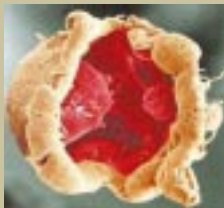


Guidelines for Stem Cell Research and Therapy



सत्यमेव जयते

Department of Biotechnology
&
Indian Council of Medical Research

2007

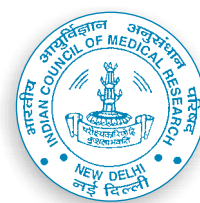


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सत्यमेव जयते



Foreword

Great promise for improvements in human health are offered by research using human stem cells, both adult and embryonic. Like many scientific advances, these technologies raise questions about balancing the promises offered against the potential harm for appropriate application.

Few advances in Science and Technology have generated as much controversy as the use of human embryonic stem cells (hESCs) harvested from the pre-implantation embryos. The potential of hESCs to replace dead or damaged cells in any tissue of the body heralds the advent of a new field of medicine that may deliver cures for diseases now thought to be incurable. In addition, hESCs offer a new model system for studies on the basic mechanisms of normal and abnormal development biology as also for drug discovery. These remarkable cells have captured the imagination of scientists and clinicians alike and given a new sense of hope to patients.

In addition, stem cell research raises many ethical, legal, scientific, and policy issues that are of concern to the policy makers and public at large. Guidelines for Stem Cell Research and Therapy has been prepared for adult, cord blood and embryonic stem cells in response to the support provided by the Government to facilitate stem cell research in India so as to improve understanding of human health and disease, and evolve strategies to treat serious diseases.

These guidelines address both ethical and scientific concerns to encourage responsible practices in the area of stem cell research and therapy. Since the latter is being contemplated with greater vigour in India it was necessary to formulate guidelines for development of clinical grade stem cells. Therefore, a separate chapter on 'Standards for Progenitor Cells Collection, Processing and Transplantation' for India has been added to facilitate development of such cells by Indian researchers.

The Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) gratefully acknowledge the valuable contributions of the Drafting Committees of ICMR and DBT.

Dr. M. K. Bhan

Secretary

Department of Biotechnology

Dr. N. K. Ganguly

Director General

Indian Council of Medical Research

Acknowledgement

This is to acknowledge with gratitude the contributions made during the last six years by the members of the Expert Groups for drafting guidelines for 'Stem Cell Research and Therapy' during the innumerable meetings held by both agencies, Indian Council of Medical Research and Department of Biotechnology, for finalizing them keeping in view the newer developments occurring in stem cell research and therapy and the relevance of their application in India. It is hoped that this spirit will continue to guide future modifications to keep pace with further new developments in this area.

The Bioethics Cell of the Council gratefully acknowledges the valuable contribution of Dr. S. S. Agarwal, Dr. A. N. Bhisey, Dr. Alok Srivastava and Dr. D. Balasubramaniam for finalization of these guidelines. Special thanks are due to Prof. Ann McLaren of Cambridge, UK for her valuable comments on the document before finalisation.

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The contributions of Dr. Geeta Jotwani in the compilation of these guidelines during the entire process of formulation and that of Dr. Nandini K. Kumar and Dr. Alka Sharma in providing the necessary inputs are highly appreciated. The support provided by Mrs. Neelam Chaudhary and Mr. J. N. Mathur for designing and publishing the document is also placed on record.

New Delhi
November 2007

Vasantha Muthuswamy
Senior Deputy Director General
Indian Council of Medical Research

Abbreviations

NAC-SCRT	- National Apex Committee for Stem Cell Research and Therapy
IC-SCRT	- Institutional Committee for Stem Cell Research and Therapy
IEC	- Institutional Ethics Committee
IAEC	- Institutional Animal Ethics Committee
IVF	- In-vitro Fertilization
SCNT	- Somatic Cell Nuclear Transfer
DCGI	- Drugs Controller General of India
ICMR	- Indian Council of Medical Research
DBT	- Department of Biotechnology
DST	- Department of Science and Technology
HMSC	- Health Minister's Screening Committee
hES Cells	- Human Embryonic Stem Cells
hEG Cells	- Human Embryonic Germ Cells
hSS	- Human Somatic Cells
GLP	- Good Laboratory Practices
GTP	- Good Tissue Practices
GMP	- Good Manufacturing Practices
GCP	- Good Clinical Practices
SOP	- Standard Operative Procedures
BMT	- Bone Marrow Transplantation
GOI	- Government of India
MOU	- Memorandum of Understanding
SCID	- Severe Combined Immunodeficiency Disease
HLA	- Human Leukocyte Antigens

Guidelines for Stem Cell Research and Therapy

1.0 Introduction

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

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

2.0 Aims and scope

- 2.1 To lay down general principles for stem cell research and therapy keeping in view the ethical issues.
- 2.2 To formulate specific guidelines for derivation, propagation, differentiation, characterization, banking, and use of human stem cells for research and therapy.

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

3.0 General principles

Any research on human beings, including human embryos, as subjects of medical or scientific experimentation, shall adhere to the general principles outlined in the "Ethical Guidelines for Biomedical Research on Human Participants" issued by the Indian Council of Medical Research

(ICMR) 2000, and revised in 2006 (www.icmr.nic.in/bioethics). The same in brief are enumerated below:

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

4.0 Mechanism for review and monitoring

The area of stem cell research being new and associated with rapid scientific developments and complicated ethical, social and legal issues requires extra care and expertise in scientific and ethical evaluation of research proposals. Hence, a separate mechanism for review and monitoring is essential for research and therapy in the field of human stem cells, one at the National level called as **National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)** and the other at the institutional level called **Institutional Committee for Stem Cell Research and Therapy (IC-SCRT)**. The composition and functions of NAC-SCRT and IC-SCRT are given in Annexure I.

- 4.1 All institutions and investigators, both public and private, carrying out research on human stem cells should be registered with the NAC-SCRT through IC-SCRT.
- 4.2 All research studies using human stem cells shall have prior approval of IC-SCRT for permissive research as given in these guidelines, and of the NAC-SCRT for restricted research, also defined in these guidelines.
- 4.3 All new human stem cell lines shall be created, with prior approval of IC-SCRT/NAC-SCRT as applicable
- 4.4 All established human stem cell lines from any source, imported or created in India, should be registered with IC-SCRT and NAC-SCRT. Permission for import/procurement from other Indian laboratories shall be obtained from IC-SCRT. The investigator shall ensure that the cell line has been established in accordance with existing guidelines of the country. An appropriate MTA shall be adopted for the purpose.
- 4.5 All clinical trials with any stem cells shall have prior approval of IC-SCRT, Institutional Ethics Committee (IEC) and Drug Controller

General of India (DCGI) for marketable product; and shall be registered with the NAC-SCRT; except that International Collaboration shall also have prior approval of NAC-SCRT and respective funding agency as per its procedure / or Health Ministry's screening committee (HMSC).

5.0 Classification of human stem cells

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

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

- 5.1.1 Blastocysts derived from surplus embryos from IVF clinics.
- 5.1.2 Blastocysts derived specifically for research or therapy using IVF.
- 5.1.3 Blastocysts derived by other techniques like SCNT etc.

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

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

6.0 Categorization of research on stem cells

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

- Permissible research areas
- Restricted research areas
- Prohibited research areas

6.1 Permissible areas of research

- 6.1.1 *In-vitro* studies on established cell lines from any type of stem cell viz. hES, hEG, hSS; or fetal/adult stem cells may be carried out with notification to IC-SCRT, provided the cell line is registered with the IC-SCRT/NAC-SCRT and GLP is followed.
- 6.1.2 *In-vivo* studies in small animals with established cell lines from any type of stem cells viz., hES, hEG, hSS, including differentiated derivatives of these cells, with prior approval of IC-SCRT and IAEC, provided such animals are not allowed to breed. This includes pre-clinical evaluation of efficacy and safety of human stem cell lines or their derivatives.
- 6.1.3 *In-vivo* studies on experimental animals (other than primates) using *fetal/adult somatic stem cells* from bone marrow, peripheral blood, umbilical cord blood, skin, limbal cells, dental cells, bone cells, cartilage cells or any other organ (including placenta), with prior approval of the IC-SCRT and IEC, and IAEC provided appropriate consent is obtained from the donor as per guidelines provided in this document.

- 6.1.4 Establishment of new hES cell lines from spare, supernumerary embryos with prior approval of the IC-SCRT and IEC provided appropriate consent is obtained from the donor as per guidelines given below. Once the cell line is established, it shall be registered with the IC-SCRT and NAC-SCRT.
- 6.1.5 Establishment of Umbilical Cord stem cell bank with prior approval of the IC-SCRT/IEC and DCGI following guidelines given in this document for collection, processing, and storage etc. Appropriate SOPs to be approved by the IC-SCRT/IEC.
- 6.1.6 Clinical trials with cells processed as per National GTP / GMP guidelines (minimally manipulated or manipulated with alteration in functionality or genetic characteristics) may be carried out with prior approval of IC-SCRT/ IEC/DCGI as applicable. All clinical trials on stem cells shall be registered with NAC-SCRT through IC-SCRT.
 - 6.1.6.1 Clinical use is not permitted
 - 6.1.6.1.1 until the efficacy and safety of the procedure is established;
 - 6.1.6.1.2 the origin, safety and composition of the product is adequately defined and labeled;
 - 6.1.6.1.3 conditions for storage and use is given in detail;
 - 6.1.6.1.4 Release form and infusion formalities are required as for blood transfusion with long term follow-up
 - 6.1.6.2 Levels of manipulations (processing) are categorized as given below
 - 6.1.6.2.1 **minimal manipulation** – no major alterations in cell population or alterations of function (use of antibodies, cytokines etc);
 - 6.1.6.2.2 **moderate manipulation** – defined alterations in cell population (T cell depletion, cancer cell depletion), expansion etc. expected alteration in function;
 - 6.1.6.2.3 **major manipulation** – such as genetic alteration by insertion of gene/siRNA etc.

6.2 Restricted areas of research

- 6.2.1 Creation of a human zygote by IVF, SCNT or any other method with the specific aim of deriving a hES cell line for any purpose.
 - Specific justification would be required to consider the request for approval by the NAC-SCRT through IC-SCRT /IEC.
 - It would be required to establish that creation of zygote is critical and essential for the proposed research
 - Informed consent procedure for donation of ova, sperm, somatic cell or other cell types as detailed in these guidelines would

need to be followed.

