National Guidelines for Stem Cell Research

Indian Council of Medical Research
&
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Contents

Abbreviations

AE	-	Adverse Event
ASCI	-	Advertising Standards Council of India
CAP	-	College of American Pathologists
CD	-	Cluster Differentiation
CDSCO	-	Central Drugs Standard Control Organization
CEO	-	Chief Executive Officer
CMC	-	Chemistry, Manufacturing and Control
CME	-	Continuing Medical Education
CSO	-	Chief Scientific Officer
COI	-	Conflict of Interest
CPCSEA	-	Committee for the Purpose of Control and Supervision of Experiments on Animals
CRISPR	-	Clustered Regularly Interspaced Short Palindromic Repeats
CSIR	-	Council of Scientific & Industrial Research
CTRI	-	Clinical Trial Registry India
BM	-	Bone Marrow
DAE	-	Department of Atomic Energy
DBT	-	Department of Biotechnology
DHR	-	Department of Health Research
DGFT	-	Directorate General of Foreign Trade
DGHS	-	Directorate General of Health Services
DNA	-	Deoxy-ribonucleic Acid
DRDO	-	Defence Research and Development Organization
DSIR	-	Department for Scientific & Industrial Research
DSMB	-	Data and Safety Monitoring Board
DST	-	Department of Science and Technology
EBV	-	Epstein–Barr Virus
ELISA	-	Enzyme-Linked Immunosorbent Assay
FACS	-	Fluorescence Activated Cell Sorting
GCP	-	Good Clinical Practices
GLP	-	Good Laboratory Practices
GMP	-	Good Manufacturing Practices
GTP	-	Good Tissue Practices
ESC	-	Embryonic Stem Cells
Hb	-	Hemoglobin
hESC	-	Human Embryonic Stem Cells
HBV	-	Hepatitis B Virus
HCV	-	Hepatitis C Virus
HIV	-	Human Immunodeficiency Virus
HLA	-	Human Leukocyte Antigens
HMSC	-	Health Minister's Screening Committee
HSC	-	Hematopoietic Stem Cell
HSCT	-	Haematopoietic Stem Cell Transplantation
IAEC	-	Institutional Animal Ethics Committee
IBSC	-	Institutional Biosafety Committee

IC-SCR	-	Institutional Committee for Stem Cell Research
ICM	-	Inner Cell Mass
ICMR	-	Indian Council of Medical Research
ICSI	-	Intra-cytoplasmic sperm injection
ICF	-	Informed Consent Form
ID	-	Identity document
IEC	-	Institutional Ethics Committee
IMA	-	Indian Medical Association
IND	-	Investigational New Drug
INE	-	Investigational New Entity
IPR	-	Intellectual Property Rights
iPSC	-	Induced Pluripotent Stem Cells
IVF	-	In-vitro Fertilization
LAL	-	Limulus Amebocyte Lysate
MCI	-	Medical Council of India
MD	-	Managing Director
MNCs	-	Mono Nuclear Cells
MOU	-	Memorandum of Understanding
MSC	-	Mesenchymal Stem Cells
MTA	-	Material Transfer Agreement
MTP	-	Medical Termination of Pregnancy
NABL	-	National Accreditation Board for Testing and Calibration Laboratories
NAC-SCRT	-	National Apex Committee for Stem Cell Research and Therapy
NBE	-	New Biological Entity
NGSCR	-	National Guidelines for Stem Cell Research
NOAEL	-	No Observed Adverse Effect Level
NOC	-	No Objection Certificate
QA	-	Quality Assurance
QC	-	Quality Control
PBSCs	-	Peripheral Blood Stem Cells
PCR	-	Polymerase Chain Reaction
PSC	-	Pluripotent Stem Cell
RCGM	-	Review Committee on Genetic Manipulation
RHS	-	Railway Health Services
R&D	-	Research and Development
SAE	-	Severe Adverse Event
SCNT	-	Somatic Cell Nuclear Transfer
SOP	-	Standard Operating Procedures
SSCs	-	Somatic Stem Cells
SVF	-	Stromal Vascular Fraction
TOP	-	Termination of Pregnancy
UCB	-	Umbilical Cord Blood

1. Preamble

In recent years, stem cell biology has emerged as an important area of biomedical research with potential applications in developmental biology, disease modelling, tissue engineering, drug development, toxicity testing and others. Use of stem cells in regenerative medicine holds promise for improving human health by restoring the function of cells and tissues damaged due to degeneration and/or injury. Like all other medical innovations, emerging research on stem cells and translational biology not only requires a sound scientific rationale, but also strict adherence to ethical, legal and social issues. Apart from challenges of selecting appropriate stem cells for a particular condition, there are important concerns related to the use of embryos for creating human embryonic stem cell (hESC) lines as these may lead to commoditization of human cells and tissues. Further, there is an inherent risk of exploitation of individuals particularly those belonging to the underprivileged groups. Besides, there are challenges related to the contentious issue of human germ-line engineering and reproductive cloning.

The National Guidelines for Stem Cell Research (NGSCR)-2017 takes into consideration all of the above mentioned issues, including recent developments in germ-line modification/editing. The guidelines take note of the fact that pluripotent stem cells derived from a variety of sources are now easily accessible for clinical trials, often without rationale and hence suitable procedures for their use and handling are required.

2. Issues and Concerns

Indiscriminate use of stem cells without establishing efficacy for therapy and before obtaining adequate data on their safety has created unprecedented difficulties related to therapeutic profligacy with vulnerable patients getting exploited. In recent years, the use of stem cells in clinical indications that has not yet been substantiated scientifically, has posed serious problems to patients in terms of their well-being and financial exploitation. Besides, 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 areas of serious concern. Of equal importance is the assurance of safety and rights of those donating stem cells of any type for basic and/or clinical research. Hence, adequate safeguards must be in place so that subjects receiving these cells in clinical trials are fully protected. Societal concerns regarding

compensation for research related injuries and unforeseen adverse effects are additional concerns that need to be adequately addressed.

As with any new scientific development having potential for improving human health, stem cell research must be regulated with special attention on the above issues. Globally, there is excitement to explore the use of adult stem cells or pluripotent stem cells like embroynic stem cells (ESC) and induced pluripotent stem cells (iPSC) for a number of diseases. However caution must be exercised for their use and the same should be based on robust scientific evidence. The guiding philosophy should be to generate new knowledge based on scientific rationale of the proposal addressing all ethical concerns. The primary objective must be to prevent potential exploitation of vulnerable individuals and premature commercialization. Because of their therapeutic potential, the stem cells fall under the definition of an 'Investigational New Drug (IND)'or 'Investigational New Entity (INE)' and hence guiding principles and regulatory norms must be followed accordingly before initiating clinical trials.

The Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) through joint effort first framed the Guidelines for Stem Cell Research and Therapy in 2007. The committee of experts decided to update these guidelines from time to time based on new knowledge generated in the field. Hence these were further revised in 2013 as National Guidelines for Stem Cell Research (NGSCR). This document has been revised incorporating recent advances, and published as NGSCR 2017.

3. Aims and Scope

These guidelines are applicable to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and all others associated with both basic and clinical research involving any kind ofhuman stem cells and their derivatives. The guidelines do not apply to research using non-human stem cells or tissues. Further, **these do not apply to use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders since these have 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. The guidelines specify unique provisions of stem cells, because of their inherent potential for unlimited proliferation, differentiation to cells of the germ layers, regeneration of

tissues, oncogenic potential, unrecognised toxicities and possible involvement in pre-implantation stages of human development.

The guideline therefore focuses on:

1. Monitoring mechanism and regulatory pathway for basic, clinical research and product development based on categories of research and level of manipulation
2. Procurement of gametes, embryos and somatic cells for derivation and propagation of any stem cell lines, their banking and distribution.
3. Other important areas like international collaboration, exchange of cell/ lines and education for stakeholders and advertisement.

The guidelines have been laid down to ensure that all research with human stem cells is conducted in an ethical and scientifically responsible manner. All researchers and stakeholders are required to comply 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; hence the guidelines will be updated at regular intervals. It is the responsibility of the researcher and members of the Institutional Review Committees to understand the basic principles of these guidelines and keep themselves abreast with the current guidelines and regulations in the country, and ensure compliance.

4. General Principles

Research on human participants involving cells and tissues derived from human embryos, fetusesor any other sources must safeguard human rights, safety, dignity, and fundamental freedom. This includes processes related to obtaining human tissues/cells for research, diagnosis and clinical trials. It is important that the fundamental tenets of beneficence, non-malfeasance, justice and autonomy are adhered to for any research involving human participants. Research involving the use of stem cells must be conducted under specific requirements and guidelines related to these cells as described in Section 5.

It is equally important to follow the general principles as laid down in the “Ethical Guidelines for Biomedical Research on Human Participants” published in 2006 (http://icmr.nic.in/ethical_guidelines.pdf) by the Indian Council of Medical Research

(ICMR) and the current revised National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017.

The General Principles of these are highlighted below:

- Principle of Essentiality
- Principles of Voluntariness
- Principle of Non-exploitation
- Priciple of Social Responsibility
- Principle of ensuring Privacy and Confidentiality
- Principle of Risk Minimization
- Principle of Professional Competence
- Principle of Maximization of Benefit
- Principle of Institutional Arrangements
- Principle of Transparency and Accountability
- Principle of Totality of Responsibility
- Principle of Environmental Protection.

5. Ethical and Scientific Considerations Determining Specific Requirements Related to Stem Cell Research:

Stem cells are unique in many ways. While they present several potential clinical benefits as reported through controlled clinical trials, there are equally unforeseen hazards for their use. However the biological properties of these cells and the effect of their processing and *ex vivo* handling raise specific concerns. Major concerns are specific to their collection, processing, storage and use for clinical research. It must be understood that the donor has the exclusive right to get apprised of all details related to his/her health and safety. The considerations include the following:

5.1. Ethical Consideration

5.1.1. Health, Safety and Rights of the Donor

Prior to procurement of biological material for isolation of stem cells, it is mandatory to obtain informed consent from the voluntary donor. This shall include video consent. The researchers and stakeholders are expected to follow the ethical principles defined in Section 4 above. The donation of gametes, embryos and fetal tissues raise special ethical and moral concerns; hence it is necessary to ensure that the donors are neither exploited nor commoditized.

While confidentiality and privacy are sacrosanct, the researcher shall ensure that provisions are in place for traceability in a contingency situation.

5.1.1.1. The donor must be informed about the need for screening of transmittable diseases (about which s/he may or may not be aware of) and of any other risk factors including possible genetic disorders as is practised for blood and other organ/tissue/cells donation.

5.1.1.2. Further, procedural risks involved during collection of organ/tissue/cells (e.g. ovum, bone marrow etc), under local or general anaesthesia should be adequately explained. These details must be included in the information sheet and should be understood by the donor in his/her preferred language.

5.1.1.3. The donor shall also be informed that under exceptional circumstances, cell lines/ products may be generated from the donated material and that these may be banked and shared with other scientific groups.

5.1.1.4. The cell lines/products may also undergo genetic manipulation and have the potential for commercialization. In the latter event, the Intellectual Property Rights (IPR) of the biological material will not vest with the donor. However, efforts should be made if any benefit can be passed on to the donor/community wherever possible .

5.1.1.5. The donors should be made aware that they may be contacted in future for any specific requirements.

5.1.1.6. The inclusion and exclusion criteria for selection of an individual to be a donor along with various laboratory investigations required are given in *Annexure IV*.

5.2. Scientific Considerations

5.2.1. Manufacture and Quality Assurance of Stem Cell and its Products/Derivatives

That human adult tissues have an inherent population of stem cells is now universally accepted. In order to obtain these cells in sufficient numbers, some degree of processing, enrichment and/or *in vitro* expansion may be necessary. Such manipulations may also be needed to enhance their utility. One of the challenges in testing the potency of stem cells is the lack of suitable animal model system. Accordingly, innovative surrogate assays are needed for the purpose. It is mandatory that the stem cells or their products/derivatives are processed in CDSCO licensed Good Manufacturing Practices (GMP) compliant

facility. *Annexure V* gives details on the requirements for manufacturing of stem cells and their derivatives.

5.2.1.1. Pluripotent stem cells carry additional risks due to their inherent property of pluripotency. These include ability to acquire mutations when maintained for prolonged periods in culture, to grow and differentiate into inappropriate cellular phenotypes, to form benign teratoma or malignant outgrowths, and to fail to mature. These confer additional risks to patients/subjects. Accordingly appropriate measures should be taken and tests performed to ensure that the stem cell derived product is safe for human application.

