IEC/IAEC.
- 7.2.5. 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. This also would require approval of NAC-SCR through IC-SCR/IEC.

7.3 Prohibited areas of research

- 7.3.1. Any research related to human germ line genetic engineering or reproductive cloning.
- 7.3.2. Any in-vitro culture of intact human embryo, or any organized cellular structures that have the potential of developing into human organs and tissues, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier?

- 7.3.3. Transfer of human blastocysts generated by any means including SCNT or parthenogenetic or androgenetic techniques into a human or non-human uterus.
- 7.3.4. Any research involving implantation of human embryo into uterus after in-vitro manipulation, at any stage of development, in humans or primates.
- 7.3.5. Animals in which any of human stem cells have been introduced at any stage of development should not be allowed to breed.
- 7.3.6. Research involving directed non-autologous donation of any stem cells to a particular individual is also prohibited.

8.0 Basic Research

Stem cells have been successfully derived from various sources and they are extensively used in basic research for the fundamental understanding of how cells multiply and differentiate to other cell types.

Clinical grade stem cells are also produced under GLP/GMP conditions and these are used for drug discovery and drug screening research. They are also exploited for clinical research/trials for human disease. These procedures require approval of IC-SCR/IEC and NAC-SCR.

8.1 Classification of stem cells

On the basis of origin of stem cells, there are a number of categories of stem cells. These are derived from human and non-human sources. Depending on the source of their derivation and their differentiation capabilities, stem cells are classified into adult stem cells (ASCs) and pluripotent stem cells (PSC).

- 8.1.1 ASCs and PSCs are derived from both animal and human sources.
- 8.1.2 ASCs are resident self-renewable population of stem cells in various tissues. ASCs include hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs), to name a few.
- 8.1.3 PSCs include ES-cells and induced pluripotent stem cells (iPS-cells). See section 8.1.10.
- 8.1.4 PSCs have two unique characteristics. First, they can be maintained and expanded as pure populations of undifferentiated cells for extended periods of time. Second, they have the full capacity for differentiation and produce cell derivatives of all three primary embryonic germ layers: ectoderm, mesoderm, and endoderm. They can

- contribute to embryonic chimeras when reintroduced into the blastocyst.
- 8.1.5 ES-cells are derived from the inner cell mass (ICM) of blastocysts. These are derived from various animal sources and from human blastocysts. See section 8.2.
 - 8.1.6 Human ES-cells are derived from spare blastocysts, obtained in IVF clinics, with informed donor consent with appropriate approvals from IC-SCR and IEC.
 - 8.1.7 iPS-cells are derived by genetic reprogramming of somatic cells by introducing four transcription factors Oct-4, Sox-2, Klf4, cMyc or other new generation methodologies.
 - 8.1.8 iPS-cells have been successfully derived from the mouse and human species.
 - 8.1.9 PSCs remain capable of re-entering into embryogenesis and contribute to chimeras. They are amenable to exogenous DNA introduction for genetic manipulation of PSCs. These come under the category of restricted research (see sections 7.1 and 7.2).
 - 8.1.10 Classification of human stem cells includes the following.

Human embryonic stem cells (hES-cells) cells, derived from blastocysts arising from (i) surplus embryos from IVF clinics; (ii) specifically generated for research or therapy using IVF; (iii) other techniques like SCNT etc.

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

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

Human induced pluripotent stem cells (iPS) cells, which are derived from fetal or adult diploid somatic cells by forced expression of pluripotency inducing factors such as Sox2, c-Myc, Oct-4 and Klf-2. They are genetically reprogrammed PSCs and they exhibit properties similar to a typical ES-cell line.

- 8.1.10.1 Patient-specific (autologous) iPSCs can be produced which are expected to provide a potential advantage for autologous cell therapy. These are purely experimental and require approvals of IC-SCR/IEC and NAC-SCR.
- 8.1.10.2 The potential use of iPSCs in regenerative medicine will largely dependent on the outcome of basic research data and preclinical data on their differentiation potential and their stability, safety and efficacy.
- 8.1.10.3 At this time, iPS-cells and their derived-progenitors are not being considered as a cell-therapy product.