- 6.2.2 Clinical trials using cells after major manipulation (defined under 13.0), or those sponsored by multinationals involving stem cell products imported from abroad shall require prior approval of the NAC-SCRT through IC-SCRT/IEC, DCGI and respective funding agency as per its procedure or Health Ministry's Screening Committee (HMSC). The process of this consideration must be completed within 3 months of the receipt of the proposal.
- 6.2.3 Research involving introduction of hES/hEG/hSS cells/cell lines into animals including primates, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into non- human animal tissues.
 - If there is a possibility that human cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for the experiments must be strong. *The animals derived from these experiments shall not be allowed to breed.*
 - Such proposals would need approval of the NAC-SCRT for additional oversight and review through Institutional Animal Ethics Committee (IAEC) and IC-SCRT/IEC.
- 6.2.4 Studies on chimeras where stem cells from two or more species are mixed and introduced into animals including primates, at any stage of development viz., embryonic, fetal or postnatal, for studies on pattern of development and differentiation.
- 6.2.5 Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator.

6.3 Prohibited areas of research

- 6.3.1 Any research related to human germ line genetic engineering or reproductive cloning.
- 6.3.2 Any *in-vitro* culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier
- 6.3.3 Transfer of human blastocysts generated by SCNT or parthenogenetic or androgenetic techniques into a human or non-human uterus.
- 6.3.4 Any research involving implantation of human embryo into uterus after *in-vitro* manipulation, at any stage of development in humans or primates.
- 6.3.5 Animals in which any of the human stem cells have been introduced at any stage of development should not be allowed to breed.

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

7.0 Clinical use of umbilical cord blood stem cells

Cord blood stem cell banking is permissible. However, all Cord blood banks should be registered with the DCGI as per guidelines applicable to the blood banks. Commercial exploitation of stored blood should be regulated strictly. No trading shall be permitted in this area as in organ donation. Special care must be taken in collection, processing and storage of umbilical cord stem cells to avoid transmission of infections. Maternal screening should be carried out for transmissible infections. Purpose of banking should be clearly explained to couples interested in storing cord blood. The ideal use of these cells at present is for allogenic hematopoietic stem cell transplantation. Expansion of umbilical cord stem cells for transplantation in adult and use for non-hematopoietic indications is still in experimental stage. Specific mention shall be made that at present the use of stored umbilical cord blood for self is practically nil. The ethical issues include concern about ownership, and risk of transmission of potential genetic disorders, besides other general issues of confidentiality, justice and beneficence. When it comes to registries and banking, the commercial aspects pose additional problems. The advertisement related to collection of samples should be carefully looked into with respect to, conflict of interest, utility of samples, accessibility and affordability.

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

- 7.1 No harm should occur to the fetus or the neonate.
- 7.2 Exact timing of the clamping of umbilical cord should be defined.
- 7.3 Parents should be correctly informed regarding risks and benefits involved.
- 7.4 Free informed consent should be obtained from both parents. If there is disagreement between the parents, the mother's wish shall prevail.
- 7.5 ID card should be issued for voluntary donation to enable access/benefit in future in case required for self/relatives.
- 7.6 Standard Operative Procedures (SOPs) for collection, transportation, processing, storage (cryo-preservation) and clinical use of umbilical cord blood/cells should be laid down with approval of the IC-SCRT/IEC.
- 7.7 If processed stem cells are proposed to be used, detailed protocol for isolation, expansion and characterization of stem cells should be approved by IC-SCRT/IEC.

- 7.8 Period of preservation for self- use later in life should be defined.
- 7.9 Detailed protocol for clinical use of umbilical cord stem cells should be in place. This should include follow up plans for assessing safety and efficacy of cord blood stem cell therapy.

8.0 Research using fetal stem cells/placenta

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

- a. Termination of pregnancy should not be sought with a view to donate fetal tissue in return for possible financial or therapeutic benefits.
- b. Informed consent to have a termination of pregnancy and the donation of fetal material for purpose of research or therapy should be taken separately.
- c. The medical person responsible for the care of the pregnant woman planning to undergo termination of pregnancy and the person who will be using the fetal material should not be the same.
- d. The woman shall not have the option to specify the use of the donated material for a particular person or in a particular manner.
- e. The identity of the donor and the recipient should be kept confidential.

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

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

- 9.1 The goal of research is to increase knowledge about embryo development and causes of miscarriages and birth defects.
- 9.2 Develop methods to detect abnormalities in embryos before implantation.
- 9.3 Advance knowledge, which can be used for infertility treatment or improving contraception techniques.
- 9.4 Increase knowledge about causation of serious diseases and their treatment including tissue therapies.
- 9.5 Developing methods of therapy for diseased or damaged tissues or organs.
- 9.6 Develop ethnically diverse hES cell lines, provided –
 - 9.6.1 the proposed research cannot be carried out with existing cell lines;
 - 9.6.2 justification for the minimum number of embryos/blastocysts required must be clearly defined;
 - 9.6.3 research teams involved should have appropriate expertise and training in derivation, characterization and culture of ES cells.

10.0 Responsibility of investigators and institutions

- 10.1 The investigators and the institutions where the stem cell research is being conducted bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. In particular, scientists whose research involves hES cells should work closely with monitoring/regulatory bodies, demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for SCNT, and be sensitive to public concerns about research that involves human embryos.
- 10.2 Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding use of hES cells.
- 10.3 Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for its functioning or ensure that its IEC has adequate expertise to handle proposals related to research with stem cells.
- 10.4 All records pertaining to adult stem cell research must be maintained for at least 5 years and those for hES cell research for 10 years.

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

- 11.1 The IC-SCRT/IEC, should review the process of procurement of gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines, including procurement of blastocysts in excess of clinical need from infertility clinics. Blastocysts made through IVF specifically for research purposes, and oocytes, sperm, and somatic cells donated for development of hES cell lines derived through SCNT or by parthenogenesis or androgenesis or any other technique should have approval of NAC-SCRT.
- 11.2 Consent for donation of supernumerary embryos should be obtained from each donor at least 24 hours in advance and not at the time of donation itself. Even people who have given prior indication of their intent to donate blastocysts that remain unutilized after clinical care should give fresh informed consent at the time of donation of the embryo for establishment of hES cell line. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.
- 11.3 There should be no commodification of human oocyte, human sperm or human embryo by way of payment or services, except for reimbursement of reasonable expenses incurred by the person (amount to be decided by IC-SCRT/ IEC. Similarly, no payments should be made for donation of somatic cells for use in SCNT except for reimbursement for attending the clinic.

- 11.4 Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for SCNT) may be reimbursed for direct expenses incurred as a result of the procedure, as determined by the IC-SCRT/ IEC. They should be informed about potential hazards, complications etc which are related to the hormonal induction process.
- 11.5 The attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells preferably should not be the same person. To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research.
- 11.6 In the context of donation of gametes or blastocysts for hES cell research or therapy, the informed consent process, should at a minimum, provide the following information:
 - a. A statement that the blastocysts or gametes will be used to derive hES cells/cell lines for research purposes.
 - b. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of cells derived from it.
 - c. Identity of the donor and recipient shall be kept confidential.
 - d. An assurance that investigators in research projects will follow applicable best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells. (Traceable information, however, will be kept secured to ensure confidentiality)
 - e. Investigators must document how they will maintain the confidentiality of any coded or identifiable information associated with the lines.
 - f. A statement that the derived hES cell line may be used for development of new drugs/diagnostics etc. which may have commercial value, but no direct financial benefit to the donors.
 - g. A statement that derived stem cells or cell lines and the information related to it may be archived for 15 years or more.
 - h. A statement that research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous transplantation.
 - i. A statement that embryos will be fully utilized in the process of deriving hES cells.
 - j. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of present or future medical care provided to potential donors.

- k. A statement of the risks involved to the oocyte donor and acceptance of the responsibility to provide appropriate health care in case any complication arises during the procedure.
- 11.7 Any clinic/research personnel who have a conscientious objection to hES cell research should not be coerced to participate or impart information.

12.0 Banking and distribution of hES cell lines

There are several models for banking of human biological materials, including hES cells. All guidelines developed in this regard adhere to key ethical principles that focus on need for consent of donors and a system for monitoring adherence to ethical, legal, and scientific requirements. As hES cell research advances, it will be increasingly important for institutions that are obtaining, storing, and using cell lines to have confidence in the value of stored cells. For this purpose, it is necessary to ensure that:

- a. they were obtained ethically and with informed consent of donors,
 - b. they are well characterized and screened for safety, (see Annexure II)
 - c. the conditions under which they are maintained and stored meet the current standards of GLP/GTP/GMP in India (to be annexed) with appropriate SOPs.
- 12.1 Institutions that are banking or plan to bank hES cell lines should establish uniform guidelines to ensure that donors of material give informed consent through a process approved by the IC-SCRT/IEC and meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and guidelines for distribution of cells should be established as per accepted standard procedures.
 - 12.2 Any facility engaged in obtaining and storing hES cell lines should consider the following:
 - 12.2.1 Creation of clear and standardized protocols for banking and withdrawals.
 - 12.2.2 Documentation requirements for investigators and sites that deposit cell lines, including:
 - a. A copy of the donor consent.
 - b. Proof of IC-SCRT/IEC approval of the procurement process.
 - c. Available medical information on donors, along with infectious disease screening details.
 - d. Available clinical, observational or diagnostic information about the donor(s).
 - e. Critical information about culture conditions (such as media, cell passage, and safety information).

- f. Available cell line characterization (such as karyotype and genetic markers).
 - 12.2.3 A repository has the right of refusal if prior culture conditions or other items do not meet its standards.
- 12.3 A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to
 - a. Plans for maintaining confidentiality (such as a coding system).
 - b. A secure system for inventory track from primary cell lines to those submitted to the repository.
 - c. A policy governing whether and how to deliver clinically significant information obtained through research/investigations back to donors.
- 12.4 The following Standard Operating Procedures (SOPs)/ Standard of practices should be defined and maintained:
 - a. Assignment of a unique identifier to each sample.
 - b. Procedure for derivation of hES lines
 - c. Process for characterizing cell lines.
 - d. Process for expanding, maintaining, and storing cell lines.
 - e. System for quality assurance and control.
 - f. Website that contains scientific descriptions and data related to the available cell lines. Central Registry should be set up by the NAC-SCRT.
 - g. Procedure for reviewing request applications for cell lines.
 - h. Process for tracking disbursed cell lines and recording their status when shipped (such as number of passages).
 - i. System for auditing compliance.
 - j. Schedule of charges.
 - k. Statement of intellectual property policies.
 - l. When appropriate, creation of a clear Material Transfer Agreement or user agreement.
 - m. Liability statement.
 - n. System for disposal of material.
 - o. Clear criteria for distribution of cell lines

13.0 Use of stem cells for therapeutic purposes

- 13.1 As of date, there is no approved indication for stem cell therapy as a part of routine medical practice, other than Bone Marrow Transplantation (BMT). Accordingly all stem cell therapy other than BMT (for accepted indications) shall be treated as experimental. It should be conducted only as clinical trial after approval of the IC-

SCRT/IEC and DCGI (for marketable products). All experimental trials shall be registered with the NAC-SCRT.