5.2.1.2. Factors that could confer risk to the patient/subject from transpalantaion of cells include their differentiation potential, source (autologous, allogeneic), type of genetic manipulation (if any), homologous versus non-homologous or ectopic use, their persistence in the patient/subject, specificity of the cell type, and their possible differentiation into tissues or organs.

5.2.1.3. For cryopreserved or otherwise stored products, possible impact of short or long-term storage on product viability and potency must be determined.

5.2.1.4. The rigor of quality control and quality assurance (QC/QA) for the product development including cell processing and manufacturing stages is critical and should be compliant with requirements as per Schedule M of Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules, 1945. This is mandatory for all clinical trials.

5.2.2. Release Criteria

Stem cells or their products intended for administration in humans as a part of clinical trial should fulfil the quality criteria as defined in *Annexure VI***.** These include cell viability, final cell population (using CD markers), stability and requirements for release.

5.2.2.1. All stem cells or their products should have proper labelling before release.

5.2.2.2. It is necessary that the product is sufficiently stable for the duration as required for the study.

5.2.2.3. All procedures shall be well laid down in writing and strictly followed so as to provide reproducibility of well characterized clinical grade cells

that meet the desired standards of identity, purity, safety, potency and traceability.

5.2.2.4. The infrastructure facility shall be duly accredited or certified by CDSCO or NABL, and file the CMC (Chemistry, Manufacturing and Control) documents for regulatory purposes and necessary approvals.

5.2.3. Evidence Based Applications

At present there is lack of solid scientific evidence substantiating the clinical efficacy of stem cells in a disease state other than their use for hematopoietic stem cell transplantation (HSCT) for approved indications as listed in *Annexure III*. Accordingly the commercial use of stem cells as elements of therapy is prohibited. It must be emphasised that no stem cell administration to humans is permissible outside the well-controlled and approved clinical trials. The latter needs to be designed carefully, with well-defined and definitive primary and secondary end-points. The follow-up period should be atleast two years. It could even be longer depending on the type and source of cells used, the intended clinical application and age and gender of the recipient. It is essential that stakeholders involved in such clinical trials are fully conversant with the current regulations and best international practices in the field including provisions for GMP and GCP compliance. Further, a patient participating and enrolled for a clinical trial should not be charged for any procedure(s) related to the trial including hospital stay and laboratory based investigations.

5.2.4. Intellectual Property Rights and Social Responsibility

Outcome of research on stem cells/lines and/or application of their products may have commercial value. The option of sharing of IPR, if any, should be indicated inthe informed consent form. It is expected that a proportion of the benefit accruing from commercial use of donated tissue/cells will be returned to the community, which has directly or indirectly contributed to the product as per the norms. The word “community” here refers to all potential beneficiaries including patient groups.

6. Mechanism for Review and Oversight

In recent years, the area of stem cell research has undergone rapid strides leading to hope as well as hype in the public mind particularly patients suffering from incurable diseases. However, research in the field is associated with unique ethical, legal and social concerns that require additional oversight and expertise for efficient scientific and ethical evaluation.

6.1. A separate mechanism for review and monitoring is essential both at the institutional andat the national level.

6.2. A National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been established that monitors and oversees research activities at the national level. It also lays guidelines for all stem cell research and/or associated clinical trials.

6.3. The Institutional Committee for Stem Cell Research (IC-SCR) approves and monitors stem cell research (both basic and clinical research) at the institutional level.

6.4. 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 process of all research projects pertaining to the field of stem cell research is carried out in compliance with the national guidelines.

6.5. NAC-SCRT may nominate an observer on the IC-SCR.

6.6. It is mandatory for all institutes and entities engaged in stem cell research to establish an IC-SCR and register the same with NAC-SCRT.

7. Stem Cell Classification

Based on the cell type/tissue of origin, stem cells are classified into 'Somatic Stem Cells' (SSCs), and 'Embryonic Stem Cells' (ESCs). While the former have limited differentiation capacity and may be multipotent or unipotent, the latter on the other hand are pluripotent. The pluripotency can also be generated in the laboratory by reprogramming of somatic cells, and the products thus generated are referred to as 'Induced Pluripotent Stem Cells (iPSCs)'. The regulatory requirements for research on each of these stem cells depend on their origin and potency. The stem cells are classified and defined as:

7.1. **Somatic Stem Cells (SSCs)** are the resident, self-renewable population of cells that 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.

7.1.1. SSCs obtained from different sources, for example the fetus, umbilical cord, placenta, infant, child or adult; and from different organs/tissues, may vary in their proliferative and differentiation potential.

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

7.1.3. SSCs are generally present in relatively low numbers in most tissues, and may need enrichment and expansion prior to use. The investigator must take into consideration the following and take appropriate precautions/measures for their avoidance:

7.1.3.1. Prolonged cell culture/expansion carries the risk of contamination with microorganisms and potential genomic alterations.

7.1.3.2. Cells, culture media and other ingredients may carry the additional risk of inducing immune reactivity.

7.1.3.3. Cells, supplements or reagents of animal origin could introduce xenogeneic pathogens.

7.2. **Pluripotent Stem Cells** have the ability to differentiate into derivatives of all three germ layers, viz., ectoderm, mesoderm and endoderm, but not placenta.

7.2.1. **Embryonic Stem Cells (ESCs)** are derived from pre-implantation embryos (blastocysts). Those derived from embryos before differentiation of tropho-ectoderm and inner cell mass (i.e. morula stage) are truly totipotent, capable of giving rise to the entire organism including extra-embryonic tissues. ESCs derived from the inner cell mass (ICM) are pluripotent (not totipotent).

7.2.2. **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 iPSCs can be generated from somatic cells by a variety of genetic and epigenetic methods.

7.2.3. Both ESCs and iPSCs, including their derivatives, can be maintained and expanded as pure population of undifferentiated cells. Under appropriate conditions of stimuli, they can be differentiated into lineage-specific progenitors e.g., neurons, cardiomyocytes and other cell types.

7.2.4. The ESCs and iPSCs have tumorigenic potential which could be a major safety concern during therapeutic application of these cells.

7.2.5. The concerns raised in 7.1.3 for SSCs are also applicable for ESCs and iPSCs.

8. Levels of Manipulation

Stem cells, whether autologous or allogeneic, require variable degree of *in vitro,* or *ex vivo* processing before their use for clinical application/transplantation/translational research (Section 12) purpose. This carries the risk of contamination and may also lead to alteration in their properties which may vary according to the degree and type of manipulation. It is essential to use culture medium/reagents as per clause 12.2.1. All laboratory procedures should be carried out under aseptic conditions in a CDSCO certified GMP and GLP facility. This section describes the different levels of manipulation of stem cells:

8.1. **Minimal manipulation:** This refers to the situation where the processing neither alters the number nor the biological characteristics and function of the cells (or tissue) relating to their utility for reconstruction, repair or replacement.

8.1.1. Processing includes simple isolation/separation, washing, centrifugation and suspension in culture medium/reagents, cutting, grinding, shaping, overnight culturing without biological and chemical treatment, and decellularization.

8.1.2. Clinical trials using such cells require IC-SCR, IEC and CDSCO approvals if these are meant for homologous use for unapproved indications.

For example use of bone marrow/peripheral blood/umbilical cord blood derived mononuclear cells by intravenous route for clinical indications other than those listed (*Annexure III*).

8.1.3. If the minimally manipulated cells are to be used for non–homologous purpose, CDSCO approval is required apart from those from IC-SCR and IEC before initiating any clinical trial.

For example use of bone marrow/peripheral blood/umbilical cord blood derived mononuclear cells by any route of administration other than intravenous for neurological disorders, musculoskeletal disorders, liver disorders and cardiovascular disorders and any other such examples.

8.1.4. If cells/tissues are removed and implanted into the same individual during the same surgical procedure within a single operation, it should not undergo processing steps beyond rinsing, cleaning or sizing.

8.2. **Substantial or more than minimal manipulation**: This is defined as *ex vivo* alteration in the cell population (enhancement or depletion of specific subsets), expansion, cryopreservation, or cytokine based activation, but one that is not expected to result in alteration of cell characteristics and function.

8.2.1. Clinical trials using cells that have undergone more than minimal manipulation require CDSCO, IC-SCR and IEC approvals.

For example, adipose tissue may be more than minimally manipulated if the processing alters the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement.

Adipose tissue is sometimes processed by various means (e.g.enzymatic digestion, mechanical disruption etc.) to isolate itsnon-adipocyte or non-structural components. In some instances, these non-adipocyte or non-structural components are cultured and expanded. Processing to isolate non-adipocyte or non-structural components e.g. Stromal Vascular Fraction (SVF) from adipose tissue (with or without subsequent cell culture or expansion) is considered more than minimal manipulation and clinical trials using SVF will therefore require approval by IC-SCR, IEC and CDSCO.

8.3. **Major manipulation:** This refers to the genetic and epigenetic modification of stem cells, transient or permanent, or of cells propagated in culture leading to alteration not only in their numbers but also biological characteristics and function.

8.3.1. This includes trans-differentiation, 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. The process also includes regulated lineage specific differentiation of human ESCs and iPSCs into the desired cellular products.

8.3.2. Clinical trials using cells which have undergone major manipulation shall require approval of CDSCO after obtaining approval from NAC-SCRT through IC-SCR and IEC.

9. Categorization of Research

The stem cell research could be basic and or translational (preclinical and clinical research) as described in Section 10 and 11. Further, the research has been divided into three major areas categories based on the ethical and or safety concerns regarding source of stem cells and levels of manipulation which warrant additional review and monitoring as per existing regulations. These include permissible, restrictive and prohibited areas.

9.1. Permissible Areas of Research:

9.1.1. *In vitro* studies on pluripotent stem cell lines viz. ESCs or iPSCs, or SSCs from fetal or adult tissues, for understanding their basic biology, may be carried out with prior approval of the IC-SCR.

9.1.2. In case *in vitro* studies involve procurement of tissue from donor for isolating stem cells, informed consent from the donor and clearance from IC-SCR and IEC are required.

9.1.3. If the source of the tissue is from hospital/clinic/entity other than the institute utilising it for research, then the IEC clearance from source institute is mandatory.

9.1.4. The ESC lines used for such research should be established following the ethical guidelines as laid down in this document (Section 15) and should be registered with the NAC-SCRT through IC-SCR.

9.1.5. Stem cell lines from sources outside the country ought to have been established as per 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 and it is the responsibility of investigator to submit Material Transfer Agreement (MTA)/Memorandum of Understanding (MOU) or certificate from the vendor to IC-SCR while taking approval on the proposal.

9.1.6. *In vivo* studies in experimental animals (other than primates, see Sub Section 9.2) with established cell lines from any type of human pluripotent stem cells viz. ESCs, iPSCs, including their differentiated cells, and human SSCs (fetal, 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.

9.1.7. Establishment of new human ES cell lines from spare embryos or iPSC lines from fetal/adult somatic cells, with prior approval of the IC-SCR, provided appropriate informed consent is obtained from the donor (Section 15). Once the PSC (ESC or iPSC) lines are established, the same shall be registered with NAC-SCRT through IC-SCR with appropriate documentation. Such cell lines must be deposited in an accredited cell bank for potential use by other investigators. Similarly, all iPSC 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 also be included.

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

9.1.9. Clinical trials with minimally manipulated SSCs for homologous use in unapproved conditions can only be done with clinical grade cells that are processed in CDSCO certified GMP compliant facility. Such trials should be carried out only with prior approval of IC-SCR, IEC and CDSCO, even if the products are not intended for market authorization.

9.1.10. All clinical trials using stem cells shall be registered with the Clinical Trial Registry of India (CTRI) (http://ctri.nic.in/Clinicaltrials/login.php).

9.2. Restrictive Areas of Research:

9.2.1. Creation of human pre-implantation embryos by IVF, ICSI, SCNT or any other method with the specific aim of deriving ESC lines for any purpose. However, such research needs close supervision and strict adherence to the guidelines. The investigator needs to provide reasoning taking into consideration the following:

9.2.1.1. The proposed research cannot be carried out with existing ESC lines, or those that can be derived from spare embryos;

9.2.1.2. Minimum number of embryos/blastocysts required for such research must be clearly defined;

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

9.2.2. Clinical trials using any type of stem cells (progenitor or differentiated) after major manipulation shall require prior approval of the CDSCO after obtaining approval from IC-SCR and IEC.