- 8.1.10.4 Other categories of PSCs include EG-cells, derived from later stages of epiblasts (primordial germ cells in the fetus). EG-cells are similar to ES-cells in terms of developmental potential capacity. These are not being tested in clinical research.
- 8.1.10.5 Embryonal carcinoma (EC) cell lines are from spontaneous testicular teratocarcinomas from a day 6 embryo of 129Sv mouse strain. EC-cells retain full differentiation capacity but cannot form chimeras. These are used for experimental basic research and are to be approved by IC-SCR/IAEC.

8.2. Derivation and characterization of human pluripotent stem cells

- 8.2.1. A number of established human PSCs i.e. hES-cells and iPS-cells, either derived in India or in other countries, are currently available for use in basic or clinical research. These are to be registered at the IC-SCR/NAC-SCR.
- 8.2.2. Derivation of new ES-cell or iPS-cell lines from human embryonic or somatic cells, respectively, require prior approval from IC-SCR/IEC and NAC-SCR; this comes under restricted area of research (see section 7.2).
- 8.2.3. Gametes or embryo donations, required for ES-cell derivation, must follow ART-Guidelines (ICMR, 2009) and must have approvals of the IEC/IC-SCR and NAC-SCR.
- 8.2.4. Human fetal or adult somatic cell donations, required for possible generation of iPS-cell lines, must have approvals of the IEC/IC-SCR.
- 8.2.5. Human PSC-lines are derived for the purpose of either basic research or clinical research (trials). Accordingly, laid-down GLP/GMP guidelines are to be adhered with approvals from IC-SCR/IEC and NAC-SCR.
- 8.2.6. Human PSC-line derivation protocol must be as per the published procedure or Institutional SOPs, approved by the IC-SCR/IEC.
- 8.2.7. Reagents used for the derivation of ES-cell or iPS-cell lines must be of GLP or GMP grade and such reagents used must be of clinical-grade, in case, such human ES-cell or iPS-cell lines are proposed to be used for (pre)clinical research.
- 8.2.8. Newly derived ES-cell or iPS-cell lines must confirm to all defining criteria of a typical human PSC-line, as per the published assays and/or Institutional SOPs.

- 8.2.9. Such newly established cell lines, with appropriate IDs, must be registered by the IC-SCR/NAC-SCR.
- 8.2.10. New PSC-lines must exhibit key pluripotency-properties such as (a) proliferative/expansion capabilities over multiple passages, (b) stable karyotype, (c) expression of stemness gene markers such as SSEA-3, Oct-4, TRA-1-80, AKP and (d) capability to undergo lineage-specific differentiation to various cell types, evidenced by cell and molecular biological criteria. These procedures must follow SOPs.
- 8.2.11. Derivation of patient-specific ES-cell or iPS-cell lines is allowed for the purpose of basic or clinical research, provided scientific justification and SOPs (with GLP/GMP compliance) are approved by the IC-SCR/IEC and NAC-SCR.
- 8.2.12. Using patient-specific ES-cells or iPS-cells or their derived-progenitors for clinical trials at this stage is not permitted and this requires considered scientific inputs at the level of NAC-SCR.

8.4 Modeling of Human disease

8.5 Drug development

8.6 Approval for derivation of a new hES cell line whether from spare embryos or embryos created for the purpose

Proposals involving the following (the list is only illustrative), may be considered for approval:

- 8.6.1 The goal of research is to increase knowledge about embryo development and causes of miscarriages and birth defects.
- 8.6.2 Develop methods to detect abnormalities in embryos before implantation.
- 8.6.3 Advance knowledge, which can be used for infertility treatment or improving contraception techniques.
- 8.6.4 Increase knowledge about causation of serious diseases and their treatment including tissue therapies.
- 8.6.5 Developing methods of therapy for diseased or damaged tissues or organs.
- 8.6.6 Develop ethnically diverse hES cell lines, provided –
- 8.6.6.1 The proposed research cannot be carried out with existing cell lines;

- 8.6.6.2 Justification for the minimum number of embryos/blastocysts required must be clearly defined;
- 8.6.6.3 Research teams involved should have appropriate expertise and training in derivation, characterization and culture of ES cells.

9.0 Preclinical and Clinical Trials using Stem Cells

This document outlines guidelines for both preclinical studies and clinical trials using stem cells. The use of stem cells (adult stem cells; fetal and embryonic) for appropriate clinical applications involves the principles of clinical translation, wherein, ethical, social, clinical, scientific, and regulatory issues need to be addressed. This document pertains to use of stem cells for clinical applications, besides those that are established standard of care for treatment (e.g. HSCT and epithelial stem cell based therapy for burns and corneal disorders). Broadly, it involves both preclinical and clinical studies. In case stem cells are being delivered using implantable or injectables scaffolds, then guidelines in chapter 10 should be followed.