- 13.2 Cells used in such trials must be processed under GTP/GMP standards.
- 13.3 The injectable product should meet pharmacopial specifications for parenteral preparations. The cells used for therapy shall be free from animal products and microbial contamination.
- 13.4 The centers carrying out stem cell clinical trials and the agency/source providing such cells for the trial shall be registered with the NAC-SCRT through IC-SCRT/IEC. In case of International Collaboration, the public funding agency evaluating the study / NAC-SCRT shall ensure that the certification provided by the collaborating country fulfills the requirements laid down in these guidelines.
- 13.5 The hES cell/cell lines or the cells derived therefrom used in the trial shall be characterized as suggested in Annexure II.
- 13.6 The headings under which clinical trial protocol for stem cell therapy shall be prepared is given in Annexure III.

14.0 International Collaboration

- 14.1 National guidelines of respective countries should be followed.
- 14.2 Exchange of biological material will be permitted as per existing procedures of funding agencies (DST, DBT, ICMR etc) or the Health Ministry's screening committee (as per GOI Guidelines), even if no funding is involved after the joint proposal with appropriate MOU is approved by NAC-SCRT.
- 14.3 If there is a conflict between scientific and ethical perspectives of the International collaborator and the domestic side, then the Indian ethical guidelines or law shall prevail.

15.0 Commercialization and Patent Issues

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

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ICMR Ethical Guidelines for Biomedical Research in Human Participants 2006

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Monitoring Mechanism

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

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

1.0 NAC-SCRT

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

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

1.1 Scope

- 1.1.1 The Committee will have the responsibility to examine the scientific, technical, ethical, legal and social issues in the area of stem cell based research and therapy.
- 1.1.2 All institutions involved in any type of stem cell research and therapy shall be registered with the NAC-SCRT.
- 1.1.3 IC-SCRT/IEC has to submit annual reports to NAC-SCRT - A regular monitoring will be done by the NAC-SCRT by obtaining periodic report from all centers and site visits as and when required to ensure adherence to standards.
- 1.1.4 NAC-SCRT shall approve, monitor and oversee research in the restricted areas as given in this document.
- 1.1.5 Every scientific proposal using ES cells under restrictive category has to be cleared through IC-SCRT/IEC before referring to NAC-SCRT.
- 1.1.6 Use of chimeric tissue for research shall be approved only by NAC-SCRT after clearance from IC -SCRT/IEC.

- 1.1.7 NAC-SCRT shall revise and update guidelines periodically, considering scientific developments at the national or international level.
- 1.1.8 *NAC-SCRT will set up standards for safety and quality, quality control, procedures for collection and its schedule, processing or preparation, expansion, differentiation, preservation for storage, removal from storage to assure quality and/or sterility of human tissue, prevention of infectious contamination or cross contamination during processing, carcinogenicity, xenotransplantation.*

1.2 Membership (12-15)

Chairman, Deputy Chairman, Member Secretary, nominees from DBT, DST, CSIR, ICMR, DCGI, DAE, and biomedical experts drawn from various disciplines like Pharmacology, Immunology, Cell Biology, Hematology, Genetics, Developmental biology, Clinical medicine and Nursing. Other members would be legal expert, social scientist, and women's representative. In addition consultants/experts could be consulted for specific topics and advice.

1.3 Frequency of meetings

Quarterly, but can be more frequent, if necessary.

1.4 Processing fees

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

2.0 IC-SCRT

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

2.1 Scope

- 2.1.1 All research institutions conducting stem cell research are expected to set up a special review body to oversee this emerging field of research.
- 2.1.2 To be registered with the NAC-SCRT.
- 2.1.3 Provide overview to all issues related to stem cell research and therapy.
- 2.1.4 Review and approve the scientific merit of research protocols.
- 2.1.5 Review compliance with all relevant regulations and guidelines.
- 2.1.6 Maintain registries of hES cell research conducted at the institution and hES cell lines derived or imported by institutional investigators.
- 2.1.7 Facilitate education of investigators involved in stem cell research.
- 2.1.8 Submit annual report to NAC-SCRT.

2.2 Membership (7-9)

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

Annexure-II

Safeguards for Use of Human Embryonic Stem (HES) Cells

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

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

Safeguards	Tests/Methods
Screening Donors	HIV, HBV, HCV, CMV, HTLV, VDRL
Derivation and culture	Use control and standardized practices and procedures for establishment of human embryonic stem cell lines. GMP clean room is must if ES cells are to be used for clinical application
Animal source	Develop alternatives to culturing ES cells on animal derived feeder cells and serum.
Characterization	Perform detail characterization of stem cell lines
	Cellular markers: SSEA-1, SSEA-3, SSEA-1, OCT-4, TRA-1-60, TRA-1-81, Alaline phosphatase, ABCG2,
	Molecular markers: OCT-4, SOX2, NANOG, REX1, TERT, UTF-1, DPPA5, FGF4, FOXD3, TDGF1, BCRP1, ABCG2, GCTM2, Genesis, GDF3, GCNF
Karyotyping	Traditional karyotyping of FISH including sex chromosome
HLA Typing	A, B, DR
Microarray	Growth factors, cytokines and ECM molecules
Immunophenotyping	CD markers: DC4, CD8, CD14, CD24, CD31, CD34, CD45, CD90, CD73, DC105, CD133
Analysis of differentiation properties	Minimum 3 markers for Ectoderm, Endoderm and Mesoderm should be checked. Each cell line should be checked for differentiation potential.
Teratoma Formation	Required SCID mouse
Comprehensive toxicity	Endotoxin, mycoplasma, aerobic, anaerobic cultures for sterility; and acute, sub-acute and chronic toxicity testing

Clinical Trial Protocol for Stem Cell Therapy

Study title

Phase of the study

Institution conducting the trial

Sponsor

Names of Principal Investigator and Co-investigators

Brief CV of all the investigators

1. Synopsis of the protocol (Summary)

2. Introduction

3. Study objectives

4. Study plan

a. Study design

b. Number of patients

c. Inclusion criteria

d. Exclusion criteria

e. Chart of schedule of visits and activities at each visit

f. Ethical considerations – risks and benefits

i. Screening phase

ii. Treatment phase

iii. Post –treatment phase

iv. Withdrawal of patients prior to study completion

g. Efficacy assessment

i. Primary efficacy outcome

ii. Secondary efficacy outcome

iii. Efficacy measurements

5. Safety assessment

Adverse Events documentation in a prescribed format

i. Definitions

ii. Documentation of adverse events

iii. Reporting of serious adverse events

6. Concomitant Medications

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

7. Product information, dose scheme and administration instructions

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

8. Data evaluation/statistics

- a. Sample size determination
- b. Study population analyses
- c. Efficacy analysis/methods
- d. Safety analysis/methods
- e. Adverse events
- f. Clinical laboratory studies

9. Ethical and Administrative Issues

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

10. Requirements for study initiation and completion

11. Confidentiality and publication

12. Enclosures

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

- III. Manual for efficacy assessments, safety assessments, laboratory procedures etc.
- IV. Administrative approvals
 - a. DCGI for IND/NDA
 - b. IEC (of each center)
 - c. Approved patient information sheet and consent form
 - d. IC-SCRT/*NAC-SCRT approval if required*
 - e. MOU/MTA in case of National/International collaboration with transfer of biological materials
 - f. Funding of the project/sponsor
 - g. Conflict of interest declaration
 - h. Incentives to investigators/patients/donors
 - i. Post-trial benefits
 - j. Medical insurance coverage for SAEs
 - k. Sponsor's responsibility towards cost of trial/complications
 - l. Investigator's bio-data/acceptance

GLOSSARY

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

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

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

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

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

Clonal: Derived from a single cell

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

- ◆ **Cloning by somatic cell nuclear transfer:** involves replacing an oocyte's nucleus with the nucleus of the adult cell to be cloned (or from an embryo or fetus) and then activating oocyte's further development without fertilization. The oocyte genetically reprogramme the transferred nucleus, enabling it to direct development of a whole new organism
- ◆ **Reproductive cloning:** The embryo developed after Somatic Cell Nuclear Transfer (SCNT) is implanted into the uterus (of the donor of the ovum or a surrogate recipient) and allowed to develop into a fetus and whole organism. The organism so developed is genetically identical to the donor of the somatic cell nucleus.
- ◆ **Therapeutic cloning:** The development of the embryo after Somatic Cell Nuclear Transfer (SCNT) is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells could be differentiated into desired tissue using a cocktail of growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection.

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

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

Embryo: in humans is the developing stage from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.

Early embryo: The term "early embryo" covers stages of development up to the appearance of primitive streak i.e., until 14 days after fertilization.

Embryonic germ cell: Embryonic germ cells are primordial germ cells isolated from the gonadal ridge of 5-10 weeks fetus.

Embryonic stem cell: embryonic stem cells are derived from the inner cell mass up to the stage of blastocysts. These cells can be cultured indefinitely under *in vitro* conditions that allow proliferation without differentiation, but have the potential of differentiating into any cell of the body.

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

Fetus: In humans, it is a developing stage from eight weeks after conception to birth

Fetal stem cell: a stem cell derived from fetal tissue, including placenta. A distinction is drawn between the fetal germ cells, from which the gametes develop, and fetal somatic cells, from which rest of the organism develops.

Gamete: the male sperm or female oocyte

Germ cells: ova and sperm, and their precursors

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

In vitro and in vivo: outside and inside the body; *in vitro* (literally, in glass) generally means in the laboratory

Mesenchymal stem cells: Stem cells present in human bone marrow and umbilical cord that have been shown to differentiate into a variety of cell types

Multipotent: Multipotent stem cells are those which are capable of giving rise to several different types of specialized cells constituting a specific tissue or organ.

Pluripotent stem cell: has the ability to give rise to various types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) Pluripotent stem cell has the potential to generate into every cell type in the body, but cannot develop into an embryo on its own.

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

Somatic cell: cell of the body other than oocyte or sperm

Somatic stem cell: an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialized cell types of the tissue or organ.

Somatic cell nuclear transfer: the transfer of a cell nucleus to an oocyte (or another cell) from which the nucleus has been removed.

Stem cells: Cells capable of self-replication, proliferation and differentiation.

Stem cell Bank: A facility that is responsible for accessioning, processing, packaging, labeling, storage and delivery of a finished stem cell line issued under its name. It is required to characterize the cells, provide quality assurance and meet the laid down standards and procedures.

Supernumerary embryo or spare embryo: an embryo created by means of *in vitro* fertilization (IVF) for the purpose of assisted reproduction but subsequently not used for it.

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

STANDARDS FOR COLLECTION, PROCESSING AND STORAGE OF CELLS FOR CLINICAL USE

NOTICE

These standards are designed to provide minimum guidelines for facilities and individuals performing collection, processing and storage of cells for clinical use or providing support services for such procedures. These standards are not intended to include all procedures and practices that a facility or individual should implement if the standard of practice in the community or governmental laws or regulations establish additional requirements. Each facility and individual should analyze their practices and procedures to determine whether additional standards may apply.