9.2.3. Clinical trials sponsored by multinationals, employing cell products developed outside India, will also need prior approval from CDSCO following clearance from both IC-SCR and IEC.

9.2.4. All international collaborations require approvals from the respective funding agencies followed by approval from the Health Ministry's Screening Committee as per Government of India Guidelines (http://icmr.nic.in/guide.htm).

9.2.5. Import of any type of stem cells and/or their products requires license from CDSCO as per the established regulations.

9.2.6. Research involving introduction of human ESC/iPSC/SSCs into animals (including primates), at embryonic or fetal stages of development for studies designed to understand the patterns of differentiation and integration of human cells into non-human animal tissues shall conform to the following:

9.2.6.1. If the expected outcome of the study is suggestive of 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 such experiments must first be substantiated with data.

9.2.6.2. Animals derived from such experiments shall not be allowed to breed.

9.2.6.3. Such proposals would need approval of the NAC-SCRT for additional oversight and review after clearance has been granted by IC-SCR, IEC and IAEC (or CPCSEA).

9.2.7. Studies on chimeras where stem cells from two or more species are mixed together at any stage of early development (embryonic or fetal), for understanding patterns of development and differentiation would also require prior approval of NAC-SCRT after clearance has been granted by the IEC and IC-SCR.

9.2.8. Genome modification including gene editing (for example by CRISPR-Cas9 technology) of stem cells, germ-line stem cells or gamete and human embryos is restricted only to *in vitro* studies. It will require thorough review by the IC-SCR, IEC and IBSC and finally by RCGM. Research teams involved should have appropriate expertise, requisite training and infrastructure in gene editing/genome modification and characterization.

9.2.8.1. The source of somatic cells and/or minimum number of embryos, germ-line cells or gametes required for this research should be clearly defined.

9.2.8.2. Only spare embryos, germ-line cells or gametes should be used.

9.2.8.3. Genome modified human embryos should not be cultured beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.

9.3. Prohibited Areas of Research

In the current state of scientific knowledge and understanding, stem cell research in the following areas stands prohibited:

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

9.3.2. *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.

9.3.3. Clinical trials involving transfer of xenogeneic cells into a human host.

9.3.4. Any clinical research on Xenogeneic-Human hybrids.

9.3.5. Use of genome modified human embryos, germ-line stem cells or gametes for developmental propagation

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

9.3.7. 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 chimeric gonadal cells.

10. Responsibilities of the Investigator, Institution and Sponsor

Although appreciable advances have been made in understanding the biology of stem cells, there still exist several elements of unpredictability in the translation aspects of research in this area. Regular review of progress in this field ensures highest degree of scientific rigor and resolution of ethical concerns. Members of the IC-SCR and IEC shall regularly update themselves with regard to advances in the field.

It is mandatory that all investigators, institutions and sponsors conducting or involved with stem cell research are fully conversant with and have fully understood all aspects of the guidelines as given in this document. Given below is a summary of their responsibilities:

10.1. Institutions involved in basic research and/or clinical trials shall constitute an IC-SCR as per these guidelines and provide adequate support for its functioning. The IC-SCR should be registered with the NAC-SCRT.

10.2. 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.

10.3. Research involving hESCs, iPSCs, gene editing/modification and other contentious areas demands extra caution.

10.4. The investigator shall endeavour to avoid any activity that leads to hype, or unrealistic expectations in the minds of study subjects or general public regarding the status of stem cell research and application.

10.5. Investigators should 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 involving human embryos.

10.6. Investigators should also ensure confidentiality of the human donors to safeguard their rights and dignity.

10.7. The biological material can only be procured from clinics/hospitals only after after clearance IEC of that entity informed consent is obtained from the donor (Section 15). It should be treated with utmost respect and adequate care to avoid misuse.

10.8. Creation of human embryos falls under the restrictive areas of research (Sub Section 9.2) and shall be resorted to only whenall other alternatives have been exhausted.

10.9. Special care should be taken for research involving introduction of human cells in animals, particularly in early developmental stages, since this may lead to

development of chimeras or incorporation of stem cells into brain and gonads which can be potentially hazardous.

10.10. Research involving stem cells can be conducted only after approval both from the IC-SCR and IEC. Additional approvals as spelt in Section 9 may also be necessary depending on the research category. The proposal should first be reviewed by the IC-SCR which primarily evaluates the scientific and technical aspects of the study followed by the IEC that will review overall work plan with major focus on ethical issues.

10.11. Clinical trials can be permitted only in institutions/hospitals having registered IC-SCR (with NAC-SCRT) and IEC (with CDSCO).

10.12. It is the responsibility of the investigator to generate robust scientific evidence through well designed clinical trials that could yield valuable information for the benefit of patients. The study subject and/or legal representative should be provided adequate and unbiased information about the trial protocol, its limitations and potential adverse effects.

10.13. Clinical trial must have a medical specialist registered with MCI and holding MCI approved post graduate qualification in the subject domain of the trial. This can only be conducted in a medical institution/hospital with adequate infrastructure and clinical facilities in accordance with Para 2 (1)(ii) of Schedule Y, Drugs and Cosmetic Act 1940 and Rules 1945. All medical professionals involved in clinical trials should have a valid GCP certification.

10.14. All records pertaining to clinical trials must be maintained for a period of at least 15 years. The head of the institution should facilitate the maintenance of records through investigator and IC-SCR.

10.15. Participants enrolled for clinical trials are not liable to pay any charges towards procedures, investigations and/or hospitalisation related to the trial.

10.16. An institution or laboratory developing or processing stem cells for human use should obtain NABL accreditation for all laboratory procedures required for product development.

10.17. The cells or cell-based products used in the trial should be processed in a CDSCO certified GLP and GMP facility (Schedule L1 and M of Drugs and Cosmetic Act, 1940 and Drugs and Cosmetics Rules, 1945).

10.18. Those working with human iPSCs should be cautious with the vectors and genes used for induction of stemness against possible malignant transformation.

10.19. Sponsors shall take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in the country.

10.20. Government agencies/sponsors facilitating stem cell research must ensure that the projects submitted for financial support has prior approval of IC-SCR in addition to IEC/IAEC/ IBSC (whichever applicable).

10.21. For multi-centric clinical trials, all participating sites should obtain approvals form their own IC-SCR and IEC.

10.22. Each institution shall have an empanelled roster of investigators conducting stem cell research and ensure that national guidelines, regulations and best practices are followed.

10.23. Institutions conducting stem cell research shall establish suitable mechanism for creating awareness amongst the scientific community and the public at large.

11. Stem Cell Research: Basic Research

Basic research is an essential component of biomedical science, intended to enhance knowledge and understanding of a subject without necessarily leading to immediate practical solutions and/or therapeutic application. Similarly a focus on basic aspects of research in stem cell biology is important to advance our understanding on the mechanisms responsible for stemness, role of niche, dormancy, recruitment, plasticity and their ability to repair and regenerate. This also includes establishing *in vitro* cell culture systems to investigate stem cells and progenitors of different lineages and understand stages of cell differentiation. This is important for drug discovery and toxicity screening.

Research on human ESCs has led to new knowledge about embryo development. Breakthrough in iPSC technology has revolutionised the field of stem cell biology and has led to the generation of human disease specific models to understand the underlying pathophysiology. These technologies have provided a basis for developing possible novel cell based therapies. It is therefore necessary that the associated scientific robustness and ethical concerns are appropriately addressed/reviewed.

The guidelines for basic science studies are summarised below:

11.1. *In vitro* studies largely fall in the permissible category of research (Sub Section 9.1).

11.2. Research involving cells/tissues directly obtained from human subjects, shall require prior approval of the IC-SCR and IEC.

11.3. Studies involving established human stem cell lines registered with the IC-SCR (where no direct contact is required with human subjects for obtaining cells), are exempted from obtaining fresh informed consent by IC-SCR/IEC. Necessary GLP guidelines shall however be followed.

11.4. *In vivo* studies on experimental animals (other than primates) that fall in the permissible category should be in accordance with Clause 9.1.5.

11.5. Studies on chimeras and sub-human primates shall adhere to Sub Section 9.2.

11.6. 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.

11.7. hESC lines to be used for any basic study should be in accordance with Clause 9.1.3.

11.8. hESCs and iPSCs and/ or lines established by the investigator should be registered with the IC-SCR.

11.9. Derivation of new ESC or iPSC 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 15), and with prior approval of IC-SCR and IEC (Section 9).

11.10. Stem cells and cell lines established for basic research shall not be used for human application or clinical trials.

11.11. Investigators intending to use stem cells or cell lines for clinical trials need to process and develop these cells and cell lines in CDSCO certified GLP and GMP facility.

11.12. For pre-clinical studies, the investigators should follow guidelines as defined in Section 12.

12. Stem Cell Research: Translational Research including Clinical Trials

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 as well as other clinical applications in conditions where use of stem cells has not yet reached the standard of medical care. It involves generating a safe and effective novel product based on fundamental research that can be taken to the bedside. It is recognized that preclinical assays in animal models may not accurately predict the nature of cell behaviour and immune response in humans.

Besides the scientific, technical and entrepreneurial challenges, it is imperative to address the associated ethical, social, and regulatory concerns.

12.1. Preclinical studies:

These are essential for establishing persuasive evidence in an appropriate *in vitro* and/or animal model on the feasibility of the intended product, prior to conduct of clinical trials, as per regulatory requirements for any new biological entity (NBE). Such studies are usually carried out on small animals, with or without immuno-suppression so as to prevent immunerejection. These studies shall demonstrate safety and potential of the product and procedures involved, for achieving desired therapeutic effects. The stem cells to be employed in such trials should be well characterized, similar to the ones to be used in clinical trials, and evaluated both for early and late toxicities including immunogenicity and tumorogenicity.

To adequately evaluate different aspects of the product including safety, bio distribution, immune rejection, more than one animal species (rodents and non-rodents) might be needed.

12.1.1. Approval and Monitoring:

12.1.1.1. Preclinical studies can be permitted only after approval from IC-SCR. Additional approvals as listed below to be taken on case-to-case basis:

i. For studies involving small animals, clearance from IAEC is necessary.
ii. In specific situations and depending on nature of the study, large animals and/or non-human primates maybe permitted with prior approval from CPCSEA.
iii. For preclinical studies involving human tissue, approval from IEC is necessary.

12.1.2. **Study Design**: Like clinical trials, preclinical studiesare also associated with selection and/or publication bias. Investigators have often sought to minimize the effects of such bias and confounding factors in clinical trials by using modalities like randomized allocation, blinded outcome assessment, or power calculations. Such rigors should also apply in preclinical studies intended to support trials. Accordingly, the following guidelines should be adhered to:

12.1.2.1. Researchers should reduce bias and random variation by ensuring that the protocol fulfils the following:

i. adequate statistical power,
ii. availability of appropriate controls,
iii. randomization of the protocol,
iv. use of blinding systems,

12.1.2.2. Researchers and sponsors should ensure that

i. preclinical study models are relevant to the clinical trial settings, best match human disease and characterize disease phenotype at baseline,
ii. end-point measures best match clinical outcomes, and demonstrate a mechanism for treatment effect,
iii. outcomes in animals are robust and validated independently by third party usinga different animal model system,

12.1.2.3. Large animal models/non-human primates maybe used wherever necessary;

For example in studies involving cardiac physiology, tissue-related inflammatory and immunological injuries and degenerative disorders of weight bearing joints.

12.1.3. **Preclinical safety studies** shall demonstrate safety of the product and the procedure for achieving proposed therapeutic effects.

12.1.3.1. The stem cells to be employed in such trials should be well characterized, similar to those to be used in clinical trials, and evaluated both for early and late toxicities including immunogenicity and tumorigenicity.

12.1.3.2. Single and repeat dose toxicity studies should be performed in relevant animal models.

12.1.3.3. The study duration might be longer as compared to standard single dose studies for chemical entities, since the infused cells/biological entities may induce long-term effects. This aspect should be reflected in the design of these studies.

12.1.3.4. The route of administration should be comparable to that intended for clinical use.

12.1.3.5. The dosage levels selected should provide information on a dose–response relationship, including a toxic dose and a no observed adverse effect level (NOAEL). Repeated dose toxicity studies are relevant only if the intended clinical use includes multiple dosing.

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

12.1.3.7. Risks for tumorigenicity must be rigorously assessed for the product, particularly when developed following extensive manipulation in culture or through genetic modification, or in situations involving pluripotent stem cells. This must be achieved before initiation of the clinical trial. Tumorigenicity potential should be assessed in immune-deficient mice using different routes of administration.

