

Human Subject Protections
Concerns Regarding Stem Cell
Research and the Establishment
of an ESCRO Committee

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Objectives

- Issues surrounding Embryonic Stem Cell research from an IRB and regulatory perspective
- Recruitment of samples locally and the procurement of samples from outside sources
- The establishment of an ESCRO committee and how it interacts with the IRB

Glossary of Key Terms

- **Adult (or somatic) stem cell**—An undifferentiated cell found in a differentiated tissue that can renew itself and differentiate (with certain limitations) to give rise to all the specialized cell types of the tissue from which it originated.
- **Blastocyst**—A preimplantation embryo of about 150 cells produced by cell division following fertilization.
- **Umbilical cord blood stem cells**—stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body (hematopoietic).
- **Therapeutic cloning**—The goal of therapeutic cloning is to create cells that exactly match a patient - combining a patient's somatic cell nucleus and an enucleated egg,

Glossary of Key Terms

- **Human embryonic stem cell (hESC)**—A type of pluripotent stem cell derived from the inner cell mass (ICM) of the blastocyst.
- **Somatic cell nuclear transfer (SCNT)**—A technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo.
- **Multipotent**—Ability of a single stem cell to develop into more than one cell type of the body.
- **Pluripotent**—Ability of a single stem cell to give rise to all of the various cell types that make up the body
- **Chimera**--A substance, such as an antibody, created from the proteins or genes of two different species. (Mythical Creature)
- <http://stemcells.nih.gov/info/glossary.asp>



Use of NIH Funds or Funded Resources for hESC Research




- **Generally** - Research involving Human Embryonic Stem Cells that are not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with federal funds.
- **Facilities** - cannot be used for ineligible hESC research if acquired, built or renovated with federal funds
- **Equipment**- may not be conducted using equipment exclusively or partially acquired with federal funds, unless
 - the federal contract/grant supporting the equipment purchase has been completed (including all of its competitive segments),
 - the institution has submitted the equipment inventory report required by the award and the federal government has not invoked its right to transfer the equipment within the 120 day period; and
 - the institution retains title to the equipment without restriction.

Use of NIH Funds or Funded Resources for hESC Research

- Investigators/departments conducting such research with non-federally approved cell lines are responsible for assuring that expenses are appropriately segregated and charged to a non-federal funding source.
- Extreme care must be used in allocating salary costs and in monitoring and allocating time and effort of all employees to assure that shared employee costs are allocated to the appropriate fund source. (use of daily logs is recommended)

Historical Overview: The Belmont Report – April 18, 1979

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

Respect for Persons		<ul style="list-style-type: none"> ▪ Informed Consent ▪ Capacity to Consent ▪ Privacy and Confidentiality ▪ Vulnerable Subjects
Beneficence		<ul style="list-style-type: none"> ▪ Risk/Benefit Analysis –Do No Harm ▪ Experimental Procedures ▪ Maximize Benefit
		<ul style="list-style-type: none"> ▪ Equitable Selection of Subjects ▪ Equitable Burdens and Benefits

IRB Approval Includes Findings That

•Review, Approve (§46.111), Exercise Continuing Oversight: *

1. Risks are minimized through sound research design
2. Risks are reasonable relative to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent will be obtained
5. Informed consent will be documented

