Stem Cell Banking & Application: Guidelines & Regulatory Framework

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Stem Cell from various sources

Adult SC offers great therapeutic promise
Various Stem Cell Therapies

1. A small amount of fat - 200cc is taken from your waist area.
2. Stem Cells are separated from fat cells.
3. Your Stem Cells are activated with natural proteins.
4. The activated Stem Cells are returned back to you through an IV to repair damaged tissue.

Viabilities of various Stem Cell Therapies:

- Bone Marrow
- Adipose
- GVHD 3%
- Spinal Cord Regeneration 7%
- Reconstruction of Blood System 5%
- Bone Regeneration 4%
- Chondrocytes 2%
- Others 1%
- HIV 4%
- Cardiovascular Disorders 27%
- Diabetes 48%

Illustration by Cell Imaging Core of the Center for Reproductive Sciences.
Mesenchymal Stem Cells

• Besides HSC bone marrow has population of stromal cells differentiate into non hematopoietic lineage, commonly known as MSCs

• Other sources
  - Adipose
  - Liver
  - Brain
  - Cord blood
  - Placenta/AF
  - Dental pulp
Adipocytes
Adipose Stromal Cells
Vascular Endothelial Cells
Pericytes
Fibroblasts
Extracellular Matrix

Stromal Vascular Fraction (SVF)

Stromal cells + Vascular Endothelial + Mural cells
Blood cells – Leucocytes + Erythrocytes

~ 37% Leucocytes
~ 35% ASCs
~ 15% Endothelial Cells
## Fat over Marrow

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bone Marrow</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source /Technique</td>
<td>Bone Marrow aspiration</td>
<td>Lipoaspiration</td>
</tr>
<tr>
<td>Technique time</td>
<td>3 day Hospital admittance</td>
<td>Day care center</td>
</tr>
<tr>
<td>OT requirement</td>
<td>General/Lumbar anesthesia</td>
<td>Local anesthesia/ mild sedation</td>
</tr>
<tr>
<td>Degree of Pain</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Types of cells</td>
<td>HSCs : 0.6%</td>
<td>HSCs : 20-30%</td>
</tr>
<tr>
<td></td>
<td>MSCs : 0.002%</td>
<td>MSCs : 30-40%</td>
</tr>
<tr>
<td></td>
<td>WBCs, RBCs etc</td>
<td>Adipocytes, WBCs, RBCs etc</td>
</tr>
<tr>
<td>Max Vol of aspiration</td>
<td>100 ml</td>
<td>16000 ml</td>
</tr>
<tr>
<td>Manipulation of Stem Cells</td>
<td>Yes - Culture</td>
<td>No – use directly</td>
</tr>
</tbody>
</table>
Dental Pulp Stem Cell Banking

- Dental pulp is a rich source of Mesenchymal Stem cells
- MSCs can be isolated from falling milk teeth and extracted teeth
- Banking of Dental Pulp Stem Cells (DPSC) offers significant advantages over cord blood

<table>
<thead>
<tr>
<th>Dental Pulp</th>
<th>Cord Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy access, dentist’s clinic</td>
<td>Requires hospital setting, during childbirth</td>
</tr>
<tr>
<td>MSCs make up a large part of the cell population, i.e. better ‘quality’ stem cells</td>
<td>Very low concentration of MSCs in Cord Blood. Cord Tissue would be required</td>
</tr>
<tr>
<td>Banking requires basic regulatory approvals</td>
<td>Blood Bank license required for banking operations</td>
</tr>
<tr>
<td>Decreased risk due to multiple teeth</td>
<td>Chances of failure to culture</td>
</tr>
<tr>
<td>Untapped market, no indigenous companies (only collection centres)</td>
<td>Saturated market with &gt;10 players</td>
</tr>
</tbody>
</table>

- MSC’s isolated from dental pulp can form
- Nerve and spinal cord
- Brain
- Heart
- Liver
- Bone
- Ligaments and cartilage
- Muscle
- Skin
Placenta & Amniotic fluid