12.1.3.8. Genotoxicity and developmental toxicity may be assessed depending on the intended clinical use.

12.1.3.9. Immunogenicity assessment should also be a part of the repeated dose toxicity study.

12.1.3.10. All safety assessment studies should be carried out only in a CDSCO certified GLP facility.

12.1.4. **Bio-distribution studies** for all stem cells and its derivatives, whether injected locally or systemically should be performedboth within the local as well as distant sites.

12.1.4.1. Studies of bio-distribution, assisted by sensitive techniques for imaging and monitoring of homing, retention and subsequent migration of transplanted cell populations are imperative for interpreting both efficacy and adverse events.

12.1.4.2. Bio-distribution and toxicity studies should be performed in a CDSCO certified GLP facility.

12.1.5. **Pre-clinical efficacy studies**: Robust preclinical testing in animal models is important for stem cell and its derivatives, because cell therapies have distinctive efficacy and pharmacological characteristics. Before clinical testing, preclinical evidence should

i) establish a mechanism of action,

ii) establish optimal conditions for employing cell-based intervention (e.g. dose, co-interventions),

iii) demonstrate ability to objectively modify the progression of and/or improve a disease or injury condition when applied in suitable animal systems.

12.2. **Clinical Trials** using stem cells should be in compliance with Schedule Y of Drugs and Cosmetics Act 1940 and Drugs and Cosmetic Rules 1945 as well as GCP Guidelines of CDSCO (http://www.cdsco.nic.in/html/GCP1.html) and ICMR-Ethical Guidelines for Biomedical Research involving Human Participants (http://www.icmr.nic.in/ethical_guidelines.pdf). The investigator should follow the guidelines for protocol as per the given format (*Annexure II*). Only institutions having their IC-SCR registered with the NAC-SCRT and IEC registered with CDSCO are permitted to conduct clinical trials. Responsibilities of the investigators, institutions and the sponsor involved in such trials are given in Section 10 and must be adhered to. Other associated guidelines are given below:

12.2.1. **Reagents** used for the derivation of human ESCs/iPSCs or expansion/enrichment of SSCs, for purposes of clinical trials should be of clinical grade/Pharmacopeia grade.

12.2.1.1. When using research grade material, the quality control program should include testing for safety, purity and potency (as listed in *Annexure V*) of the reagents and their components, wherever appropriate.

12.2.1.2. Animal derived materials/reagents such as fetal calf serum, bovine serum albumin and trypsin should be tested for adventitious agents (forexample causing spongiform encephalopathy).

12.2.1.3. For all imported reagents (for example, fetal calf serum and others), the country of origin should be specified.

12.2.1.4. Researchers should be encouraged to use serum free/xeno-free medium for processing of cells.

12.2.1.5. Limits should be established for the concentration of components, including those of animal origin, in the final product.

12.2.2. **Trial Participants:**

12.2.2.1. The selection of participants for the trials shall be done as per the predefined inclusion and exclusion criteria of the duly approved protocol.

12.2.2.2. Amendments/deviations, if any in the protocol must have prior approval of the IC-SCR, IEC and CDSCO.

12.2.2.3. Participants enrolled for clinical trials are not liable to pay any charges towards procedures, investigations and/or hospitalisation related to the trial.

12.2.3. **Participant information:** The patient information sheet and the informed consent should have prior approval of IC-SCR and IEC, shall specifically address the following:

12.2.3.1. Information regarding the current status on the application of stem cells in the given condition, experimental nature of the proposed clinical study and its possible short and long-term risks and benefits.

12.2.3.2. Information stating irreversibility of the intervention.

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

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

12.2.3.5. Information on the sample size, duration of study and follow-up.

12.2.3.6. Information that the study has been duly approved by the IC-SCR and IEC.

12.2.3.7. Information on the category of the trial viz. blinded/randomised/open labelled etc.

12.2.3.8. Information that the trial participant will not be levied any charges towards procedures, investigations and/or hospitalisation related to the trial.

12.2.3.9. The participants should be provided the information sheet and consent form in the vernacular/regional language and the same should be well understood by the participant.

12.2.3.10. Video consent shall be recorded.

12.2.4. **Regulatory approval:** This section deals with mandatory approvals from IC-SCR, IEC and CDSCO before enrolling participants for clinical trials.

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

12.2.4.2. Only those institutions that have their IC-SCR and IEC registered with the NAC-SCRT and CDSCO respectively are permitted to conduct clinical trials.

12.2.4.3. Clinical trials using minimally manipulated autologous SSCs (i.e. HSCs and MSCs) for homologous use for indications other than those listed in

Annexure III or for non-homologous use for any indication should be approved by IC-SCR, IEC and CDSCO.

12.2.4.4. Clinical trials using stem cells with substantial manipulation should have prior approval of IC-SCR, IEC and CDSCO.

12.2.4.5. Clinical trials using allogeneic SSCs (with any degree of manipulation) and those using autologous SSCs with more than minimal and major manipulation should have prior approval of IC-SCR, IEC and CDSCO.

12.2.4.6. Clinical trials using human pluripotent stem cells (hESCs or iPSCs) or their derivatives should have prior IC-SCR, IEC and CDSCO.

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

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

12.2.5. **Monitoring:** Clinical trials using stem cells shall be conducted under monitoring by Data Safety Monitoring Board (DSMB) and reporting to IC-SCR and IEC.

12.2.5.1. All cases of adverse and serious adverse events (AEs/SAEs) should be reported by the investigator/clinician/institution to the DSMB, IEC, funding agency/sponsor and IC-SCR. It is the responsibility of the IEC andthe sponsor to report to CDSCO as defined in the Schedule Y of Drugs and Cosmetics Act, 1940 and Drug and Cosmetic Rules, 1945. Information on these should also be reported to NAC-SCRT by the IC-SCR.

12.2.5.2. Members of the DSMB are expected to have the requisite expertise to monitor trials for AEs/SAEs and their smooth conduct.

12.2.5.3. Members of the DSMB shall not have any conflict of interest with the study and should be independent of IC-SCR and IEC.

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

12.2.5.5. The medical records of trial participants should be maintained for a period of at least 15 years by head of the institute through investigators and IC-SCR.

12.2.6. **Follow-up of participants** is required depending on nature of the experimental stem cell-based intervention and the persistence potential of cellular products.

12.2.6.1. Long-term follow-up provides an opportunity to monitor late adverse events, and/or efficacy of the intervention.

12.2.6.2. For each indication, a minimum of two years of post-trial follow-up is necessary with respect to the safety data. The same can be extended by one year or more depending on the type/source of the cells and the degree of their manipulation. The same should be appropriately decided by the IC-SCR and IEC on case-to-case basis.

12.2.6.3. Clinical trial participants have to be physically examined/investigated.

12.2.6.4. The investigator should submit periodic report on follow-up to DSMB.

13. Therapeutic Use of Stem Cells

13.1. At present, there are no approved indications for stem cell therapy other than the HSCT for conditions stated in *Annexure III*.

13.2. Therapeutic use of stem cells other than the above shall be treated as investigational and conducted only in the form of a clinical trial after obtaining necessary regulatory approvals. Hence, their application in the following situations, outside the domain of clinical trials considered unethical and prohibited:

i. Autologous use of stem cells (HSCs, MNCs, MSCs, iPSCs etc.) for indication/disease other than those listed in *Annexure III.*

ii. Allogeneic use of SSCs, hESCs and its derivatives.

13.3. Cells used in clinical trials should be of clinical grade and be processed under CDSCO certified GMP facility.

13.4. The cells/product for transplantation to be used for clinical trial should be free from any microbial contamination.

13.5. Centres involved in clinical trials and entities providing cells/products for the trial should be registered with the NAC-SCRT through their respective IC-SCR.

13.6. For International Collaboration, the funding agencies/sponsors shall ensure that certification provided by the collaborating country fulfils the requirements as laid down in these guidelines. For example, all ICMR funded international projects are required to obtain clearance from the Health Ministry's Screening Committee (HMSC). Similar clearances would need to be obtained if the trial/study is supported by other public/private organisations.

13.7. Investigator claiming the study outcome to be considered as a possible therapy in a particular indication, shall apply to the ICMR with the trial data on which such a claim is based giving full justification for the same. The ICMR will then determine in consultation with experts in the field, whether such a claim is tenable.

14. Banking of Biological Tissues as Source of Stem Cells

At present there is no scientific evidence to substantiate clinical benefits with the use of stem cells derived from cord tissue, placenta, tooth extract, adipose tissue, dental pulp, menstrual blood and olfactory ensheating cells etc. Yet, procurement and banking of these biological is increasingly becoming a commercial activity with the specific objective of their isolation and/or *ex vivo* expansion to be utilized for scientifically unsubstantiated therapeutic interventions. Hence, care needs to be taken so that there is no exploitation and commoditization of the resources.

As of now, only UCB banking is permitted and licensed by CDSCO. Accordingly, commercial banking of all other biological materials not permitted until further notification.

14.1. Banking of Umbilical Cord Blood

UCB is a rich source of $CD34^+$ hematopoietic and mesenchymal (stromal) stem cells. Use of UCB derived HSCs for treatment of various haematological and immunological disorders is currently well established, particularly where an HLA-matched sibling is not available. However, there is a paucity of public funded UCB banks in India. On the other hand several private UCB banks have come-up, that engage themselves in promotional advertisements offering storage of cord blood with the promise of future therapeutic use. Such advertisements are often misleading for the public and lack comprehensive and accurate information to the consumer. So far there is no scientific basis for preservation of cord blood for future self-use and this practice therefore raises ethical and social concerns. Private storage of the cord blood HSCs is advisable when there is an elder child in the family with a condition treatable with these cells and the mother is expecting the next baby. In other situations, the parents should be educated about the limitations of use of such cells at this point of time.

On the other hand, public cord blood banks across the world, for several decades, are playing an important role as a source of HSCs for transplant in selected

haematological conditions. Hence, parents should be encouraged for voluntary donation to public cord blood banks for allogeneic use based on HLA matching and for research purposes. Obstetricians must educate parents to be, about the options available, especially donating cord blood to a public bank.

14.1.1. UCB banks are permitted only under license and monitoring by the CDSCO. These are expected to follow the Drugs and Cosmetics (3rd Amendment) Rules, Gazette Notification No. GSR 899(E) dated 27/12/2011 for collection, processing, testing, storage, banking, and release of stored units (http://cdsco.nic.in/html/GSR%20899.pdf).

14.1.2. Therapeutic use of stem cells derived from UCB for indications other than those listed in *Annexure III* is not permitted. These can be used only as a clinical trial after obtaining approval of IC-SCR, IEC and CDSCO.

14.1.3. Cord blood banks involved in basic research or clinical trials should constitute an IC-SCR and register the same with NAC-SCRT.

14.1.4. The release of UCB units for research and/or clinical trials should be to only those institutions that have a registered IC-SCR and IEC.

14.1.5. Procedure for collection of umbilical cord blood

14.1.5.1. Parents should be fully informed regarding risks and benefits involved voluntary informed consent should be obtained from both parents well before the scheduled delivery date, but in no case at the time of delivery or subsequently. If there is disagreement between parents, the mother's wish shall prevail.

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

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

14.1.5.4. Exact timing of clamping the umbilical cord should be defined in the SOPs and recorded in the case file. No harm should occur to the neonate and the mother.

14.1.5.5. Donor families should be compensated by providing them *Donor Cards* to enable them preferential access during emergency and for any other benefits to donor/relatives in future.

14.1.5.6. SOPs for release of UCB units should be in place.

14.2. Banking and Distribution of Human ESC/iPSC Lines

As human ESC/iPSC research advances, it is important for institutions that obtain store and use stem cell lines to have proper SOPs in place. They should ensure that the stored cells are well characterized and screened for infectious disease markers. It is also essential that these are maintained and stored as per current standards of GLP and GTP.

The following guidelines are specifically adapted for human ESC/iPSC lines. However, researchers are advised and expected to keep track of advances in the field.

14.2.1. An Institution/repository engaged in receiving and storing human ESC/iPSC lines should follow the standard practices as listed below:

14.2.1.1. Creation of clear and standardized protocols for banking and release.

14.2.1.2. Documentations to be obtained from the investigators and/or institutions that deposit cell lines:

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 details on screening of infectious disease.
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. Cell line characterization (such as but not limited to cluster differentiation (CD) phenotyping, karyotyping and genetic markers).

