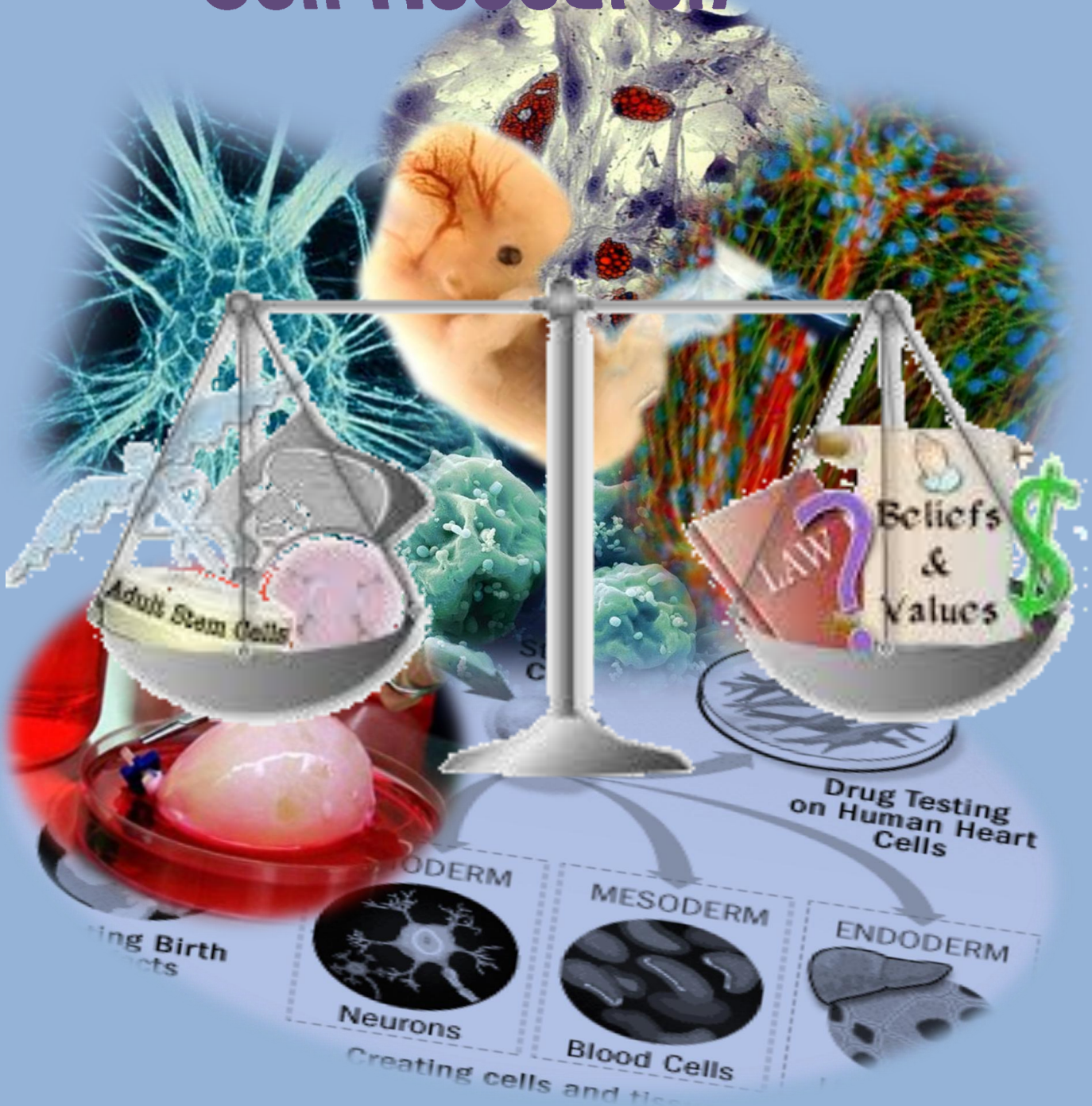
National Guidelines for Stem Cell Research



Indian Council of Medical Research
Department of Health Research
&
Department of Biotechnology
2013

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Foreword

The field of stem cell research is still young. Successful culture and characterization of human embryonic stem cells was achieved just over a decade ago. Since then, some advances have been made towards understanding the basic biology of stemness and their differentiation into different cell lineages, but harnessing of their promised potential to usher in the era of regenerative medicine is still a long way to go. Several clinical trials have been carried out using autologous or allogenic CD34+ve hematopoietic stem cells or mesenchymal stem cells (MSCs) in a variety of clinical indications but most of these have been Phase I or early Phase II trials. There is no conclusive proof of safety or therapeutic efficacy of stem cells in any condition yet. Unfortunately, some clinicians have started exploiting hapless patients by offering unproven stem cell treatments prematurely. Such fraudulent practices need to be stopped urgently, while ensuring that scientifically designed and responsible research on stem cells is not hindered. In 2007, the Indian Council of Medical Research and the Department of Biotechnology jointly released Guidelines for Stem Cell Research and Therapy, which now need to be revised to reflect new scientific and clinical findings that have significantly changed the scope of stem cell research and possible translation.

The present guidelines have retained the earlier classification of stem cell research into three categories, namely Permitted, Restricted and Prohibited categories; an additional layer of oversight, besides the Institutional Ethics Committee (IEC), in the form of Institutional Committee for Stem Cell Research (IC-SCR) and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been introduced. This mechanism of additional review has been accepted by the scientific community in the country and the required NAC-SCRT has become operational. The role and functioning of these committees is being streamlined.

Since 2007 there have been several new developments in the field of stem cell research that significantly change the landscape. This includes the development of induced Pluripotent Stem (iPS) cells by introduction of a limited number of genes into adult somatic cells, paving the way for the generation of histocompatible or patient-specific pluripotent stem cells. Also, progress has been made in growing stem cells without xenogeneic feeder cells; and in well-defined media free from foetal calf serum. However, significant challenges remain with respect to characterizing the cell product for therapy for its purity, safety and potency in an expeditious and cost-effective manner. Updated guidelines are therefore critical to incorporate these advances and to harmonize them with the internationally revised guidelines. Towards this end, the Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology have conducted a series of public consultations in different parts of the country to elicit the views of various stake holders including scientists, physicians, members of civil society, patient groups, media and industry. The Drafting Committee has taken cognizance of these deliberations and also held in-depth discussions with various expert groups over an extended period, to prepare these revised guidelines.

One major recommendation of the Committee has been to omit the word Therapy from the title of the Guidelines. This has been done to emphasize the fact that stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven. These guidelines are intended to cover only stem cell research, both basic and translational, and not therapy. It has been made clear in these Guidelines that any stem cell use in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. ***Accordingly, any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with this stringent definition, every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.*** It is hoped that this clear definition will serve to curb the malpractice of stem cell "therapy" being offered as a new tool for curing untreatable diseases.

The Indian Council of Medical Research (Department of Health Research) and the Department of Biotechnology gratefully acknowledge the contribution of Prof. Shyam Agarwal in strategizing, conceptualising and finalizing the National Guidelines for Stem Cell Research.

Dr. K. VijayRaghavan
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Department of Health Research &
Director General, Indian Council of Medical Research

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ICMR and DBT also acknowledge the participation of scientists, physicians, members of civil society, patient groups, media and industry during public consultations on Guidelines for Stem Cell Research & Therapy (2007) conducted in different parts of the country to have consensus on the document.

The Division of Basic Medical Sciences, Indian Council of Medical Research organized a series of meetings of Drafting Committee for these Guidelines. The valuable contributions of (Late) Dr. S. S. Agarwal, Chairman and Dr. A. N. Bhisey, Co-chairman of drafting committee in steering and active discussion by members during these meetings are highly appreciated. Special thanks are due to the three member sub-committee of NAC-SCRT headed by Prof. N. K. Mehra for their contribution in giving shape to this document. We gratefully appreciate Dr. Alok Srivastava, Chairman and all members of the NAC-SCRT for finalization of National Guidelines for Stem Cell Research (2013).