• Rich source of MSCs
  ➢ All three germ layers
  ➢ Maintain pluripotency
  ➢ Immunomodulatory properties
  ➢ Cryopreservation of minimally manipulated placenta/AF
Challenges

- Collection/extraction
- Transportation
- Processing/expansion
- Storage-cryopreservation:
  - Cryo protective agents: DMSO, glycerol, PVP etc
- Freezing, thawing & viability assessment
- Cryopreservation storage & shipping
Present Status

- Blood Banks
- Umbilical Cord blood Banks 7
- Banking for other tissues: Adipose, dental pulp, cord tissue 2
- Repositories for cancer tissue 2
- EBV transformed cell lines for rare genetic disorders, familial cancers 3
Stem Cell Banking

- India’s guidelines are permissive when compared to other countries
- At present only cord blood banking is regulated & licensed by Drug Controller General of India
- Banking of other biological tissues- Regulatory pathways are not defined.
REGULATIONS FOR CORD BLOOD BANKING
General Requirements

- Location
- Building/premises
- Disposal of waste/infectious material
- Health, clothing & sanitation of personnel
- Requirement for processing: testing & storage area
Requirement for processing: testing & storage area

• Separate dedicated space for
  – Reception
  – Processing
  – Haematology/serology lab
  – Infectious disease screening
  – Sterility testing
  – HLA typing
  – Sterilization/washing
  – Record room/store room
  – Cryogenic storage
  – General storage
Specific Guidelines/SOPs

- Collection & Storage of Processed components
  - Collection
  - Transportation
  - Storage

Labelling
- Collection
- Processing & Storage
- Release

- Trained Personnel
  - Medical Director
  - Lab in-charge
  - Technical Supervisor
  - Technicians

QA
Screening tests for ID
Storage
Refer samples
Current Regulatory Scenario

• Provision for two-tier of evaluation and monitoring of stem cell industry as proposed by guidelines:
  ➢ At institutional level- Institutional Committee for stem cell research and therapy (IC-SCRT) for permissible areas of research
  ➢ At the national level- National Apex Committee for Stem Cell Research and therapy (NAC-SCRT) for restricted areas

• IC-SCRT is required to register with NAC & oversee activities at institution level and report to NAC-SCRT in case of violation/unethical practices.
Current Regulatory Scenario

- **Constitution:**
  - Core Investigational New Drug (IND) evaluation committee
  - Cellular Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) by Ministry of Health (2010)

- **Intent is to**
  - Advice DCGI in matters pertaining to regulatory pathways for approval of clinical trials and market authorization of therapeutic products derived from Stem Cell, human Gene manipulation and Xenotransplantation technology
  - Establish separate wing for Stem Cell Research supported with knowledge and capacity to regulate the activities in the country.
  - Process cellular therapy-related applications till rules/guidelines are established
General Concerns

- **Concerns** with the private stem cell banks for yet-to-be-developed therapies. Even if therapies are developed, stem cells derived with today’s methods and medical approaches may be inappropriate for future applications.

- As a translational research field, stem cell development requires a high degree of linkage between basic and clinical expertise, which is another grey area.

- Lack of established criteria for final product characterization and release control.
Guidelines for Stem Cell Research

Guidelines reiterate

- General principles as applicable to all biomedical research involving human participants (Ethical Guidelines 2006)

- Specific Principles: collection/processing/storage & use
  - Health & safety of donors
  - Manufacture & quality assurance of products under cGMP
  - Design of clinical trials
General Principles

- Potential health benefits.
- Respect for human dignity, human rights and fundamental freedoms.
- Informed consent.
- Equitable distribution of burden and benefits.
- Non-malfeasance with the aim of minimization of risk and maximization of benefit.
- Freedom of conducting research with due respect to the above within the regulatory framework.
Quality assurance

- Sc in adult are rare/limited
- Requires some degree of processing
  - Enrichment/in vitro expansion
  - Manipulation to enhance the utility
- Essential to follow GMP/GLP
- Reagents and media should be of clinical grade
- Stringent characterization
  - Identity/purity/safety/genomic instability/tumorigenicity/potency
Design of Clinical Trial

- Basic characteristics of Sc
  - capacity for unlimited self renewal & differentiation
  - differentiate into cell types of all three germ layers

- Once introduced in the body
  - May survive indefinitely & differentiate unpredictably

- Give rise to teratomas

- Long term follow-up of subjects

- Records to be kept for 5yrs for Autologous and 10yrs for allogenic/ESc
Basic/Clinical Research

- Human clinical trial using stem cells must strictly adhere to accepted principles as laid down in the Schedule Y of Drugs and Cosmetic Act, GCP Guidelines of CDSCO and Ethical Guidelines for Biomedical Research involving Human Participants of ICMR.

