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 the following statements:

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

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

15.2.7.7 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 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 (Available at: 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.

16.4 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 HMSC. Similar clearances would need to be obtained if the trial/study is supported by other public/ private organizations.

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/No Objection Certificate (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.

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 human applications during 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 19 November, 1997 of the Ministry of Health) on import/export of biological materials. (Available at: http://www.icmr.nic.in/min.htm) and DGFT Notification No. 19 /2015-2020 dated, 4 August, 2016. (Available at: http://dgft.gov.in/Exim/2000/NOT/NOT16/noti1916.pdf).

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 19 November, 1997 of the Ministry of Health) (Available at: 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 used 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

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 Chapter 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* cognizance or acting on any complaint received by them. (Available at: https://www.mciindia.org/documents/rulesAndRegulations/Ethics%20Regulations-2002.pdf)

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. (Available at: http://lawmin.nic.in/ld/P-ACT/1954/A1954-21.pdf).

19.3 The advertisement of treatment of several diseases as listed in Schedule J of Drugs and Cosmetics Act, 1940 and rules therein (*Annexure VII)* 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. (Available at: 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:

1. ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017.
2. Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules, 1945.
3. Indian Medical Council (Professional Conduct, Etiquettes and Ethics) Regulation.
4. Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954.
5. 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).
6. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (Mar 1998).
7. Committee for Human Medicinal Product: Guideline on Human Cell-Based Medicinal Products (Jan 2007).
8. Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations Draft Guidance for Industry(Dec 2014)
9. Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products Draft: Guidance for Industry and Food and Drug Administration Staff (Oct 2015).
10. Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff (Dec 2014).
11. Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (Jan 2011).
12. International Society for Stem Cell Research Guidelines for Stem Cell Research and Clinical Translation (May 2016).
13. ISCT Presidential Task Force on the Use of Unproven Cellular Therapies: Reference Guide (Jan 2016).
14. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (April 1996).
15. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Aug 2007).
16. 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).
17. 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).
18. 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.
19. 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.
20. The Code for Self-Regulation of Advertising Content in India by ASCI (Available at: 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 bio-technological 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.

Drug: As per Drugs and Cosmetics Act, 1940, drug includes—

i. all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;

ii. such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of 6 [vermin] or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;

iii. all substances intended for use as components of a drug including empty gelatin capsules; and

iv. such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board

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 spongelike 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 freewill 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.

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, National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 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. It is mandatory for them 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 Examine scientific, technical, ethical, legal and social issues in the area of stem cells and/or of their derivatives.

1.1.2 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.

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

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

1.1.5 Periodically review and update the National Guidelines for Stem Cell Research and possible therapeutic applications of stem cells keeping pace with global scientific developments in the field.

1.1.6 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.

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

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

1.1.9 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.

1.1.10 NAC-SCRT may sent their nominee as an observer on IC-SCR.

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

The meeting may take place quarterly, but can be more frequent, as per the needs and requirements.

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

This is a multi disciplinary 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 NAC-SCRT.

2.1.7 Seek advice from NAC-SCRT on any contentious issue.

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 Continuing Medical Education (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. The experts should be invited as per the subject area of the projects under consideration for review.

2.3. Membership

2.3.1 The IC-SCR shall have a minimum of 11 members. Other experts as per study requirements should be included.

2.3.2 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, community/lay-person 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. The members of quorum except the Member Secretary should never have been affiliated to the institution.

2.3.3 Persons affiliated to the institution, except the Member-Secretary, cannot be members of IC-SCR. Ex-employees of the institute can become a member only after two (2) years of leaving the institution.

2.3.4 The Chairperson/Vice-Chairperson should have biomedical qualification with a postgraduate (medical)/doctorate degree (non-medical) with minimum of ten (10) years' experience after obtaining the postgraduate/doctorate degree.

2.3.5 Members from law, ethics, social sciences and community/lay-person must be from outside the institute and with no COI.

2.3.5.1 All members should have a minimum of five (5) years' experience after postgraduation in their respective areas of proficiency except for community/lay-person.

2.3.5.2 The legal expert should be a law graduate with five (5) years of experience. S/he should be well versed with the existing acts, rules, regulations and guidelines.

