Embryonic Stem Cell Research Oversight Committee (ESCRO)
Policies and Procedures

Institutional Oversight of Human Embryonic Stem Cell and Related Research at the University of Miami

It is the policy of the University of Miami (UM) that all research using human embryonic stem cells (hESCs) or somatic cell nuclear transfer (SCNT) involving human cells being conducted by UM faculty, staff or students or involving the use of UM facilities or resources shall be subject to review and oversight by the UM Embryonic Stem Cell Research Oversight (ESCRO) committee. Any and all such research must be conducted according to the specific ESCRO protocol as reviewed and approved in advance by the UM ESCRO committee.

I. Purpose of the UM ESCRO Committee

Under the ESCRO Committee Charge issued by the Vice Provost for Research, the primary purpose of the committee is to provide oversight of all issues related to derivation and use of hES cells and SCNT involving human cells and to facilitate education of investigators involved in such research.

Specifically, the UM ESCRO Committee provides oversight over all issues related to derivation and use of hESCs and hSCNT, including establishing and modifying policies and procedures; assures all research involving hESCs and hSCNT conducted at the University or by University investigators is compliant with all relevant regulations and is within the guidelines presented in the NAS/IOM report "Guidelines for Human Embryonic Stem Cell Research." (2005 and subsequent updates), or any subsequent revisions or replacements of those guidelines.

The committee also maintains registries of hESC and hSCNT research conducted at the University and of hESCs derived or imported by University investigators; ensures MTA's are on file; reviews and approves the scientific merit of hESC and hSCNT research protocols; reviews derivation details and ensures appropriate informed consent is obtained; coordinates with other University regulatory and oversight committees (i.e., IACUC, IRB, IBC, etc.); and assures that University investigators and trainees are educated regarding the responsible conduct of research with hESC and hSCNT, including University, State, and Federal regulations governing such research.

Ill. The Authority of the UM ESCRO Committee

A. Initial Approval of Human Stem Cell Research

The UM ESCRO committee shall have the authority to approve, require modifications of, or withhold approval of all research activities that fall under its jurisdiction within UM, (see UM ESCRO Committee Charge). In addition, other Divisions of the University may refer research protocols to the UM ESCRO committee for review. Research already in progress and within the purview of the UM ESCRO committee must be submitted to the committee for review within one year of the launch of the committee.

B. Continuing Oversight

1. Approved research shall be reviewed by the UM ESCRO committee every three years, or more frequently, as determined by the committee on a case-by-case basis. The investigator is responsible for submitting the progress report in a timely manner. Failure to submit the application by the deadline will result in withdrawal of approval.

2. Adverse Event Reports pertaining to UM ESCRO committee approved research and submitted to a University IRB, IACUC, and/or IBC must also be submitted to the UM ESCRO committee.

3. No modifications to a UM ESCRO committee approved research protocol shall be implemented prior to committee approval of the modifications, except when a deviation is necessary to prevent imminent harm. Such deviations should be reported to the committee within 3 business days. The committee has the authority to review and approve, require modifications of, or withhold approval of all proposed modifications to the approved research protocol prior to the implementation of such modifications by the investigator.

C. Monitoring of UM ESCRO Committee Approved Research

The UM ESCRO committee or its representatives shall have the authority to observe the conduct of any research activity subject to committee oversight. This function includes the authority to review all records associated with the conduct of the research.

D. Restrictions, Suspension, and Termination of Research

1. The UM ESCRO committee shall have the authority to place restrictions on research activities that fall under its jurisdiction. The committee will notify the Vice Provost for Research and any other relevant committees (e.g., IRB, IACUC, IBC, and other applicable Committees and Boards) of any such restrictions.

2. The UM ESCRO committee shall have the authority to suspend or terminate its approval of research that falls under its jurisdiction and that is not being performed in compliance with committee requirements, applicable governmental regulations, and/or University policies. The committee will notify all UM Institutional Official(s), as well as other relevant committees (e.g., IRB, IACUC, IBC, etc.) of any suspension or termination.

3. If the UM sponsors research at a site outside the University, or a UM researcher [1] participates as a co-investigator in research at a site outside the University, the UM ESCRO committee shall have the authority to terminate the participation of UM researchers in the research. In such cases, the UM ESCRO committee chairman will inform the responsible Institutional Official(s) at UM and at each institution involved in the research of the termination.