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Abbreviations

CDSCO	-	Central Drugs Standard Control Organization
CTRI	-	Clinical Trial Registry India
DBT	-	Department of Biotechnology
DCGI	-	Drugs Controller General of India
DNA	-	Deoxy-ribonucleic Acid
DST	-	Department of Science and Technology
ECM	-	Extra Cellular Matrix
GCP	-	Good Clinical Practices
GLP	-	Good Laboratory Practices
GMP	-	Good Manufacturing Practices
GOI	-	Government of India
GTP	-	Good Tissue Practices
EGC	-	Embryonic Germ Cells
ESC	-	Embryonic Stem Cells
iPSC	-	Induced Pluripotent Stem Cells
HLA	-	Human Leukocyte Antigens
HMSC	-	Health Minister's Screening Committee
HSC	-	Hematopoietic Stem Cell
HSCT	-	Haematopoietic Stem Cell Transplantation
IAEC	-	Institutional Animal Ethics Committee
IC-SCR	-	Institutional Committee for Stem Cell Research
ICM	-	Inner Cell Mass
ICMR	-	Indian Council of Medical Research
IEC	-	Institutional Ethics Committee
IND	-	Investigational New Drug
IPR	-	Intellectual Property Rights
IVF	-	In-vitro Fertilization
MOU	-	Memorandum of Understanding
MSC	-	Mesenchymal Stem Cells
MTA	-	Material Transfer Agreement
MTP	-	Medical Termination of Pregnancy
NAC-SCRT	-	National Apex Committee for Stem Cell Research and Therapy
NBE	-	New Biological Entity
PSC	-	Pluripotent Stem Cell
SCNT	-	Somatic Cell Nuclear Transfer
SOP	-	Standard Operating Procedures
SSCs	-	Somatic Stem Cells
TOP	-	Termination of Pregnancy

Guidelines for Stem Cell Research

1.0 Preamble

Use of stem cells in regenerative medicine holds promise for improving human health by restoring the function of cells and organs damaged due to degeneration or injury. Stem cell biology has potential application in several areas of biomedical research that includes drug development, toxicity testing, developmental biology, disease modelling, tissue engineering etc. Like many innovations, stem cell research also involves scientific, ethical and social issues. Apart from challenges of using appropriate stem cells for a particular condition, there are important issues related to the use of embryos for creating human embryonic stem (hES) cell lines. As these may lead to commoditization of human tissues and cells, there is inherent risk of exploitation of individuals particularly those belonging to the underprivileged groups, and challenges related to the contentious issue of human germ-line engineering and reproductive cloning.

Premature use of stem cells for therapy before obtaining adequate data on their safety and efficacy has created an unprecedented problem related to therapeutic profligacy with vulnerable patients being exploited. The potential danger of tumorigenicity of stem cells considering their capacity for unlimited proliferation, possibility of genomic changes arising during *in-vitro* manipulations, and limitations related to immunological tissue incompatibility between individuals are all causes for concern. Of equal importance is the assurance of safety and rights of those donating stem cells of all types for basic and clinical research. Safeguards must be in place to protect subjects receiving stem cells through enrolment in clinical trials. Societal concerns regarding compensation for research related injuries and adverse effects are all also issues that need to be addressed.

As with any new scientific development having the potential for improving human health, research in this field must be regulated with special attention to these issues. The guiding philosophy should be to promote scientific and ethical stem cell research while preventing premature commercialization and potential exploitation of vulnerable patients.

The revised version of the National Guidelines for Stem Cell Research 2013 takes into consideration the above mentioned issues. It also takes note of the fact that

pluripotent stem cells of different kinds have entered clinical trials and hence appropriate guidelines are required for their use.

2.0 Aim and Scope

These Guidelines apply to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and any others associated with both basic and clinical research on all types of human stem cells and their derivatives. These guidelines do not apply to research using non-human stem cells or tissues. Further, they do not regulate the use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders which has already been established as a standard of medical care.

The guidelines reiterate that the general principles of biomedical research involving human participants shall also be applicable to all human stem cell research.

2.1 The Guidelines specify unique provisions of stem cells, because of their potential for unlimited proliferation, differentiation to cells of the germ layers, regeneration of tissues, and their involvement in pre-implantation stages of human development. The guidelines therefore include:

2.1.1. Procurement of gametes, embryos and somatic cells for derivation and propagation of pluripotent and multipotent stem cell lines, their banking and distribution.

2.1.2. Regulated differentiation into desired progenitor cells and their characterization,

2.1.3. Use of human stem cells and other progenitors derived from them, or their products for basic and clinical research.

The guidelines have been laid down to ensure that research with human stem cells is conducted in a responsible and ethical manner and complies with all regulatory requirements pertaining to biomedical research in general and of stem cell research in particular.

It is important to recognize that this is a rapidly evolving field hence; the recommendations may change over time. It is the responsibility of the researcher and the Institutional Review Committees to understand the principles of these guidelines and keep abreast with the existing regulations in the country.

3.0 General Principles

Research on human subjects involving cells and tissues derived from human embryos and foetuses must safeguard human rights, dignity, and fundamental freedom. This includes processes related to obtaining human tissues and cells for research, diagnosis and therapy. The fundamental tenets of beneficence, non-malfeasance, justice and autonomy should be adhered to in all research involving human subjects. To achieve these objectives, all research involving the use of stem cells must be guided by the general principles laid down in the *"Ethical Guidelines for Biomedical Research on Human Participants"* published in 2006 by the Indian Council of Medical Research (ICMR) and specific principles related to stem cells as detailed in Section 4 of these guidelines must be followed.

The general principles to be followed are given below:

- Principle of essentiality
- Principles of voluntariness, informed consent and community agreement
- Principle of non-exploitation
- Principle of privacy and confidentiality
- Principle of precaution and risk minimization
- Principle of professional competence
- Principle of accountability and transparency
- Principle of maximization of public interest and distributive justice
- Principle of institutional arrangements
- Principle of public domain
- Principle of totality of responsibility
- Principle of compliance

The details of the above may be seen in the parent document (http://www.icmr.nic.in/ethical_guidelines.pdf)

4.0 Ethical Considerations Determining Specific Principles Related to Stem Cell Research

Stem cells are unique in many ways. The two basic characteristics of stem pluripotent cells are their capacity for self-renewal and multi lineage differentiation. They may survive indefinitely and differentiate unpredictably when introduced into

the human host. They may also give rise to tumours such as teratomas. Some of the major concerns that are specific to their collection, processing, storage and use, particularly of the human ES cells for translational research are listed below:

4.1 **Health and Safety of Donors**: Prior to procurement of stem cells for research, it is mandatory to obtain informed consent from the donor. The donor must be informed about the need for screening of transmittable diseases (about which the donor may or may not be aware of) and possible risks involved in donation particularly during major invasive procedures such as ovum or bone marrow donation, under local or general anaesthesia. The donor shall also be informed that cell lines may be generated from the donated material and that these may be banked and shared with other scientific groups. The cell lines may also undergo genetic manipulation, and have the potential for commercialization. In the latter event however, the Intellectual Property Rights (IPR) will not vest with the donor. Also, while confidentiality and privacy are sacrosanct, provision must be made for traceability in a contingency situation. The donor should be made aware that he/she may be contacted in future for specific requirements.

Special care needs to be taken when cells are obtained from embryos and foetuses. Also, donation of gametes and embryos raise special ethical and moral concerns. It is necessary to ensure that the donors are not exploited and commoditized.

4.2 **Manufacture and Quality Assurance of Stem Cell Products**: It is recognised that human adult tissues also have an inherent population of stem cells. In order to obtain these cells in sufficient numbers, some degree of processing, enrichment and/or *in vitro* expansion may be required. Further, manipulations may be needed to enhance their utility. One of the challenges in testing the potency of stem cells is the lack of suitable animal models. Innovative surrogate assays are needed for the purpose.

4.2.1 In case of human ES or iPS cells, targeted differentiation may be required to generate appropriate cells of interest and to separate them from undifferentiated cells. For individualized preparation of iPS cells, abbreviated tests of safety and efficacy are needed to provide timely release of the therapeutic product.

4.2.2 Cell culture techniques require stringent controls to avoid contamination and batch to batch variation. In case autologous or histocompatible iPS cells are used, the cell product should be processed individually for each patient.

4.2.3 Therapeutic cell products should be prepared as in compliance with the GLP/GMP/GTP guidelines and other laboratory conditions depending on the purpose of each use.

4.2.4 All reagents and media used in the process should be of 'clinical grade', intended to be administered to humans.

4.2.5 Stringent characterization of the product with reference to its identity, purity and safety as well as genomic stability, tumorigenicity and potency is essential before its release for human use.

4.2.6 Appropriate quality control and assurances should be in place.

4.3 **Design of Clinical Trials**: Clinical trials using stem cells need to be planned carefully, with follow-up periods suitable for the subject being evaluated, and should also incorporate appropriate end points. It is essential that stakeholders involved in the clinical trials related to stem cells are fully conversant with the current regulations in the field. It is important to ensure that no unproven stem cell therapy is offered outside of the well-controlled clinical trials.