9.1 Preclinical

Preclinical studies are essential to establish safety and proof-of-principle, prior to conduct of human clinical trials as per regulatory requirements for any new biological entity (NBE). Preclinical studies would involve both *in-vitro* and/or animal experiments. The latter would largely constitute small animals and in certain special situations, large animals and non-human primates, on a case-to-case basis.

- 9.1.1 Preclinical studies shall demonstrate safety of the procedure and proof-of-principle for desired therapeutic effect. The stem cells to be employed in such trials shall be well characterized and evaluated for potential toxicities (both early and late e.g. immunogenicity and tumorigenicity)
- 9.1.2 Diseased human tissues may also be used for preclinical studies.

9.1.3 *Approval and Monitoring:*

Preclinical studies need to be approved by IC-SCR/IEC followed by a robust independent peer review. Approval from IAEC and CPCSEA shall also be obtained for small and large animal studies respectively. 2.3.2. (Should be reconsidered)

9.1.4 *Study Design:*

- 9.1.4.1 The stem cells shall be well characterized and the source, dose and route of administration (local/systemic) shall be clearly specified appropriate to the proposed clinical application. The final product to be administered should be a clinical grade product prepared under rolling cGMP facility.
- 9.1.4.2 Besides routine safety studies, distribution of cells, their survival, integration and functional outcome should also be incorporated in animal models wherever possible. Large animal models shall be used where necessary (eg in studies of cardiac physiology; tissue-related inflammatory and immunological injuries and degenerative disorders of weight bearing joints etc.). **The selected animal model must offer an appropriate context for studying the human disease and conditions of specific interest.**
- 9.1.4.3 Toxicity studies shall be done in a certified **GLP facility**.
- 9.1.4.4 The interaction of stem cells with drugs being used to treat the underlying medical condition, and immunosuppressant's (where relevant), shall be tested in animal models/cell culture system.
- 9.1.4.5 Study design shall preferably incorporate a plan to analyze potential toxicities arising from culture-acquired abnormalities.
- 9.1.5 It is acknowledged, that preclinical assays in animal models are unpredictable regarding the nature of cell behavior and immune response in humans.

9.2 Clinical Research

Human clinical trial using stem cells must strictly adhere to accepted principles as laid down in the Schedule Y of Drugs and Cosmetic Act, GCP Guidelines of CDSCO and Ethical Guidelines for Biomedical Research involving Human Participants of ICMR. Clinical research protocol shall be formulated as per the format given in Annexure III.

- 9.2.1 To establish the therapeutic potential of well characterized stem cells in various clinical disorders, hitherto, considered incurable by standard protocol of care following robust preclinical data on safety and proof-of –concept.

9.2.2 *Trial Subjects*

Subject Selection shall be done according to the inclusion and exclusion criteria as per the approved clinical research protocol.

9.2.2.1 The information sheet for the Patient's consent shall specifically address the following: Information regarding the present status of use the stem cells in the given condition, experimental nature of the proposed clinical study and its possible short term and long term risks.

9.2.2.2 Information stating irreversibility of the intervention.

9.2.2.3 Information regarding the source of stem cells and ex-vivo manipulation.

9.2.2.4 Information on the established standard of care must be made available

9.2.2.5 Information on the sample size and duration of study

9.2.2.6 The consent form needs to be approved by IEC and IC-SCR.

9.2.3 Approval and Monitoring:

9.2.3.1 Approval and monitoring of clinical trials will take into consideration the following factors but not limited to:

2. Source and type of stem cells- adult, embryonic, fetal, iPSc etc.
3. Autologous or allogeneic applications
4. Degree of manipulation- minimal, more than minimal or major
5. Stage of research - in-vitro, in-vivo, preclinical or clinical research
6. Evidence of progress of similar research at national and international level
7. Whether the proposed cell based research is intended for manufacturing of a marketable product

9.2.3.2 Regulatory approvals

9.2.3.2.1 Clinical trial proposals using minimally manipulated autologous adult stem cells, will need approval by IC-SCR and IEC.