- Subject Selection shall be done according to the inclusion and exclusion criteria as per the approved clinical research protocol.
Approval & Monitoring Clinical Research

- Evidence of progress of similar research at national and international level
- Whether the proposed cell based research is intended for manufacturing of a marketable product
- Approval and monitoring of clinical trials will take into consideration the following factors but not limited to:
  - Source and type of stem cells- adult, embryonic, fetal, iPSc etc.
  - Autologous or allogenic applications
  - Degree of manipulation- minimal, more than minimal or major
  - Stage of research - in-vitro, in-vivo, preclinical or clinical research
Regulatory Approvals

- Clinical trial proposals using minimally manipulated autologous adult stem cells will need approval by IC-SCR and IEC.

- Clinical research using autologous stem cells requiring more than minimal or major manipulation, and use of allogenic stem cells with any degree of manipulation will need approval from NAC-SCR through IC-SCR.

- Any stem cell based product already approved and marketed outside India will require approval of DCGI.

- Any clinical trial likely to lead to a marketable product shall have prior approval of DCGI through IC-SCR and NAC-SCR.
Use of Stem Cell: Therapeutic Purpose

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

• Cells used in such trials must be processed under GTP/GMP standards.

• The injectable product should meet pharmacopial specifications for parental preparations.

• The cells used for therapy shall be free from animal products and microbial contamination.

• The centers carrying out stem cell clinical trials and the agency/source providing such cells for the trial shall be registered with the NAC-SCR through IC-SCR/IEC.
Additional Areas Addressed

- Tissue engineering and scaffolds in stem cell research
- Banking and distribution of biological tissues including umbilical cord blood banking
- Research using fetal stem cells/placenta
- Procurement of gametes, blastocysts or somatic cells for generation of hES cell lines
- Commercialization and patent issues
Contd...

- International collaborations
- Import / Export of Stem Cells
- Public Participation
- Periodic Review of Guidelines
Volume II

Supplements:

• Basic principles of GLP/GMP/GTP/GCP related to SCR
• Standards For Collection, Processing And Storage Of Cells For Clinical Research
• Model Consent Form For Gamete/Embryo Donation
• SOPs & Manual
• Basic Principles of Stem Cell Banking (UCB, ESC, Adipose, Dental Pulp etc.
• Practical Code for Development of Human-derived therapeutic Cell Product
Stem Cell Therapies: India

**Proven Therapies**
1. Hematopoietic stem cell transplants – for hematological indications

2. Corneal repair with Limbal stem cells

**Unproven Treatments**
Large number of clinics offering treatments with adult stem cells (autologous BM / allogeneic CB or MSC) for a variety of indications, should be conducted in the form of well defined controlled trials

Taking advantage of current absence specific laws / regulatory oversight
## Approved Indications