[1] UM researchers are UM faculty, staff or students acting in their capacity as UM faculty, staff, or students.

E. Review of Research within the Jurisdiction of the UM ESCRO Committee by Other University Committees or Officials

1. Research requiring UM ESCRO committee review ordinarily will be submitted for review and approval concurrently with submission of the research to any other UM entity (e.g., IRB, IACUC, IBC, etc.) that may have responsibility for oversight of other aspects of the research.

2. Research activities approved by the UM ESCRO committee may be subject to further review, modification of, approval and/or disapproval by all relevant bodies, such as IRB;IBC; IACUC; and the UM Vice Provost for Research. However, those committees and officials may not approve the conduct of research within the UM ESCRO committee's jurisdiction if approval was previously withheld by the committee.

F. Education and Training

All study team members engaged in research, subject to oversight by the UM ESCRO committee shall complete educational activities related to the responsible conduct of such research, as specified by the committee.

IV. Conflicts of Interest - UM ESCRO Committee Chairman, Members and Consultants

A. Disclosure

UM ESCRO committee chairman and committee members are required to disclose conflicts of interest at the beginning of each committee meeting or when assigned as a reviewer. Conflicts of interest include being a listed investigator, having a financial interest in the sponsor of the research or the technology being evaluated, as defined by the faculty manual,UM Policy on Conflict of Interest, or having any other interest or relationship that might reasonably be perceived to inhibit or impede a fair and unbiased review of the research.

B. Abstention from Deliberations and Absence from the Meeting Room

UM ESCRO committee members who have conflicts of interest with respect to protocols submitted for review will abstain from participating in committee deliberations and decisions relative to those protocols. Such members may be consulted on the research.

C. Consultants and Conflict of Interest Disclosure

Consultants shall be asked and are required to disclose, at the time they are contacted to review a research study, if they have a conflict of interest with the study on which they are being asked to consult. Such conflicts shall generally be considered disqualifying.

V. Research Requiring Review and Approval by the UM ESCRO Committee

All research under the jurisdiction of the UM ESCRO committee shall be subject to review by the committee, in addition to all other relevant bodies with oversight, such as the IRB and the IACUC.

VI. Prohibited Research

In accordance with prevailing ethical and policy guidance and applicable law, the following categories of research are currently prohibited at UM:

- Research involving the introduction of ESCs into human blastocysts;
- Research involving the introduction of hESCs into non-human blastocysts;
- Research involving in vitro culture of any intact human embryo for longer than 14 days or until formation of the primitive streak begins, whichever occurs first; and
- Breeding of animals that have had hESCs introduced into the germ line.

Note: The above list of prohibited research does not imply that similar research with human pluripotent stem (hPS) cells or induced pluripotent stem cells (iPSC) is allowed by default. Such research while not under ESCRO Committee jurisdiction still requires IRB and/or IACUC approval. The IRB and IACUC may refer cases to ESCRO for review prior to granting approval.

This list may be revised to reflect changes in prevailing ethical and policy guidance and applicable law.

VII. Standards for UM ESCRO Committee Review

In conducting review of proposed research, the UM ESCRO committee will take into account considerations that include the following.

A. Procurement of Gametes, Blastocysts, or Somatic Cells for hESC Generation

For the purposes of UM ESCRO committee review, sources of human embryonic stem cell materials will be considered human research subjects (per 45 CFR 46), regardless of the context in which the materials are procured. Human subject research is required to have IRB approval.

The ethical and legal issues related to hESC research will depend in part on the context in which human materials are procured (for example, infertility treatment, research, clinical care). The context of procurement will involve established standards of care that will be taken into consideration during committee deliberations. Therefore, protocols must describe:

1. Ethical considerations for procurement of human materials in the context of clinical care:
    a. Plans to ensure that an individual's decision about donation will not affect the quality of care s/he receives
    b. Plans to ensure that infertility treatment teams will not generate more oocytes than clinically necessary

2. Voluntariness of Consent:

    a. Plans to ensure that undue inducements will not be provided for donation (e.g., financial or special considerations for services)

    b. Plans to ensure that decisions to donate are made free from undue influence (e.g., the investigator and the attending physician responsible for the infertility treatment are not the same person).