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Introduction

This document defines the standards for collection, processing and storage of cells for clinical use. The aim is to provide minimum standards for these procedures in India. These guidelines therefore apply to those cells on which considerable literature is available on clinical use.

At present, this is mainly confined to adult cells derived from blood and marrow, corneal limbus and cartilage. These guidelines could also apply to collection, processing and storage of other adult cells. This document is not intended to replace standard operation procedures (SOPs) for each laboratory involved in processing cells for cellular therapy. The intention of this document is to guide the laboratory to the minimum standards required in these procedures and also to help them prepare SOPs for different processes that are involved. The standards required for the clinical use of these cells are variable depending on the applications. This document does not purport to define those standards.

Use of embryonic cells has not reached wide clinical use as yet and the literature on it is inadequate at present. This document therefore does not address the use of cells of embryonic origin for clinical use. For cells that do not come within the purview of the guidelines in this document, investigators must define appropriate standards and obtain specific approvals from institutional committees and designated central authorities for the protocols that they plan to follow in their studies.

Finally, this document has been adapted with permission from the standards for haematopoietic progenitor cell (HPC) collection, processing and transplantation of the Foundation for the Accreditation of Cellular Therapy (FACT) in USA.

PART A: Terminology, Abbreviations and Definitions

A1.0 Terminology

For purposes of these Standards, the term *shall*, means that the Standard is to be complied with at all times. The term *should* indicate an activity that is recommended or advised, but for which there may be effective alternatives.

A2.0 Abbreviations

The following abbreviations cover terms used in these Standards.

<i>ABO</i>	Human erythrocyte antigens, A, B, O.
<i>C</i>	Centigrade.
<i>DBT</i>	Department of Biotechnology, Govt of India
<i>DCGI</i>	Drugs Controller General of India
<i>HPC</i>	Hematopoietic progenitor cells.
<i>ICMR</i>	Indian Council of Medical Research
<i>IRB</i>	Institutional Review Board.
<i>SOPs</i>	Standard Operating Procedures
<i>TP</i>	Therapeutic cells

A3.0 Definitions

Allogeneic refers to cells obtained from a donor and intended for infusion into a genetically distinct recipient.

Autologous refers to cells obtained from a patient and intended for infusion into that patient.

Cells include primitive pluripotent hematopoietic cells capable of self-renewal as well as maturation into any of the hematopoietic lineages, including committed and lineage-restricted progenitor cells, unless otherwise specified, regardless of tissue source.

Cell therapy refers to the infusion of cellular products with the intent of providing effector functions in the treatment of disease or support of other therapy.

Collection includes any procedure for harvesting cells regardless of technique or source.

Competency is the adequate ability to perform a specific procedure according to direction.

Cord blood refers to HPCs collected from placental and umbilical cord blood vessels after the umbilical cord is clamped and/or severed.

Expansion refers to growth of one or more cell populations in an *in vitro* culture system.

Head / Officer in-charge: For purposes of these Standards includes individuals with the following qualifications:

Collection or Processing Facility Head / Officer in-charge is an individual with a doctoral degree, qualified by postdoctoral training or experience for the scope of activities carried out in the facility. This individual is responsible for all technical procedures and administrative operations of the collection facility. This individual should participate regularly in educational activities related to the field of cell collection and / or processing. The Collection or Processing Facility *Head / Officer in-charge* may also serve as the Medical *Head / Officer in-charge* if appropriately qualified.

Collection or Processing Facility Medical Head / Officer in-charge is a licensed physician. This individual is directly responsible for the pre-collection evaluation of the donor, final approval of the prospective donor for the collection procedure, conduct of the collection / processing procedure, care of any complications arising from collection and compliance of the collection facility with these Standards. The Collection or Processing Facility *Medical Head / Officer in-charge* should participate regularly in educational activities related to the field of cell collection and/or processing.

Laboratory Head / Officer in-charge is an individual with a relevant doctoral degree, and qualified by training or experience for the scope of activities carried out in the cell processing facility. The *Laboratory Head / Officer in-charge* is responsible for all procedures and administrative operations of the cell processing facility, including compliance with these Standards. The *Laboratory Head / Officer in-charge* should participate regularly in educational activities related to the field of hematopoietic cell processing and/or transplantation. The *Laboratory Head / Office in-charge* may also serve as the *Medical Head / Office in-charge* if appropriately credentialed.

Program Head / Officer in-charge is the physician responsible for all administrative and medical operations of the clinical transplantation program, including compliance with these Standards. The *Program Head/ Office in-charge* shall be appropriately licensed to practice medicine in India.

Human tissue refers to cells obtained from any living or cadaveric human donor or organ.

Labeling process includes steps taken to identify the original cell collection, any products, and any product modifications; to complete the required reviews; and to attach the appropriate labels.

Manipulation refers to an *ex vivo* procedure(s) that functionally or genetically alters cell populations.

Manufacturing includes, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cellular or tissue-based product, and the screening and testing of a cell or tissue donor.

Manipulated cell products refers to cell products that have been functionally, quantitatively or genetically altered *ex vivo*, including *ex vivo* expanded cells.

Minimally manipulated cell products refers to cell products that have not been subjected to an *ex vivo* procedure that functionally or genetically alters specific nucleated cell populations.

Potency is the therapeutic activity of a product as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

Processing includes all aspects of manipulation, labeling, and infusion of products, regardless of source.

Products : The proper name of each product is as follows:

Hematopoietic Progenitor Cells, Apheresis (HPC-A) - hematopoietic progenitor cells collected from the peripheral blood of a donor using an apheresis technique.

Hematopoietic Progenitor Cells, Marrow (HPC-M) - hematopoietic progenitor cells aspirated from the iliac crests, sternum or other bones of a human donor.

Hematopoietic Progenitor Cells, Cord Blood (HPC-C)

Therapeutic Cells (TC) - cell products harvested or manufactured for the purpose of providing therapeutic benefit.

Therapeutic Cells, T- cells (TC-T)

Therapeutic Cells, Dendritic (TC-D)

Therapeutic Cells, Natural Killer (TC-NK)

Therapeutic Cells, Cytotoxic Lymphocyte (TC-CTL)

Therapeutic Cells, MSC (TC-MS)

Therapeutic Cells, other (such as tumor-derived cells, Limbic stem cells) (TC-other)

Proficiency test refers to an evaluation of the ability to perform laboratory procedures within acceptable limits of accuracy, through the analysis of unknown specimens distributed at periodic intervals by a source outside the facility performing the proficiency test.

Purity refers to relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

Quality refers to conformance of a product or process with pre-established specifications or standards.

Quality assessment describes the actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

Quality assurance describes the actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product are working as expected individually and collectively.

Quality control refers to a product of a quality program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of HPC products, including testing and product release.

Quality improvement describes the actions planned and performed to develop a system to review and improve the quality of a product or process.

Quality management refers to an integrated program of quality assessment, assurance, control and improvement.

Safety refers to relative freedom from harmful effects to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

Standard Operating Procedures(SOP) Manual refers to a compilation of written detailed instructions required to perform procedures.

Standards refer to current Indian Council of Medical Research – Department of Biotechnology (ICMR-DBT) guidelines for collection, processing and storage of cells for therapeutic use.

Syngeneic refers to cells collected from the patient's genetically identical twin.

Time of collection refers to the end of the cell collection procedure.

Transplantation refers to the administration of autologous, syngeneic or allogeneic cells with the intent of providing transient or permanent engraftment in support of therapy of disease.

Unmanipulated hematopoietic progenitor cells refers to HPCs as obtained at the time of collection and not subjected to any form of manipulation.

Validation refers to establishment of documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

PART B: Progenitor and Other Adult Cell Collection Standards

B1.0 General

- B1.1 These Standards apply to progenitor and other cell collection activities.
- B1.2 The Collection Facility shall abide by all applicable governmental laws and regulations.

B2.0 Progenitor cell collection facility

- B2.1 There shall be adequate and confidential space for donor examination and evaluation.
- B2.2 There shall be emergency medical care available for the donor
- B2.3 There shall be a designated area for appropriate preparation and storage of the reagents and equipment needed and for the performance of the collection procedure.
- B2.4 Procedures that will require general or regional anesthesia shall be performed by a qualified anesthesiologist.
- B2.5 Where applicable, central venous catheters shall be placed by a licensed physician qualified to perform the procedure.
- B2.6 Where applicable, growth factor administration shall be under the supervision of a physician experienced in the management of persons receiving these agents.

B2.7 Safety

- B2.7.1 Each collection facility shall be operated in a manner to minimize risks to the health and safety of employees, donors, volunteers, and patients. Suitable environment and equipment shall be available to maintain safe operations.
- B2.7.2 There shall be procedures for biological, chemical, and radiation safety, as appropriate, and a system for monitoring training and compliance.
- B2.7.3 Cell collections shall be handled and discarded with precautions that recognize the potential for transmission of infectious agents.
- B2.7.4 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the collection facility staff.
- B2.7.5 Prospective donors shall be evaluated by medical history, physical examination by a trained physician and laboratory testing for the risks of the collection procedure including the possible need for central venous access and/or mobilization

therapy for collection of blood cells and anesthesia for collection of marrow. This evaluation shall be documented.

B3.0 Personnel

B3.1 There shall be a *Collection Facility Head / Officer in-charge* who is an individual with a doctoral degree, qualified by postdoctoral training or experience for the scope of activities carried out in the facility. This individual is responsible for all technical procedures and administrative operations of the collection facility. This individual should participate regularly in educational activities related to the field of cell collection and / or processing. The *Collection or Processing Facility Head / Officer in-charge* may also serve as the *Medical Head / Officer in-charge* if appropriately credentialed.

B3.1.1 The *Collection Facility Head / Office in-charge* shall have at least one year's experience in the collection procedure. This individual shall have performed or supervised at least 10 collection procedures of each type that are to be carried out at the facility.

B3.2 There shall be a *Collection Facility Medical Head / Officer in-charge* who is a physician licensed in the jurisdiction in which the facility is located. This individual is directly responsible for the pre-collection evaluation of the donor, final approval of the prospective donor for the collection procedure, conduct of the collection / processing procedure, care of any complications arising from collection and compliance of the collection facility with these Standards. The *Collection or Processing Facility Medical Head / Officer in-charge* should participate regularly in educational activities related to the field of cell collection for clinical use.

B3.3 There shall be adequate numbers of trained support personnel available at the facility where the collection is performed.

B3.3.1 The training, continued education and continued competency for the performance of operations shall be documented.