9.2.3.2.2 Clinical research using autologous stem cells requiring more than minimal or major manipulation, and use of allogeneic stem cells with any degree of manipulation will need approval from NAC-SCR through IC-SCR.

9.2.3.2.3 Any stem cell based product already approved and marketed out-side India will require approval of DCGI.

9.2.3.2.4 Any clinical trial likely to lead to a marketable product shall have prior approval of DCGI through IC-SCR and NAC-SCR.

9.2.3.2.5 6.2.2

9.2.3.3 Monitoring of Clinical Trials

- a. Institutional, by IEC and IC-SCR and respective Funding Agency.
- b. NAC-SCR will function to give general oversight and will review specific controversial or ethically more sensitive clinical research trials (eg. hESCs).
- c. Data Safety Monitoring Board (DSMB) shall comprise independent members not associated with IC-SCR/NAC-SCR and shall be constituted by the respective funding agency for all clinical trials involving human subjects in case of extramural funding or by the institutions/industry for in-house supported clinical trials.
- d. These members shall have the requisite expertise to monitor trials for adverse events and their smooth conduct.

9.2.3.4 Stem cell therapy (other than HSCT and epithelial –stem cell-based treatments for burns and corneal disorders) is considered/deemed to be experimental therapy as of now and should be conducted in the form of clinical trials. Those conducted outside clinical trial is unethical and hence not permissible.

9.3 Use of stem cells for therapeutic purposes

- 9.3.1 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-SCR/IEC and DCGI (for marketable products). All experimental trials shall be registered with the NAC-SCR.
- 9.3.2 Cells used in such trials must be processed under GTP/GMP standards.
- 9.3.3 The inject able product should meet pharmacopial specifications for parental preparations. The cells used for therapy shall be free from animal products and microbial contamination.
- 9.3.4 The centers carrying out stem cell clinical trials and the agency/ source providing such cells for the trial shall be registered with the NAC-SCR through IC-SCR/IEC. In case of International Collaboration, the public funding agency evaluating the study / NAC-SCR shall ensure that the certification provided by the collaborating country fulfills the requirements laid down in these guidelines.

- 9.3.5 The hES cell/cell lines or the cells derived there from used in the trial shall be characterized as suggested in Annexure II.
- 9.3.6 The headings under which clinical trial protocol for stem cell therapy shall be prepared is given in Annexure III.

10.0 Tissue Engineering and Scaffolds in Stem Cell Research

This Chapter describes the recommended specifications and characterization of raw or starting materials of natural and synthetic origin or their combination. These could be metallic, ceramic, polymeric, natural or composite materials that are degradable or non-degradable and can be used for the delivery of stem cells into experimental animals or in human studies for the purpose of basic or clinical research.

- 10.1 A material that can be used as a scaffold must satisfy a number of properties during the tissue regeneration process. The properties include overall biocompatibility of the material, biodegradation into non toxic products, malleability to complicated shapes with or without appropriate porosity, ability to support cell growth and proliferation, and appropriate mechanical properties. Since tissue differentiation and functionality are highly dependent on the local environment, it is important to characterize the raw materials and finished products for their physicochemical properties, such as chemical identity, structure, topography, mechanical properties, thermal characteristics, sterilisability and biodegradation.

10.2 Biological Evaluations

Biological evaluation of tissue engineering scaffolds must be performed to determine the potential toxicity resulting from contact of the component materials of the materials with the body. The materials or their constituents could (a) produce adverse local or systemic effects; (b) be carcinogenic; or (c) produce adverse reproductive and developmental effect. Therefore, to biologically validate that the properties of a scaffold material and to certify the overall performance of the product, the following criteria must be tested:

1. Absence of components that might be toxic to cell growth and/or to the intended performance;
2. Biocompatibility of the structural material with the cells or biological specimens to confirm that the system maintains the desired cell differentiation, functionality and genotype during production and until use;

3. Release kinetics and/or rate of degradation of any bioactive molecules, to verify that they are appropriate for the achievement of the intended effect.
4. Where the safety of a material has been previously established for other implantable medical applications, elements of that evaluation could be used for evaluating the safety and suitability as a cellular therapy product.
5. Guidance for doing the above mentioned evaluations and safety can be found in the standards issued by organizations like ASTM International, NIST and ISO. The levels of characterization that may be conducted for the materials is voluntary, however sufficient information on the characteristics and safety of the material, in its original and finished form, should be available as part of the official dossier of properties of the materials.