3. Informed Consent:

In addition to the required elements of informed consent specified in 45 CFR 46. 116, the informed consent process and document must disclose the following:

a. That blastocysts or gametes will be used to derive hESCs for research that may include research on human transplantation
b. That embryos will be destroyed in the process of deriving hESCs
c. That embryos will not be used to produce a pregnancy and will not be allowed to develop in culture for longer than 14 days from fertilization
d. That resulting cell lines will be genetically similar or identical to the donor
e. That restricted and/or directed donation (e.g. to individuals or groups) are/is not permitted
f. Whether the donors' identities will be ascertainable;
g. If the donors' identities are retained (even if coded), whether donors can elect to be contacted to receive information obtained through studies of the cell lines;
h. That derived hESCs and/or cell lines might be kept for many years;
i. That the hESCs and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and non-human cells in animal models;
j. That the results of study of the hESCs may have commercial potential and that the investigator and institution may benefit; however, the donor will not receive financial or any other benefits from any commercial development;
k. That the research is not intended to provide direct medical benefit to the donors;
l. That neither consenting nor refusing to donate embryos for research will affect the quality of any care provided to potential donors
m. Risks to donors.
n. obtaining the embryos, evidence of and adherence to basic ethical and legal principles of procurement, and compliance with applicable laws.

A. Transfer of Human Materials from Outside Entities

To determine the scientific and ethical integrity of hESC research the UM ESCRO committee must examine the circumstances under which human materials were (or will be) procured for use in hESC research and the details of the derivation of hESC lines. The applications must include documentation of the provenance of all hESC lines, whether the cell lines were imported into the institution or derived locally.

B. Derivation of hESCs

Protocols must describe:

- Appropriate expertise of the research team in the derivation or culture of either human or non-human ESCs
- The scientific rationale for the need to generate new hESCs, as well as the basis for the number of blastocysts used in the derivation process
- Any plans for compliance with an established set of good manufacturing practices (GMPs), and if so with which GMPs
- How any new hESC lines will be characterized, validated, stored, and distributed.

C. Transfer of hESCs into Non-human Animals

Protocols must describe:

- Why hESCs are required in lieu of ESCs from primates or other animals
- Relevant animal work that precedes the proposed work involving hESCs
- Quality control of ESC lines and their derivatives, (such as genetic stability, freedom from contamination)
- The part of the non-human animal's body to which the cells will be transferred;
- The developmental stage of the non-human animal to which the cells will be transferred;
- When the proposed research involves potential for neural grafting, describe procedures that will assess whether the animal may acquire cognitive characteristics that are thought of as distinctly human, as well as how non-human primates will be evaluated (pre- and post-transplant)

D. Safety Considerations in Trials with Humans

Protocols must comply with all FDA, IRB and any other relevant Federal, State and local laws and must describe:

- Pre-clinical testing with animal models;
- Quality control of ESC lines and their derivatives;
- Selection of subjects (e.g., the appropriateness of using healthy volunteers in early human trials);
- Risk of infectious disease (e.g., from cells cultured in mouse feeder layers);
- Risk of transfer of genetic disorders;
- Risks of misdifferentiation, mistargeting, tumor formation, and immune rejection;
- Risk of uncontrolled cell growth.

E. Justice

Protocols must describe mechanisms established for subject selection. The process for selection among groups and individuals to participate must be equitable.

F. International Collaboration

Where UM faculty, staff or students acting in their capacity as faculty, staff or students respectively, collaborate with a researcher at a foreign institution, protocols must describe protections afforded and procedures prescribed by the foreign institution.

VIII. Procedures for Research Requiring UM ESCRO Committee Review

The review process and the records of the UM ESCRO committee will be maintained as confidential to the extent permitted by law.

A. UM ESCRO Committee Review of Research Proposals

1. A protocol consisting of hES cells currently on the NIH registry and only for any in- vitro work is eligible to have an expedited, designated review of their project. The reviewers will consist of one (1) committee member, along with the Chair and will not need a convened meeting for approval.

2. Each research study requiring review and approval by the convened UM ESCRO committee shall be addressed separately at the committee meeting.

