BHARATHIDASAN UNIVERSITY

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Tamil Nadu, India

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TOPIC: National Policies Governing ES Cell Research for Science and the Scientist

Dr. A. S. VIJAYAKUMAR

Guest lecturer
Department of Biomedical Science

National Policies Governing ES Cell Research for Science and the Scientist

Introduction

- Stem cells and their derivatives fall under definition of 'Drug' as per the Drugs and Cosmetics Act 1940
- They are categorized as 'Investigational New Drug (IND)' or 'Investigational New Entity (INE)' when used for clinical application.
- Last decade has witnessed a proliferation of indiscriminate use of stem cell based therapies without establishing either their safety or therapeutic efficacy has led to the exploitation of vulnerable patients.
- National Guidelines for Stem Cell Research (NGSCR)-2017 takes into consideration the above mentioned issues.

Introduction

- Guiding philosophy of this document is:
  - Prevention of premature commercialization of unproven stem cell therapy
  - Generation of new knowledge based on sound scientific rationale while addressing all ethical concerns

Aim and Scope

- These guidelines are applicable to

- ✓ Individual researchers
- ✓ Organizations
- ✓ Sponsors
- ✓ Oversight regulatory committees
- ✓ All others associated with both basic and clinical research involving any kind of human stem cells and their derivatives.

- Not applicable for research using non-human stem cells and their derivatives.
- Not applicable use for hematopoietic stem cells for treatment of various hematological, immunological and metabolic disorders since these have already been established as a standard of medical care

Aim and Scope

- The guideline therefore focuses on:

1. Monitoring mechanism and regulatory pathway for basic, clinical research and product development based on categories of research and level of manipulation

2. Procurement of gametes, embryos and somatic cells for derivation and propagation of any stem cell lines, their banking and distribution

3. Other important areas like international collaboration, exchange of cell/lines and education for stakeholders and advertisement

Ethical Consideration

- Health ,Safety and Rights of the Donors

- It is mandatory to obtain informed consent from voluntary donor
- This shall include video consent as per CDSCO guidelines(9th Jan 2014)
- Confidentiality and privacy are sacrosanct (traceability in contingency)

Information to be provided to donor:

Need for screening TTD
Further procedural risks during collection of organ/tissue/cells (eg ovum , bone marrow) under LA/GA
If commercialization brings any benefits(financial) , efforts should be made to pass on the same to the donor

Scientific Consideration

- Manufacture and Quality Assurance of Stem Cell and its Products/Derivatives

- It is mandatory that the stem cells or their products/derivatives are processed in CDSCO licensed GMP compliant facility.

- Pleuripotent stem cell carry additional risks(mutations,benign teratoma,malignancy,failure to mature) , appropriate measures to be taken to ensure safe product

- For cryopreserved products ,possible impact of short/long term storage must be determined

- Compliance of QC/QA as per Schedule M of Drugs & Cosmetics Act,1940 and rules therein

- Release Criteria

- All stem cells or their products should have proper labeling before release

- Products should be of well characterized clinical grade that meet the desired standards of identity,purity,safety and traceability

- Product should be sufficiently stable for the duration as required

- The infrastructure facility shall be duly certified by CDSCO

Evidence Based Applications

- Clinical efficacy of stem cells in a disease state other than their use for HSCT for approved indications is not established

- It must be emphasized that no stem cell administration to humans is permissible outside the purview of clinical trials

Review & Oversight

- Research in this field is associated with unique ethical , legal and social concerns that require additional oversight and expertise for efficient scientific and ethical evaluation

- Separate mechanism for review and monitoring is essential both at institutional and national levels
- NAC-SCRT monitors and oversees research activities at the national level and lays guidelines for basic and clinical research
- IC-SCR approves and monitors stem cell research at the institutional level
- It is mandatory for all institutes and entities engaged in stem cell research to establish an IC-SCR and register the same with NAC-SCRT

Stem Cells Classification

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

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

- Embryonic Stem Cells (ESCs) are derived from pre-implantation embryos (blastocysts). Those derived from embryos before differentiation of trophoectoderm and inner cell mass (i.e. morula stage) are truly totipotent capable of giving rise to the entire organism including extra-embryonic tissues.

- Induced Pluripotent Stem Cells (iPSCs) as the name suggests are pluripotent in nature, quite similar to the ESCs. They are capable of indefinite expansion and differentiation into ectodermal, mesodermal and endodermal cells.

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

Levels of Manipulation

- Stem cells, whether autologous or allogeneic, require variable degree of *in vitro or ex vivo* processing before their use for clinical application/transplantation/translational research.
- Risk of contamination/alteration in the properties

1. Minimal Manipulation : The processing neither alters the number nor the biological characteristics and function of the cells (or tissue) relating to their utility for reconstruction, repair or replacement. Eg washing,centrifugation,separation and isolation.