When Appropriate

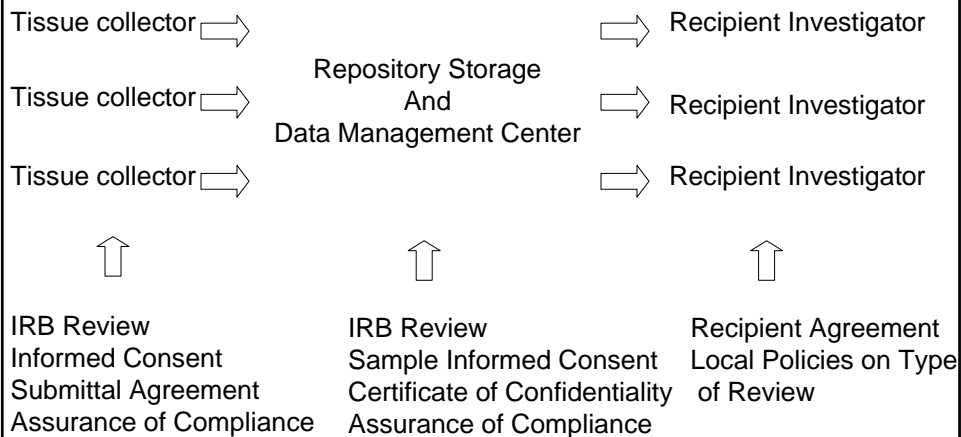
1. Privacy and Confidentiality provisions are adequate
2. Data safety monitoring is adequate
3. Appropriate safeguards are included for vulnerable subjects

Human Subjects Protections

45 CFR 46(Common Rule) 21 CFR 50, 56

- Human subjects protections are triggered when there is:
 - An identifiable living individual who is the subject of research
 - The research is funded by HHS or any other federal agency that has signed on to the “Common Rule”
 - The research is regulated by the FDA as part of the process for obtaining approval of a new human therapeutic drug, device or biologic.
 - The research takes place at an institution that has an FWA pledging to apply federal human subjects protections even to research not funded or regulated by the federal government.

Use OHRP Repository Guidance Model



Research Using Coded Data/Biologic Samples

- Under 45 CFR part 46, if an investigator obtains for research purposes private information about, or biologic samples that have come from, living individuals and the private information or biologic sample retains a link to individually identifying information, such private information ordinarily would be considered by OHRP to be individually identifiable to the investigator.

Research Using Coded Data/Biologic Samples

- However, OHRP does not consider research involving only coded private information or specimens to involve human subjects if the following conditions are both met:
 - (1) Private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

Research Using Coded Data/Biologic Samples

- (2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because for example
 - (a) the key to the code is destroyed before the research begins;
 - (b) the investigator enters into an agreement with the key holder preventing the release of the key under any circumstances, until individuals are deceased;

Research Using Coded Data/Biologic Samples

- (c) there are IRB-approved Protocol policies **(SOP's/Assurances)** and operating procedures for the repository that prohibit the release of the key to the investigators under any circumstance; or
- (d) there are other legal requirements prohibiting the release of the key to the investigator until the death of the individual.

Human Subjects Protections and hESC Donation

- Even though the use of Coded Biologic materials may not be considered to be within the definition of human subjects research and the donors may not be the subject of research, most institutions and state laws regarding hESC have asked for IRB oversight of the donation process.
- IRBs have experience looking at inducements, risks, and consent processes, all relevant to the recruitment of somatic cell, gamete and embryo donors.

HIPAA and hESC Donation

- Donor suitability rules may require access and collection of medical record information about gamete and blastocyst donors whose biological materials were used to derive new embryonic stem cell lines
- HIPAA may apply to the research uses of this medical record information

Human Subjects Protections and Consent for hESC Donation*

- IRB's will be challenged to develop consents that adequately address the potential uses in a manner that is understandable at a 6-8th grade level.
 - Permission to use frozen (previously obtained/leftover IVF embryos)
 - Separately donated gametes used to create embryos
 - hESC developed from SCNT – check state law where donation occurred
- How much Detail must be given regarding future use?
 - *NJ Law requires IRB review for Derivation and Use**

Cal. Consent for Donors

CHSC(125315(c))*

Must Include statement That:

- (1) hESC will be used to derive human pluripotent **stem** cells may be used, at some future time, for human transplantation research.
- (2) all identifiers will be removed
- (3) donors will not receive any information
- (4) de-identified **cell** lines, may be kept for many years.
- (5) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial benefit
- (6) the hESC research is not intended to provide direct benefit to the donor.
- (7) hESC donated will not survive the derivation process,