B4.0 Quality management

B4.1 The *Collection Facility* shall have a written Quality Management Plan that describes, at a minimum, the methods for oversight of donor care (including detection of errors, accidents and adverse reactions), significant outcome parameters, the means for review of aggregate data on a regular basis (audits), validation of significant processes of the Collection Program and requirements for meetings, review, documentation, corrective actions and reporting.

B4.1.1 The collection facility *Head / Office in-charge* is responsible for the Quality Management Plan as it pertains to the Collection Facility.

- B4.1.2 The Collection Facility shall establish and maintain a program of quality management, under the supervision of a designated person. The individual shall review and approve policies and procedures that document compliance with regulatory requirements and standards, and the performance of quality audits.
- B4.1.3 Protocols shall be developed, implemented, and documented for the validation or qualification of significant products of facilities, processes, equipment, reagents, labels, containers, packaging materials, and computer systems. Determination of which elements are to be validated or qualified shall be made by the Collection Facility Director.
- B4.1.4 Evaluation of validation studies and audits shall be reviewed with documentation of approval by the appropriate individual from the quality management program.

B4.2 Laboratory testing

- B4.2.1 Tests required by these Standards shall be performed in a laboratory in accordance with governmental laws and regulations.

B4.3 Supplies and reagents

- B4.3.1 Reagents used in collection of products shall be of appropriate grade for the intended use and shall be sterile.
- B4.3.2 Procedures for production of in-house reagents shall be validated.
- B4.3.3 Each supply and reagent used in the collection of the product shall be examined visually for damage or evidence of contamination as it comes into inventory and this review shall be documented. Such examination shall include inspection for breakage of seals, abnormal color and expiration date.
- B4.3.4 All supplies and reagents used in the collection of products shall be stored in a safe, sanitary, and orderly manner.
- B4.3.5 Lot numbers and expiration dates of reagents and disposables shall be recorded.

B4.4 Equipments

- B4.4.1 Equipments used in the collection of products shall be maintained in a clean and orderly manner and located so as to facilitate cleaning, calibration and maintenance.
- B4.4.2 The equipments shall be observed, standardized and calibrated on a regularly scheduled basis as described in the SOPs Manual and according to the Manufacturer's recommendations.

B4.5 Review of collection records

- B4.5.1 Records pertinent to the product collected shall be regularly reviewed by the Collection Facility Officer-in-charge or designee.
- B4.5.2 A thorough investigation, including resolution and outcome of any adverse event or the failure of a product to meet any of its specifications shall be made and documented.

B4.6 Errors, accidents and adverse reactions

- B4.6.1 Each Collection Facility shall have a system for detecting, evaluating, documenting and reporting errors, accidents, suspected adverse reactions, biological product deviations and complaints. Corrective actions shall be documented and reviewed by the Collection Facility Officer-in-charge.
- B4.6.2 All suspected clinical adverse reactions to the collection of cells shall be evaluated promptly according to SOPs, and reviewed by the Collection Facility Officer- in-charge.
- B4.6.3 A written evaluation of reported adverse reactions to the collection of cells shall be included as part of the cell collection record and made available to the donor's physician.
- B4.6.4 Where applicable, the event shall also be reported to the appropriate regulatory agency, clinical program and cell processing laboratory as appropriate.

B4.7 Outcome analysis

- B4.7.1 Documentation and review of product quality shall be part of the ongoing quality program.
- B4.7.2 There shall be ongoing review of the products collected.
- B4.7.3 All suspected adverse reactions to the collection of a product shall be evaluated promptly and reviewed by the collection facility in-charge.
- B4.7.4 Documentation and review of clinical outcome after cell therapy shall be part of the on-going quality management program,

B5.0 Policies and procedures

- B5.1 The Collection Program shall have written policies and procedures addressing all aspects of the operation including, but not limited to, screening, consent, collection, treatment, emergency and safety procedures, donor and patient confidentiality, quality management and improvement, errors, accidents and adverse reactions; biological product deviations, corrective actions, personnel training, competency assessment, outcome analysis, audits, labeling, storage,

transportation, expiration dates, release and exceptional release, disposal of medical and biohazard waste, equipment and supplies, maintenance and monitoring, cleaning and sanitation procedures, and a disaster plan.

B5.2 The Collection Program shall maintain a detailed SOP Manual.

B5.2.1 The SOP Manual shall include:

B5.2.1.1 A procedure for preparing, implementing and reviewing all procedures.

B5.2.1.2 A standardized format for procedures, including worksheets, reports and forms.

B5.2.1.3 A system of numbering and/or titling of individual procedures.

B5.2.2 Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure requires:

B5.2.2.1 A clearly written description of the purpose.

B5.2.2.2 A clear description of equipment and supplies used.

B5.2.2.3 The objectives of the procedure, and acceptable end-points and the range of expected results where applicable.

B5.2.2.4 A reference section listing appropriate literature.

B5.2.2.5 Documented approval of procedure and each procedural modification by the Collection Facility Officer-in-charge or designee prior to implementation and annually thereafter.

B5.2.2.6 Examples of correctly completed orders, reports, labels and forms, where applicable.

B5.3 Copies of the SOP Manual shall be available in the immediate area to the facility staff at all times.

B5.4 All personnel in the facility shall follow the SOPs detailed in the manual.

B5.5 New and revised policies and procedures shall be reviewed by the staff prior to implementation. This review and associated training shall be documented.

B5.6 Archived procedures and their historical sequence shall be maintained indefinitely, including the inclusive dates of use.

B5.7 Deviations from SOPs shall be documented and approved, if appropriate, by the Collection Facility Officer-in-charge or designee.

B5.8 SOPs for all procedures shall comply with these Standards.

B6.0 Donor evaluation, selection and management

- B6.1 There shall be donor evaluation procedures in place to protect the safety of the cell donor and recipient. Both the potentials for disease transmission from the donor to the recipient and the risks to the donor from the collection procedure shall be assessed. Donor evaluation and selection test results shall be documented.
 - B6.1.1 There shall be written criteria for donor evaluation and selection.
 - B6.1.2 Any abnormal findings shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.
 - B6.1.3 The use of a donor not meeting the criteria shall require documentation of the rationale for his/her selection by the transplant physician and the informed consent of the donor and the recipient.
 - B6.1.3.1 Procedures shall be in place to ensure both confidentiality of donor and patient health information.
 - B6.1.4 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the collection facility staff.
 - B6.1.5 Prospective donors shall be evaluated by medical history, physical examination and laboratory testing for the risks of the collection procedure including the possible need for central venous access and/or mobilization therapy for collection of blood cells and anesthesia for collection of marrow. This evaluation shall be documented.
 - B6.1.6 The medical history shall include at least the following:
 - B6.1.6.1 Vaccination history.
 - B6.1.6.2 Travel history.
 - B6.1.6.3 Blood transfusion history.
 - B6.1.6.4 Questions to identify persons at high risk for significant transmissible infections as defined by DCGI for donors of cellular and tissue-based products.
 - B6.1.7 Within 7 days prior to collection, each donor shall be tested for evidence of infection by the following communicable disease agents:
 - B6.1.7.1 Human immunodeficiency virus, type 1
 - B6.1.7.2 Human immunodeficiency virus, type 2

B6.1.7.3 Hepatitis B virus

B6.1.7.4 Hepatitis C virus

B6.1.7.5 Treponema pallidum (syphilis)

B6.1.7.6 Cytomegalovirus (unless previously documented to be positive)

B6.2 There shall be written documentation of an interim assessment of donor suitability for the collection procedure by a qualified person immediately prior to each collection procedure.

B6.3 For donors of peripheral blood apheresis products, a complete blood count, including platelet count, shall be performed within 72 hours prior to the first collection and within 24 hours before each subsequent apheresis.

B6.4 Donor consent

B6.4.1 Allogeneic donors

B6.4.1.1 Informed consent from the donor shall be obtained and documented by a licensed physician or other health care provider familiar with the collection procedure before the high dose therapy of the recipient is initiated.

B6.4.1.2 The procedure shall be explained in terms the donor can understand, and shall include information about the significant risks and benefits of the procedure and tests performed to protect the health of the donor and recipient and the rights of the donor to review the results of such tests.

B6.4.1.3 The donor shall have an opportunity to ask questions and the right to refuse to donate.

B6.4.1.4 In the case of a minor donor, informed consent shall be obtained from the donor's parents or legal guardian in accord with applicable law and shall be documented.

B6.4.1.5 If the donor's name is to be added to a hematopoietic progenitor cell donor registry, specific informed consent and authorization to release the donor's health information as appropriate shall be obtained and documented in advance.

B6.4.2 Autologous donors

B6.4.2.1 Informed consent from the patient shall be obtained and documented by a licensed physician or other health care provider familiar with the collection procedure.

- B6.4.2.2 The procedure shall be explained in terms the patient can understand, and shall include information about the significant risks and benefits of the procedure and tests performed to protect the health of the patient and the rights of the patient to review the results of such tests.
- B6.4.2.3 The patient shall have an opportunity to ask questions and the right to refuse to donate.
- B6.4.2.4 In the case of a minor patient, informed consent shall be obtained from the patient's parents or legal guardian in accord with applicable law and shall be documented.

B7.0 Progenitor and Other Adult Cell Collection

- B7.1 Collection of progenitor and other adult cells shall be performed according to written procedures in the facility's SOP Manual.
- B7.2 Before collection of peripheral and other adult cells is undertaken, there shall be a written order for the collection from a physician regarding timing and procedural details of collection and goals of collection.
- B7.3 Methods for collection shall employ aseptic technique and shall use procedures validated to result in acceptable progenitor cell viability and recovery.
- B7.4 The collected cells shall be packaged in a closed sterile container / transfer packs approved for human cells and labeled.
 - B7.4.1 Bone Marrow shall be filtered to remove particulate material prior to final packaging, distribution or transplantation using sterile filters that are non-reactive with blood.
- B7.5 Procedures for transportation of the collected product shall be designed to protect the integrity of the product being shipped and the health and safety of facility personnel.
 - B7.5.1 The primary product container shall be placed in a secondary container and sealed to prevent leakage.
 - B7.5.2 The outer shipping container should be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation.
 - B7.5.3 The product shall be shipped to the processing laboratory at a temperature defined in the SOP Manual.

B8.0 Labels

B8.1 Labeling operations

- B8.1.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling of products.
- B8.1.2 The labeling operation shall include the following quality management elements:
 - B8.1.2.1 Container labels shall be held upon receipt from the manufacturer pending review and proofing against a copy approved by the Collection Facility In-charge or designee to ensure accuracy regarding identity, content, and conformity.
 - B8.1.2.2 Stocks of unused labels representing different products shall be stored in an orderly manner to prevent errors. Stocks of obsolete labels shall be destroyed.
 - B8.1.2.3 A system of checks in labeling procedures shall be used to prevent errors in translating information to container labels.
 - B8.1.2.4 All labeling shall be clear and legible and printed using moisture-proof ink.
- B8.1.3 Labels shall be affixed or attached firmly to the container.
- B8.1.4 The proper name and significant modification(s) shall be noted on the label.
- B8.1.5 Products that are subsequently re-packaged into new containers shall be labeled with new labels as appropriate. Records to allow tracking of products including collection or processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, donor and recipient information on the original container shall be maintained.
- B8.1.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.
- B8.1.7 The product label shall be complete. Not applicable (NA) may be used when appropriate.
- B8.1.8 Labeling requirements, if any, required by applicable governmental laws or regulations shall be observed.