4.4 **Specific Requirements:** Keeping the above considerations in mind, it is emphasized that besides general principles of biomedical research, specific principles need to be evolved to regulate stem cell research, particularly in relation to its translational role. This document is an effort in this direction, to ensure that progress in the field for potential benefit to mankind does not get stymied. To achieve this objective three fundamental principles as under must be followed:

4.4.1 An extra layer of oversight by those who are knowledgeable about the special issues related to stem cells

4.4.2 Periodic evaluation of advances in the field by expert groups and appropriate modification of regulations as and when deemed necessary

4.4.3 Categorizing of stem cell research into three areas viz. permitted, restricted and prohibited, according to the expected risk and level of supervision required for each category. For details, please refer to Section 6 of this document.

4.5 **Intellectual Property Rights and Social Responsibility:** Research on stem cells/ lines and their applications may have considerable commercial value. Appropriate IPR protection may be considered on the merits of each case. If the IPR is commercially exploited, a proportion of the benefits shall be returned to the community, which

has directly or indirectly contributed to the product. "Community" includes all potential beneficiaries such as patient and research groups.

5.0 Classification of Stem Cells

Based on the cell type/tissue of origin, stem cells are classified into *Somatic Stem Cells (SSCs)*, and *Embryonic Stem Cells (ESCs)*. SSCs have limited differentiation capacity and may be multipotent or unipotent. ESCs on the other hand are pluripotent and this characteristic can also be generated by reprogramming of somatic cells, giving rise to induced Pluripotent Stem Cells (iPSCs). The regulatory requirements for research on stem cells depend on their origin and potency.

5.1 ***Somatic Stem Cells (SSCs)*** are a resident, self-renewable population of cells which are present in virtually all organs/tissues of the body. They are essentially undifferentiated, resident in differentiated tissues and are committed to the lineage of that organ. They may, however, have limited plasticity.

5.1.1. SSCs obtained from different sources viz., the foetus, umbilical cord, placenta, infant, child or adult; and from different organs/tissues, may vary in their proliferative and differentiation potential.

5.1.2. The SSCs in bone marrow, skin and gastrointestinal tract continuously divide and differentiate throughout life, but in other organs they remain dormant until they are required for repair and replacement.

5.1.3. SSCs are present in relatively low numbers in most tissues, and may therefore need to be enriched and expanded prior to use. Prolonged cell culture/expansion carries the risk of contamination with microorganisms and potential genomic alterations which should be avoided. Further, cells, culture media and other ingredients, particularly those of animal origin, may carry the risk of introducing xenogeneic pathogens and inducing immune reactivity.

5.1.4. Research on SSCs largely falls under the permitted category and can be carried out with prior approval of the Institutional Committee for Stem Cell research (IC-SCR).

5.2 ***Embryonic Stem Cells (ESCs)*** are derived from pre-implantation embryos. Those derived from embryos before differentiation of trophoectoderm and inner cell mass (i.e. morula stage) are truly totipotent, capable of giving rise to the entire organism and extraembryonic tissues. However, ESCs derived from the inner cell mass (ICM) are pluripotent (not totipotent), having ability to differentiate into derivatives of all three germ layers, viz., ectoderm, mesoderm and endoderm, but not placenta.

5.3 ***Induced Pluripotent Stem Cells*** **(iPSCs),** as the name suggests are pluripotent in nature, quite similar to the ESCs but may not be exactly the same. They are capable of indefinite expansion and differentiation into ectodermal, mesodermal and endodermal cells. The iPS cells can be generated from somatic cells by a variety of genetic and epigenetic methods.

Both ESCs and iPSCs, and their derivatives, can be maintained and expanded as pure populations of undifferentiated cells under appropriate conditions. With appropriate stimuli they can be differentiated into lineage specific progenitor and differentiated cells, e.g., neurons, cardiomyocytes and others. The tumorigenic potential of ESCs and iPSCs is a major safety concern for therapeutic applications.

6.0 Categories of Research on Stem Cells

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

6.1 Permitted Areas of Research

6.1.1 *In vitro* studies on pluripotent stem cell lines viz. ES or iPS cells, or SSCs from foetal or adult tissues, for understanding their basic biology, may be carried out with prior approval of IC-SCR.

6.1.1.1 The ES cell lines used for such research should be established following the ethical guidelines as laid down in this document and should be registered with the NAC-SCRT through IC-SCR.

6.1.1.2 Stem cell lines from sources outside the country should have been established as per the regulatory requirements of the country of origin. These should also meet the National Guidelines as per this document. Documentation/Certification to this effect should be available with the investigator.

6.1.2 *In vivo* studies in experimental animals (other than primates, see Clause 6.2) with established cell lines from any type of human pluripotent stem cells viz., ES, iPS, including differentiated derivatives of these cells, and human SSCs (foetal, neonatal or adult) from any tissue, with prior approval of IC-SCR and IAEC. Such animals shall not be allowed to breed if the stem cells are likely to be incorporated in the gonads. These studies are needed for pre-clinical evaluation of efficacy and safety of human stem cells or their derivatives.

6.1.3 Establishment of new human ES cell lines from spare embryos or iPS cell lines from foetal/adult somatic cells, with prior approval of the IC-SCR, provided appropriate consent is obtained from the donor as per guidelines given in this document (Section 13). Once the ES cell line is established, it shall be registered with NAC-SCRT through IC-SCR with appropriate documentation. Such cell lines to be deposited in an accredited cell bank for use by other investigators. Similarly all iPS cell lines so derived shall be registered with the NAC-SCRT through IC-SCR, if intended for use in clinical research/ trials. Details of their derivation and characterization should be included.

6.1.4 Establishment and licensing of Umbilical Cord Blood stem cell banks falls under purview of the Drug Controller General of India (DCGI). The guidelines notified by CDSCO available at http://cdsco.nic.in/html/GSR%20899.pdf should be followed.

6.1.5 Clinical trials with clinical grade SSCs processed as per National GLP/ GMP / GTP guidelines as applicable (but without major manipulation: see clause 6.1.6.3 below), may be carried out with prior approval of IC-SCR and IEC. Prior approval of DCGI is required if it is intended to seek market authorization for the investigational product. All clinical trials on stem cells shall be registered with Clinical Trial Registry India (CTRI). http://ctri.nic.in/Clinicaltrials/login.php)

6.1.6 **Levels of manipulation**: Before use of stem cells for translation; almost all stem cells, whether autologous or allogeneic, need some degree of in-vitro, or ex-vivo processing before being re-introduced into human body. This carries the risk of contamination and/or alteration in the properties of cells, which may vary according to the degree and type of manipulation. Different degrees of manipulation are defined below:

6.1.6.1 ***Minimal manipulation:*** No intended alteration in cell population or function. This may include separation of mononuclear cells, washing, centrifugation and suspension in acceptable medium and a maximum of overnight storage under appropriate conditions. All laboratory procedures should be carried out under aseptic conditions in a GLP and GMP certified facility.

6.1.6.2 ***Substantial manipulation (or More than minimal manipulation):*** Defined as ex vivo alterations in the cell population (enhancement or depletion of specific subsets), expansion, cryopreservation, or cytokine based activation which is not expected to result in alteration of function. All laboratory processes should be compliant with GLP and GMP certified facilities.

6.1.6.3 ***Major manipulation:*** Genetic and epigenetic modification of stem cells, transient or permanent, which results in alternation of function, is considered to be a major manipulation. This includes transdifferentiation, transduction / transfection by retro / lenti viruses or other gene delivery vehicles to achieve specific selection and expansion of cells of interest. These alterations may also be carried out at transcriptional or translational level. This also includes regulated lineage specific differentiation of human ES and iPS cells into the desired cellular products. Clinical trials using cells which have undergone major manipulation shall require approval of DCGI after obtaining approval from NAC-SCRT through IC-SCR and IEC.

6.1.7 Special care should be taken for cells propagated in culture since they may acquire random genetic alterations. Appropriate screens such as but not limited to cytogenetic and molecular assays should be incorporated as a part of the characterization of cells.

6.1.8 All products intended for administration in humans shall be properly labelled and fulfil the laid down acceptance, release and stability criteria. All procedures shall be well laid down in writing and strictly followed to provide reproducible production of large quantities of well-defined clinical grade cells which meet the desired standards of identity, purity, safety, potency and traceability. The laboratory shall be duly accredited or certified, and file the CMC (Chemistry, Manufacturing and Control) documents for regulatory purposes and necessary approvals.

6.2 Restricted Areas of Research

6.2.1 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving ES cell line for any purpose. This shall require the following:

6.2.1.1 The proposed research cannot be carried out with existing ES cell lines, or those that can be derived from spare embryos;

6.2.1.2 Minimum numbers of embryos/blastocysts required for this research are clearly defined;

6.2.1.3 Research teams involved have appropriate expertise and training in derivation, characterization and culture of ESCs.