* See also CHSC 125341

Recruitment/Consent for Egg Donation

- IVF Clinics offer up to \$40,000 for eggs* – Potential for Coercion
 1. What is the optimal age of donors?
 2. Reproductive *donor* age?
 3. How many times to donate?
 4. How much stimulation?
- What are the Risks
 - **Acute Risks**
 - OHSS -Ovarian Hyperstimulation Syndrome
 - Surgical
 - Anesthetic
 - Psychological
 - **Chronic Risks**
 - Breast, ovarian, endometrial cancer
 - Future Fertility

* Cal.Code 125350 –No sale of for oocyte or embryo for research

Other IRB Issues

- Who owns Leftover Oocytes from Donor Egg IVF
 - Immature oocytes from IVF retrievals
 - Failed-to-fertilize oocytes from IVF procedures.
 - Will oocytes require donor data to assist in determining donor suitability
- Shared use issues – Consent, MTA's, Contracts
- Specific description for future use
- Exculpatory Language
- Compliance

Embryonic Stem Cell Research Oversight (ESCRO) NAS 2005

- Non-binding recommendations for establishment of oversight committee charged with oversight of Embryonic Stem Cell Research
- Oversight responsibilities include education, policy determinations legal and ethical oversight

hESC Ethical Issues

- Blastocysts as a potential human life
- “Respect” for fetal-embryonic materials.
- Nuclear transfer technology raises the possibility of human reproductive cloning.
- Research use of human-animal ‘chimeras’ might alter our definition of ‘human’.
- Defining the rights of the donors of the genetic material (hESC, sperm, egg,) (request to destroy, IP interests).

NAS Guidelines for Human Embryonic Stem Cell Research 2005

- hES cell research already actively underway with both federal and non-federal funding - several states are initiating major research efforts
- Significant public support (and opposition) for hES cell research
- A patchwork of regulations
 - Limited federal support / little federal regulation
 - No federal regulations governing hES cell research funded from other sources
 - Disparate state regulations
- No system for oversight of hES cell research
- Uncertainty about appropriate procedures
 - Public concerns
 - Uncertain scientific environment

Issues Considered

- 1) Recruitment of donors of blastocysts, gametes, or somatic cells
 - informed consent
 - financial incentives
 - conflicts of interest
 - donor confidentiality
 - risks associated with oocyte retrieval
 - handling of genetic info arising from the research
- 2) Characterization and standardization of stem cells
- 3) Safe handling/storage of blastocysts and stem cell material
- 4) Conditions for transfer of such material among laboratories
- 5) Appropriate uses of hES cells in research or therapy
- 6) Limitations on the use of hES cells
- 7) Safeguards against misuse

NATIONAL ACADEMIES GUIDELINES FOR RESEARCH ON HUMAN EMBRYONIC STEM CELLS

- 1.0 Introduction
- 2.0 Establishment of an Institutional Embryonic Stem Cell Research Oversight Committee
- 3.0 Procurement of Gametes, Blastocysts or Cells for hES Generation
- 4.0 Derivation of hES Cell Lines
- 5.0 Banking and Distribution of hES Cell Lines
- 6.0 Research Use of hES Cell Lines
- 7.0 International Collaboration
- 8.0 Conclusion and Need for a National Panel

1.1(a) What The Guidelines Cover

These guidelines cover all derivation of hES cell lines and all research that uses hES cells derived from

- (1) Blastocysts made for reproductive purposes and later obtained for research from in vitro fertilization (IVF) clinics.
- (2) Blastocysts made specifically for research using IVF.
- (3) Somatic cell nuclear transfer (NT) into oocytes.

Many, but not all, of the guidelines and concerns are common to other areas of human stem cell research, such as

- (a) Research that uses human adult stem cells.
- (b) Research that uses fetal stem cells or embryonic germ cells derived from fetal tissue

1.1(b) Reproductive Uses of Nuclear Transfer

The guidelines do not address reproductive uses of nuclear transfer - those are addressed in the 2002 report *Scientific and Medical Aspects of Human Reproductive Cloning*, in which the National Academies recommended that “Human reproductive cloning should not now be practiced. It is dangerous and likely to fail.”

