ICMR’s Guidelines for Biomedical Research and National Guidelines for Stem Cell Research

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The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979
1980 ICMR Guidelines

- Ethics Committee
- Informed consent
- Clinical trials
- Research on children, mentally disadvantaged, those with diminished autonomy
- Traditional Medicine
- Publications
Ethical issues in New Biology & Technology
Biomedical Ethics - Guidelines

- CECHR under Chief Justice of India, hon’ble M. N. Venkatachaliah - AUG 1996
- Draft consultative document - Dec 1997
- Nation wide circulation - Jan 1998
- Regional public debates - 1998 - 1999
- Meetings of sub-committees - 1999
- Finalisation of document - 2000
Major areas identified by the Central Ethics committee on Human Research (1996)

- Clinical evaluation of drug/devices/diagnostics/vaccines/herbal remedies
- Epidemiological research
- Human Genetic Research
- Transplantation research including fetal tissue transplantation
- Assisted Reproductive technologies

Released in 2000
The National Ethical Guidelines
FWA : US - Compliance with the following procedural standards:

- 45 CFR 46 and all of its subparts (A,B,C,D)
- 45 CFR 46, subpart A (Common Rule)
- 21 CFR 50 and 21 CFR 56
- CIOMS International Ethical Guidelines
- ICH-GCP-E6 Sections 1 through 4
- Canadian Tri-Council Policy
- Indian Council of Medical Research
- Other (please submit copy to OHRP with this Assurance)

OHRP website – Compilation of documents related to Human Protection
Differences between 2000 and 2006 Ethical Guidelines of ICMR
Difference – General Principles

• Essentiality
• Voluntariness, informed consent and community agreement *(ECs shall decide about waiver)*
• Non-exploitation
• Privacy and confidentiality
• Precaution and risk minimisation

• Professional competence
• Accountability and transparency
• Maximisation of the public interest
• Institutional arrangements
• Public domain
• Totality of responsibility
• Compliance
Difference - Ethical Review Mechanism

Basic responsibilities of Ecs – Special situations

Composition – No. changed with specification for drug trial as per Schedule Y of Drugs & Cosmetics Act

Terms of Reference
Training
Regulation
Review Procedures – Exemption from review, expedited review, full review
Submission of Application
Decision Making Process
Review Process
Periodic Review
Continuing Review
Interim Review
Monitoring
Record Keeping
Administration and Management
Special Considerations
General Issues

- Informed consent of subject – Fresh /re-consent
- Waiver of consent
- Obligations of investigators
- Essential information for prospective research participants
- Compensation of participation
- Conflict of interest
- Selection of special group of research participants
- Essential information on confidentiality for prospective research participants
- Compensation from accidental injury
- Post – trial access
- International Collaborative Research/ Assistance in Biomedical/ Health Research
- Researcher’s relations with the media and publication practices
Ethical Review Procedures
Specific Principles

• Clinical Trials of Drugs, Devices, Vaccines, Diagnostic agents, Herbal Drugs

• Epidemiological Studies

• Human Genetics Research

• Transplantation Research including Fetal tissue and Xeno- transplantation

• Assisted Reproductive Technologies
Issues in Clinical trials

• DRUG TRIALS – special considerations increased
  – Phases of clinical trials – Combined Phase I & II & special studies
  – Multicentric trials - special concerns increased
  – Contraceptive trials
  – Monitoring ADRs / Aes – text changed

• Vaccine trials including r-DNA and combination vaccines - special concerns increased

• Devices/ Surgical procedures – text changed

• Herbal remedies – text changed
Epidemiological Studies

- Definition/ Types of studies
- General Principles
- Specific Principles - Informed consent – individuals & communities, inducements, risks, benefits, ethical review procedures, conflict of interest – community participation
- Privacy/ Confidentiality
- Program Evaluation
Human Genetics Research

- General issues
- Pedigree studies
- Privacy/confidentiality
- Genetic screening
- Therapeutic trials including Gene therapy
- Human Genome Project

- DNA and cell line Banking/repository - Excerpt from Draft Guidelines on Biobanking added
- DNA diagnosis
- Pre-natal diagnosis
- Assisted reproductive technologies – removed
- Human Genome Diversity - removed
Organ Transplantation

- Definitions
- Live donor transplants
- Cadaver donor transplants
- Research on recipients
- Fetal tissue transplantation
- Xeno-transplantation
- Transplantation for cosmetic purposes

Stem cell research & therapy - Excerpt from National Guidelines added
Assisted Reproductive Technologies