6.2.2 Clinical trials using cells derived from the differentiation of human ES or iPS cells, or any stem cell after major manipulation (as defined under Clause 6.1.6.3) shall require approval of DCGI after obtaining approval fromNAC-SCRT through IC-SCR and IEC.

6.2.3 Clinical trials sponsored by multinationals, employing cell products developed outside India, will also need prior approval from DCGI through IC-SCR and IEC.

6.2.4 International collaborative research projects should get clearance from the respective funding agencies as per their established procedure e.g. Health Ministry's Screening Committee (HMSC).

6.2.5 The imports of biological materials for research and development is regulated by Government of India vide their notification (No. L./950/53/97-H1 (Pt.) dated 19th Nov 1997.

6.2.6 Import of 'drugs' (therapeutic products – including cells) requires license from the DCGI as per the regulations.

6.2.7 Research involving introduction of human ES / iPS / SS cells into animals (including primates), *at embryonic or foetal stages of development* for studies on pattern of differentiation and integration of human cells into non-human animal tissues shall conform to the following:

6.2.7.1 If there is a possibility that human stem 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 substantiated. Animals derived from these experiments shall not be allowed to breed.

6.2.7.2 Such proposals would need approval of the NAC-SCRT for additional oversight and review through IAEC and IC-SCR.

6.2.8 Studies on chimeras where stem cells from two or more species are mixed at any stage of development viz., embryonic, foetal or postnatal, for studies on pattern of development and differentiation would require prior approval of NAC-SCRT through IC-SCR and IAEC.

6.2.9 Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the human ES/iPS cells were derived is readily ascertainable or could become known to the investigator would also require prior approval of NAC-SCRT through IC-SCR and IEC.

6.3 Prohibited Areas of Research

In the current state of our scientific and technological understanding, research in the following areas is prohibited:

6.3.1 Research related to human germ line gene therapy and reproductive cloning.

6.3.2 *In vitro* culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.

6.3.3 Clinical trials involving transfer of xenogeneic cells into a human host. Any clinical research on Xenogeneic-Human hybrids is also prohibited.

6.3.4 Research involving implantation of human embryos (generated by any means) into uterus after *in vitro* manipulation, at any stage of development, in humans or primates.

6.3.5 Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to gonadal cells.

7.0 Responsibility for Conduct of Stem Cell Research (of Investigator, Institution and Sponsor):

7.1 The investigators and institutions where stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with the national regulations and guidelines. In particular, scientists whose research involves human ES 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 stem cell research, and be sensitive to public concerns about research that involves human embryos. Those working with human iPS cells shall be particularly careful with the vectors and genes used for induction of stemness against malignant transformation. Sponsors shall also take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in the country.

7.2 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, there exist 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. Members of the regulatory committee shall regularly update their knowledge with regards to advances in the field.

7.3 Each institution shall maintain a register of its investigators conducting stem cell research and ensure that all registered users are kept up to date with existing guidelines and regulations regarding the use of these cells. It shall also be the responsibility of the institution to ensure that most current standards are applied.

7.4 Each institution shall constitute an IC-SCR as provided in these guidelines and provide adequate support for its functioning. All records pertaining to clinical adult stem cell research must be maintained for a period of at least 5 years and those for ES/iPS cell research for atleast10 years.

7.5 The physician/scientist engaged in stem cell research shall endeavour to avoid any activity that leads to unnecessary hype, or unrealistic expectations in the minds of study subjects or public at large regarding stem cell therapy. The study subject and other responsible family members must be given adequate and unbiased information about the trial protocol, its limitations and potential adverse effects. They must also be informed about the given indication for therapy. The investigator's responsibility is to generate robust scientific evidence through good clinical trials which may then be applied for the benefit of the patients.

7.6 The institutions conducting stem cell research shall establish suitable mechanisms for creating awareness and communicating scientific evidences to the public.

7.7 The basic scientists engaged in human stem cell research shall be vigilant to safeguard rights and dignity of human donors and aborted foetuses from who samples for research 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.

7.8 Several types of research with pluripotent stem cells in the present state of our knowledge and understanding are prohibited (clause 6.3). Guidelines in this document should be strictly complied with, regardless of the arguments of potential benefits that can come from such research.

8.0 Mechanism for Review and Regulatory Oversight of Stem Cell Research

In recent years, the area of stem cell research has undergone rapid developments promising new leads in the treatment of several incurable diseases. Research in the field is associated with unique ethical, legal and social issues that require additional oversight and expertise for efficient scientific and ethical evaluation. Hence, a separate mechanism for review and monitoring is essential both at the institutional as well as the national level. A National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) will monitor and oversee activities at national level and Institutional Committee for Stem Cell Research (IC-SCR) at institutional level. The composition, functions and responsibilities of NAC-SCRT and IC-SCR are given in Annexure I. These oversight committees shall ensure that review, approval and monitoring of all research projects in the field of stem cell research is done rigorously and effectively as per the national guidelines.

8.1 All institutes engaged in stem cell research must establish an Institutional Committee for Stem Cell Research (IC-SCR) with necessary expertise in the field as detailed in Annexure I. Alternatively, IC-SCR can be constituted by inducting additional expertise in the existing IEC with the nomenclature as IC-SCR, as per the requirement of these guidelines. The IC-SCR shall discharge all its function as envisaged under these guidelines.

8.2 All institutions and investigators, both public and private, carrying out research on human stem cells should be registered with the NAC-SCRT through IC-SCR.

8.3 Research using human stem cells shall have prior approval of IC-SCR for permitted research and of the NAC-SCRT for restricted research.

8.4 All new human pluripotent stem cell lines, irrespective of the source and methodology used, can be created with prior approval of IC-SCR. However, the use of human embryonic and iPS cells in clinical trials shall have prior approval of the NAC-SCRT. The requirements for taking decisions regarding creation of embryos for the purpose of establishment of stem cell lines are given in details in these guidelines (Clause 6.1.3 and 6.2.1).

8.5 Permission for procurement of human embryonic stem cell lines from abroad or from laboratories/banks in India shall be obtained from IC-SCR. Import must follow the guidelines as per Clause 6.2.5.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 Indian guidelines. An appropriate MTA shall be adopted for the purpose.

8.6 All clinical trials with SSCs, other than those with genetic modifications, shall have prior approval of IC-SCR and Institutional Ethics Committee (IEC). Clinical trials using genetically modified SSCs, and ES or iPS cells or derivatives should have prior approval from the NAC-SCRT after obtaining clearance from IC-SCR and IEC.

8.7 All clinical trials using cells that have undergone more than minimal manipulation (Clause 6.1.6.2) shall have to obtained approval from IC-SCR, IEC and DCGI.

8.8 Approval of the Drug Controller General of India (DCGI) is mandatory for stem cell based IND products and application for new indications (cells for therapies are deemed as drugs) with prior clearance from IC-SCR and IEC.

8.9 For market authorization of stem cell derived products, all clinical trials approved by the DCGI shall be registered with the Clinical Trials Registry of India established by ICMR. (http://ctri.nic.in/Clinicaltrials/login.php).

8.10 International collaborations shall have prior approval of respective funding agency as per its procedure or Health Ministry's Screening Committee (HMSC).

9.0 Basic Research

9.1 Derivation and Characterization of Human Pluripotent Stem Cells: General Considerations

9.1.1 All human ESC lines to be used for basic research should be in accordance with the details provided under Clause 6.1.3 of this document. Human iPSC lines to be used for basic research should be registered with IC-SCR.

9.1.2 Derivation of new ES or iPS cell lines from human embryonic or somatic cells respectively, shall adhere to the conditions for gamete, embryo and somatic cell donation as laid down in these guidelines (Section 13), and with prior approval (Clause 6.1.3).

9.2 Basic Stem Cell Biology:

9.2.1 Research on human ESCs and iPSC to increase knowledge about embryo development, infertility treatment causes of miscarriage and birth defects and improving contraception techniques.

9.2.2 Developing methods to detect abnormalities in embryos before implantation.

9.2.3 Developing human disease models (generation of disease specific iPSC) to understand pathophysiological mechanisms at cellular and molecular level.