B8.2 Product identification

- B8.2.1 Each product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to relate any product to its donor, the donor's medical record, and to all records describing the handling and final disposition of the

product. If a single product is divided in multiple containers, there shall be a system of identifying each container.

B8.2.2 Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the product.

Supplementary identifiers shall not obscure the original identifier. The facility associated with each identifier shall be designated.

B8.2.2.1 Products shipped by registries may obscure the donor name and collection facility identifiers to maintain confidentiality as long as there is sufficient documentation to allow tracking to the original donor.

B8.2.3 Products shall be identified according to the proper name of the product as defined in 3.0 (*products*), including the appropriate modifiers.

B8.3 Label content

B8.3.1 Partial label

B8.3.1.1 If the container is capable of bearing only a partial label, the container shall show as a minimum the unique identifier of the product, proper name of the product as well as the name and identifier of the intended recipient, if known.

B8.3.1.2 Additional information, as required in *Section B8.3*, shall be provided with the product when the product is distributed.

B8.3.2 Labeling at the end of collection

B8.3.2.1 Labeling at the end of collection shall occur before the container is removed from the proximity of the donor.

B8.3.2.2 At the end of collection in the operating room or apheresis unit, the label on the primary container shall bear the information in *Section B8.3.1*.

B8.3.3 Bio-hazard label

B8.3.3.1 A bio-hazard label shall be applied to each product prior to release from the Collection Facility if any test shows evidence of infection due to communicable disease agent(s) as designated in *Section B6.1.7.1 – B6.1.7.6*.

B8.3.3.2 A bio-hazard label shall be applied to each product if testing was not performed or final results are not available.

B9.0 Records

B9.1 Collection Facility Records

Records related to quality control, personnel training or competency, facility maintenance, facility management, or other general facility issues shall be retained for 10 years by the Collection Facility, although not all need be immediately available.

B9.2 Patient Care Records

Patient care records including consents shall be maintained in a confidential manner as required by applicable governmental laws and regulations.

B9.3 Research Records

Research records shall be maintained in a confidential manner as required by applicable governmental laws and regulations.

B9.4 Records in case of divided responsibility

B9.4.1 If two or more facilities participate in the collection, processing or transplantation of the product, the records of each facility shall show plainly the extent of its responsibility.

B9.4.2 The Collection Facility shall furnish to the facility of final disposition a copy of all records relating to the collection and processing procedures performed in so far as they concern the safety, purity and potency of the product involved.

PART C: Cell Processing Standards

C1.0 General

- C1.1 These Standards apply to the processing of cells by the Collection Facility and/or laboratory.
- C1.2 The Processing Facility shall abide by all applicable governmental laws and regulations.

C2.0 Laboratory facilities for cell processing

- C2.1 The facility responsible for cell processing shall be of adequate space and design for the intended procedures.
- C2.2 The operation of the facility shall be divided into defined areas of adequate size for each operation to prevent improper labeling and/or contamination of the product.
- C2.3 The facility shall be operated in a manner to minimize risks to the health and safety of employees, patients, donors and visitors.
 - C2.3.1 The facility shall have written policies and procedures for infection control, biosafety, chemical and radiological safety, emergency response to worksite accidents, and waste disposal.
 - C2.3.1.1 Instructions for action in case of exposure to communicable disease, or to chemical, biological and radiological hazards shall be included in the safety manual.
 - C2.3.2 Decontamination and disposal techniques for medical waste shall be described. Human tissue shall be disposed in such a manner as to minimize any hazard to facility personnel or the environment in accordance with applicable governmental laws and regulations.
 - C2.3.3 Eating, drinking, smoking, the application of cosmetics or the insertion or removal of contact lenses shall not be permitted in work areas.
 - C2.3.4 Gloves and protective clothing shall be worn while handling human specimens. Such protective clothing shall not be worn outside the work area.
- C2.4 There shall be adequate equipment for the procedures performed at the facility.
- C2.5 The facility shall be maintained in a clean and orderly manner as established in SOPs.
- C2.6 The facility shall be secure to prevent the admittance of unauthorized personnel.

C3.0 Personnel

- C3.1 There shall be a *Laboratory Head / Officer in-charge* who is an individual with a relevant doctoral degree, and qualified by training or experience for the scope of activities carried out in the cell processing facility. The *Laboratory Head / Officer in-charge* is responsible for all procedures and administrative operations of the cell processing facility, including compliance with these Standards. The *Laboratory Head / Officer in-charge* should participate regularly in educational activities related to the field of hematopoietic cell processing and/or transplantation. The *Laboratory Head / Office in-charge* may also serve as the *Medical Head / Office in-charge* if appropriately credentialed.
- C3.2 There shall be a *Processing Facility Medical Head / Officer in-charge* who is a physician licensed in the jurisdiction in which the facility is located. This individual is directly responsible for the pre-collection evaluation of the donor, final approval of the prospective donor for the collection procedure, conduct of the collection / processing procedure, care of any complications arising from collection and compliance of the collection facility with these Standards. The *Collection or Processing Facility Medical Head / Officer in-charge* should participate regularly in educational activities related to the field of cell collection and/or processing.
- C3.3 There shall be a *Laboratory Quality Management Supervisor* designated by the *Laboratory Head* to establish and maintain systems to review, modify as necessary, and approve all procedures intended to monitor compliance with these Standards and/or the performance of the facility. The *Laboratory Quality Management Supervisor* should participate regularly in educational activities related to the field of cell processing and quality management.
- C3.4 There shall be adequate numbers of trained support personnel available at the facility where the collection is performed.
- C3.4.1 The training, continued education and continued competency for the performance of operations shall be documented.

C4.0 Quality management

- C4.1 The Cell Processing Laboratory shall establish and maintain a program of quality management as it pertains to the laboratory, under the supervision of a designated person. The individual shall review and approve policies and procedures that document compliance with regulatory requirements and standards, and the performance of quality audits.

- C4.1.1 Protocols shall be developed, implemented and documented for the validation or qualification of significant procedures of facilities, processes, equipment, reagents, labels, containers, packaging materials, and computer systems. Determination of which elements are to be validated or qualified shall be made by the Laboratory Head / Office in-charge.
- C4.1.2 Evaluation of validation studies and audits shall be reviewed with documentation of approval by the appropriate individual from the Quality Management Program.
- C4.1.3 Outcome Analysis
Documentation and review of clinical outcomes shall be part of the on-going quality management program.

C4.2 Testing of products

- C4.2.1 The Laboratory Head shall prescribe tests and procedures for measuring, assaying, or monitoring properties of the cell products essential to the evaluation of their safety and usefulness. Results of all such tests and procedures shall become part of the permanent record of the product processed.
- C4.2.2 There shall be documentation of on-going proficiency testing for tests performed within the cell processing laboratory as designated by the Laboratory Head.
- C4.2.3 Tests required by these Standards, not performed by the cell collection or laboratory facility, shall be performed in a laboratory accredited or licensed in accordance with applicable governmental laws and regulations.
- C4.2.4 A nucleated cell count shall be performed for any product after collection and as specified in SOPs.
- C4.2.5 The processing facility shall monitor and document microbial contamination of cell therapy products after processing and as specified in SOPs.
 - C4.2.5.1 The results of microbial cultures shall be reviewed by the Laboratory Head or designee in a timely manner.
 - C4.2.5.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.
- C4.2.6 For products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, should be employed for evaluation of the target cell population before and after the processing procedure(s).

C4.3 Supplies and reagents

- C4.3.1 Protocols shall be developed, implemented, and documented for the validation or qualification of significant, processes, equipment, reagents, labels, containers, packaging materials, and computer systems. Determination of which elements are to be validated or qualified shall be made by the Laboratory Director.
- C4.3.2 Reagents used in processing and preservation of products shall be of appropriate grade for the intended use and shall be sterile.
- C4.3.3 Procedures for production of in-house reagents shall be validated.
- C4.3.4 Each supply and reagent used in the processing and infusion of the product shall be examined visually for damage or evidence of contamination as it comes into inventory. Such examination shall include inspection for breakage of seals, abnormal color and expiration date.
- C4.3.5 All supplies and reagents used in the processing, testing, freezing, storage, and transplantation of products shall be stored in a safe, sanitary, and orderly manner.
- C4.3.6 All supplies and reagents coming into contact with products during processing, storage, and transplantation shall be sterile.
- C4.3.7 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.

C4.4 Equipments

- C4.4.1 Equipments used in the processing, testing, freezing, storage, transportation, and transplantation of products shall be maintained in a clean and orderly manner and located so as to facilitate cleaning, calibration and maintenance.
- C4.4.2 The equipments shall be observed, standardized and calibrated on a regularly scheduled basis as described in the SOPs Manual and according to the Manufacturer's recommendations.
- C4.4.3 Sterilization equipments shall be designed, maintained and used to ensure the destruction of contaminating microorganisms.
- C4.4.4 Refrigerators and freezers used for the storage of specimens, cell products, blood products, human tissues, or reagents shall not be used for any other purpose.

C4.5 Review of processing records

- C4.5.1 Records pertinent to the product shall be regularly reviewed by the Laboratory Head or designee.
- C4.5.2 The review may be performed at appropriate periods during or after product processing, testing, freezing, and storing.

- C4.5.3 A thorough investigation, including resolution and outcome, of any unexplained discrepancy or the failure of a product to meet any of its specifications shall be made and documented.

C4.6 Errors, accidents and adverse reactions

- C4.6.1 Each cell processing facility shall have a system for detecting, evaluating, documenting and reporting errors, accidents, suspected adverse reactions, and complaints. Corrective actions shall be documented and reviewed by the Laboratory Head .
- C4.6.2 All suspected clinical adverse reactions shall be evaluated promptly according to SOPs, and reviewed by the Processing Facility Medical Head
- C4.6.3 A written evaluation of reported adverse reactions shall be included as part of the processing record and made available to the patient's physician.
- C4.6.4 Where applicable, the event shall also be reported to the clinical program, the collection facility and appropriate regulatory agency.