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

14.2.2. 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:

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

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

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

14.2.3. The following SOPs/Standard of practices should be defined and maintained:

14.2.3.1. Assignment of a unique identifier to each sample.

14.2.3.2. System for quality assurance and control.

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

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

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

14.2.3.6. System for auditing compliance.

14.2.3.7. Schedule of charges.

14.2.3.8. Statement of intellectual property policies.

14.2.3.9. When appropriate, creation of a clear MTA or user agreement.

14.2.3.10. Liability statement.

14.2.3.11. System for disposal of material.

14.2.3.12. Clear criteria for distribution of cell lines

14.2.3.13. Release Certificate to be issued with each dispatch.

15. 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. If the source of the tissue is from hospital/clinic/entity other than the institute utilizing it for research, then the IEC clearance from the source institute is mandatory.

The biological material includes gametes, blastocysts, embryos, fetal and placental tissues, as well as somatic cells.

15.1. Fetal /Placental Tissue

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

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

15.1.2. Informed consent for donation:

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

15.1.2.2. The consent for donation of fetal 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.

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

15.1.3. The purpose and use of donated fetal 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.

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

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

15.1.6. 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 fetal tissue are proposed to be used for therapy.

15.2. Gametes used for embryogenesis, Blastocysts, Pre-implantation Embryos or Somatic Cells for Generation of Human - ESC/iPSC Lines

15.2.1. 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 ESC/iPSC lines. IC-SCR and IEC should verify that the blastocysts obtained from infertility clinics are in excess (spare embryos) of the clinical needs of the couple.

15.2.2. Creation of human ESC lines from blastocysts and iPSC 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.

15.2.3. Consent for donation of blastocysts for establishment of human ESC 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.

15.2.4. 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 iPSC lines except for reimbursement towards travel expenses for attending the clinic.

15.2.5. 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 ESC in research.

15.2.6. If the research involves collection of biological samples from other institutions/clinics, IEC approval should be taken at the source institution, which shall maintain proper documentation for the same.

15.2.7. Informed consent for donation should include:

15.2.7.1. A statement that the donated material will be used to derive hESC/cell lines for research purposes.

15.2.7.2. 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.

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

15.2.7.4. A statement that the derived hESC line may be used for development of new product(s) that may have a commercial value. However, no direct financial benefit or IPR will accrue to the donors.

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

15.2.7.6. A statement that research is not intended to provide direct medical benefit to the donor(s) except situations involving autologous transplantation.

15.2.7.7. 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.

15.2.7.8. 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.

15.2.8. 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.

15.2.9. The IC-SCR and IEC while reviewing and approving proposals for gametes/blastocysts/embryos and somatic cell donation shall ensure that the subjects do not belong to vulnerable groups.

15.2.10. There shall be no coercion to undertake human ESC research or any activity related to stem cell research. Autonomy of the researcher/physician must be respected.

16. International Collaboration

Stem cell research is an emerging field of biomedical sciences and may require national and international collaboration. Such collaborations help the participating institutions for advancement of the field, capacity building and global competence. Participating institutions should consider the following:

16.1. National guidelines and regulations of respective countries shall be followed.

16.2. All international collaborations require approvals of the respective funding agencies followed by approval from the Health Ministry's Screening Committee as per Government of India Guidelines (http://icmr.nic.in/guide.htm).

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

17. Exchange/Procurement of Tissues,Stem Cells and Cell lines

Exchange or procurement of tissues, stem cells or cell lines may be required for basic and clinical research. These may not be currently available in the country and hence may have to be procured from either academic institutions or sourced commercially. A critical limitation of the use of stem cells for research and development is the need to maintain them in a viable state. Since their viability can be affected during transit,

appropriate international guidelines should be followed for their packaging, labelling, handling and transport at ports.

17.1. Import of stem cell lines for basic research does not require prior approval/NOC from any government agencies and should be permitted by customs authorities at the port of entry/exit without prior approvals

17.2. Traceability of all cell lines including those imported must be maintained by the investigator.

17.3. For the purpose of basic stem cell research and its technology development, the investigators can obtain primary cultures of adult stem cells at defined passages and/or pluripotent stem cell (PSC) lines that are well characterized and having dedicated ID or Code numbers.

17.4. The purpose of procuring such cells should be clearly defined. These should be used only for the purpose defined complying with laboratory-SOPs. Such cells are not permitted for commercial purposes or for clinical trials.

17.4.1. For import of cell lines developed by researchers, the investigator must obtain adequate documentation from the source to demonstrate that the cells/cell lines were created following existing guidelines of the country of origin.

17.4.2. For export of indigenously developed cell lines, necessary clearances from IEC and IC-SCR must be obtained and submitted along with the MTA during the review of such research proposals.

17.4.3. All proposals for import/export of stem cells and their derivatives required for research and development including those for clinical trials shall be examined by the IC-SCR and IEC.

17.4.4. Biological material required for clinical trials and originating from countries outside India requires import clearance from CDSCO. The procured material should not be used for any commercial/therapeutic purpose.

17.4.5. Import and export of stem cells and cell lines for commercial use need to be considered on case-to-case basis as per the Government of India guidelines (Circular No. L/950/53/97-H1 (Pt.) dated November 19th, 1997 of the Ministry of Health) on import/export of biological materials. http://www.icmr.nic.in/min.htm and DGFT Notification No. 19 /2015-2020 dated, 4 August, 2016.

17.4.6. Import/export of HLA tested unrelated donor derived BM/PBSCs/cord blood as a source of hematopoietic stem cells for transplantation in approved indications (*Annexure-III*) is exempted for clearance from any authority as per

the Govt. of India's guidelines (Circular No. L/950/53/97-H1 (Pt.) dated November 19th, 1997 of the Ministry of Health) http://www.icmr.nic.in/min.htm if this exchange is considered necessary by the physician in-charge of the patient.

18. Awareness and Education of Stakeholders

18.1. It is the democratic right of the people to be aware of treatment modalities and the risks versus benefit of new/upcoming technologies such as cell based therapies including stem cells. The scientific community including scientists and clinicians working in the field, policy makers including regulators own the responsibility to create awareness and update **about the rightful status of** the stem cells and their applications on the basis of peer reviewed scientific evidences.

18.2. Public awareness need to be created through periodic interactions with the public/stakeholders held across the country. 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. Different print and electronic media modules can be exploited to this effect.

18.3. Continuous education module need to be introduced for updating the medical and scientific community.

18.4. The status of new scientific developments and innovative technologies, ethical issues related to these technologies and regulatory pathways need to be made a part of the curriculum for medical graduates.

19. Publicity and Advertisements in All Media including Electronic and Print

It may be noted that actions can be taken against the erring clinicians/entities as per the following existing rules and regulations.

19.1. The advertising and publicity through any mode by clinicians is not permitted as per Section 6 of the Indian Medical Council (Professional Conduct, Etiquettes and Ethics) Regulation. It is mandated that the MCI and Medical Councils of respective state should initiate action on the erring clinicians for violation of code of ethics prescribed by it either taking *suo moto* cognisance or acting on any complaint received by them.

19.2. The Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954 – prohibits misleading advertisements relating to drugs and magical remedies.

DGHS and relevant state authorities are mandated to take necessary action for violation of this act.

19.3. The advertisement of treatment of several diseases as listed in Schedule J of Drugs and Cosmetics Act, 1940 and Drug and Cosmetic Rules, 1945 is not permissible. Hence publicity claiming available cure for these conditions using stem cells and its derivatives is prohibited. CDSCO, DGHS and relevant state authorities are mandated to take necessary action for violation of this act.

19.4. No advertisement which violates the code for self regulation in advertising, as adopted by the Advertising Standards Council of India (ASCI), Mumbai for public exhibition, from time to time, shall be published.
https://ascionline.org/images/pdf/code_book.pdf

20. 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. The ICMR will determine from time to time the need and mechanism for implementing revisions to the document.

Documents Referred:

i. ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017.
ii. Drugs and Cosmetics Act, 1940 and Drugs and Coemetics Rules, 1945.
iii. Indian Medical Council (Professional Conduct, Etiquettes and Ethics) Regulation.
iv. Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954.
v. Guidance for FDA Reviewers and Sponsors Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)(April 2008).
vi. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (Mar 1998).
vii. Committee for Human Medicinal Product: Guideline on Human Cell-Based Medicinal Products (Jan 2007).
viii. Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations Draft Guidance for Industry(Dec 2014)
ix. Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products Draft: Guidance for Industry and Food and Drug Administration Staff (Oct 2015).
x. Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff (Dec 2014).
xi. Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (Jan 2011).
xii. International Society for Stem Cell Research Guidelines for Stem Cell Research and Clinical Translation (May 2016).
xiii. ISCT Presidential Task Force on the Use of Unproven Cellular Therapies: Reference Guide (Jan 2016).
xiv. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (April 1996).
xv. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Aug 2007).
xvi. Guidance for Industry : Certain Human Cells, Tissues, and Cellular and Tissue- Based Products (HCT/Ps) Recovered From Donors Who Were Tested For Communicable Diseases Using Pooled Specimens or Diagnostic Tests, CBER, FDA (04/2008).
xvii. Commission Directive 2006/17/EC: Implementing Directive, 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human cells. OJ, L-38/40 (February 2006).
xviii. Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). June 2002.
xix. Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products. May 2010.
xx. The Code for Self-Regulation of Advertising Content in India by ASCI https://ascionline.org/images/pdf/code_book.pdf.

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.

Adventitious agents: These are microorganisms that have been unintentionally introduced into the manufacturing process of a biological product. Include bacteria, fungi, mycoplasmas, rickettsia, protozoa, parasites, TSE agents, and viruses.

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

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 cell types of different genetic composition, produced as a result of organ transplant, grafting, or genetic engineering.

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

Clinical grade: Compatible and certified for administration into humans.

Clinical Research/Trial: 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 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 fetus) and then activating reconstituted oocyte for further development. 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 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 donor-sourced Somatic Cell Nuclear Transfer (SCNT) until 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.

***Conflict of Interest*:** A situation in which a person is in a position to derive personal benefit from actions or decisions made in their official capacity.

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 specialized cells of organs such as a heart, liver, or muscle. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions either inside or outside the cell, usually through signalling pathways involving receptor-proteins embedded in the cell surface.

Donor: A person who provides blood, an organ, or tissue or cells for transplantation, transfusion, etc.

Early embryo: The term “early embryo” covers stages of development upto 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 (which are capable of becoming 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 embryonic germ layers (ectoderm, mesoderm and endoderm).

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

Fetus: In humans, it is a developing stage from eight weeks, post fertilization, till birth.

Fetal stem cell: Stem cells derived from fetal 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 fetal germ cells, from which the gametes develop, and fetal somatic cells, from which rest of the organism develops.

Gamete: A mature male or female reproductive cell usually possessing a haploid set of chromosomes 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 a sperm (in the male).

Germ cells: Ova and sperm, and their precursors.

Germline Editing: It is a form of genetic modification that involves changing genes in eggs, sperm, or very early embryos. This type of genome modification is heritable, meaning that the modified genes could appear not only in the offspring that result from the procedure, but also in the subsequent generations.

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

Human Embryo: It is developing stage from time of fertilization until the end of the eighth week of gestation, after which it is known as a fetus.

Implantation: The embedding of a blastocyst into the uterine endometrium. In humans implantation takes place between 7-9 days after fertilization.

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

Investigator: A person who carries out a formal inquiry or investigation.

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.

Legal Guardian: A person who has the legal authority (and the corresponding duty) to care for the personal and property interests of another person, called a ward.

Mesenchymal stem cells: These are multi-potent progenitor cells originally identified in the bone marrow stroma and now isolated from different sources including umbilical cord blood, cord tissue, adipose tissue, dental pulp and other sources 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. They are capable of generating chimeric embryo/offspring and can generate a teratoma after injection into an immune-suppressed mouse.

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

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

Somatic cell: A 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.

Spongiform encephalopathy: Is kind of degenerative diseases of the brain characterized by the development of porous sponge like lesions in brain tissue and by deterioration in neurological functioning; specifically: prion disease.

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.