10.3 Physicochemical Evaluation

For the purpose of material evaluation it is suggested that all products, protocols and procedures must be carried out as per the American Society for Testing and Materials (ASTM) document No. F2312-11, F2211-04, F2383-11, F2150-07, F2027-08, F2883-11 and F2664-11 (www.astm.org), Details of these are available from the links shown in parenthesis. Details of the some of the available standards are given in the appendix at the end of this Chapter.

10.4 Biological Evaluation

When selecting the appropriate tests for biological evaluation, one must consider the chemical characteristics of materials and the nature, degree, frequency and duration of its exposure to the body. In general, the tests include

- (a) acute, subacute, sub-chronic and chronic toxicity;
- (b) irritation to skin, eyes and mucosal surfaces;
- (c) sensitization;
- (d) hemo-compatibility;
- (e) genotoxicity;
- (f) carcinogenicity and
- (g) effects on reproduction including developmental effects.

- (h) Additional tests for specific target organ toxicity such as neurotoxicity and immunotoxicity may be necessary for some devices.

The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate and ISO documents nos. 10993 Part 1 to Part 12 (www.iso.ch/en).

Details of these are available from the links shown in parenthesis. Details of the some of the available standards are given in the appendix at the end of this Chapter.

10.5 Scope of the Guidelines

Although many tissues engineered products are used for implants and other devices these guides are primarily for materials and scaffolds that are used or new ones being developed for the delivery and *in vivo* functions of stem cells. Representative examples of scaffolding materials and synthetic tissues and biological substitutes that have been used for delivery of stem cells for basic and clinical research and their guidance standards are given below

10.6 Examples of Scaffold Materials

10.6.1 *Synthetic materials*

A vast majority of biodegradable polymers studied belong to the polyester family, which includes polyglycolides and polylactides and their co-polymers. Other degradable polymers such as polyorthoesters, polyanhydrides, polyphosphazenes, and polyurethanes. Bioceramics and Bioglass belong to another class of synthetic materials that have been used for this purpose.

10.6.2 *Natural materials*

Natural polymers used as scaffolds for stem cell delivery include materials such as chitosan, alginate, collagen, albumin, hyaluronic acid, fibrin, de-cellularised tissues and peptides. Specific standards for manufacturing some of these materials are provided in ASTM F2103-11, F2212-02, F2347-11, F2605-08 standards.

10.6.3 *Biological Substitutes*

ECM biomaterials are derived from the extracellular matrix of human or animal tissues, and processed to remove unwanted components of the tissues and retaining

desired components. Versions of these USFDA approved materials for soft tissue repair devices and for demineralized bone grafts are given below:

8. Human dermis
9. Bovine dermis
10. Porcine dermis
11. Human Demineralized Bone Matrix
12. Equine pericardium
13. Bovine pericardium
14. Small intestine submucosa

11.0 Banking of Biological tissues

There are several models for banking of various biological tissues. Recent advances have indicated their potential use for future applicability, with specific interest in banking, isolation and ex vivo expansion of the stem cells from them.

Hematopoietic stem cells are an example of well researched cell type. They are already in clinical use for hematopoietic reconstitution. Hitherto, bone marrow was the only source of such cells; however alternate sources like mobilized peripheral blood, and cord blood are now being increasingly recognized for their potential clinical use. Hence regular banking of such cell types is fairly well established. Few examples of tissues of current interest in stem cell isolation and expansion are adipose tissues, Wharton's jelly, Dental pulp, endometrial tissues, Placental tissues, to name a few. In the future, this list is expected to increase. Accordingly, it is important to define standards for their banking.

The following guidelines are comprehensive and concise. They are applicable to Umbilical cord blood stem cell banking, which is the result of a collective experience and increasing clinical literature on its usage. Researchers are advised to refer to Annexure () and international standards, and regulatory documents for more information.

The same outline may be considered for other tissues as well; however tissue specific /cell specific requirements may vary.

Cord Blood stem cell banking requires registration and license from the Government Regulatory Agency namely DCGI.

11.1 Clinical use of umbilical cord blood stem cells

Cord blood stem cell banking is permissible. All Cord blood banks should be registered with the DCGI as per their guidelines (ref). Commercial exploitation of stored blood should be regulated strictly. Special care must be taken towards maternal screening and for collection, processing and storage of umbilical cord stem cells to avoid transmission of 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 hematopoietic stem cell transplantation. Expansion of umbilical cord stem cells for transplantation in adult and use for non-hematopoietic 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, 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.