2.3.5.3 The social scientist should have a postgraduate/doctorate degree in social sciences/social work.

2.3.5.4 The ethics expert should have a minimum six months training or demonstrable experience in bioethics.

2.3.6 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.

2.3.7 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.

2.3.8 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.

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

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

2.3.11 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.

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

2.3.13 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 (Available at: 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.

Annexure– II

Clinical Trial Protocol Template

Section	Description
1.	Study title:
	Protocol ID: Phase of the study: Sponsor: Contract Research Organization (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 b. Exclusion
	Study activities: Phase a. Screening b. Treatment c. Post –treatment 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: Outcome a. Primary efficacy b. Secondary efficacy
10.	Concomitant Medications a. Documentation of medications – name, dose, duration b. Intercurrent illness c. Prohibited medications
11.	Investigational New Entity a. Chemistry Manufacturing and Control (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 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.	Intellectual Property Rights (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

Annexure– III

Approved Indications for Hematopoetic Stem Cell Transplantation (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'sAnemia (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's tumor, 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 Hemophagocytic Disorders 13.13 Lymphoproliferative Disorders 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 mobilized 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 *Genetic and Travel History*: Detailed travel and genetic history of the donor should be recorded before initiating screening and testing.

1.4 *Testing:* In addition to infectious disease markers (Table 4.1), 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 4.2.

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 agents in addition to those listed in Table 4.1.

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 anesthesia/local anesthesia (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 ≤ 11.0 gm%, serum creatinine ≥ 2.0 mg%, serum total bilirubin ≥ 1.0 mg%.
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 anonymized, 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. **Management of Records:** 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	1. 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)

S. No.	Test	Method
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 rules therein.

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 summarized 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 and Rules therein.

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 sub-populations 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 which includes –

1. Product 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 determine the identity of 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) Quantitative assessment of product identity 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 out depending 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, wherever 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 thesewith respect to time in culture. This profile should be used to define limits of the culture period.

3. Non-cellular Components or 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. Product 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 cell 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 viable and non-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.

i. 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.

ii. Lot release and shelf life specifications for potency should be determined and amended during product development, if appropriate.

iii. 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).

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

v. 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.

vi. 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.

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:

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

ii. 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.

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

iv. 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 Description	Test Method	Specification
1	Morphology	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
	Adipocyte		
	Osteocyte		
	Chondrocyte	Micro mass culture and staining	
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		
	CMV		
	EBV	PCR	
	Parvo virus B 19		

S. No.	Test Description	Test Method	Specification
	Appropriate potency assay	Method to be described	Limits to be specified
	BSA estimation (if fetal calf serum used)	ELISA	
	Trypsin estimation (if used)		

9. Labelling and Packaging

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

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

ii. To minimize the potential mix-ups, label should contain the date of manufacture, storage conditions, expiry 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 is 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

i. If the product is shipped from the manufacturing to the clinical site, specify the time and describe 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.

ii. 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.

Annexure VII

SCHEDULE J of Drugs and Cosmetics Rules, 1945

Diseases and ailments (by whatever name described) which a drug may not purport to prevent or cure or make claims to prevent or cure.

1. AIDS
2. Angina Pectoris
3. Appendicitis
4. Arteriosclerosis
5. Baldness
6. Blindness
7. Bronchial Asthma
8. Cancer and Benign tumour
9. Cataract
10. Change in colour of the hair and growth of new hair.
11. Change of foetal sex by drugs.
12. Congenital malformations
13. Deafness
14. Diabetes
15. Diseases and disorders of uterus.
16. Epileptic fits and psychiatric disorders
17. Encephalitis
18. Fairness of the skin
19. Form, structure of breast
20. Gangrene
21. Genetic disorders
22. Glaucoma
23. Goitre
24. Hernia
25. High/low Blood Pressure
26. Hydrocele
27. Insanity
28. Increase in brain capacity and improvement of memory.
29. Improvement in height of children/adults.
30. Improvement in size and shape of the sexual organ and in duration of sexual performance
31. Improvement in the strength of the natural teeth.
32. Improvement in vision
33. Jaundice/Hepatitis/Liver disorders
34. Leukaemia
35. Leucoderma
36. Maintenanceor improvement of the capacity of the human being for sexual pleasure.
37. Mental retardation, subnormalities and growth
38. Myocardial infarction
39. Obesity
40. Paralysis
41. Parkinsonism
42. Piles and Fistulae
43. Power to rejuvenate
44. Prematureageing
45. Premature greying of hair
46. Rheumatic Heart Diseases
47. Sexual Impotence, Premature ejaculation and spermatorrhoea
48. Spondylitis
49. Stammering
50. Stones in gall-bladder, kidney, bladder
51. Vericose Vein