9.2.4 Developing targeted therapies for genetic and developmental diseases

9.2.5 Developing *in vitro* cell culture systems of stem cells and their progenitors during different stages of cell differentiation for drug discovery and toxicity screening

9.2.6 Advancing current understanding of novel cell-based therapies by studying distribution, differentiation, integration, functioning and survival of implanted cells in experimental animals

9.2.7 Understanding mechanisms responsible for stemness, role of niche, dormancy, recruitment, plasticity and the ability to repair and regenerate

9.2.8 Pre-clinical evaluation of safety and efficacy of cell products developed as new drugs

9.2.8.1 All *in vitro* studies that fall in the permitted category of research (Clause 6.1).

9.2.8.2 Studies carried out on established human stem cell lines registered with the IC-SCR/NAC-SCRT (where no direct contact is required with human subjects to obtain cells), and approved by the scientific review committee may be

exempted from obtaining fresh informed consent by IC-SCR/IEC. Necessary GLP guidelines shall however be followed.

9.2.8.3 Studies performed on cells/tissues directly obtained from human subjects, shall require approval from the IC-SCR and IEC before their initiation.

9.2.8.4 *In vivo* studies on experimental animals (other than primates) that fall in the permitted category should be in accordance with Clause 6.1.2.

9.2.8.5 Studies on chimeras and sub-human primates shall follow Clause 6.2.5.

9.2.9 No *in vitro* studies on pre-implantation human embryos shall be carried out beyond 14 days of fertilization or formation of primitive streak, whichever is earlier. Similarly no *in vitro* manipulated cells shall be implanted in human/animal uterus with the intent of developing a whole organism.

10.0 Translational Research including Clinical Trials Using Stem Cells

This section outlines guidelines for both preclinical studies and clinical trials using stem cells and their derivatives, for repair or regeneration of damaged tissues and organs in situations where application of this mode of therapy has not yet reached an accepted standard of medical care. It involves translational research for generating a safe and effective novel product based on fundamental research that can be taken to the bedside. Besides the scientific, technical and entrepreneurial challenges, it is necessary to address the ethical, social, and regulatory issues associated with this emerging branch of medicine.

In case stem cells are being delivered using implantable or injectable scaffolds, guidelines given in Section 11 should additionally be followed.

10.1 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). These studies involve both *in vitro* and/or experiments using animal model systems. The latter are usually carried out in small animals, with or without immuno-suppression to prevent cell rejection. Only in specific situations and depending on the nature of the study, large animals and/or non-human primates maybe used with prior permission (Clause 10.1.3).

10.1.1 Preclinical studies shall demonstrate safety of the product and the procedure, as well as the proof-of-principle for achieving desired therapeutic effects. The stem cells to be employed in such trials shall be well characterized, similar to the ones to be used in clinical trials, and evaluated both for early and late toxicities including immunogenicity and tumorigenicity.

10.1.2 Diseased human tissues can be permitted for *in vitro* preclinical studies.

10.1.3 ***Approval and Monitoring:*** Preclinical studies shall be approved by IC-SCR and IEC following independent peer review. Approval from IAEC and CPCSEA shall also be obtained for studies involving small and large animals respectively.

10.1.4 ***Study Design:***

10.1.4.1 The stem cells shall be well characterized and the source, dose and route of their administration (local/systemic) shall be clearly defined appropriate to the proposed clinical application. The final product to be administered must be a clinical grade product prepared in a rolling cGMP facility.

10.1.4.2 Besides routine safety studies, distribution of cells, their survival, integration and functional outcome should be evaluated in animal models wherever possible.

10.1.4.3 Large animal models/non-human primates maybe used wherever necessary for example studies involving cardiac physiology; tissue-related inflammatory and immunological injuries and degenerative disorders of weight bearing joints etc. The selected animal model should offer an appropriate context for studying the human disease and conditions of specific interest.

10.1.4.4 For products seeking market authorization, preclinical toxicity studies shall be done in a certified GLP facility.

10.1.4.5 The interaction of stem cells with drugs (including immuno-suppressants wherever relevant) to treat the underlying medical condition shall be tested in animal model/cell culture systems.

10.1.4.6 Study design shall preferably incorporate a plan to analyse potential toxicities arising due to abnormalities acquired during *in vitro* processing

10.1.5 It is recognized that preclinical assays in animal models may not accurately predict the nature of cell behaviour and immune response in humans.

10.2 Clinical Research/Trial

Clinical trials using human stem cells should be in compliance with Schedule Y of Drugs and Cosmetics Act and GCP Guidelines of CDSCO (www.cdsco.nic.in) as well as ICMR-Ethical Guidelines for Biomedical Research involving Human Participants (http://www.icmr.nic.in/ethical_guidelines.pdf). Clinical trial protocol shall be formulated as per the format given in Annexure II.

10.2.1 Reagents used for the derivation of human ES or iPS cell lines, or expansion/enrichment of SSCs, for purposes of clinical trials should be of clinical-grade.

10.2.2 ***Trial Subjects:*** Subject selection shall be done according to the predefined inclusion and exclusion criteria, as laid down in the approved clinical research protocol.

10.2.2.1 The patient information sheet and the informed consent form shall specifically address the following:

a. Information regarding the present status of use of stem cells in the given condition, experimental nature of the proposed clinical study and its possible short and long term risks.

b. Information stating irreversibility of the intervention.

c. Information regarding source and characteristics of stem cells and degree of their *ex vivo* manipulation, if any.

d. Information on the established standard of care for a given condition

e. Information on the sample size and duration of study

f. The information sheet and the consent form should be approved by IEC and IC-SCR and the same should be clearly mentioned in these documents.

10.2.3 ***Approval and Monitoring****:*

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

10.2.3.1 Source and type of stem cells- somatic, embryonic, iPSC etc.

10.2.3.2 Autologous or allogeneic application

10.2.3.3 Degree of manipulation: minimal, substantial (more than minimal), or major (Clause 6.1.6)

10.2.3.4 Stage of research –*in vitro*, *in vivo*, preclinical or clinical

10.2.3.5 Whether the proposed cell based research is intended for developing a marketable product or an academic institutional research for advancement of knowledge

10.2.4 ***Regulatory Approvals:***

10.2.4.1 All clinical trials using stem cells shall be registered with CTRI http://ctri.nic.in/Clinicaltrials/login.php

10.2.4.2 Clinical trial proposals using minimally manipulated autologous SSCs shall be approved by IC-SCR and IEC.

10.2.4.3 Clinical trials using stem cells with substantial manipulation shall be approved by DCGI after obtaining clearance from IC-SCR and IEC.

10.2.4.4 Clinical trials using allogeneic SSCs (with any degree of manipulation) or autologous SSCs with major manipulation shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC.

10.2.4.5 Clinical trials using human ES cells (or their derivatives) shall be approved by DCGI after obtaining clearance from NAC-SCRT through IC-SCR and IEC.

10.2.4.6 Any stem cell based product already approved and marketed outside India (or for concurrent clinical trial in India) will require approval of DCGI through IC-SCR and IEC for pre-license clinical trial.

10.2.4.7 Any clinical trial with a product intended to be licensed and marketed shall have prior approval of DCGI through IC-SCR and IEC.

10.2.5 ***Monitoring of Clinical Trials:***

10.2.5.1 All clinical trials using stem cells involving human subjects shall be monitored by IEC and IC-SCR. All cases of adverse events should be reported to the Data Safety Monitoring Board (DSMB), NAC-SCRT and Funding Agency/Sponsor.

10.2.5.2 Institutes involved in clinical trials using stem cells should constitute separate DSMB for each trial, as appropriate.

10.2.5.3 DSMB shall have the requisite expertise to monitor trials for adverse events and their smooth conduct.

10.2.5.4 Members of the DSMB shall not have any conflict of interest with the study and they should not be associated with IC-SCR/IEC.

10.2.5.5 The IC-SCR and IEC shall ensure that the subjects recruited under clinical trial shall not be charged.

10.2.5.6 The institution and/or sponsor conducting clinical trials shall be responsible for insurance and compensation of the subjects recruited under the trial

10.3 Use of Stem Cells for Therapeutic Purposes

10.3.1 At present, there are no approved indications for stem cell therapy other than the hematopoietic stem cell transplantation (HSCT) for haematological disorders. Accordingly all stem cell therapy other than the above shall be treated as investigational and conducted only in the form of a clinical trial after obtaining necessary regulatory approvals. Use of stem cells for any other purpose outside the domain of clinical trial will be considered unethical and hence is not permissible.

10.3.2 Cells used in clinical trials must be of clinical grade and processed under rolling GTP/GMP standards as considered necessary by the IC-SCR and NAC-SCRT.

10.3.3 The product for transplantation to be used for clinical trial shall be free from animal products and microbial contamination.

10.3.4 Centres carrying out stem cell clinical trials and the agency/ source providing such cells for the trial shall be registered with the NAC-SCRT through IC-SCR.