The following points should be specifically considered while collecting umbilical cord blood for banking:

- 11.1.1 No harm should occur to the donor/fetus or the neonate.
- 11.1.2 Exact timing of the clamping of umbilical cord should be defined.
- 11.1.3 Parents should be correctly informed regarding risks and benefits involved.
- 11.1.4 Free informed consent should be obtained from both parents. If there is disagreement between the parents, the mother's wish shall prevail.
- 11.1.5 ID card should be issued for voluntary donation to enable preferential access/benefit in future in case required for self/relatives. Such units may also be used for unrelated

individuals.

- 11.1.6 Standard Operative Procedures (SOPs) for collection, transportation, processing, storage (cryo-preservation) and release for clinical use of umbilical cord blood/cells should be clearly laid down.
- 11.1.7 If processed stem cells are proposed to be used, detailed protocol for isolation, expansion and characterization of stem cells should be approved by IC-SCR/IEC.
- 11.1.8 Period of preservation for self- use later in life should be defined.
- 11.1.9 Detailed protocol for release of umbilical cord units for clinical use should be in place. This should include follow up plans for assessing safety and efficacy of cord blood stem cell therapy.

11.2 Banking and distribution of Cell lines

Cell lines from various tissues are being used by researchers worldwide. These include embryonic stem cells (both normal and Parthenotic), neonatal tissues (Wharton's Jelly), iPS cell lines, adult stem cell lines derived from Mesenchymal stem cells, fibroblasts, myoblasts, to name a few.

The following guidelines are specifically outlined for hESCs. Researchers are advised to follow these for other cell lines as well. However, specific requirements may vary from cell/tissue type.

11.2.1 Banking and distribution of hES cell lines

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: i) they are well characterized and screened for safety, (see Annexure II) ii) the conditions under which they are maintained and stored meet the current standards of GLP/ GTP/ GMP in India (to be annexed) with appropriate SOPs.

The following guidelines are specifically for hES cell lines; however the researchers are advised to follow these for other sources of stem cells as well.

- 11.2.1.1 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 the IC-SCR/IEC 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.
- 11.2.1.2 Any facility engaged in obtaining and storing hES cell lines should consider the following:
 - a. Creation of clear and standardized protocols for banking and withdrawals.
 - b. Documentation requirements for investigators and sites that deposit cell lines, including:
 - A copy of the donor consent.
 - Proof of IC-SCR/IEC approval of the procurement process.
 - Available medical information on donors, along with infectious disease screening details.
 - Available clinical, observational or diagnostic information about the donor(s).
 - Critical information about culture conditions (such as media, cell passage, and safety information).
 - Available cell line characterization (such as karyotype and genetic markers).
- 11.2.2 A repository has the right of refusal if prior culture conditions or other items do not meet its standards.
- 11.3 A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to
 - 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 obtained through research/investigations back to donors.

11.4 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. Process for characterizing cell lines.
- d. Process for expanding, maintaining, and storing cell lines.
- e. System for quality assurance and control.
- f. Website that contains scientific descriptions and data related to the available cell lines. Central Registry should be set up by the NAC-SCRT.
- g. Procedure for reviewing request applications for cell lines.
- h. Process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
- i. System for auditing compliance.
- j. Schedule of charges.
- k. Statement of intellectual property policies.
- l. When appropriate, creation of a clear Material Transfer Agreement or user agreement.
- m. Liability statement.
- n. System for disposal of material.
- o. Clear criteria for distribution of cell lines

12.0 Research using fetal stem cells/placenta

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

- 12.1. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.
- 12.2. Informed consent to have a termination of pregnancy and the donation of fetal material for purpose of research or therapy should be taken separately.

- 12.3 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.
- 12.4 The woman shall not have the option to specify the use of the donated material for a particular person or in a particular manner.
- 12.5 The identity of the donor and the recipient should be kept confidential.

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

- 13.1 The IC-SCRT/IEC, 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 or any other technique should have approval of NAC-SCR.
- 13.2 Consent for donation of supernumerary embryos should be obtained from each donor at least 24 hours in advance and not 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.
- 13.3 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-SCR/ IEC. Similarly, no payments should be made for donation of somatic cells for use in SCNT except for reimbursement for attending the clinic.
- 13.4 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-SCR/ IEC. They should be informed about potential hazards, complications etc which are related to the hormonal induction process.
- 13.5 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.