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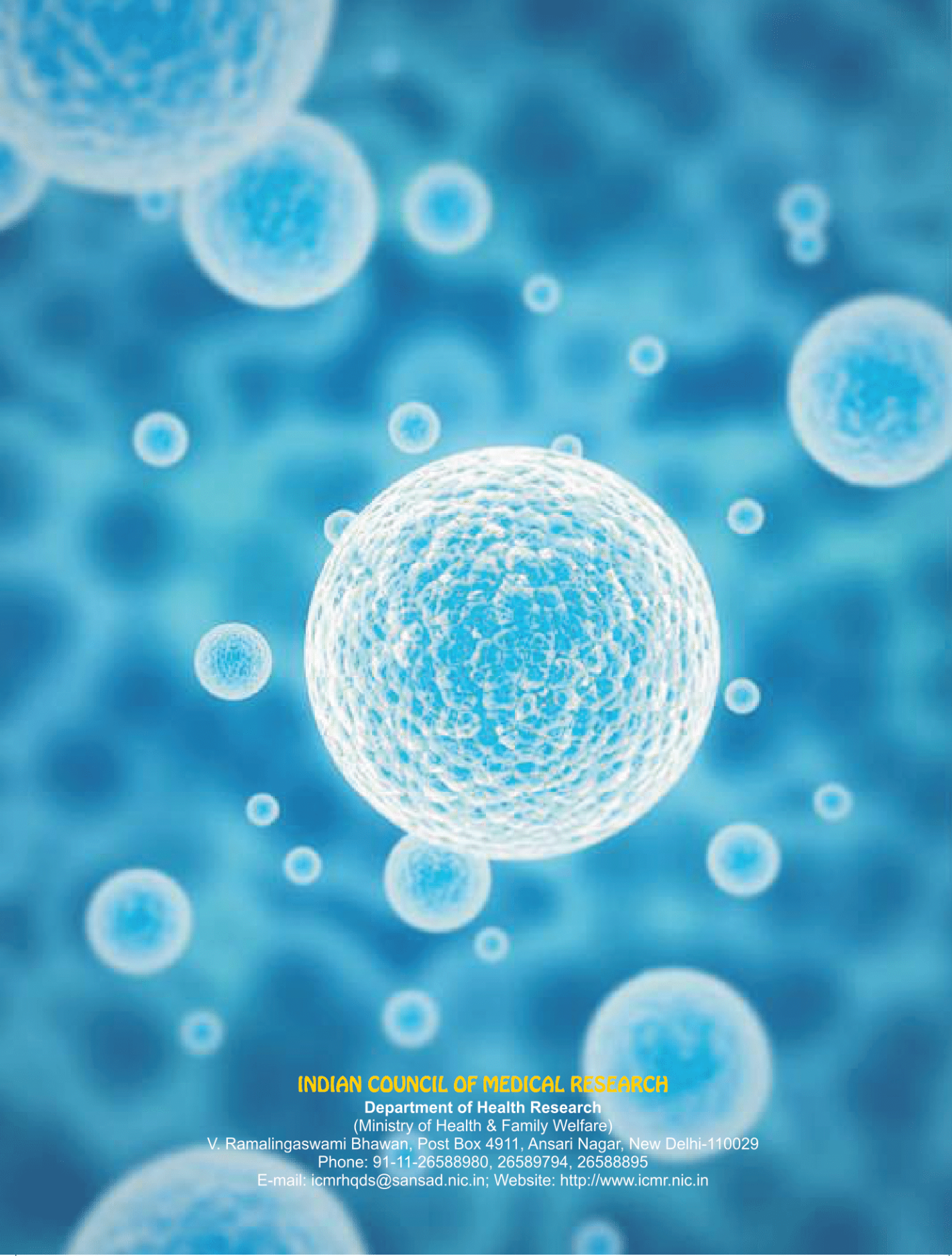

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