10.3.5 For International Collaboration, the public funding agency evaluating the study or the Health Ministry's Screening Committee shall ensure that the certification provided by the collaborating country fulfils the requirements as laid down in these guidelines.

10.3.6 For a trial protocol to become an approved therapy, the investigator shall apply to the NAC-SCRT with the data on which such a claim is based and a justification for the same. The NAC-SCRT will then determine, in independent consultation with experts in the field, whether such a claim may be approved.

11.0 Tissue Engineering and Scaffolds in Stem Cell Research

Tissue engineering is an emerging area of biomedical research with the primary goal

of repair/regeneration and restoration of functions of the damaged tissue that fail to heal spontaneously by using cells, growth factors and natural or synthetic scaffolds either alone or in combination. Scaffolds act as the artificial extracellular matrix (ECM), which provide structural support for the cells as they expand and guide their growth in a three-dimensional (3D) space into a specific tissue. To guide the organization, growth, and differentiation of cells in tissue-engineered constructs, the scaffold should be able to provide not only physical support for the cells but also the chemical and biological cues required for function restoration.

An ideal scaffold should possess all the qualities of a native ECM, be biocompatible and should provide a 3D template for the cells to attach and guide their growth. It should have a porous architecture with a high surface area allowing for maximum loading of cells, cell-matrix interaction, tissue in growth and transportation of nutrients and oxygen. It should be mechanically strong to withstand local *in vivo* biological forces but biodegradable. However, the degradation rate should match the rate of regeneration. It should be made of material that can be sterilized without compromising any structural or functional properties. Most importantly, it should allow the cells it supports to perform intended functions. The manufacturing process of scaffold with all the above unique characteristics must be accomplished in a practical, reproducible and scalable manner.

The detailed guidelines for the use of scaffolds in stem cell research are beyond the scope of this document. The investigator is advised to refer to the following:

http://www.astm.org/Standards/F2150.htm

http://www.astm.org/Standards/F2450.htm

http://www.astm.org/Standards/F2027.htm

http://www.astm.org/Standards/F2739.htm

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=28650

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=28653

12.0 Banking of Umbilical Cord Blood and Other Biological Tissues Including Cell Lines:

12.1 Procurement and banking of various biological tissues such as umbilical cord blood, placenta, extracted tooth, adipose tissue and other sources of stem cells with the specific objective of their isolation and/or *ex vivo* expansion is increasingly becoming

a commercial activity. However, care needs to be taken such that there is no exploitation and commoditization of these resources. Each proposal for banking or for academic application of the banked tissue shall be carefully examined by the IC-SCR and IEC from the ethical angle to ensure access, equity and justice. Use of the banked material for commercial purposes may require national consultation regarding intellectual property rights of the donor.

12.2 *Banking of Umbilical Cord Blood*

12.2.1 Umbilical cord blood is a rich source of CD34+ hematopoietic and mesenchymal (stromal) stem cells. The use of the HSC for treatment of various haematological and immunological disorders is currently well established, particularly where an HLA-matched sibling is not available for HSC donation. To meet this demand, several public (untargeted, non-profit) umbilical cord blood banks have become established all over the world. Such banks are permitted to be established in India, so long as they are licensed by the CDSCO and fulfil the requirements laid down by it. As far as collection and distribution policy and procedure of the umbilical cord blood units for HSCT is concerned, they should follow the standard practices. However, any other use of cord blood stem cells, HSC or MSC is experimental at present and shall be permitted only under conditions of controlled clinical trial by the IC-SCR/IEC or NAC-SCRT through the IC-SCR as required under the provisions of these guidelines.

12.2.2 All cord blood banks must be licensed and monitored by the CDSCO. They should follow the Drugs and Cosmetics (3rd Amendment) Rules, 2011 (Gazette Notification No. GSR 899(E) dated 27/12/2011) for collection, processing, testing, storage, banking, and release of umbilical cord blood (http://cdsco.nic.in/html/GSR%20899.pdf).

There are ethical concerns about the promotional advertisements by private banks offering storage of cord blood for possible future use. Such advertisements are often misleading for the public and lack comprehensive and accurate information to the consumer. It may be mentioned that there is no scientific basis for preservation of cord blood for future self-use and this practice is not recommended. On the other hand, parents should be encouraged for voluntary donation to public cord blood banks for allogeneic transplantation and research purposes. In such cases, ID cards should be issued by the banks, to the donor to enable preferential access/benefits to donor/relatives, in future.

12.2.3 *Precautions for collection of umbilical cord blood for stem cells*

The following points should specifically be considered while collecting UCB:

12.2.3.1 No harm should occur to the donor neonate.

12.2.3.2 Exact timing of clamping the umbilical cord should be defined in the SOP and recorded in the case file.

12.2.3.3 Parents should be fully informed regarding risks and benefits involved.

12.2.3.4 Voluntary informed consent should be obtained from both parents well before the scheduled delivery date, but in no case at the time of delivery. If there is disagreement between parents, the mother's wish shall prevail.

12.2.3.5 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.

12.2.3.6 Standard operating Procedures for collection, transportation, processing, storage (cryopreservation) and release for clinical use of umbilical cord blood/ cells should be clearly laid down and approved by IC-SCR and IEC.

12.2.3.7 If stem cells are proposed to be processed before use (without major manipulation), detailed protocol for their isolation, expansion, and characterization should be approved by IC-SCR and IEC. If any major manipulation is envisaged, the approval should also be taken from the NAC-SCRT.

12.2.3.8 Period of preservation for self-use later in life should be clearly defined.

12.2.3.9 Detailed SOPs for release of umbilical cord units for clinical use should be in place. This should include follow up plans to monitor the outcome of HSCT for assessing safety and efficacy of cord blood stem cell therapy.

12.3 Banking and Distribution of Human ES/iPS Cell Lines

As human ES/iPS cell research advances, it will be increasingly important for institutions that obtain store and use stem 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 infectious disease markers and
ii. They are maintained and stored as per current standards of GLP/GTP/GMP with appropriate SOPs.

The following guidelines are specifically adapted for human ES/iPS stem cell lines. However researchers are advised and expected to keep track of advances in the field.

12.3.1 Institutions that are banking or plan to bank human ES/iPS stem cell lines should establish uniform guidelines to ensure that donors of biological material give informed consent through a process approved by the IC-SCR and 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.

12.3.2 Any facility engaged in obtaining and storing human ES/iPS stem cell lines should follow the standard practices. These include:

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

12.3.2.2 Documentation requirements for investigators and sites that deposit cell lines, including:

a. A copy of the donor consent form.

b. Proof of IC-SCR and IEC approval for the procurement process.

c. Available medical information on donors, along with infectious disease screening details.

d. Available clinical, observational or other diagnostic information about the donor.

e. Personal information anonymised (such that the identity cannot be frivolously disclosed), but traceable if required.

f. Critical information about culture conditions (such as media, additives, cell passage, and safety information).

g. Available cell line characterization (such as but not limited to cluster differentiation (CD) phenotyping, karyotyping and genetic markers).

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

12.3.3 A secure system for protecting the privacy of donors where the material is assigned a unique code and all other identifiable information is stored securely at the source of origin, with details on the following:

12.3.3.1 Plans for maintaining confidentiality (such as a coding system).

12.3.3.2 A secure system for inventory track from primary cell lines to those submitted to the repository and their subsequent use.

12.3.3.3 A policy governing whether and how to deliver clinically significant information obtained through research/investigations back to donors.

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

12.3.4.1 Assignment of a unique identifier to each sample.

12.3.4.2 Procedure for derivation of stem cell lines

12.3.4.3 Process for characterizing cell lines.

12.3.4.4 Process for expanding, maintaining, and storing cell lines.

12.3.4.5 System for quality assurance and control.

12.3.4.6 Website that contains scientific descriptions and data related to the available stem cell lines.

12.3.4.7 Procedure for reviewing request applications for deposit/requisition of cell lines.

12.3.4.8 Process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).

12.3.4.9 System for auditing compliance.

12.3.4.10 Schedule of charges.

12.3.4.11 Statement of intellectual property policies.

12.3.4.12 When appropriate, creation of a clear Material Transfer Agreement or user agreement.

12.3.4.13 Liability statement.

12.3.4.14 System for disposal of material.

12.3.4.15 Clear criteria for distribution of cell lines

12.3.4.16 An approved Release Certificate to be issued with each dispatch

13.0 Procurement of Biological Material for Research:

Procurement of biological material as a source of stem cells for basic or translational research is permissible subject to approval by IC-SCR and IEC. The biological material includes foetal and placental tissues, as well as gametes, blastocysts and somatic cells.