- Definitions
- Informed consent
- Privacy/confidentiality
- Selection of donor
- Legitimacy of the child
- Surrogate motherhood
- Research on embryos/spare embryos

Excerpt from National Guidelines added
Guidelines

Draft Guidelines

- Mental Health
- Dataset protection
- Disaster situations

Ethical Guidelines for Social Science Research (2000)
ICMR’s Ethical Guidelines

THE BIOMEDICAL RESEARCH ON HUMAN PARTICIPATION (PROMOTION AND REGULATION) BILL, 2007

Title different? 2014
Contents modified
Indirectly mandated

- 2002 - Indian Medical Council Act, amendment
- 2005 - Drugs & Cosmetics Act – Schedule Y

Included in Indian (CDSCO) GCP - 2001
Role Among Developing Countries

- Referred by many developing countries before own national guidelines were prepared
- Accepted by US as equally protective to human participants
- Indian guidelines more stringent due to over-precaution
- Guidelines for research using traditional medicine accepted by WHO for phase II trials in humans if traditionally used for traditional indication – adopted in China
- Draft Research ethics guidelines for disaster situations prepared by regional working group included in ICMR guidelines
Guidelines on Stem Cell Research 2013
What are Stem Cells

- Cells which can make exact copies of itself indefinitely (self-renewal), and can differentiate into specialised cells for various tissues of body
- Repairs, Replaces, Regenerates, Restores
- Cannot cure but may eliminate symptoms
Types of Stem Cells

- Adult Stem Cells – undifferentiated and multipotent
  - eg. Adult mesenchymal cells, bone marrow, hematopoietic, neural etc

- Embryonic Stem Cells (hES, hEG, hSS, iPS)
  - From eggs fertilized *in vitro*
  - Not from eggs, fertilized in woman
Potential of Stem Cells

• **Totipotent (total):**
  – Differentiate into any adult cell type
  – Form specialized tissue needed for embryonic development

• **Pluripotent (plural - PSCs):**
  – Includes embryonic cells (ES cells) and induced PS(iPS)
  – Potential to form most or all 210 differentiated adult cell types and iPS for embryogenesis

• **Multipotent (multiple):**
  – Limited potential
  – Forms only multiple adult cell types – Oligodendrocytes, Neurons, Myocyte etc.
Mesenchymal Stem Cells (MSC)

Mesodermal Progenitor Cells (MPC)

Skin-derived Precursors (SKP)

Multipotential adult progenitor cells (MAPC)

Embryonic origin

Adult origin

Chondrocytes

Adipocytes and Hemopoietic supportive stroma

Myoblasts

Cardiac

Skeletal

Osteoblasts

Endothelium

Neurons

Glia

Blood cells
Embryonic Stem Cells
Research Areas

- Drug development
- Toxicity testing
- Developmental biology
- Disease modeling
- Tissue engineering
Tissue Culture

Cardiomyocytes

Oligodendrites

Motor neurons

Bladder
Human Embryonic Cell (hES cell)

- Surplus embryos from IVF clinic
- Specifically generated for research
- Other techniques like SCNT to test therapeutic response
Cloning

- Therapeutic Cloning (SCNT)
- Reproductive Cloning
Countries with a permissive or flexible policy on embryonic stem cell research (in red)

- Denotes Genome Sequencing Center
Global Regulatory Scenario – Developed Countries

- **US** – The US Federal Government has approved ES cell research now
- **UK** – World’s most liberal ES cell policy, permits research on embryos up to 14 days old for medical purposes.
- **France** – Less liberal policies, use of excess embryos from IVF allowed
- **Germany** – Very strict policies, use of excess embryos or its creation is barred but can import embryos
- **Japan** – Research liberal, but regulation of therapy strict, Accreditation & no implantation of manipulated eggs
- **Australia** – Nation wide policy not yet made, no cloning in 3 states, stem cell legalized in some parts
Global Regulatory Scenario – Developing Countries

- **Korea**
  - research on surplus embryos
  - prohibited reproductive cloning

- **China**
  - No embryonic stem cell research
  - Cord blood stem cell study allowed
  - Regulation lax in military and police hospitals

- **Singapore**
  - Stem cell research allowed

- **Malaysia**
  - Therapeutic cloning allowed
  - National regulatory body

- **Israel**
  - Creation of embryos allowed
  - No regulation
  - No cloning for 5 years
Pro-life Group

- Consider destruction of lab fertilized embryos as ‘murder’
Pro-choice Group

• “Utilitarianism - destruction of smaller group for the sake of a larger group is justifiable.”