Vulnerable / special population: It simply implies the disadvantaged sub-segment of the community requiring utmost care, specific ancillary considerations and augmented protections in research. The vulnerable individuals' freedom and capability to protect one-self from intended or inherent risks is variably abbreviated, from decreased free will to inability to make informed choices. Vulnerable communities need assiduous attention during designing studies with unique recruitment considerations and quality scrutiny measurements of overall safety and efficacy strategies ensuing research. Vulnerable population and methods for their safeguard) include the economically disadvantaged, racial and ethnic minorities, the uninsured, low-income children, the elderly, the homeless, those with human immunodeficiency virus (HIV), and those with other chronic health conditions, including severe mental illness.

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ANNEXURES

Annexure - I

Composition and Functioning of NAC-SCRT and IC-SCR

The NGSCR have been formulated to encourage research involving stem cells and regenerative medicine leading to a pool of scientists in the country in this ever growing area of biomedical research. Because of the special characteristics of the stem cells, it is important that such research is conducted under strict compliance of NGSCR, Ethical Guidelines for Biomedical Research involving Human Participants 2006 and the existing regulatory framework.

Two levels of monitoring mechanism have been established: one at the national level focussing primarily on policy and the other, a more self-regulatory system of review at the institutional level. The National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been constituted and notified by Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India as an independent body of experts representing diverse areas of biomedical research, concerned government agencies and other stakeholders.

The Institutional Committee of Stem Cell Research (IC-SCR), on the other hand, operates at the institutional level with members having specific expertise as per these guidelines. All institutional committees are required to register with NAC-SCRT and submit periodic report on their scientific activities for effective functioning.

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

This is a multi-disciplinary committee with its Secretariat at the ICMR Headquarters, New Delhi. Main objectives of the committee are i) to serve as an advisory body to promote and facilitate stem cell research in the country; ii) to perform a comprehensive review of the therapeutic use of stem cells and formulate policies to curb unethical practices; iii) to review specific controversial or ethically sensitive issues referred to the committee.

The committee periodically assesses the adequacy of the document in light of advancements in the field and also provides a forum for discussion of issues involved in basic and clinical research. The committee reviews specific concerns referred by the IC-SCR including studies falling under the 'restrictive category'. Further, all unforeseen issues of public interest are referred to it from time to time.

1.1. Scope

1.1.1. Facilitate stem cell research for unmet need in the country

1.1.2. Examine scientific, technical, ethical, legal and social issues in the area of stem cells and/or of their derivatives.

1.1.3. Maintain a register of all institutions involved in any type of stem cell research and clinical trials undertaken. Accordingly all IC-SCRs are mandated to register with NAC-SCRT.

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

1.1.5. Approve, monitor and oversee research in 'restrictive areas' as defined in this document.

1.1.6. Periodically review and update the National Guidelines for Stem Cell Research and their possible therapeutic applications keeping pace with global scientific developments in the field.

1.1.7. In co-ordination with the CDSCO and keeping in view other existing regulations, set-up standards for safety and efficacy, quality control, procedures for collection of human stem cells or their derivatives and their schedule, processing or preparation, expansion, differentiation, preservation for storage, removal from storage to assure quality.

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

1.1.9. Address suggestions and feedback received from other government agencies and stakeholders.

1.1.10. Review unethical practices related to stem cell research (and/or therapy) being undertaken at an organization or by an individual and bring the same to the notice of competent authorities for necessary action.

1.2. Composition

The committee is constituted of the following:

Chairman, Alternative Chairman, Member Secretary, nominees from DBT, DST, CSIR/DSIR, ICMR, DGHS, CDSCO, DAE, DRDO, RHS, MCI, IMA, and biomedical experts drawn from appropriate disciplines such as Hematology, Pharmacology, Immunology, Cell Biology, Microbiology, Genetics, Developmental biology, Clinical medicine and Nursing. Other members include a legal expert, social scientist, and

women's representative. Additional subject experts could be consulted for specific topics and advice.

1.3. Frequency of meetings

Quarterly, but can be more frequent, as per the needs and requirements.

2. Institutional committee for Stem Cell Research (IC-SCR)

This is a multidisciplinary self regulatory, independently functioning body at the institutional level that oversees all stem cell related research activities and/or clinical trials in compliance with the NGSCR and existing regulatory framework. Institutions involved in stem cell research (basic science and clinical) are required to establish IC-SCR as per NGSCR and register the same with NAC-SCRT.

IC-SCR approval is mandatory for undertaking any stem cell research including clinical trials.

2.1. Scope

2.1.1. Review and approve the scientific merit of research protocols.

2.1.2. Function in compliance with the existing regulations and guidelines for stem cell research.

2.1.3. Maintain a record of all research activities involving stem cells conducted at the institution.

2.1.4. Maintain a registry of pluripotent stem cell lines (hESC/iPSC) derived or imported by individual investigators and notify the same to NAC-SCRT.

2.1.5. Submit report of the institutional stem cell research activities to NAC-SCRT annually.

2.1.6. Report all AEs/SAEs to asper the Schedule Y of Drugs and Cosmetics Rules, 1945clause 2.(2) (iv)(page 505).

2.1.7. Report all contentious issues to NAC-SCRT.

2.1.8. Facilitate training of investigators and other stakeholders engaged in stem cell research about current knowledge, international status, relevant guidelines and regulations through regular CME programs, public lectures and seminars.

2.2. Composition

The committee includes representatives of the public and persons with expertise in clinical medicine, hematology, immunology, developmental biology, stem cell

research, molecular biology, assisted reproduction technology, toxicology, other related disciplines (as per the institutional research mandate), and ethics, social sciences and law. All members should have a minimum of 5 years' experience in their respective areas of expertise.

2.3. Membership

2.3.1. The IC-SCR shall have a minimum of 9 members. Presence of Chairperson/Vice Chairperson, Legal Expert, Social Scientist, Ethics expert, 2 Stem Cell/Cell Molecular Biologists, lay-person and a Member-Secretary is mandatory. Other experts as per study requirements should be included.

2.3.2. The Chairperson/Vice-Chairperson should be from outside the institute, have a biomedical qualification with a postgraduate (medical)/doctorate degree (non-medical) and must have a minimum of ten (10) years' experience after obtaining the postgraduate/doctorate degree. The Chairman should not be affiliated to the institution and have no conflict of interest (COI).

2.3.3. Members from Law, Ethics, Social Sciences and lay-person must be from outside the institute and with no COI.

2.3.4. IC-SCR should have at least two stem cell/cell and molecular biology experts who should be from outside the institution. They should have a postgraduate (medical)/doctorate degree (non-medical) with a minimum of five (5) years' experience in the field of stem cell research after obtaining postgraduate/doctorate degree.

2.3.5. The Ethics expert should have a minimum six months training or demonstrable experience in bioethics.

2.3.6. The Social Scientist should have a postgraduate/doctorate degree in social sciences/social work.

2.3.7. The legal expert should be a law graduate with five years of experience. S/he should be well versed with the existing acts, rules, regulations and guidelines.

2.3.8. The Member Secretary should be affiliated to the institute but should not be a part of the scientific/clinical management team and must not have any COI related to stem cell research activities.

2.3.9. Persons affiliated to the institute/company such as President/Vice-President/Chairperson/Director/CEO/Dean/CSO/MD/Financial and Legal Advisers/Administrative Heads/etc. cannot be members of the IC-SCR. They cannot attend meetings of IC-SCR in any capacity.

2.3.10. Persons affiliated to the institution, except the member-secretary, cannot be members of IC-SCR. Ex-employees of the institute can become member only after 2 years of leaving the institution.

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

2.3.12. Members from funding agency (ICMR/DBT/DST/CSIR etc.) must abstain from the discussion and decision making process of any proposal funded by them.

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

2.3.14. Subject experts with no COI and not affiliated to the same institute may be invited for specific projects. The invitee will not have voting rights.

2.3.15. NAC-SCRT may nominate an observer on the IC-SCR to educate and to create awareness regarding existing guidelines and regulations.

2.3.16. Presence of the following members is mandatory for quorum and for decision making: Chairperson/Vice Chairperson, Member Secretary, Experts from Law, Ethics and Social Sciences, layperson and two stem cell/cell and molecular biology expert with appropriate expertise and no COI. In the absence of Chairperson, the Vice Chairperson can conduct the meeting.

2.3.17. The IC-SCR shall not act as an IEC. Separate approvals must be obtained from both committees for human stem cell related projects.

2.4. SOPs for functioning of IC-SCR

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

2.4.1 Composition of IC-SCR
2.4.2 Terms of reference of members
2.4.3 Review and approval process
2.4.4 Quorum and frequency of meetings
2.4.5 Monitoring and progress review of on-going research activities
2.4.6 Maintenance of records
2.4.7 Record of Conflict of Interest (COI)
2.4.8 Record of confidentiality agreement

2.5. Registration of IC-SCR

Registration of IC-SCR with NAC-SCRT is mandatory. NAC-SCRT website (http://bic.icmr.org.in/nacscrt/IC-SCR_Registration.html) should be consulted for further details. The application along with supporting documents should be

submitted to NAC-SCRT Secretariat. This will be reviewed by the committee and if satisfactory, a registration certificate is issued. The validity of certification is three years subject to compliance with the National Guidelines for Stem Cell Research.

It may be noted that the certificate is issued for the sole purpose of registration of IC-SCR with NAC-SCRT. The committee should ensure that the investigator/institution is not misusing the certificate for undue publicity or commercial gains. **The registration may be withdrawn if the practices of investigator/institute/IC-SCR are not in compliance with the NGSCR requirements.**

The IC-SCR shall inform the Secretariat in writing of any alterations in the committee composition/functioning/category of stem cell research undertaken/any other information/concerns.

Representatives of the NAC-SCRT/regulatory authorities can inspect records, data or documents related to research activities of the institute and seek clarifications/explanation to the queries, if any.

1627 ***Annexure– II***

1628 ## Clinical Trial Protocol Template

Section	Description
1.	Study title:
	Protocol ID: Phase of the study: Sponsor: CRO:
	Investigator/s and Institution/s
2.	Synopsis of the protocol (Summary)
3.	Introduction (including preclinical and clinical experience)
4.	Study rationale (including potential risks and benefits)
5.	Study objectives (primary and secondary objectives)
6.	Study design
	Number of patients
	Eligibility criteria a. Inclusion criteria b. Exclusion criteria
	Study activities a. Screening phase b. Treatment phase c. Post –treatment phase d. Follow-up
	Schedule of visits and activities at each visit
7.	Withdrawal of patients prior to study completion
8.	Safety assessment a. Definitions

	b. Documentation of adverse events c. Reporting of serious adverse events
9.	Efficacy assessment a. Primary efficacy outcome b. Secondary efficacy outcome
10.	Concomitant Medications a. Documentation of medications – name, dose, duration b. Intercurrent illness c. Prohibited medications
11.	Investigational New Entity a. CMC information b. Dosage c. Route of administration d. Cell preparation and administration instructions e. Accountability of Investigational drug/product
12.	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
13.	Ethical and Administrative Issues a. Informed consent including audio video consent from Patient /Parent/Relative b. Risks and benefits c. Approval of IEC, IC-SCR and CDSCO
14.	Data and Safety Monitoring Board (DSMB)
15.	Adherence to the protocol a. Protocol deviation/amendment
16.	Data collection, source documentation and retention of patient records
17.	Monitoring of the study and audit

18.	IPR issues (patent obtained/filed)
19.	Confidentiality
20.	References
21.	Enclosures a. CMC in case of stem cell or cell based product (if not included in Investigator brochure) b. Investigator brochure including background, rationale, product details, pre-clinical study results, human trials, references and publication list and reprints c. Case Record Form d. Manual for efficacy assessments, safety assessments, laboratory procedures etc. e. Approved patient information sheet and consent form (including audio video consent) f. MOU/MTA in case of National/International collaboration with transfer of biological materials g. Funding of the project/sponsor h. Conflict of interest declaration i. Clearances of IEC, IC-SCR and CDSCO j. Charter of DSMB k. Certificate of Registration of IEC and IC-SCR

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Annexure– III

Approved Indications for HSCT

I. Adults (generally ≥18 years of age):

S. No	Indication
1.	Acute Myeloid Leukemia (AML)
2.	Acute Promyelocyte Leukemia (APML)
3.	Acute Lymphoblastic Leukemia (ALL)
4.	Chronic Myeloid Leukemia (CLL)
5.	Myelodysplastic Syndromes (MDS)
6.	Therapy related AML/MDS
7.	Myelofibrosis & Myeloproliferative diseases
8.	Plasma Cell Disorders 8.1 Myeloma 8.2 Plasma Cell Leukemia 8.3 Relapse after autologous transplant
9.	Hodgkin Lymphoma (HL)
10.	Diffuse Large B-cell Lymphoma
11.	Follicular Lymphoma
12.	Mantle Cell Lymphoma
13.	T-cell Lymphomas
14.	**Lymphoplasmacytic Lymphomas** 14.1 Primary refractory, sensitive 14.2 Primary refractory, resistant 14.3 First or greater relapse, sensitive 14.4 First or greater relapse, resistant 14.5 Relapse after autologous transplant