13.1 Foetal /Placental Tissue

For procurement of foetal or placental tissue as a source of stem cells, the following guidelines should be adhered to:

13.1.1 *Termination of pregnancy (TOP)* should comply with all obligations under the MTP Act. However, TOP with a view to donate foetal tissue in return for financial or any other inducement is not permissible.

13.1.2 *Informed consent for donation*

13.1.2.1 Independent informed consent should be obtained for termination of pregnancy and for donation of the foetal material for research.

13.1.2.2 The consent for donation of foetal tissue should be obtained in advance and not just before or at the time of the procedure. The parent should be given sufficient time to take decision regarding the donation.

13.1.2.3 The consent for donation should include permission for screening of the donor for transmissible infections and obtaining family history of genetic disorders.

13.1.3 The purpose and use of donated foetal tissue should be fully explained to the parents. It should not be vague and open ended. The information sheet for the purpose should be carefully scrutinized and vetted by the IC-SCR and IEC.

13.1.4 The medical person responsible for care of the pregnant woman willing to undergo termination of pregnancy and the investigator using the foetal material shall not be the same.

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

13.1.6 The identity of the donor should be kept confidential. Personal information of the donor, however, should be kept available for traceability in situations where the cells derived from the donated foetal tissue are proposed to be used for therapy.

13.2 Gametes, Blastocysts (Pre-implantation Embryos) or Somatic Cells for Generation of Human ES/iPS Cell Lines

13.2.1 The IC-SCR and IEC, should review and approve the process of procurement of gametes, blastocysts, or somatic cells for the purpose of generating new human ES/iPScell lines. IC-SCR and IEC should verify that the blastocysts obtained from infertility clinics are in excess (spare embryos) of the clinical need of the couple.

13.2.2 Creation of human ES cell lines from blastocysts and iPS cell lines from somatic cells should be approved by IC-SCR and IEC. However, creation of the same

through IVF or other methods, specifically for research purposes, should have prior approval of NAC-SCRT through IC-SCR and IEC.

13.2.3 Consent for donation of blastocysts for establishment of human ES cells lines should be obtained from the donor at least 24 hours in advance and not at the time of the donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

13.2.4 There should be no inducement for donation of gametes or embryos by way of payment or in lieu of medical services, except for reimbursement of reasonable expenses for travel and loss of wages 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 or creation of iPS cell lines except for reimbursement towards travel expenses for attending the clinic.

13.2.5 The attending physician responsible for the infertility treatment and the investigator deriving or proposing to use ES cells shall not be the same individual. To facilitate autonomy of the donor, decisions related to the creation of embryos for infertility treatment should be independent of the influence of investigators who propose to derive or use ES cells in research.

13.2.6 *Informed consent for donation* should include:

13.2.6.1 A statement that the blastocysts or gametes will be used to derive human ES cells/cell lines for research purposes.

13.2.6.2 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.

13.2.6.3 An assurance that the investigator will follow the ethical practices for procurement, culture, and storage of cells and tissues.

13.2.6.4 A statement that the derived ES cell line may be used for development of new drugs/diagnostics or other uses which may have commercial value, but no direct financial benefit will accrue to the donors.

13.2.6.5 A statement that derived stem cells or cell lines and the information related to them may be archived for 10 years or more.

13.2.6.6 A statement that research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous transplantation.

13.2.6.7 A statement that neither consenting nor refusing to donate gametes/embryos/somatic cells for research will affect the quality of present or future medical care provided to potential donors.

13.2.6.8 A statement of the risks involved to the oocyte donor and acceptance of the responsibility to provide appropriate health care and compensation in case any complication arises during/or anytime after the procedure.

13.2.7 Identity of the donor shall be kept confidential at all times. Wherever traceability of the stem cells is required, the same shall be kept secured to ensure confidentiality. The investigator shall also document the process of maintenance of the confidentiality of any coded or identifiable information associated with the cell lines.

13.2.8 The IC-SCR and IEC while reviewing and approving the proposals for gamete/blastocyst/somatic cell donation shall ensure that the subjects do not belong to vulnerable groups.

13.2.9 There shall be no coercion to undertake human ES cell research or any activity related to SCR. Autonomy of the researcher/physician must be respected.

14.0 International Collaboration

14.1 National guidelines of respective countries shall be followed.

14.2 All international collaboration will be permitted as per the approved procedure of funding agencies (DST, DBT, ICMR etc.) or the Health Ministry's Screening Committee (as per GOI Guidelines), following joint proposal with appropriate MOU.

14.3 In situation involving a conflict (scientific and/or ethical) between the collaborators, the Indian ethical guidelines and regulations shall prevail for the work to be carried out in India.

15.0 Exchange of Biological Material for Research

15.1 All proposals for import/export of stem cells and their derivatives required for research and development including for clinical trials shall be examined by the IC-SCR, and if felt necessary by the NAC-SCRT. After satisfying the scientific and ethical considerations, the statutory requirements of approval from DCGI and the Govt. of

India's guidelines (Circular No. L/950/53/97-H1 (Pt.) dated November 19th, 1997 of the Ministry of Health) on import/export of biological materials should be followed.

15.2 A critical limitation of the use of stem cells for research and development is to maintain them in a viable state. Since their viability can be affected by X ray – irradiation, appropriate international guidelines need to be followed for their packaging, labelling, handling and transport at ports without compromising their quality.

15.3 Transport of hematopoietic stem/progenitor cells from established bone marrow/cord blood banks for unrelated donor transplantation required for therapeutic indications should follow the established procedures.

16.0 Public Participation

16.1 An interactive portal on the web shall be created by NAC-SCRT, both for the public as well as scientists and professionals to provide reliable and up-to-date information about recent developments in the field. The portal will encourage suggestions and feedback for continuous improvement.

16.2 To create awareness and update about the stem cells and their applications, periodic interactions with the public/stakeholders will be held across the country by the experts and regulators. The focus of such interactive sessions will be to educate the masses so as to avoid their exploitation and to provide a forum for free and frank exchange of views.

17.0 Periodic Review of Guidelines

The field of stem cells has seen rapid strides both in basic and translational aspects. With the unfolding of new developments and knowledge, it is essential to periodically review and update the guideline document. Accordingly periodic changes to specific clauses and sections will be notified in the form of amendments. It is one of the assigned functions of the NAC-SCRT to determine the need and mechanism for implementing revisions to the document.

References for Further Reading

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Annexure - I

Function of NAC-SCRT and IC-SCR

The National Apex Committee for Stem Cell Research has been established by Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India. The committee periodically assesses the adequacy of the guidelines proposed in this document and also provides a forum for continuing discussion of issues involved in hES/hiPS cell research in the light of ever growing advances in science. The committee also reviews and approves specific research protocols falling under restricted category or as provided in the guidelines. It also addresses new unforeseen issues of public interest from time to time. The body is independent and should be respected by both the lay and scientific communities. The IC-SCR shall function at the institutional level and have appropriate expertise as suggested to support this effort, and shall registered with and report to the NAC-SCRT.

1.0 National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)

This is a multidisciplinary committee with a Secretariat. It will have two main functions:

a) General oversight of the field of stem cell research and therapy in India and formulation of policy related to it

b) Review of specific controversial or ethically sensitive research and proposals for therapeutic use of stem cells/differentiated derivatives

1.1 Scope

1.1.1 The Committee has the responsibility to examine scientific, technical, ethical, legal and social issues in the area of stem cell or their derivatives based research and therapy.

1.1.2 Maintain a register of all institutions involved in any type of stem cell research and therapy including details of their IC-SCR.

1.1.3 Review annual reports of these IC-SCRs for compliance with national guidelines and ethical practices.

1.1.4 NAC-SCRT shall approve, monitor and oversee research in the restricted areas as given in this document.

1.1.5 Use of chimeric tissue for research shall be reviewed by NAC-SCRT

1.1.7 NAC-SCRT shall review and update the national guidelines for stem cell research and therapy periodically, considering scientific developments at the national or international levels.

1.1.8 NAC-SCRT in collaboration with the CDSCO 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 of human stem cells or their derivatives.

1.1.9 Respond to queries/ representations from all the stakeholders in the community (investigators, industry, R&D Institutions, entrepreneurs, media, patient groups, government agencies etc.)

1.1.10 Respond to controversial issues raised /received from NGOs, patients, individuals etc., and diverted to NAC-SCRT by other agencies (ICMR, DBT, DST, MCI, DCGI etc.)

1.1.11 Monitor any unethical practices related to stem cell research and/or therapy being followed at any organization or any individual and bring them to the notice of relevant authorities.