Although the guidelines do not specifically address human reproductive cloning, it continues to be the view of the National Academies that research aimed at the reproductive cloning of a human being should not be conducted at this time.

Donations of blastocysts, oocytes, sperm and somatic cells

- Should always be reviewed by an Institutional Review Board
- Should be governed by informed consent of all donors
- Separation of decision to donate from all clinical decisions
- No payments to donors beyond reimbursement
of direct expenses
- No purchase or sale of donated materials
- Protection of donor privacy

Recommendations for Oversight of Human Embryonic Stem (hES) Cell Research

**1. Local oversight - each institution should establish an
Embryonic Stem Cell Research Oversight (ESCRO)
committee to review and monitor all proposals to
conduct hES cell research.**

The committee should include representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research.

Recommendations for Oversight of Human Embryonic Stem (hES) Cell Research

- **2. A national panel should be established to assess periodically the adequacy of the guidelines and to provide a forum for a continuing discussion of issues involved in hES cell research.**
 - politically independent and without conflicts of interest
 - respected in the lay and scientific communities
 - able to call on suitable expertise to support this effort.

Functions of Embryonic Stem Cell Research Oversight (ESCRO) Committees

- To provide local oversight over all issues related to derivation and research use of hES cell lines
- To ensure adherence to the basic ethical and legal principles of informed consent and protection of donor confidentiality.
- To review compliance of all hES cell research with all relevant regulations and guidelines.
- To maintain registries of hES cell research conducted at the institution and of all hES cell lines
- To facilitate education of investigators involved in hES cell research (And the Community)
- The ESCRO committee will not substitute for an Institutional Review Board (IRB) but rather will provide an additional level of review and scrutiny warranted for hES cell research and review proposals not requiring IRB review.

Functions of Embryonic Stem Cell Research Oversight (ESCRO) Committees – cont.

- To review and approve the scientific merit of research proposals and divide into three categories in setting limits on research and determining the requisite level of oversight:
 - a) Research that is permissible after notification of the ESCRO committee and completion of all reviews mandated by current requirements;
 - e.g., all purely *in vitro* hES cell research with pre-existing coded or anonymous hES cell lines.
 - b) Research that is permissible only after additional review and approval by the ESCRO committee
 - (i) all derivations of new hES cell lines from donated blastocysts, from *in vitro* fertilized oocytes, or by nuclear transfer.
 - (ii) all research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development.
 - (iii) all research in which identifiable information about donors is readily ascertainable or could become known by the investigator

c) Research that should not be permitted at this time:

(i) Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.

(ii) Research in which hES cells are introduced into nonhuman primate blastocysts or in which any ES cells are introduced into human blastocysts.

(iii) No animal into which hES cells have been introduced at any stage of development should be allowed to breed.

Mechanisms for Ensuring Compliance

Stakeholders in hES cell research—sponsors, funding sources, research institutions, relevant oversight committees, professional societies, and scientific journals, as well as investigators—should develop policies and practices that are consistent with the principles inherent in these guidelines.

- ESCROs and IRBs should require evidence of compliance when protocols are reviewed for renewal
- Funding agencies should assess compliance when reviewing applications for support
- Journals should require that evidence of compliance accompanies publication of results

2007 Amendments to the NAS Guidelines for hESC Research

- (1) clarifying the phrase “provenance of the cell lines” (changes to Part 1.2);
- (2) use of the hES cells approved for use in federally-funded research (addition of Part 1.4);
- (3) importation of hES cell lines into an institution or jurisdiction (addition of Part 1.5); and
- (4) allowing ESCRO committees to serve multiple institutions (changes to Part 2.0 and addition of Part 2.1).