• Contributes significant information about the cause, new treatment possibilities, and potential cure for many diseases.
Adult Stem Cell - issues

• Scientific Concerns
  – Possibility of transmission of infectious agents
  – Low capacity of differentiation

• Informed consent issues
Cord Blood - issues

- Informed consent from mother or both parents
- Ensure no harm to the neonate
- Professionals with expertise to do it with permission from authority
- Cord Blood banking issues
  - anonymisation, commercialization, export/import of cord blood stem cells
  - Collection for own purpose or for donation
- Quality Control issues in Banking
  - Medical History, Accreditation of cord blood banks, Labeling issues
Embryonic Stem cells

- Creation of embryos
  - for HLA match for older affected sibling for therapy
  - creating embryos for research
  - Storage and disposal of supernumerary embryos
  - Status of cryo-preserved embryos - for how long?
  - Commodification
  - embryo’s right to life.
Hwang Ho (S. Korea) – Fabrication and Falsification (Research Misconduct)
Japanese Scandal of Research Misconduct

- Best known for developing new methods to grow stem cells into organ-like structures
- First stem cell researchers to grow optic cup from human cells
- With author Haruko Obokata on the two stem-cell papers published in *Nature* - falsification of data
- Hung himself in RIKEN Institute

Yoshiki Sasai
Indian Guidelines on Stem Cell Research 2013
Guidelines

• General Principles of ICMR’s Ethical Guidelines to be followed

• Specific Principles
  – Health & safety of donors – consent
  – Manufacture & quality assurance of stem cell products
  – Design of clinical trials to be based on current guidelines and or/ regulations
  – IPR to ‘community’
Guidelines

• Categories of research on stem cells
  • Permitted
  • Restricted
  • Prohibited

• All cell lines to be registered with NAC-SCRT through IC-SCR

• Establishment & licensing of umbilical cord blood stem cells under DCGI’s purview
Guidelines

• Levels of Manipulation
  – Minimal - IC-SCR & IEC when using minimally manipulated autologous adult stem cells
  – Substantial or more than minimal - IC-SCR & NAC-SCRT approval
  – Major – requires NAC-SCRT (through IC-SCR), IEC and DCGI’s approval

• GMP, GLP standards t be maintained
Guidelines – salient features

• Clinical trial using products developed outside India – prior approval from DCGI through ICSR & IEC

• International collaboration – HMSC approval in addition

• Registry of investigators, institutions with NAC-SCRT through IC-SCR

• CTRI registration if product is to be approved by DCGI

• Institution to set up IC-SCR or IEC with additional expertise could function as IC-SCR
Guidelines - Salient Features

- Archiving of adult cell stem cell research for 5 yrs and hES/iPS cell research for 10 yrs

- Communication – no hype communicated to parent, family and awareness programs by the institution

- Use of human embryo only if there is no other alternative

- For clinical trials DSMB a must.

- Cord blood banks to be registered with DCGI
Mechanism for Review and Regulatory Oversight

• NAC- ISCRT : National Apex Committee for Stem Cell Research and Therapy at national level

• IC-ISCR : Institutional Committee for Stem Cell Research at institutional level

• IEC

• DCGI
IC- SCR Approval

- Preclinical studies (with IAEC approval)
- Permitted research
- Creation of all new human pluripotent stem cell lines, irrespective of the source and methodology used
- Permission for procurement of human stem cell lines from abroad or from laboratories/banks in India
- All clinical trials with SSCs, other than those with genetic modifications (with IEC approval)
- Clinical trials using cells that have undergone more than minimal manipulation (with IEC & DCGI approval)
- Stem cell based IND products and application for new indications (with IEC & DCGI approval)
NAC - SCRT Approval

• Restricted research

• Use of human embryonic and iPS cells in clinical trials

• Clinical trials using genetically modified SSCs, and ES or iPS cells or derivatives

• Receive all ADRs

• Maintain registry of Centres carrying out stem cell clinical trials and the agency/ source providing such cells
Highlights in Informed Consent Document

a. Information regarding the present status of use of stem cells in the given condition, experimental nature of the proposed clinical study and its possible short and long term risks.

b. Information stating irreversibility of the intervention.

c. Information regarding source and characteristics of stem cells and degree of their ex-vivo manipulation, if any.

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

e. Information on the sample size and duration of study

f. The information sheet and the consent form should be approved by IEC and IC-SCR and the same should be clearly mentioned in these documents.
"Don't worry, I won't let anyone get your stem cells."

Thank You