2. Substantial Manipulation: this involves ex vivo alteration in the cell population,expansion,cryopreservation or cytokine based activation but will not result in alteration of cell characteristics and function

3. Major Manipulation: this refers to the genetic and epigenetic modification of stem cells , transient or permanent, or of cells propagated in culture leading to alteration not only in their numbers but also biological characteristics and function. eg : transdifferentiation , transduction.

Clinical trials using cells that have undergone more than minimal manipulation require approvals from CDSCO only after obtaining clearances from IC-SCR and IEC.

Categorization of research

- The research has been categorized into three major areas
- Basis : - Ethical/safety concerns
  - Source of stem cells
  - Levels of manipulation

- **Permissible Area:** - In vitro studies using stem cells isolated from tissues can be done with prior approval of IC-SCR and IEC.

  - Establishment of new human ESC lines from spare embryos or iPSC lines from fetal/adult somatic cells or SSCs from fetal or adult tissues, with prior approval of the IC-SCR and IEC.

  -If the tissue is obtained from hospital/clinic, other than the institute of the investigator, then the IEC clearance from the source institute is mandatory.

Categorization of research

- In vivo studies in experimental animals are permitted with prior approval of IC-SCR and Institutional Animal Ethical Committee(IAEC)

- **Restrictive Area** : It include, basic and translational research activities requiring additional arm of oversight/monitoring due to contentious issues involved.

  - Creation of human pre-implantation embryos by IVF, ICSI and SCNT with the specific aim of deriving ESC lines for any purpose .

  - Studies on chimeras where stem cells from two or more species are mixed together at any stage of early development (embryonic or fetal), for understanding patterns of development and differentiation

Categorization of research

- **Prohibited Areas :**

- Human germ line gene therapy and reproductive cloning

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

- Clinical trials involving xenogeneic cells.

- Any clinical research on Xenogeneic-Human hybrids

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

Categorization of research

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

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

Responsibilities of Investigators/Institutions & Sponsors

- Institutions involved in basic research/clinical trials should constitute an IC-SCR which should be registered with NAC-SCRT.
- Research involving hESCs, iPSCs, gene editing/modification and other contentious areas demands extra caution.
- Avoid activities leading to unrealistic expectations in the minds of participants and general public.
- Investigators should demonstrate respect for autonomy and privacy of those who donate gametes, blastocysts, embryos or somatic cells for stem cell research.
- Ensure confidentiality of the human donors
- Biological material can be procured only from clinics/hospitals that have IEC.

Responsibilities of Investigators/Institutions & Sponsors

- Clinical trials can be permitted only in institutions/hospitals having registered IC-SCR (with NAC-SCRT) and IEC (with CDSCO).
- All medical professionals involved in clinical trials should have a valid GCP certification obtained from agencies such as Central Drug Service Agency (CDSA) or online courses conducted by National Institutes of Health (NIH) USA.
- All records pertaining to clinical trials must be maintained for a period of at least 15 years.
- An institution or laboratory developing or processing stem cells for human use should obtain National Accreditation Board for Testing and Calibration (NABL) accreditation for Lab

Responsibilities of Investigators/Institutions & Sponsors

- The cells or cell-based products used in the trial should be processed in a CDSCO certified GLP and GMP facility
- For multi-centric clinical trials, all participating sites should obtain approvals form their own IC-SCR and IEC.

Stem Cells: Basic Research

- It is intended to enhance knowledge and understanding of a subject without necessarily leading to immediate practical solutions/therapeutic application.
- Guidelines for basic studies:

- In vitro studies largely fall in the permissible category of research.
- In vivo studies on experimental animals (other than primates) that fall in the permissible category
- No in vitro studies on pre-implantation human embryos shall be carried out beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.
- No in vitro manipulated cells shall be implanted in human/animal uterus with the intent of developing a whole organism.

Stem Cells: Basic Research

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

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

Stem Cells: Translational Research including Clinical trials

- It involves generating a safe and effective novel product based on fundamental research that can be taken to the bedside.