C5.0 Policies and procedures

- C5.1 The Cell Processing Facility shall have written policies and procedures addressing all appropriate aspects of the operation including processing; emergency and safety procedures; donor and patient confidentiality; quality management and improvement; errors, accidents and adverse reactions; corrective actions; personnel training; competency assessment; outcome analysis; audits; labeling; storage, including alternative storage if the primary storage device fails; transportation; expiration dates; release and exceptional release; disposal of medical and biohazard waste; equipment and supplies; maintenance and monitoring; cleaning and sanitation; and a disaster plan.
- C5.2 The Cell Processing Laboratory shall maintain a detailed SOP Manual.
 - C5.2.1 The SOP Manual shall include:
 - C5.2.1.1 A procedure for preparing, implementing and reviewing all procedures.
 - C5.2.1.2 A standardized format for procedures, including worksheets, reports and forms.
 - C5.2.1.3 A system of numbering and/or titling of individual procedures.
 - C5.2.2 Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure requires:

- C5.2.2.1 A clearly written description of the purpose.
- C5.2.2.2 A clear description of equipment and supplies used.
- C5.2.2.3 The objectives of the procedure, and acceptable end-points and the range of expected results where applicable.
- C5.2.2.4 A reference section listing appropriate literature.
- C5.2.2.5 Documented approval of procedure and each procedural modification by the Laboratory Head or Processing Facility Medical Head appropriate prior to implementation and annually thereafter, including the associated validation studies.
- C5.2.2.6 Examples of correctly completed orders, worksheets, reports, labels and forms, where applicable.
- C5.3 Copies of the SOP Manual shall be available in the immediate area to the facility staff at all times.
- C5.4 All personnel in the facility shall follow the SOPs detailed in the manual.
- C5.5 New and revised policies and procedures shall be reviewed by the staff prior to implementation. This review and associated training shall be documented.
- C5.6 Archived procedures and their historical sequence shall be maintained indefinitely, including the inclusive dates of use.
- C5.7 Deviations from SOPs shall be documented and approved, if appropriate, by the Laboratory Head or designee.
- C5.8 SOPs for all procedures shall comply with these Standards.

C6.0 Adult cell processing

- C6.1 Laboratory control procedures shall include:
 - C6.1.1 The establishment of validated and appropriate assays, standards and test procedures for the evaluation of products.
 - C6.1.2 Provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.
 - C6.1.3 Identification and handling of all test samples so that they are accurately related to the corresponding product being tested, or to its donor, or to the corresponding recipient, where applicable.

C6.2 Cell processing

- C6.2.1 All open cell handling procedures must be performed in class 100 environment.
- C6.2.2 More than minimal manipulation of products should only be performed in a clean-room environment. Environmental monitoring of such rooms must be performed and documented.
- C6.2.3 There shall be a written request from the recipient's physician before processing is initiated.
- C6.2.4 Processing of cellular therapy products shall be performed according to protocols defined in the facility's SOPs.
- C6.2.5 Methods for processing shall employ aseptic technique and be validated to result in acceptable cell viability and recovery.
- C6.2.6 The objectives and acceptable end-points for each procedure shall be specified.
- C6.2.7 Worksheets shall be maintained for all procedures.
 - C6.2.7.1 The individual responsible for each significant step of processing shall be documented.
 - C6.2.7.2 Lot numbers and expiration dates of reagents and disposables and a record of key equipment used in processing shall be documented.
- C6.2.8 The Laboratory Head or designee shall review the processing record for every product.
 - C6.2.8.1 The appropriate transplant physician shall be notified when the clinically relevant processing end-points are not met.
 - C6.2.8.2 Notification and appropriate remedial actions, if taken, shall be documented in the processing record.
- C6.2.9 Process using more than minimal manipulation shall only be performed with the institutional review board (IRB) approval and with the written informed consent of the recipient of the product and in compliance with governmental laws and regulations, as applicable
- C6.3 There shall be a policy and procedure to cover the processing of ABO incompatible products, when applicable
- C6.4 Laboratory control procedures shall include:
 - C6.4.1 The establishment of validated and appropriate assays, standards and test procedures for the evaluation of products.
 - C6.4.2 Provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.

- C6.4.3 Identification and handling of all test samples so that they are accurately related to the corresponding product being tested, or to its donor, or to the corresponding recipient, where applicable.

C7.0 Cryopreservation

C7.1 Samples

- C7.1.1 Sample aliquots of the product, cryopreserved and stored under the same conditions as the product, should be available for testing for 5 years.

C7.2 Procedures

- C7.2.1 Cryopreservation procedures shall be included in the cell processing facility's SOPs and shall describe:
 - C7.2.1.1 The name and freezing criteria of the cell product or aliquot.
 - C7.2.1.2 The cryoprotectant solution and its final concentration.
 - C7.2.1.3 Cryopreservation container.
 - C7.2.1.4 Acceptable range of product volume for reproducible cryopreservation.
 - C7.2.1.5 Acceptable range of nucleated cell concentration of the final product after cryopreservation.
 - C7.2.1.6 Cooling rate.
 - C7.2.1.7 Product temperature at endpoint of controlled cooling.
 - C7.2.1.8 Acceptable temperature range for storage.

C7.3 Cooling rate

- C7.3.1 The cryopreservation procedure shall be validated.
- C7.3.2 The cooling rate achieved shall be recorded, if a rate-controlling device is used.

C8.0 Labels

C8.1 Labelling operations

- C8.1.1 Labelling operations shall be conducted in a manner adequate to prevent mislabeling of products.
- C8.1.2 The labelling operation shall include the following quality management elements:
 - C8.1.2.1 Container labels shall be held upon receipt from the manufacturer pending review and proofing against a copy

- approved by the Laboratory Director or designee to ensure accuracy regarding identity, content, and conformity.
- C8.1.2.2 Stocks of unused labels representing different products shall be stored in an orderly manner to prevent errors. Stocks of obsolete labels shall be destroyed.
 - C8.1.2.3 A system of checks in labeling procedures shall be used to prevent errors in translating information to container labels.
 - C8.1.2.4 All labeling shall be clear and legible and printed using moisture-proof ink.
- C8.1.3 Labels shall be affixed or attached firmly to the container.
 - C8.1.4 The cell therapy product name and significant product modification(s) shall be noted on the label.
 - C8.1.5 Products that are subsequently re-packaged into new containers shall be labeled with new labels as appropriate. Records to allow tracking of products including collection or processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, donor and recipient information on the original container shall be maintained.
 - C8.1.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.
 - C8.1.7 The product label shall be complete. Not applicable (NA) may be used when appropriate.
 - C8.1.8 Labeling requirements, if any, required by governmental laws or regulations shall be observed.

C8.2 Product identification

- C8.2.1 Each product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to relate any product to its donor, the donor's medical record, and to all records describing the handling and final disposition of the product. If a single product is stored in multiple containers, there shall be a system of identifying each container.
- C8.2.2 Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the product. Supplementary identifiers shall not obscure the original identifier. The facility associated with each identifier shall be designated.

C8.2.3 If applicable, significant modifications made to the product subsequent to collection and prior to cryo-preservation shall be noted.

C8.3 Partial label

C8.3.1 If the container is capable of bearing only a partial label, the container shall show as a minimum the unique identifier of the product, proper name of the product as well as the name and identifier of the intended recipient, if known.

C8.4 Bio-hazard label

C8.4.1 A bio-hazard label shall be applied to each product if any test shows evidence of infection due to communicable disease agent(s).

C8.4.2 A bio-hazard label shall be applied to each product if testing was not performed or final results are not available.

C8.5 Label during processing

C8.5.1 Any container used during processing shall contain at a minimum the information required in 8.310

C8.6 Labeling at completion of processing

C8.6.1 At the end of processing, the label on the product container shall bear the information in 8.310.

C8.7 Labeling prior to distribution

C8.7.1 At the time of distribution the name and unique patient identifier of the intended recipient shall be attached to the product container if this information is not already on the primary container label.

C9.0 Issue of Products Prior to Distribution

C9.1 Inspection of products prior to distribution

C9.1.1 Each product issued for infusion shall be inspected by two trained personnel immediately before release to verify appropriate labeling and integrity of the product container.

C9.1.2 The Laboratory Head, or designee, shall give specific authorization for use when the container is compromised and/or recipient information is not verified.

C9.2 Return of products from issue

C9.2.1 Products accepted for return shall meet the following conditions:

- C9.2.1.1 The integrity of the primary container has not been compromised subsequent to issue from the laboratory.
- C9.2.1.2 The product has been maintained subsequent to issue at the specified temperature range during storage and transportation.
- C9.2.2 If the conditions in 9.211 and 9.212 have not been met, the Laboratory Head or designee shall give specific authorization to accept the products for return.
- C9.2.3 The Laboratory Head or designee shall consult with the patient's physician regarding reissue or discard of the returned product.
- C9.2.4 Documentation of the events requiring return, the results of inspection upon return, and subsequent action taken to insure product safety and viability shall be maintained in the laboratory record.

C9.3 Instructions for administration

- C9.3.1 For each type of product, the laboratory shall maintain a current document containing the following as appropriate:
 - C9.3.1.1 The use of the cell product, indications, contraindications, side effects and hazards, dosage and administration recommendations.
- C9.3.2 The instructions for administration shall be available to the clinical staff caring for the recipient.

C9.4 Infusion forms

- C9.4.1 The laboratory shall provide a written form to be completed for products issued containing at a minimum the name and unique identifier of the intended recipient, the proper product name and product identifier, and the initials of the medical staff receiving the product.

C10.0 Conditions for Storage

C10.1 Storage duration

- C10.1.1 Facilities storing cell products shall establish policies for the duration and conditions of storage and indications for discard. Patients, donors, and associated transplant centers should be informed about these policies before cell collection.

C10.2 Temperature

- C10.2.1 Storage temperatures shall be defined in the SOP Manual.

C10.2.2 Cells stored in a liquid state shall be maintained within a specific temperature range and for a period of time specified in a SOP.

C10.2.3 Cryopreserved products shall be stored within a temperature range appropriate for the cell product and cryoprotectant solution used and as defined in the SOPs.

C10.3 Product safety

C10.3.1 Materials that may adversely affect cell products shall not be stored in the same refrigerators or freezers.

C10.3.2 For products immersed in liquid nitrogen, procedures to minimize the risk of microbial cross-contamination of products shall be employed.

C10.4 Monitoring

C10.4.1 Refrigerators and freezers for product storage shall have a system to monitor the temperature continuously or at least every 8 hours.

C10.4.1.1 For products fully immersed in liquid nitrogen continuous temperature monitoring is not required.

C10.4.2 There shall be a mechanism to ensure that levels of liquid nitrogen in liquid nitrogen freezers are maintained.

C10.5 Alarm systems

C10.5.1 Storage devices for products or reagents for product processing shall have alarm systems that are continuously active.

C10.5.2 Alarm systems shall have audible signals.

C10.5.3 If laboratory personnel are not always present in the immediate area of the storage device, a remote alarm device shall be required at a location staffed 24 hours a day.