13.6 In the context of donation of gametes or blastocysts for hES cell research or therapy, 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 shall 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 the derived hES cell line may be used for development of new drugs/diagnostics etc. which may have commercial value, but no direct financial benefit to the donors.
- g. A statement that derived stem cells or cell lines and the information related to it may be archived for 15 years or more.
- 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.

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

14.0 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 groups, research groups etc.

15.0 International Collaboration

- 15.1 National guidelines of respective countries should be followed.
- 15.2 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-SCR.
- 15.3 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.

16.0 Import / Export of Stem Cells

17.0 Public Participation

18.0 Periodic Review of Guidelines

19.0 References

Opinion on Ethical Aspects of Human Stem Cell Research and Use. The European Group on Ethics. Paris: 2000

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ISSCR Guidelines for the Clinical Translation of Stem Cells, December 2008.

National guidelines for DSMB jointly prepared by WHO and CDCSO, Ministry of Health and Family Welfare, November, 2007

DSMB guidelines, NIH, USA November, 2011

Regulation (EC) No.1394/2007 of the European Parliament and Council, November, 2007

Requirement and Guidelines on clinical trials for import and manufacture of new drug Schedule Y, CDSCO

Good clinical practices for clinical research in India, CDSCO

F2312-11 Standard Terminology relating to Tissue Engineered Medical Products

F2211-04 Standard Classification for Tissue Engineered Medical Products (TEMPs)

F2027-08 Standard Guide for Characterization and Testing of Raw or Starting Biomaterials for Tissue-Engineered Medical Products

F2150-07 Standard Guide for Characterization and Testing of Biomaterials Scaffolds used in Tissue-Engineered Medical Products

F 2383-11 Standard Guide for Characterization and Testing Assessment of Adventitious Agents in Tissue Engineered Medical Products (TEMPs)

F 2883-11 Standard Guide for Characterization of Ceramic and Mineral Based Scaffolds used for Tissue-Engineered Medical Products (TEMPs) and as Device for Surgical Implant Applications

F 2103-11 Standard Guide for Characterization and Testing of Chitosan Salts as Starting Materials intended for use in Biomedical and Tissue-Engineered Medical Product Applications

F2212-02 Standard Guide for Characterization Type I Collagen as starting Material for Surgical Implants and Substrates for Tissue-Engineered Medical Products (TEMPs)

F2347-11 Standard Guide for Characterization and Testing of Hyaluronan as starting material intended for use in Biomedical and Tissue-Engineered Medical Product Applications.

F2605-08 Standard Test Method for determining the molar mass of sodium alginate by Size Exclusion Chromatography with Mutli-Angle Light Scattering detection (SEC-MALS).

F2664-11 Standard Guide for assessing the attachment of cells to biomaterial surfaces by physical methods

F2739-08 Standard Guide for quantitating cell viability within biomaterial scaffolds.

F2210-02 Standard Guide for processing Cells, Tissues and Organs for use in Tissue-Engineered Medical Products

ISO standards for biocompatibility testing of materials used in medical devices

ISO 10993--1:19971:1997 Biological evaluation of medical devices ---Part 1: Evaluation and testing

ISO 10993--2:19922:1992 Biological evaluation of medical devices ---Part 2: Animal welfare requirements

ISO 10993--3:19923:1992 Biological evaluation of medical devices ---Part 3: Tests for genotoxicity, carcinogenicity and, reproductive toxicity

ISO 10993--4:20024:2002 Biological evaluation of medical devices ---Part 4: Selection of tests for interactions with blood

ISO 10993--5:19995:1999 Biological evaluation of medical devices---Part 5: Tests for in vitro cytotoxicity

ISO 10993--6:19946:1994 Biological evaluation of medical devices ---Part 6: Tests for local effects after implantation

ISO 10993--7:19957:1995 Biological evaluation of medical devices ---Part 7: Ethylene oxide sterilization residuals

ISO 10993--8:20008:2000 Biological evaluation of medical devices ---Part 8: Selection and qualification of reference materials f

ISO10993--9:19999:1999 Biological evaluation of medical devices ---Part 9: Framework for identification and quantification