1.2 Membership (at least 15)

Committee composition will include Chairman, Alternative Chairman, Member Secretary, nominees from DBT, DST, CSIR, DSIR, ICMR, DCGI, DAE, MCI, DGHS and biomedical experts drawn from appropriate disciplines such as Haematology, Pharmacology, Immunology, Cell Biology, Microbiology, Genetics, Developmental biology, Clinical medicine and Nursing. Other members would include a legal expert, social scientist, and women's representative. In addition consultants/experts could be consulted / invited for specific topics and advice.

1.3 Frequency of meetings

Quarterly, but can be more frequent, if necessary.

2.0 Institutional committee for Stem Cell Research (IC-SCR)

This is a multidisciplinary body at the institutional level.

2.1 Scope

2.1.1 Institutions involved in stem cell research are required to set-up a special review board to oversee research (basic science and clinical) in this field.

2.1.2 To be registered with the NAC-SCRT.

2.1.3 Provide overview of all issues related to stem cell research at the institutional level.

2.1.4 Review and approve the scientific merit of research protocols.

2.1.5 Shall function in compliance with all relevant regulations and guidelines.

2.1.6 Maintain a register of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators and notify NAC-SCRT.

2.1.7 Facilitate training of investigators involved in stem cell research.

2.1.8 Submit annual report to NAC-SCRT.

2.2 Membership (at least 7)

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.

2.3 Guidelines for the constitution of IC-SCR

2.3.1 The Chairman must have relevant medical/scientific background and be from outside the institute with no conflict of interest (COI).

2.3.2 Members from Law, Ethics and Social Sciences must be from outside the institute and with no COI.

2.3.3 Stem cell experts, if possible from outside the institute, can be the scientific/technical members.

2.3.4 Member Secretary can be from the same institute and must not have any COI.

2.3.5 Any member having COI with a particular proposal must abstain from the discussion and decision making process of that proposal.

2.3.6 IC-SCR members must be familiar with the current bioethical guidelines and guidelines for stem cell research.

2.3.7 The quorum should consist of the following members, without which the decision should not be taken:

- 2.3.7.a Chairman, and Member Secretary (if not abstaining due to COI)
- 2.3.7.b Experts from Law, Ethics and Social Sciences
- 2.3.7.c At least one stem cell expert with appropriate expertise and no COI

2.3.8 A group of institutions may have a common IC-SCR with the approval from head of each institution if:

- 2.3.8.a It designates at least one person from each institute as member (with no COI)
- 2.3.8.b Provides details of that person to NAC-SCRT
- 2.3.8.c The designated person is present during the discussion of the proposals submitted by the institute

2.4 Guidelines for framing SOP for functioning of IC-SCR

SOP for functioning of IC-SCR must be framed including, but not limited to, the following information:

2.4.1 Constitution and functioning of IC-SCR

2.4.2 Terms of reference of members

2.4.3 Detailed review and approval process

2.4.4 Frequency of meetings
2.4.5 Monitoring and follow-up of approved projects
2.4.6 Maintenance of records

2.5 The institute under which the IC-SCR functions must ensure that the IC-SCR is always independent and appropriately competent to review the proposals being submitted to them.

2.6 It is the responsibility of the IC-SCR to ensure that the research conducted under its ambit is scientific and ethical.

2.7 The IC-SCRs fulfilling aforesaid guidelines may be registered by the NAC-SCRT.

Annexure– II

Clinical Trial Protocol for Stem Cell Therapy

The document should include study title, Phase of the study, Institution conducting the trial, Sponsor Names of the Principal Investigator and Co-investigators and 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. Informed consent from Patient /Parent/Relative

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 study results, human trials, references and publication list and reprints

II. Case Record Form

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

IV. Administrative approvals from the following:

a. DCGI for IND/NDA
b. IEC (of each centre)
c. Approved patient information sheet and consent form
d. IC-SCR and NAC-SCRT as applicable
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

Glossary

Adult stem cell: (also known as somatic stem cell)**:** A relatively rare undifferentiated cell found in many organs and differentiated tissues with a limited capacity for both self-renewal (in the laboratory) and differentiation. Such cells vary in their differentiation capacity, but it is usually limited to cell types in the organ of origin. This is an active area of investigation.

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)

Bone Marrow: The soft, spongy tissue found in the centre of most large bones that produces the cellular components of blood which is known as hematopoietic stem cells (white cells, red cells and platelets). It is also a source of mesenchymal and endothelial stem cells.

Chimera: An organism, organ, or part consisting of two or more tissues of different genetic composition, produced as a result of organ transplant, grafting, or genetic engineering.

Cell line: A cell culture selected for uniformity from a cell population derived from a usually homogeneous tissue source (as an organ)

Clinical grade: Compatible and certified for administration into humans.

Clinical Research/Trial: is a branch of healthcare science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease. Clinical Research is different than clinical practice. In clinical practice one uses established treatments, while in clinical research evidence is collected to establish a treatment.

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

Clonal: cells derived from a single parent cell

Cloning: The process of creating genetically identical copy of a biological unit (e.g. a DNA sequence, cell, or organism) from which it was derived, especially by way of biotechnological methods.

- 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 foetus) and then activating oocyte's further development without fertilization. The oocyte genetically reprograms 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 foetus 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: A process by which a subject voluntarily confirms his or her (or their next of kin/legal heir) willingness to participate in a particular study/clinical trial, after having been informed of the aims, methods, required data collection procedures and schedule, anticipated benefits and potential hazards of the study and the discomfort it may entail. Informed consent is documented by means of a written, signed and dated informed consent form. 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 isolated from the umbilical cord blood collected at the time of birth. Cord blood contains hematopoietic and mesenchymal (stromal) stem cells. 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.

Differentiation: The process whereby an unspecialized embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions outside the cell, usually through signalling pathways involving proteins embedded in the cell surface.

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 foetus (those that would become sperm and eggs).

Embryonic stem cell: cells 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 three germinal layers 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 till birth

Fetal stem cell: Stem cells derived from foetal tissue including placenta that retain the ability to divide, proliferate and provide progenitor cells that can differentiate into specialized cells. A distinction is drawn between the foetal germ cells, from which the gametes develop, and foetal somatic cells, from which rest of the organism develops.

Gamete: A mature male or female reproductive cell usually possessing a haploid chromosome set and capable of initiating formation of a new diploid individual by fusion with a gamete of the opposite sex. An egg (in the female) and sperm (in the male).

Germ cells: ova and sperm, and their precursors

Hematopoietic stem cell: A stem cell that gives rise to all red and white blood cells and platelets.

Human Embryo: It is developing stage between the times of fertilization until the end of the eighth week of gestation, after which it is known as a foetus.

Implantation: The embedding of a blastocyst in the wall of uterus. In humans implantation takes place between 7-14 days after fertilization.

Induced Pluripotent Stem Cell (iPSC): These are adult differentiated cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the properties of pluripotent stem cells.

***In vitro*:** Of processes or reactions taking place in a test tube, culture dish, or elsewhere outside a living organism.

***In vivo*:** Of processes taking place in a living organism

Mesenchymal stem cells: Is multipotent progenitor cells that were originally identified in the bone marrow stroma and now isolated from different sources including umbilical cord blood and adipose tissue etc.

Multipotent stem cells: The cells have the potential to differentiate into different types of specialized cells constituting a specific tissue or organ.

Pluripotent stem cell: Having the ability to give rise to all of the various cell types of the body. Pluripotent cells cannot make extra-embryonic tissues such as the amnion,

chorion, and other components of the placenta. Scientists demonstrate pluripotency by providing evidence of stable developmental potential, even after prolonged culture, to form derivatives of all three embryonic germ layers from the progeny of a single cell and to generate a teratoma after injection into an immunosuppressed mouse.

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

Regenerative medicine: A field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues

Somatic cell: cell of the body other than gamete

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: see cloning

'Spare' embryo: An embryo created during the course of IVF treatment of the infertile couple which is not utilized for the purpose also known as **supernumerary embryo.**

Stem cells: Stem cells are undifferentiated cells with a capacity for self-renewal, proliferation and differentiation into many different types of functional cell

Stem cell Bank: A facility that is responsible for accessioning, processing, packaging, labelling, storage and delivery of appropriately defined different kinds of stem cells.

Teratoma: A tumour derived from more than one embryonic layer and made up of a heterogeneous mixture of tissues (as epithelium, bone, cartilage, or muscle.

Totipotent: Having the ability to give rise to all the cell types of the body plus all of the cell types that make up the extra embryonic tissues such as the placenta.

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