<table>
<thead>
<tr>
<th>Disease Prevalence in India</th>
<th>Success in other parts of the world</th>
<th>Success in our centres in India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbal stem cell deficiency (LSCD) due to chemical burns</td>
<td>76.6% Largest study from Italy is about 250 cases</td>
<td>71% &gt;800 patients in last 12 years at LV Prasad Eye Institute, Hyderabad</td>
</tr>
<tr>
<td><strong>Prevalence in India</strong>: India needs 1 Lakh corneal transplants a year. Of these about 6000 <em>need limbal stem cell</em> treatment a year.</td>
<td></td>
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</tr>
<tr>
<td>Haematological disorders:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Thalassemia Major</td>
<td>60-65%</td>
<td>60-65%</td>
</tr>
<tr>
<td><strong>Prevalence in India</strong>: 1/10,000</td>
<td></td>
<td></td>
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<tr>
<td>2. Acute Myeloid Leukemia (not cured by Chemotherapy) <strong>Prevalence in India</strong>: 0.5-0.6/10,000</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>3. Non Hodgkin Lymphoma <strong>Prevalence in India</strong>: 20/10,000</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>4. Aplastic Anemia <strong>Prevalence in India</strong>: 0.1/10,000</td>
<td>70-80%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>5. Acute Lymphoblastic Leukemia <strong>Prevalence in India</strong>: 0.5-0.6/10,000</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>6. Myeloma <strong>Prevalence in India</strong>: 0.2-0.3/10,000</td>
<td>90%</td>
<td>90%</td>
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</table>
## Ongoing Trials

<table>
<thead>
<tr>
<th>Indication</th>
<th>Phase</th>
<th>Total subjects</th>
<th>Status</th>
<th>Global</th>
<th>Phase</th>
<th>Type of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myocardial Infarction (AMI) MI</td>
<td>I/II</td>
<td>20</td>
<td>Completed</td>
<td>68</td>
<td>Phase III - 6</td>
<td>BMMSC / CD34+ / SVF / EPC</td>
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<tr>
<td></td>
<td>II</td>
<td>25</td>
<td>Completed</td>
<td></td>
<td>Phase II/III - 9</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Phase II – 19</td>
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<td></td>
<td>Others – Phase I</td>
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<tr>
<td>Critical Limb Ischemia</td>
<td>I/II</td>
<td>20</td>
<td>Completed</td>
<td>31</td>
<td>Phase III – 1</td>
<td>BMMSC / CD34+ / SVF / EPC</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>126</td>
<td>Ongoing</td>
<td></td>
<td>Phase II and Phase II/III – 6</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Others – Phase I and Phase I/II</td>
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</tr>
<tr>
<td>Osteoarthritis</td>
<td>II</td>
<td>60</td>
<td>Ongoing</td>
<td>23</td>
<td>Phase III – 1</td>
<td>BMMSC / CD34+ / SVF / EPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II and Phase II/III – 8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Others – Phase I and Phase I/II</td>
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</tr>
<tr>
<td>COPD</td>
<td>II</td>
<td>30</td>
<td>Approved</td>
<td>12</td>
<td>Phase III – 1</td>
<td>BMMSC / CD34+ / SVF / EPC</td>
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<tr>
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<td>Phase II – 7</td>
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<td></td>
<td></td>
<td></td>
<td>Others – Phase I/II</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>II</td>
<td>60</td>
<td>Ongoing</td>
<td>35</td>
<td>Phase III – 1</td>
<td>BMMSC / CD34+ / SVF / EPC</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Phase II and Phase II/III – 7</td>
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<td></td>
<td></td>
<td>Others – Phase I and Phase I/II</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus Type 2</td>
<td>II</td>
<td>30</td>
<td>Approved</td>
<td></td>
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</tr>
</tbody>
</table>
# Ongoing Trials

<table>
<thead>
<tr>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Limbal stem cell deficiency (LSCD) due to chemical burns</td>
<td></td>
<td>&gt;800 71%</td>
<td>&gt;250 76.6%</td>
<td>Being offered as standard therapy</td>
<td></td>
<td>autologous Limbal epithelial stem cell</td>
</tr>
<tr>
<td>Limbal stem cell deficiency (LSCD)</td>
<td>I/II</td>
<td>25</td>
<td>Completed 44%</td>
<td>Being offered as standard therapy</td>
<td></td>
<td>ReliNethra® (an autologous Limbal epithelial stem cell graft)</td>
</tr>
<tr>
<td>Conjunctival disorders including recurrent pterygium, Stevens-Johnson syndrome, symblepheron, etc.</td>
<td>II</td>
<td>25</td>
<td>Completed 82%</td>
<td>2</td>
<td>Being offered as standard therapy</td>
<td>ReliNethra® C (an autologous Conjunctival epithelial stem cell graft)</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>II</td>
<td>20</td>
<td>Completed 67%</td>
<td>2+2</td>
<td></td>
<td>NeuroRel™ (an autologous bone-marrow derived MSCs)</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>II</td>
<td></td>
<td>On going</td>
<td>1</td>
<td></td>
<td>NeuroRel™ (an autologous bone-marrow derived MSCs)</td>
</tr>
</tbody>
</table>
Clinical Trials (CT) with Stem Cells in India