1. **PRECLINICAL STUDIES** :

These are essential for establishing persuasive evidence in an appropriate *in vitro and*/or animal model on the feasibility of the intended product, prior to conduct of clinical trials, as per regulatory requirements for any new biological entity (NBE).

more than one animal species (rodents & non rodents) might be needed

Stem Cells: Translational Research including Clinical trials

- **PRECLINICAL STUDIES**

- Approval & monitoring> permitted only after approval from IC-SCR

  > small animals → IAEC

  > large animals/non-human primates → CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals)

  > Human tissue → IEC

- Study Design > researchers should reduce bias and random variation by ensuring :

  a) adequate statistical power
  b) randomization of protocol
  c) appropriate control
  d) blinding

Stem Cells: Translational Research including Clinical trials

- **PRECLINICAL STUDIES**

- Safety Studies > stem cells used should be evaluated for early and late toxicities (immunogenicity & tumorogenicity)

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

  > The interaction of stem cells with drugs (including immunosuppressant) to treat the underlying medical condition shall be tested

  > Risks for tumorigenicity must be rigorously assessed for the product, particularly when developed following extensive manipulation in culture or through genetic modification, or in situations involving pluripotent stem cells.

Stem Cells: Translational Research including Clinical trials

- **PRECLINICAL STUDIES**

- Bio-distribution Studies >for all stem cells and its derivatives, whether injected locally or systemically should be performed both within the local as well as distant sites.

  > Studies of bio-distribution involves imaging and monitoring of homing , retention and subsequent migration of transplanted cell populations

Stem Cells: Translational Research including Clinical trials

- **CLINICAL TRIALS :**

- It should be in compliance with schedule Y of Drugs & Cosmetics Act 1940 and rules therein as well as GCP guidelines of CDSCO and ICMR

- Only institutions having their IC-SCR registered with the NAC-SCRT and IEC registered with CDSCO are permitted to conduct clinical trials.

- Reagents > it should be of clinical grade

  > Animal derived materials (fetal calf serum) should be tested for adventitious agents(bovine spongiform encephalopathy)

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

Stem Cells: Translational Research including Clinical trials

- **CLINICAL TRIALS :**

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

  >Irreversibility of the intervention.

  > The source and characteristics of stem cells and the degree of their *ex vivo manipulation*, if any.

  >The established standard of care for a given condition.

  >The sample size, duration of study and follow-up.

  >IC-SCR and IEC approvals.

Stem Cells: Translational Research including Clinical trials

- **CLINICAL TRIALS :**

  > The trial participant will not be levied any charges towards Procedures, investigations and/or hospitalization related to the trial

  > The participants should be provided the information sheet and Consent form in the vernacular/regional language

- Regulatory Approval > All clinical trials using stem cells shall be registered with the CTRI

  > All types of clinical trial using minimal/substantial manipulation , involving hESC,iPSC,SSC should have prior approval of IC-SCR, IEC and CDSCO.

Stem Cells: Translational Research including Clinical trials

- **CLINICAL TRIALS :**

- Monitoring > Separate Data Safety Monitoring Board (DSMB) should be established for each clinical trial

  > All cases of adverse and serious adverse events (AEs/SAEs) should be reported by the investigator/clinician/institution to the IEC and CDSCO

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

  > Medical records of trial participants should be maintained for a period of at least 15 years

Stem Cells: Translational Research including Clinical trials

- **CLINICAL TRIALS :**

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

  > Post trial follow up → 2 years for each indication ; 1 year can be extended depending on level of manipulation.

  > Submit periodic report to dsmb

Therapeutic Use of Stem Cells

- No approved indications other than HSCT
- Therapeutic use of stem cells other than approved indications(HSCT) should be conducted only in the form of clinical trial
- An investigator claiming the study outcome to be considered as a possible therapy in a particular indication, shall apply to the Director General, ICMR(Trial data & Justification)
- The ICMR will then determine in consultation with experts in the field, whether such a claim is tenable

Stem Cell Derived Secretotome

- Stem cell derived conditioned medium also k/a secretome (eg mesenchymal stem cell cultures of adipose tissue,Wharton's jelly etc)
- Possible application in cosmetics & wound healing
- It comprises *growth factors , cytokines , chemokines , ECM proteins*
- *Data* regarding pharmaceutical properties,quantification of growth factors,cytokines,precinical & clinical studies should be submitted to CDSCO
- Based on data submitted approval for use will be granted on case-to-case basis.

Stem Cell Banking

- As of now, only UCB banking is permitted and licensed by CDSCO.

- Umblical Cord Blood Banking : > rich source of CD34+ hematopoietic and mesenchymal (stromal) stem cells.

  > well established role in various hematological & immunological disorders(esp when HLA match sibling not available)

  > paucity of public funded UCB banks in India

  > commercialization of private UCB banks with promise of future therapeutic use

  > there is no scientific basis

  > Private storage of the cord blood HSCs is advisable when there is an elder child in the family with a condition treatable with these cells and the mother is expecting the next baby

Stem Cell Banking

- Umblical Cord Blood Banking : > public UCB banks across the world serves as a source of HSCs

  > parents should be encouraged for voluntary donations

  >UCB banks are permitted only under license and monitoring by the CDSCO. These are expected to follow the Drugs and Cosmetics act(3rd Amendment)

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

Stem Cell Banking

- **Umblical Cord Blood Banking :**

- Procedure for collection of Umblical Cord Blood > voluntary informed consent to me obtained (Mother's wish shall prevail out of both)

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

  > No harm should occur to the neonate and the mother.