2007 Amend – §1.2
“provenance of the cell lines,”

- Purely *in vitro* hES cell research that uses previously derived hES cell lines is permissible provided that the ESCRO committee or equivalent body designated by the investigator’s institution (see Section 2.0) receives documentation *of the provenance of the cell lines including:*
 - *_i) documentation of the use of an acceptable informed consent process that was approved by an Institutional Review Board (IRB) or foreign equivalent for their derivation (consistent with part 3.6); and*
 - *ii) documentation of compliance with any additional required review by an Institutional Animal Care and Use Committee (IACUC), Institutional Biosafety Committee (IBC), or other institutionally mandated review.*

Amend 2007 – §1.4
Use of the NIH-approved hES Cell Lines

- ***1.4 Use of NIH-approved hES cell lines***
- *(a) It is acceptable to use hES cell lines that were approved in August 2001 for use in U.S. federally funded research.*
- *(b) ESCRO committees should include on their registry a list of NIH-approved cell lines that have been used at their institution in accord with the requirement in section 2.0 of the Guidelines.*
- *(c) Presence on the list of NIH-approved cell lines constitutes adequate documentation of provenance, as per Section 6.1 of the Guidelines.*

Amend 2007 – §1.5

Importation of hES Cell Lines into an Institution or Jurisdiction

- Institutions following the National Academies' Guidelines who wish to import of cell lines derived according to different rules, (e.g. United Kingdom, Canada, CIRM.
- "If a U.S.-based investigator collaborates with an investigator in another country, the ESCRO committee may determine that the procedures prescribed by the foreign institution afford protections consistent with these guidelines, and the ESCRO committee may approve the substitution of some of or all of the foreign procedures for its own."
- Analogous to 45 CFR 46.101(h) relating to acceptance of standards of collaborating institutions in other countries (*except 46.101(h) refers to Dept./Agency approval)

§ 1.5 Acceptability of research using hES cell lines imported from other institutions or Jurisdictions

- (a) Before approving use of hES cell lines imported from other institutions or jurisdictions, ESCRO committees should consider whether such cell lines have been "acceptably derived."
- (b) "Acceptably derived" means that the cell lines were derived from gametes or embryos for which
 - (1) the donation protocol was reviewed and approved by an IRB or, in the case of donations taking place outside the United States, a substantially equivalent oversight body;
 - (2) consent to donate was voluntary and informed;
 - (3) donation was made with reimbursement policies consistent with these Guidelines; and
 - (4) donation and derivation complied with the extant legal requirements of the relevant jurisdiction.
- (c) ESCRO committees should include on their registry a list of cell lines that have been imported from other institutions or jurisdictions and information on the specific guidelines, regulations, or statutes under which the derivation of the imported cell lines was conducted.

Amend 2007 – §1.5 ESCRO Committees Serving Multiple Institutions

- **2.0** ... *each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee. This committee could be internal to a single institution or established jointly with one or more other institutions. Alternatively, an institution may have its proposals reviewed by an ESCRO committee of another institution, or by an independent ESCRO committee. ...*
- *An institution that uses an external ESCRO committee should nevertheless ensure that the registry and educational functions of an internal ESCRO committee are carried out by the external ESCRO committee on its behalf or internally by other administrative units.*
- **2.1.** *For projects that involve more than one institution, review of the scientific merit, justification, and compliance status of the research may be carried out by a single ESCRO committee if all participating institutions agree to accept the results of the review.*

Amend 2007 - Frozen IVF blastocysts derived from anonymous sperm donors: Absence of informed consent = **No Amendment**

- Specifically, section 3.3 of the Guidelines states that “When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors.” This requirement might preclude the use of previously existing frozen blastocysts from IVF clinics, which do not customarily request informed consent from sperm donors.
 - To evaluate these effects, the Committee contacted the Society for Assisted Reproductive Technology (SART), which is actively involved in the collection of data on outcomes from its member IVF clinics.
 - The information returned in response to the Committee’s request indicated that the number of blastocysts created with anonymous donor sperm in SART member practices is only about 3.5 percent and should not significantly affect the availability of blastocysts for donation to research.
 - Given this small number, the Committee has concluded that it is not necessary to modify the Guidelines by “grandfathering” the frozen embryo population in IVF clinics and exempting them from the informed consent requirement for sperm donors.
- * **Consider the difficulties of consenting for sperm and egg IVF donation**