15.	Burkitt's Lymphoma
16.	Cutaneous T-cell Lymphoma
17.	Plasmablastic Lymphoma
18.	Chronic Lymphocytic Leukemia (CLL)
19.	**Solid tumors** 19.1 Germ cell tumor, relapse 19.2 Germ cell tumor, refractory 19.3 Ewing's sarcoma, high risk
20.	**Non – Malignant diseases** 20.1 Severe Aplastic Anemia, new diagnosis 20.2 Severe Aplastic Anemia, relapse/refractory 20.3 Fanconi's Anemia (FA) 20.4 Dyskeratosis Congenita 20.5 Sickle Cell Disease (SCD) 20.6 Hemophagocytic Syndromes, refractory 20.7 Mast Cell Diseases 20.8 Common Variable Immunodeficiency(CVID) 20.9 Wiskott-Aldrich Syndrome (WAS) 20.10 Chronic Granulomatous Disease (CGD)

II. Pediatric (generally <18 years of age)

S. No.	Indications
1.	Acute Myeloid Leukemia (AML)
3.	Acute Lymphoblastic Leukemia (ALL)
4.	Chronic Myeloid Leukemia (CML)
5.	Myelodysplastic Syndromes (MDS)
7.	T-cell Non-Hodgkins' Lymphoma (T-NHL)

8.	Lymphoblastic B-cell Non-Hodgkins' Lymphoma (non-Burkitt)
9.	Burkitt's Lymphoma
10.	Hodgkins'Lymphoma
11.	Anaplastic Large Cell Lymphoma
12.	**Solid tumors** 12.1 Germ cell tumor, relapse 12.2 Germ cell tumor, refractory 12.3 Ewing's sarcoma, high risk or relapse 12.4 Neuroblastoma, high risk or relapse 12.5 Wilm'stumor, relapse 12.6 Osteosarcoma, high risk 12.7 Medulloblastoma, high risk 12.8 Other malignant brain tumors
13.	**Non – Malignant diseases** 13.1 Severe Aplastic Anemia, new diagnosis 13.2 Severe Aplastic Anemia, relapse/refractory 13.3 Fanconi's Anemia (FA) 13.4 Dyskeratosis Congenita 13.5 Blackfan-Diamond Anemia 13.6 Sickle Cell Disease (SCD) 13.7 Thalassemia Major 13.8 Congenital Amegakaryocytic Thrombocytopenia 13.9 Severe Combined Immunodeficiency (SCID) 13.10 T Cell Immunodeficiency, SCID variants 13.11 Wiskott-Aldrich Syndrome (WAS) 13.12 HemophagocyticDisorders 13.13 LymphoproliferativeDisorders 13.14 Severe Congenital Neutropenia 13.15 Chronic Granulomatous Disease (CGD) 13.16 Other Phagocytic Cell Disorders 13.17 Immune Dysregulation Polyendocrinopathy Enteropathy, X – linked (IPEX) Syndrome 13.18 Juvenile Rheumatoid Arthritis (JRA) 13.19 Systemic Sclerosis (SS) 13.20 Other Autoimmune and Immune Dysregulation Disorders 13.21 Mucopolysaccharoidoses (MPS-I and MPS-VI) 13.22 Other Metabolic Diseases

	13.23 Osteopetrosis 13.24 Globoid Cell Leukodystrophy (Krabbe) 13.25 Metachromatic Leukodystrophy 13.26 Cerebral X-linked Adrenoleukodystrophy

Source: Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, Omel JL, Orchard PJ, Palmer J, Saber W, Savani BN, Veys PA, Bredeson CN, Giralt SA, LeMaistre CF; American Society for Blood and Marrow Transplantation. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015 Nov;21(11):1863-9

Annexure IV

Screening of Donors for Allogeneic Transplantation

1. Cell Source and Traceability

The cells can be obtained from the following two sources:

a) *autologous:* These include mononuclear, $CD34^+$ enriched cells or mesenchymal stromal cells (MSCs) or iPS cells or stromal vascular fragment (SVF) from adipose tissue obtained from the same individual, and

b) *allogeneic:* These include mononuclear cells, preferably HLA matched $CD34^+$ HSCs or MSCs that have been isolated from various tissues under GTP practices from any healthy individual other than the recipient.

1.1 *Cell Source*: The starting cell source is bone marrow/Wharton's jelly/UCB/lipoaspirate/peripheral blood mobilised stem cells/embryos or other appropriate cell sources from healthy donors.

1.2 *Screening requirements*: Donor screening and testing can be done only after obtaining written informed consent including audio – video consent from the donor. The overall procedure for cell/tissue donation should be conducted as per the Ethics Committee approved standard operating procedures (SOPs).

1.3 *Testing:* In addition to infectious disease markers (Table 1), the donors are screened for complete hemogram, coagulation studies, blood sugar, liver function tests, renal function tests, routine urine examination, echocardiogram, and chest X-ray as given in Table 4.1.

Note: Stem cells/tissues obtained from sources such as embryos/fetuses/fetal tissues/umbilical cord and blood/placenta and others must be free from HPV/EBV/TORCH/ Parvo virus B19, and any other emerging infectious agentsin addition to those listed in Table1.

2. Inclusion criteria:

a. Healthy individuals of both sexes in the age group of 18-40 yrs.
b. Willingness and ability of the donor to comply with the program.
c. The donor should be able to comprehend the Institutional Ethics Committee (IEC) approved information, need for informed consent including audio-video consent, donor rights, voluntary nature of donation and then sign the informed consent form (ICF).

3. **Exclusion criteria:**
    a. Refusal or inability to give informed consent.
    b. An illness that precludes the use of general anaesthesia /local anaesthesia (whichever applicable).
    c. Illness like tuberculosis, malaria or any other infection.
    d. Autoimmune disorders (diabetes mellitus), hypertension, heart disease.
    e. Past history of any malignancy.
    f. Features of any genetic or chromosomal disorders.
    g. Family history of any inherited disorders.
    h. Abnormal laboratory investigations: Hb ≤ 11.0gm%, serum creatinine ≥ 2.0mg%, serum total bilirubin ≥1.0mg%.
    i. Pregnant and nursing women.
    j. Donors found positive for any of the infectious disease markers (Table 4.1).
    k. Participation in a similar donation program within the last six months.
4. **Follow up interviews:** Should be conducted with every donor at six monthly intervals after the first donation for a period of at least five years so as to record general well-being of the donor.
5. **Traceability:** All donors must be anonymised, although under special circumstances, their traceability may be needed. There should be a system in place allowing traceability of the final product to the original donor, thus facilitating tracing of cells and final disposition of each tissue derived from the donor.
6. **Cell/tissue collection:** Procedure to obtain cells/tissues along with the name and location of the collection facility, and transport conditions (if shipped to a processing facility for further manufacturing) should be documented.
7. **Record Management:** Records to be maintained concurrently with the performance of each required step in determining donor eligibility so that all steps can be clearly traced if needed. Compliance with the GTP requirements, records pertaining to cell source are to be retained at least 15 years from the date of administration to the recipient.

Table 4.1: Screening for Communicable Diseases (To be performed in NABL/CAP accredited laboratory)

S. No	Infectious agents	Tests to be done
1.	HIV, type 1& 2	Anti-HIV-1& 2
		HIV-1 Polymerase chain reaction (PCR) test or HIV-1 and HBV and HCV combination PCR test (Combination NAT)
2.	HBV (HBsAg + anti-HBc)	HBsAg
		Total anti-HBc (IgG and IgM)
		HBV nucleic acid assay (HBV deoxyribonucleic acid [DNA] by PCR) or HIV-1 and HBV and HCV combination PCR test (Combination NAT)
3.	HCV	Anti-HCV
		HCV NAT (HCV ribonucleic acid [RNA] by PCR) or HIV-1 and HBV and HCV combination PCR test (Combination NAT)
4.	Treponemapallidum	TPHA test
5.	Human T-lymphotropic virus (HTLV), types I and II	Anti – HTLV I/II
6.	CMV (Cytomegalovirus)	Anti – CMV (IgM)
		CMV PCR qualitative

Note: Emerging infectious agents should be included as and when notified.

Table 4.2: Hematological and Biochemical Investigations (To be performed in NABL/CAP accredited laboratory)

S. No.	Test	Method
1.	Blood grouping	1. ABO grouping and Rh typing
2.	Complete Haemogram	1. Hemoglobin (Hb) 2. Total Leucocyte Count (TLC) 3. Differential Leucocyte Count (DLC) 4. Platelet count 5. Peripheral smear examination
3.	Blood Sugar	1. Fasting Blood Sugar (FBS), 2. Post-prandial blood sugar (PPBS) – 2 hours after meals
4.	HbA1c	3. Blood –Glycosylated Hemoglobin (HbA1c)
5.	Renal function tests	1. BUN 2. Serum creatinine 3. Serum Sodium 4. Serum Potassium
6.	Liver function Tests	1. Total bilirubin 2. Direct bilirubin 3. Total proteins 4. Serum albumin 5. Serum globulin 6. A:G ratio 7. Alanine Aminotransferase (ALT) 8. Aspartate Aminotransferase (AST) 9. Alkaline Phosphatase (ALP)
7.	Lipid Profile	1. Lipid Profile 2. Total Cholesterol 3. Triglycerides 4. High density lipoproteins (HDL) 5. Low density lipoproteins (LDL) 6. Very low density lipoprotein (VLDL)
8.	Coagulation Studies	1. Prothrombin time (PT) 2. International Normalized Ratio (INR) 3. Activated Partial Thromboplastin Time (aPTT)
9.	Urine Routine	Microscopy and Urine routine examination (Urine pregnancy test for female donors of child bearing potential during the screening)
10.	ECG	12 Lead ECG (Electrocardiogram)
11.	Chest X ray	Posterio-anterior (PA) view

Source: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). U.S. Department of Health and Human Services. Food and Drug Administration, Center for Biologics Evaluation and Research, May 2004 &August 2007

Annexure V

Manufacturing of Stem Cells and /or their Derivatives

Institutions/entities involved in clinical research/trials using stem cells and/or their derivatives should prepare detailed SOPs on the development and manufacturing processes involved and validate the same. All requirements should be defined and justified as per the Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules, 1945.

A flow diagram explaining the entire process starting from biological specimen indicating critical steps and intermediate products (e.g. intermediate cell batches), helps to provide the above information in a succinct manner. The Chemistry, Manufacturing and Control (CMC) requirements of the product are summarised below:

a) Describe the degree of manipulation(s) required for cell processing and document the physiological function of cells.
b) Document information on procedures used for transportation/shipment of the materials during the manufacturing process of the product, including storage conditions and holding times.
c) Attention should be paid to biodegradable materials, which may have the potential for undergoing environmental changes (raised pH, temperature, humidity, specific handling etc.) for the cells during the manufacturing process.
d) The manufacturing area should be separated from the procurement area so as to avoid the risk of cross contamination during each step of the procedure, e.g. via processing equipment or in storage containers such as liquid nitrogen tanks.
e) Facility requirements should be complied with the GMP, prescribed for aseptic manufacturing as per Schedule M of Drugs and Cosmetics Act, 1940.
f) Equipment and premises used for manufacturing should fulfil conditions of aseptic production. It is recommended that dedicated, product-specific or single-use equipment be used in the production process, whenever possible.

The following procedures should be included in the CMC:

1. Cell Collection/Processing/Culture Conditions:

i. The volume and number of cells/tissue collected.
ii. Detailed procedure for collection (with respect to the type of enzyme, media, etc.) along with validation.

iii. Procedure(s) used to isolate and/or purify the cell population of interest along with validation for the intended use.
iv. Use of cell selection or separation device, including density gradient, magnetic beads, or fluorescence activated cell sorting (FACS) systems.
v. Culture systems whether closed or open along with use of flasks, bags etc.
vi. All in-process quality control testing parameters and procedures. Consideration should be given to the degree of disruption applied to the tissue in order to preserve the intended functional integrity of the cellular preparation and to minimize cell-derived impurities in the product (cell debris, cross contamination with other cell types).