C10.5.4 Alarms shall be set to activate at temperatures or an unsafe level of liquid nitrogen to allow time to salvage products.

C10.5.5 There shall be written instructions to be followed if the storage device fails. These instructions shall be displayed in the immediate area containing the storage device.

C10.5.5.1 A procedure for notifying laboratory personnel shall be placed at each remote alarm location and in the immediate area of the storage device.

C10.5.6 Alarm systems shall be checked periodically for function.

- C10.5.7 Additional storage devices of appropriate temperature shall be available for product storage if the primary storage device fails.

C10.6 Security

- C10.6.1 The storage device shall be located in a secure area. Locking capability for the device or the storage location should be used when the area is unattended.

C10.7 Inventory control

- C10.7.1 An inventory control system to identify the location of each product and associated sample aliquots shall be in use.

- C10.7.2 The inventory control system records shall include:

- C10.7.2.1 Donor name or identifier
- C10.7.2.2 Patient name or identifier (if known)
- C10.7.2.3 Product unique identifier
- C10.7.2.4 Product or specimen name
- C10.7.2.5 Date of collection
- C10.7.2.6 Storage device identifier
- C10.7.2.7 Location within the storage device
- C10.7.2.8 Dates of issue
- C10.7.2.9 Disposition

C11.0 Transportation

- C11.1 Procedures for transportation of non-frozen and/or cryopreserved products shall be designed to protect the integrity of the product being shipped and the health and safety of facility personnel.
- C11.2 The primary product container for non-frozen products shall be placed in a secondary plastic bag and sealed to prevent leakage.
- C11.3 Frozen or non-frozen products that leave the facility or are transported on public roads shall be shipped in an outer shipping container.
 - C11.3.1 The outer shipping container shall be thermally insulated and shall conform to the regulations regarding the mode of transport.
 - C11.3.2 The outer shipping container shall be made of material adequate to withstand leakage of contents, shocks, pressure

changes, and other conditions incident to ordinary handling in transportation.

- C11.3.3 The shipping container shall be of appropriate design and construction for transportation of the cryogenic material used.
 - C11.3.4 Cryopreserved products with an indicated storage temperature below -80°C shall be shipped in a validated liquid nitrogen "dry shipper" that contains adequate absorbed liquid nitrogen to maintain temperature at least 48 hours beyond the expected time of arrival at the receiving facility.
 - C11.3.5 During transport, the product temperature shall be maintained at the storage temperature specified by the Processing Laboratory.
 - C11.3.6 The sending facility shall include a temperature monitor in the shipper.
 - C11.3.7 Outer shipping container shall be labeled as defined in *Section C8.3*.
 - C11.3.8 There shall also be a label inside the shipping container that includes all the information required on the outer shipping container as defined in *Section C8.3*.
 - C11.3.9 The shipping container shall be labeled in accordance with applicable regulations regarding the cryogenic material used and the transportation of biologic materials.
- C11.4 The receiving facility shall verify the presence of cryogenic material (absorbed liquid nitrogen) in the shipper and the status of the temperature monitor shall be recorded upon arrival.

C11.5 Method of transport

- C11.5.1 The transit time should be minimized.
- C11.5.2 If the intended recipient has received high-dose therapy, the product shall be hand-carried by a suitably informed courier in the passenger compartment.
- C11.5.3 There shall be plans for alternative transport in an emergency.
- C11.5.4 The products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container shall be inspected by hand.

C11.6 Transport records

- C11.6.1 Transport records shall permit tracing of the product from one facility to another.
- C11.6.2 Transport records shall identify the date and time product is shipped and received.
- C11.6.3 Transport records shall identify the source facility, the receiving facility, and the personnel responsible for shipping and receiving the product.
- C11.6.4 Transport records shall document the identity of the courier and any delays or problems occurring during transportation of the product.

C12.0 Disposal

- C12.1 There shall be a written policy for disposal of cell products.
- C12.2 There shall be a written agreement between the patient or designated recipient and the storage facility defining the circumstances for disposal or transfer of cells.
 - C12.2.1 If the patient or designated recipient is still alive, his/her written consent for disposal or transfer of the products shall be obtained. If consent is denied, the patient shall be offered the opportunity to ship the product to another facility.
- C12.3 There shall be written documentation of patient death or no further need for the product before any product is discarded.
- C12.4 The records for discarded products shall indicate the product discarded, date of discard, and method of disposal.
- C12.5 The Laboratory Medical Head of the processing facility, in consultation with the patient's transplant physician, shall approve of product discard and method of disposal.
- C12.6 The method of disposal and decontamination shall meet the governmental laws and regulations, for disposal of biohazardous materials.

C13.0 Records

C13.1 General requirements

- C13.1.1 All records and communications among the collection, processing and transplant facilities and their patients shall be regarded as privileged and confidential. Safeguards to assure this confidentiality shall be established and followed

in compliance with applicable governmental laws and regulations.

- C13.1.2 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and infusion or disposal of each product in such a way that all steps may be accurately traced.
- C13.1.3 Records shall be legible and indelible, shall identify the person immediately responsible for each significant step, and shall include dates (and times where appropriate) of various steps and shall show the test results as well as the interpretation of each result where appropriate.
- C13.1.4 Records of each step shall be as detailed as necessary for a clear understanding of each step by a person experienced in hematopoietic progenitor cell processing and transplantation, and shall be available for inspection by authorized individuals.
- C13.1.5 Appropriate records shall be available from which to determine the lot numbers and manufacturer of supplies and reagents used for the processing of specific products.
- C13.1.6 Records shall be maintained in such a way as to assure their integrity and preservation.

C13.2 Records to be maintained indefinitely

Records related directly to the processing, testing, storage or release of HPCs shall be maintained indefinitely.

C13.2.1 Processing records

- C13.2.1.1 Identity of any facility involved in the collection, processing, storage or transplantation of the product.
- C13.2.1.2 Product processing, including lot numbers and expiration dates of reagents and disposables and a record of key equipment used in processing shall be documented.
- C13.2.1.3 Authorization by the recipient's physician for the processing of products.
- C13.2.1.4 Results and interpretation of all tests and re-tests.
- C13.2.1.5 Information on characterization of materials and devices used in the manipulation of products including but not limited to antibodies, serum, cytokines, toxins, antibiotics, pharmacologic agents,

other chemicals or solid supports. Records shall include the manufacturer's name and lot numbers of all reagents used.

C13.2.1.6 Records of laboratory personnel involved in the labeling, processing, storage or distribution of the product, including their name, signature, initials, identification and inclusive dates of employment.

C13.2.1.7 Documentation of donor's infectious disease testing results.

C13.2.1.8 Signature of the Laboratory Medical Head authorizing the release of products in cases where there is a nonconforming product.

C13.2.2 Storage and distribution records

C13.2.2.1 Distribution or disposition, as appropriate, of products.

C13.2.2.2 Visual inspection of liquid products immediately before distribution.

C13.2.2.3 Product storage temperature, including initialed temperature recorder charts.

C13.2.2.4 Reissue, including records of proper temperature maintenance, documentation of events requiring return, results of inspection upon return and actions taken to insure product safety and viability prior to reissue.

C13.2.3 Compatibility test records

C13.2.3.1 Results of all compatibility tests, including red cell compatibility testing of patient samples, antibody screening and identification as specified in the facility SOP.

C13.2.4 Errors, accidents, adverse reactions and complaints:

C13.2.4.1 Records of errors, accidents and corrective action regarding processing, storage or infusion occurring within the facility.

C13.2.5 All superseded procedures and policies.

C13.3 Records to be maintained for 10 years

Records related to quality control, personnel training or competency, equipment maintenance, sterilization of supplies and

reagents, disposition of rejected supplies and reagents, management, or other general facility issues shall be retained for 10 years by the processing facility, although not all need be immediately available. If governmental laws or regulations require a longer retention period, records shall be retained for the period required by such laws or regulations.

- C13.3.1 Temperature charts and records for storage of reagents.
- C13.3.2 Calibration and standardization of equipment including initial installation.
- C13.3.3 Performance checks of equipment and reagents.
- C13.3.4 Periodic tests of capacity and integrity of shipping containers to maintain proper temperature in transit.
- C13.3.5 Periodic check on aseptic technique and competency.
- C13.3.6 Proficiency test results.
- C13.3.7 Results of inspection and accreditation visits.
- C13.3.8 General facility records.
 - C13.3.8.1 Sterilization records of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.
 - C13.3.8.2 Technical personnel training, continuing education, and periodic competency testing.
 - C13.3.8.3 Maintenance records for equipment including preventive maintenance and general physical plant.
 - C13.3.8.4 Documentation of acceptance for supplies and reagents, including name of manufacturer or supplier, lot numbers, date of receipt and expiration date as established in the facility SOP.
 - C13.3.8.5 Disposition of rejected supplies and reagents used in the collection, processing, testing, freezing and storage of products.

C13.4 Electronic records

An electronic record is any record or document consisting of any combination of text or graphics or other data that is created, stored, modified, or transmitted in digital form by a computer.

- C13.4.1 If a computer record-keeping system is used, there shall be a system to ensure the authenticity, integrity and confidentiality of all records.

- C13.4.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.
- C13.4.3 The facility shall have an alternative system that ensures continuous operation in the event that computerized data are not available. The alternative system shall be tested periodically.
- C13.4.4 There shall be established written procedures for record entry, verification and revision. A system shall be established for display of data before final acceptance.
 - C13.4.4.1 The quality assurance system shall include an assessment of computer functions to ensure that errors and problems are reported and resolved.
- C13.4.5 There shall be a system whereby access is limited to authorized individuals.
- C13.4.6 There shall be the ability to generate true copies of the records in both paper and computer form suitable for inspection and review.
- C13.4.7 When the software is not commercially available and computer system is used, there shall be validated procedures for and documentation of:
 - C13.4.7.1 Systems development, if carried out internally.
 - C13.4.7.2 Numerical designation of system versions if applicable.
 - C13.4.7.3 Prospective validation of system, including hardware, software, and database.
 - C13.4.7.4 Installation of the system.
 - C13.4.7.5 Training and continuing competency of personnel in systems use.
 - C13.4.7.6 Validation and monitoring of data integrity.
 - C13.4.7.7 Policies and procedures for system maintenance and operations. Documentation shall be complete, in language understandable by users.
- C13.4.8 All system modifications shall be authorized, documented, and validated prior to implementation.
- C13.4.9 The computer system shall ensure that all donor, product and patient identifiers are unique.

C13.5 Records in case of divided responsibility

- C13.5.1 If two or more facilities participate in the collection, processing or transplantation of the product, the records of the Cell Processing Laboratory shall show plainly the extent of its responsibility.
- C13.5.2 The Cell Processing Laboratory shall furnish to the facility of final disposition a copy of all records relating to the collection and processing procedures performed in so far as they concern the safety, purity and potency of the product involved.

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