  > Donor families should be compensated by providing them *Donor Cards* (allow them preferential access during emergency)

Stem Cell Banking

- **Banking of Human ESC/iPSC Lines :**

- following SOPs should be defined and maintained

>Assignment of unique identifier to each cell line

> Website that contains scientific description and data related to available stem cell lines

> Process for tracking disbursed cell lines and recording their status when shipped

> System for auditing compliance

> System for disposal of material.

> Release certificate to be issued with each dispatch.

- **Banking of Human ESC/iPSC Lines :**

- Secure system for protecting the privacy of donors > Plans for maintaining confidentiality
- A secure system for inventory track from primary cell lines to those submitted to the repository and their subsequent use.

Procurement of Biological Material for Research

- Fetal / Placental Tissue : - Termination of pregnancy (TOP) should comply with all obligations under MTP act

- Informed consent for donation > it should be obtained for termination of pregnancy and for donation of fetal material for research
  > Parents should be given sufficient time to take decision

- The purpose and use of donated fetal tissue should be fully explained to the parents.

- Medical person responsible for care of the pregnant woman willing To undergo termination of pregnancy and the investigator using the fetal Material shall not be the same.

- Donor shall not have the option to specify the use of the donated material

Procurement of Biological Material for Research

- <u>Gametes/Blastocysts/Embryos/Somatic Cells for Generation of Human - ESC/iPSC Lines</u>

- IC-SCR and IEC should verify that the blastocysts obtained from infertility clinics are in excess (spare embryos) of the clinical needs of the couple.
- Blastocyst→Human ESC
- Somatic cell → iPSC

} should be approved by IC-SCR & IEC

- Consent for donation of blastocysts should be obtained at least 24hrs in advance.

Procurement of Biological Material for Research

- There should be no inducement for donation of gametes or embryos by way of payment or in lieu of medical services,
  except for reimbursement of reasonable expenses for travel and loss of wages

- Attending physician responsible for the infertility treatment and the investigator deriving or proposing to use ES cells shall not be the same individual.

Procurement of Biological Material for Research

- Informed consent for donation should include the following statements:

- ✓ Donated material will be used to derive hESC for research purposes
- ✓ Donation is made without any restriction or direction regarding who may be the recipient
- ✓ that the derived hESC line may be used for development of new product(s) that may have a commercial value
- ✓ that derived stem cells or cell lines and the information related to them may be archived for 10 years or more
- ✓ that research is not intended to provide direct medical benefit to the donor(s) except situations involving autologous transplantation.

- Informed consent for donation should include the following statements:

- That neither consenting nor refusing to donate cells for research will affect the quality of present or future medical care provided

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

International Collaboration

- Collaborations help the participating institutions for advancement of the field, capacity building and global competence

- Participating institutions should consider the following:

- National guidelines and regulations of respective countries shall be followed.
- In situation involving a conflict (scientific and/or ethical) between the collaborators, the existing Indian guidelines, acts and regulations shall prevail
- Funding agencies/sponsors shall ensure that certification provided by the collaborating country fulfils the requirements as laid down in these guidelines.

Exchange/Procurement of Tissues, Stem Cells and Cell lines

- Exchange or procurement of tissues, stem cells or cell lines may be required for basic and clinical research.
- Not available currently in the country
- Import of stem cell lines for basic research does not require prior approval/No Objection Certificate (NOC) from any government agencies
- Traceability of all cell lines including those imported must be maintained by the investigator.
- Such cells are not permitted for commercial purposes or for human applications during clinical trials.

Awareness & Education of Stakeholders

- Democratic right, to be aware about treatment modalities, risks and benefits of upcoming technologies like stem cells
- Public awareness need to be created through periodic interactions
- The status of new scientific developments and innovative technologies, ethical issues related to these technologies and regulatory pathways need to be made a part of the curriculum for medical graduates.

Publicity & Advertisements

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

- The advertising and publicity through any mode by clinicians is not permitted as per Chapter 6 of the Indian Medical Council (Professional Conduct, Etiquettes and Ethics) Regulation.

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

Periodic Review of Guidelines

- Field of stem cells has seen rapid strides both in basic and translational aspects.
- It is essential to periodically review and update the guideline document
- Accordingly periodic changes to specific clauses and sections will be notified in the form of amendments
- ICMR will determine from time to time the need and mechanism for implementing revisions to the document

Reference:

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THANK YOU