2. Cell culture

During *in vitro* cell cultures, consideration should be given to the use of clinical grade reagents and culture media. Ensure acceptable kinetic growth and manipulation of the isolated cells. Level of manipulation of cells through physical, chemical and/or genetic treatments, if any, should be documented.

i. Processing steps required to preserve the integrity and function of the cells.
ii. Detailed procedures employed for any manipulation, with close monitoring as per the specific process controls.
iii. Duration of cell culture and the number of cell passages along with validation.
iv. Relevant genotypic and phenotypic characteristics of the primary cell cultures, of the established cell lines and of the derived cell clones and their stability with respect to culture longevity.
v. Consistency/reproducibility of the cell culture process and culture conditions including the media and duration with respect to the intended clinical function of the cells.
vi. Special consideration should be given to the growth potential of cells in response to growth factors since cell subpopulations may gain a growth advantage under defined *in vitro* culturing conditions.

3. Final Cell Harvest

i. If the final cell harvest is centrifuged prior to final formulation, description of the wash conditions and media used.

ii. Whether cells/products are manufactured for immediate use or cryopreserved after formulation.

iii. If the final harvest is stored, description of the storage conditions, length of storage, and appropriate supporting data.

4. Process Timing and Intermediate Storage

Approximate time elapsed for each step from cell collection to final harvest to be recorded

i. Time limit of each step involved in production to be noted to determine in-process checks, if any.

ii. If cells are cryopreserved, this information to be included along with stability and viability data.

iii. Time and conditions of storage of the product prior to patient administration.

5. Final Formulation

Describe formulation of the final product, including excipients such as growth factors or human serum albumin. List of all excipients/components with defined specifications and source used during manufacturing of the final product that are intended to be present in the final product should be provided.

i. State the source of these components.

ii. Identify the vendor and final concentration of excipients and describe the cell density or cell concentration used in the final product.

iii. If the final product is delivered to the clinical site in frozen state, before administration to the patient, mention procedures/instructions about shipment and thawing before use. Data generated about the stability/viability of product during such processes should be released.

Annexure -VI

Release Criteria for stem cells and/or their derivatives

The release criteria for stem cells and derivatives are of critical importance and researchers/stakeholders are required to follow the specifications under which the final product is considered for their intended use. The characteristics of the final product as mentioned in the release criteria must be complied with and includes –

1. Cell identity

For the final product, identity testing is important to ensure that the contents of the vial are labeled appropriately. It is recommended to verify the identity of the Master Cell Bank, Working Cell Bank, and the final product by assays that will identify the product and distinguish it from others being processed in the same facility. The identity of the cells should be confirmed by appropriate genotypic and/or phenotypic markers, and the fraction of the cell population having such identity markers measured as an indication of purity.

a) Assess cell identity quantitatively by monitoring cell surface antigens or biochemical markers. Method of identification should be able to detect contamination or replacement by other cells in use in the facility.
b) Define acceptable limits for culture composition.
c) Identify and validate quantitative assays for functional potency.
d) Monitor the desired function when the cells are subjected to manipulation. Tests should be carried out periodically to assure that the desired trait is retained.

2. Cellular Component

Identity of the cellular components in relation to phenotypic and/or genotypic profile should be carried outdepending on the cell population and origin.

a) Employ relevant markers for cell phenotyping. These markers are based on gene expression, antigen presentation, biochemical activity, response to exogenous stimuli, capability to produce biologically active or otherwise measurable molecules.
b) For adherent cells, morphological analysis may be a useful tool in conjunction with other tests. Where applicable, provide detailed description of the procedures that could lead to modification of the

product characteristics including adhesion, absorption, degradation, and components of the culture media.

c) For identity of cellular components of allogeneic origin, include histocompatibility testing, whereever applicable, and perform other genetic polymorphisms with specific reference to the intended use.

d) Define essential characteristics of the cultured cell population (phenotypic markers such as cell surface antigens, functional properties, activity in bioassays, as appropriate), and establish stability of these with respect to time in culture. This profile should be used to define limits of the culture period.

3. Non-cellular Components of the active substance:

All non-cellular components should be appropriately characterized and identity parameters established:

a) If the finished product contains a distinct active substance in addition to the cellular component, the same should be characterized with respect to identity in accordance to relevant guidelines, depending on the nature of the active substance, whether chemical or of biological origin.

b) Structural components designed to support the cellular components such as scaffolds or membranes should be identified and characterized with respect to their composition and structural characteristics.

4. Cell purity

Product purity is defined as relative freedom from extraneous material in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity testing includes assays for pyrogenicity/endotoxin, residual proteins or peptides used to stimulate or pulse cells, reagents/components used during manufacture, such as cytokines, growth factors, antibodies and serum and unintended cellular phenotypes.

a) The cellular population of interest could contain other cells that are of different lineages and/or differentiation stage or that may be unrelated to the intended population.

b) Where a specific cell type is required for the indication, the unwanted cells (such as cell debris, or based on CD markers) should be defined and their amount in the final product controlled by appropriate

specifications. Acceptance criteria for the amount of contaminating cells should be set.

c) Where the desired biological activity and efficacy of the product requires a complex mixture of cells, the same should be characterized and its composition controlled by appropriate in-process controls and release testing.

d) Irrespective of the cell type, the cell population can get contaminated with non-viable cells. Since cell viability is an important parameter for product integrity and is directly correlated to the biologic activity, the ratio between non-viable and viable cells should be determined and specification limits should be defined.

5. Impurities

The appropriate purity testing should include assays for residual peptides and proteins used during production and purification, and reagents used during manufacture, such as cytokines, growth factors, antibodies, beads, and serum. Appropriate purity testing should include a measurement of contaminating cell types or cell debris.

a) Product or process-related: During the production of stem cells and/or derivatives, variable amounts of impurities, product and process-related, may be introduced into the final product. Any reagents known to be harmful in humans should be analyzed in the final product (or in individual components if otherwise not possible) and acceptance criteria should be defined. Specification limits should be justified by levels detected in batches used for toxicological and/or clinical studies. Any material capable of introducing degradation products into the product during production (e.g. biodegradable materials), should be thoroughly characterized and the impact, if any, of the degradation products to the cell component(s) should be addressed.

b) Adventitious agents: A critical aspect is to establish that the product is free from adventitious microbial agents (viruses, mycoplasma, bacteria, and fungi). The contamination could originate from the starting or raw material stage or adventitiously introduced during the manufacturing process.

i. A risk assessment should be performed to evaluate the possibility of reactivation of cryptic (integrated, quiescent) forms of adventitious agents.
ii. A thorough testing for the absence of bacteria, fungi and mycoplasma should be performed at the level of finished product.
iii. In cases where the short shelf life of the product is prohibitive for the testing of absence of bacteria, alternative validated testing methods may be acceptable, if justified.

c) Pyrogenicity/Endotoxin: Define the pyrogenicity/endotoxin testing conducted, and the acceptance criterion for release.
i. The Limulus Amebocyte Lysate test method (LAL) is the required method for testing biological products for pyrogenic substances (validated prior to licensure).
ii. The rabbit pyrogen test method is also one of the methods for testing biological products for pyrogenic substances.

6. **Viability:** The viability of the cells should be quantitated and a lower limit for acceptability established.

7. **Potency:**

Potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties. The assay demonstrating the biological activity should be based on the intended biological effect which should ideally be related to the clinical response. If development of a quantitative biological assay is not possible, then a quantitative physical assay which correlates with and is used in conjunction with a qualitative biological assay can be used.

a) A suitable potency assay should already be in place when material for the first clinical trial is produced and it should be validated prior to pivotal clinical trials.
b) Lot release and shelf life specifications for potency should be determined and amended during product development, if appropriate.
c) Major cellular functions such as viability, self renewal, death and differentiation are pivotal to the quality, function and sustainability of the product. The product needs to be monitored during production and at release using surrogate markers and appropriate technology (e.g. gene

expression profiles by microarrays, flow cytometric immune fluorescent analysis, cell cloning, PCR and many others).

d) Markers for purity and those for potency should not be mixed in the same assay.

e) A combination of multiple methods may be needed to adequately define the potency of cell-based products during development. Certain assays may be needed to control process changes, whereas others are more suitable for release testing.

f) Potency assays of stem cell based pharmaceutical product intended for immunotherapeutic use will be based on complex immune mechanisms which may be complicated by multi-antigen formulations and inherent variability of the starting material.

8. Tumorigenicity

The tumorigenicity of stem cell product differs from the classical pharmaceutics. The transformation can happen due to chromosomal instability of stem cell and its derivatives and due to host factors in the treated individual. Therefore testing of chromosomal integrity and tumorigenicity of product is necessary before final product release.

The outcome of these release criteria testing should be available prior to administration to a human subject. If results from final product testing will not be available prior to release, it is recommended that the same is indicated in the clinical trial application, together with your specifications, and include a description of the reporting notification process if the acceptance criteria are not met.

Certain release tests can be performed only on key intermediates and/or as in-process tests. In all such cases, an adequate quality control should be in place from the manufacturing process, supported by the results of the clinical studies. These exceptions may include the following:

a. Some release tests might not be feasible on the combined components of the active substance/ finished product for technical reasons.

b. A complete release testing cannot be finalized before the product is administered to the recipient due to time restrictions (e.g. in case of autologous products, which are administered immediately after

completion of the production and initial testing). However, a critical set of essential tests that can be performed in the limited time prior to clinical use must be defined and justified. Whenever feasible, retention samples should be stored for future analysis.

c. In case of allogeneic stem cells, product can be released only after complete testing as per defined specifications.

d. The amount of available product is limited to the clinically necessary dose (e.g. due to very limited cell numbers at collection or low proliferation rates). Release of the product should be justified by the validation of cell manipulation process and in-process controls.

The release criteria specifications for the final product (tests for safety, purity, potency, and identity and acceptance criteria) should be provided in format as given in Table 6.1:

Table 6.1: Release criteria for stem cell products for clinical applications

S. No.	Test	Test Method	Specification
1	Description	Microscopic Observation	Description of cells seen
2	Cell count	Automated Dye Exclusion (done by automated counter)	Cell numbers to be specified
3	Viability	DNA Staining by 7AAD (Flow cytometry)	≥ 70 %
4	Bacterial Endotoxins	Gel clot	Specification to be set
5	Mycoplasma	PCR ELISA	Not Detected
6	Sterility Test	Direct inoculation	Must comply
7	Purity	Immunophenotyping (Flow Cytometry)	≥ 80% of final cell population to express appropriate cell surface markers, ≤ 10% of undesirable cell types
8	DNA Ploidy	Propidium Iodide Staining (Flow cytometry)	Normal
9	Differentiation assay (if applicable)	Monolayer culture and staining	Description

S. No.	Test	Test Method	Specification
	Adipocyte		
	Osteocyte	Monolayer culture and staining	Description
	Chondrocyte	Micro mass culture and staining	Description
10	Karyotyping	GTG-Banding	Normal
11	Infectious Disease Testing: HIV – I	Quantitative real time PCR	Negative
	HIV – II	Qualitative real time PCR	
	HBV	Quantitative real time PCR	
	HCV	Quantitative real time PCR	
	CMV	Quantitative real time PCR	
	EBV	PCR	
	Parvo virus B 19	PCR	
12.	Appropriate potency assay	Method to be described	Limits to be specified
13.	BSA estimation (if fetal calf serum used)	ELISA	Limits to be specified
14.	Trypsin Estimation (if used)	ELISA	Limits to be specified

9. Labelling, Packaging

The product labelingshould be maintained throughout the manufacturing process and should be described on the final product container.

a. The label for an investigational product must contain the following statement: “Caution: New Drug – Only for Investigational Use.”

b. To minimize the potential mix-ups, label should contain the date of manufacture, storage conditions, expiration date and time (if appropriate), product name, and two non-personal patient identifiers For autologous donors and other situations for which a donor eligibility determination is not required, appropriate applicable labelling to be done. For example, for autologous cells intended for autologous use one

must label the product "FOR AUTOLOGOUS USE ONLY" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" if donor testing and screening is not performed.

10. Shipping and Transport

a. If the product is shipped from the manufacturing site to the clinical site, describe the time and shipping conditions (e.g., packaging, temperature). The stability protocol should be adequate to demonstrate that product integrity, sterility, and potency are maintained under the proposed shipping conditions.

b. If the final product is delivered in frozen state to the clinical site, it is recommended to include a description of how the product will be shipped and data to show that the product can be thawed with consistent results.