Amend 2007 **Additional guidance on how to evaluate research proposals that are submitted for ESCRO**

Sample Questions for Reviewing hES Cell Research

- What is the scientific question being asked by the proposed research involving human embryonic stem cells? Does the underlying hypothesis address an important scientific question? Could the question reasonably be addressed in any other way?
- Does the research team have the appropriate expertise and training in deriving or culturing either human or nonhuman stem cells? If training is the primary purpose of the proposal, is the training being conducted under the supervision of appropriate experts?

Sample Questions for Reviewing hES Cell Research cont.

- Has the investigator articulated a compelling rationale for using human stem cells instead of non-human stem cells?
- Has the investigator articulated a compelling rationale for using human embryonic stem cells instead of other types of stem cells?
- Has the investigator justified the selection of the stem cell line(s) to be used?
- Has the investigator articulated a rationale for creating a new stem cell line or could the proposed research be conducted with existing cell lines? If more than one cell line is to be derived, has the investigator justified the number he/she proposes to make?

When Does the FDA Regulate Drugs and Devices?

If the article is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, then it is regulated by FDA. How is the article regulated?

<i>Drug</i>	Operates through metabolism, chemical reactions, etc.
<i>Device</i>	Is not metabolized
<i>Biologic</i>	Cells, vaccines, etc. (it is or was alive, or came from something that is or was alive)
<i>Combination</i>	Some combination, e.g., HIV test kit

Regulatory Framework

- Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
- Prevent improper handling or processing that might contaminate or damage tissues
- Ensure that clinical safety and effectiveness is demonstrated for cells and tissues that are highly processed, used for purposes other than re-placement, combined with non-tissue components, or that have systemic effects

Stems Cells Subject to Regulation Under the PHS Act

- Under Public Health Service Act – a biological product is defined as
 - A virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or derivative...
 - Applicable to the prevention, treatment, or cure of a disease or condition of human beings – (Sect 351(a))
- Control of Communicable Diseases (Sect. 361)
 - Secretary is authorized to make and enforce regulations...to prevent the introduction, transmission or spread of communicable diseases
- Risk determines level of regulation
 - Lower Risk – Tissue Regulations Suffice: Section 361, PHS Act, 21 CFR Part 1271- Human Cells, Tissue and Cellular and Tissue-Based Products (donor tests)
 - Higher Risk – Preapproval Required: Section 351, PHS Act (Biologic); Section 505 Food, Drug and Cosmetic Act (Drug), Investigational New Drug Requirements – 21 CFR Part 312

-Regulatory Process for Stem Cells

- IND/BLA
 - Complete development plan
 - Meet informed consent requirements
 - IRB review and approval
 - Follow good laboratory practices
 - Chemistry, manufacturing and controls information
 - Labeling
 - Investigators must file Financial Disclosure Statement
 - To obtain BLA (Biological License Application) approval the manufacturer is required to submit data from non-clinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, stability, and potency 21 CFR 600

Other Regulatory Areas

- Laboratory standards for pre-clinical work on products requiring FDA approval
- Safety reviews for work involving genetic alteration of stem cell lines (IBC)
- Animal care committee reviews (IACUC)

Non-Federal Sources of Regulation or Oversight

- State laws (e.g. CA, NJ, CT, IL, IN, MD, MA)
- Patent owners' licensing restrictions on use of licensed products or methods
- Institutional oversight bodies other than IRBs, IBCs and animal welfare committees (e.g. University of Wisconsin Bioethics Advisory Committee; conflict of interest committees)
- Voluntary guidelines from professional societies and other NGOs (e.g. NAS guidelines; ASRM)
- Rules imposed as condition of collaboration with foreign research center (e.g. HFEA UK- Human Fertilisation and Embryology Authority)
- International sources of guidance or regulation (e.g. W.H.O., UNESCO, Council of Europe, European Union, International Society for Stem Cell Research (6-30-06))