Clinical Trial Proposal

Corporate Sponsors

DCGI (Regulator)

ICMR (MOH)

Academic Investigator / RFA response

DBT (MOS & T)

For opinion

Reject / Approve

• Drugs & Cosmetics Act
• Tx of Human Organs Act
*no laws to cover autologous BM / allogeneic CB stem cells / MSC OR use of embryonic stem cells, YET

Review by
1) Local IRB (submitted with CT proposal)
2) Expert Committee of ICMR
3) NAC – SCRT (if needed, for certain categories)
⇒ Reject / Approve

Further Review by
1) Task Force on Stem cells (Science)
2) Clinical Trials Committee (Epidemiology / Trial design)
3) DBT Ethics Committee (apart from Local IEC)
4) NAC – SCRT (if needed, for certain categories)
⇒ Reject / Approve ⇒ Provide funding
⇒ Appoint CRO & DSMB
⇒ Regular meeting of Investigators with DBT
The Clinical Trials Registry- India (CTRI) has been set up by the ICMR's National Institute of Medical Statistics (NIMS) and is funded by the Department of Science and Technology (DST) through the Indian Council of Medical Research (ICMR). It also receives financial and technical support through the WHO, WHO-SEARO, and the WHO India Country office. [Read more...]

**Mission**

The mission of the Clinical Trials Registry- India (CTRI) is to encourage all clinical trials conducted in India to be prospectively registered before the enrollment of the first participant and to disclose details of the 20 mandatory items of the WHO International Clinical Trials Registry Platform (ICTRP) dataset. [Read more...]

**Vision**

The vision of the CTRI is to ensure that every clinical trial conducted in the region is prospectively registered with full disclosure of the 20-item WHO ICTR dataset, as well all items of the CTRI dataset, in order to 1) improve transparency and accountability, 2) improve the internal validity, details of the clinical trials can be made publicly available. The CTRI will be...
<table>
<thead>
<tr>
<th>Functions undertaken by Central Government</th>
<th>Functions undertaken by State Governments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statistic Functions</strong></td>
<td><strong>Statistic Functions</strong></td>
</tr>
<tr>
<td>• Laying down standards of drugs, cosmetics, diagnostics and devices.</td>
<td>• Licensing of drug manufacturing and sales establishments.</td>
</tr>
<tr>
<td>• Laying down regulatory measures, amendments to Acts and Rules.</td>
<td>• Licensing of drug testing laboratories.</td>
</tr>
<tr>
<td>• <strong>To regulate market authorization of new drugs</strong></td>
<td>• Approval of drug formulations for manufacture.</td>
</tr>
<tr>
<td>• To regulate clinical research in India.</td>
<td>• Monitoring of quality of Drugs &amp; Cosmetics, manufactured by respective state units and those marketed in the state.</td>
</tr>
<tr>
<td>• To approve licenses to manufacture certain categories of drugs as Central Licence Approving Authority i.e. for Blood Banks, Large Volume Parenterals and Vaccines &amp; Sera.</td>
<td>• Investigation and prosecution in respect of contravention of legal provisions.</td>
</tr>
<tr>
<td>• To regulate the standards of imported drugs.</td>
<td>• Administrative actions.</td>
</tr>
<tr>
<td>• Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).</td>
<td>• Pre- and post- licensing inspection.</td>
</tr>
<tr>
<td>• Testing of drugs by Central Drugs Labs.</td>
<td>• Recall of sub-standard drugs.</td>
</tr>
<tr>
<td>• Publication of Indian Pharmacopoeia</td>
<td></td>
</tr>
</tbody>
</table>
Thank you