ISO10993--10:200210:2002 Biological evaluation of medical devices ---Part 10: Tests for irritation and delayed hypersensitivity

ISO10993--11:199311:1993 Biological evaluation of medical devices ---Part 11: Tests for systemic toxicity

ISO10993--12:200212:2002 Biological evaluation of medical devices ---Part 12: Sample preparation and reference material

20.0 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 oocyte that has had its nucleus removed to asexually create an embryo without the fusion of sperm and oocyte. 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 oocyte's nucleus with the nucleus of the adult cell to be cloned (or from an embryo or fetus) and then activating oocyte's further development without fertilization. The oocyte genetically reprogramme 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 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 blastocysts. 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.

Feeder layer: cells used in co-culture to maintain pluripotent nature of the stem cells

Fetus: In humans, it 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 oocyte

Germ cells: ova and sperm, and their precursors

Implantation: the embedding of a blastocyst in the wall of uterus. In humans implantation takes place between 7-14 days 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: Stem cells present in human bone marrow and umbilical cord that have been shown to differentiate into a variety of cell types

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 an embryo on its own.

Primitive streak: a collection of cells, which appears at about 14 days after fertilization from which the fetal body plan develops

Somatic cell: cell of the body other than oocyte 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 oocyte (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.

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 the light of ever growing advances in science. The committee will also review and approve specific research protocols falling under restricted category or as provided in the guidelines. 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. The IC-SCRT/IEC shall function at the institutional level and have appropriate expertise as suggested to support this effort.

1.0 NAC-SCRT

This is a multidisciplinary with a secretariat. It will have two main

functions:

- a) General oversight and policy monitoring function
- b) Review of specific controversial or ethically more sensitive research proposals

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 stem cell based research and therapy.
- 1.1.2 All institutions involved in any type of stem cell research and therapy shall be registered with the NAC-SCRT.
- 1.1.3 IC-SCRT/IEC has to submit annual 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 research in the restricted areas as given in this document.
- 1.1.5 Every scientific proposal using ES cells under restrictive category has to be cleared through IC-SCRT/IEC before referring to NACSCRT.
- 1.1.6 Use of chimeric tissue for research shall be approved only by NACSCRT after clearance from IC -SCRT/IEC.
- 1.1.7 NAC-SCRT shall revise and update guidelines periodically, considering scientific developments at the national or international level.
- 1.1.8 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).

2.0 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 To 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 annual report to NAC-SCRT.

2.2 Membership (7-9)

The committee should include representatives of the public and persons with expertise in clinical medicine, 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

Clinical Trial Protocol for Stem Cell Therapy

Study title Phase of the study Institution conducting the trial Sponsor Names of Principal Investigator and Co-investigators Brief CV of all the investigators

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
 - i. Screening phase
 - ii. Treatment phase
 - iii. Post –treatment phase
 - iv. Withdrawal of patients prior to study completion
- g. Efficacy assessment
 - i. Primary efficacy outcome
 - ii. Secondary efficacy outcome
 - iii. Efficacy measurements

5. Safety assessment

Adverse Events documentation in a prescribed format

- i. Definitions
- ii. Documentation of adverse events
- iii. Reporting of serious adverse events

6. Concomitant Medications

- i. Documentation of medications – name, dose, duration
- ii. Intercurrent illness
- iii. Prohibited medications

7. Product information, dose scheme and administration instructions

- i. Product information
- ii. Dose scheme
- iii. Route of administration
- iv. Cell preparation and administration instructions

8. 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

9. 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)

10. Requirements for study initiation and completion

11. Confidentiality and publication

12. Enclosures

- I. Investigator brochure including background, rationale, product details, pre-clinical studies results, human experiences, references and publication reprints

II. Case Record Form

III. Manual for efficacy assessments, safety assessments, laboratory procedures etc.

IV. Administrative approvals

- a. DCGI for IND/NDA
- b. IEC (of each center)
- c. Approved patient information sheet and consent form

- d. IC-SCRT/NAC-SCRT approval if required
- e. MOU/MTA in case of National/International collaboration with transfer of biological materials
- f. Funding of the project/sponsor
- g. Conflict of interest declaration
- h. Incentives to investigators/patients/donors
- i. Post-trial benefits
- j. Medical insurance coverage for SAEs
- k. Sponsor's responsibility towards cost of trial/complications
- l. Investigator's bio-data/acceptance