3. The Principal Investigator must be a University of Miami faculty member. May be waived under University policy. All waivers must be approved in writing by the Vice Provost for Research.

4. Submitted protocols will be made available to UM ESCRO committee members in advance of committee meetings to allow sufficient time for review.

5. The primary reviewer for each protocol shall summarize the proposed research followed by an open discussion of the research by the UM ESCRO committee members.

6. All proposals will have a secondary reviewer assigned.

7. The primary and secondary reviewers may direct questions about the submitted protocol to the Principal Investigator via ESCRO administration. In such cases, the Principal Investigator will have an opportunity to submit revisions before full UM ESCRO committee review.

8. Reviewers who are absent from a full UM ESCRO committee meeting may provide written comments regarding the proposed research, but absent members shall not be counted in the UM ESCRO committee vote.

9. Following open discussion, the UM ESCRO committee chairman shall call for a vote of the committee to grant:

    a. Full Approval: No changes are required to the proposed research;

    b. Approval Pending Concurrence with UM ESCRO committee-directed Changes: The proposed research may be granted full approval by the UM ESCRO committee chairman pending principal investigator concurrence with specific revisions stipulated by the committee. The research may not receive full approval until such time that the research procedures have been modified to comply with the specific revisions stipulated by the committee and such revisions have been reviewed and approved by the UM ESCRO committee chairman or their designee;

    c. Reconsideration: Approval of the proposed research requires substantive clarifications or modifications of the research design or procedures. The principal investigator must respond to the identified clarifications, modifications, or revisions and resubmit the revised research protocol for re-review by the UM ESCRO committee; or

    d. Approval withheld: The proposed research has fundamental design problems and/or presents significant ethical, legal or regulatory compliance concerns. The principal investigator must undertake a major revision of the proposed research before it can be resubmitted for re-review by the UM ESCRO committee.

10. The vote of the majority of the UM ESCRO committee members present at the meeting shall determine the final determination status (i.e. full approval, approval pending concurrence with UM ESCRO committee-directed changes, reconsideration, or approval withheld) of the proposed research. The UM Vice Provost for Research may impose additional restrictions on approved research, but may not approve research for which approval was withheld by the UM ESCRO committee.

11. Following an UM ESCRO committee vote for full approval or approval pending concurrence with UM ESCRO committee directed changes:

    a. UM ESCRO committee members voting to reconsider or withhold approval of the research in the face of a majority vote for full approval or approval pending concurrence with committee-directed changes shall be requested to summarize the reasons for their contravention.

12. The UM ESCRO committee shall notify the investigators in writing of the committee's decision to approve, reconsider, or withhold approval of the research, or of the committee-directed changes required to secure committee approval of the research.

IX. Process for Protocols Following UM ESCRO Committee Vote

B. Protocols Granted FullApproval

For research granted full approval by the UM ESCRO committee, the Principal Investigator will be notified. The Principal Investigator shall be responsible for ensuring that all other applicable institutional requirements are met (e.g., IRB, IACUC, or IBC approval) .

C. Protocols Approved Subject to Concurrence with UM ESCRO Committee-Directed Changes

If the convened UM ESCRO committee decides to approve the proposed research pending concurrence with committee-directed changes, the principal investigator will be provided:

1. Notification addressing the specific revisions stipulated by the committee in order to obtain full approval of the research.

2. Notification instructing the investigator to revise the research protocol to concur with the specific revisions stipulated by the committee and to resubmit for full approval.

3. Notification specifying that the principal investigator must respond to the committee's request for revisions within six (6) weeks of the date of the notification, and that failure to respond within this six (6) week period may result in termination of the respective research submission.

For research approved by the UM ESCRO committee pending concurrence with committee-directed changes, the revised research submitted in response to the specific revisions stipulated shall be reviewed by the committee chair or his/her designee and, based on an appropriate response, granted full approval. Any problems or concerns related to the principal investigator's response shall be communicated, in writing or by e-mail, to the principal investigator. In the event that the principal investigator does not agree with certain specific revisions stipulated by the UM ESCRO committee, the research proposal (to include any directed changes agreed on by the principal investigator) and the investigator's justification for not complying with certain change(s) shall be referred to convened meeting review. The investigator shall be notified that s/he will be afforded an opportunity to appear in person at the committee meeting during which the research will be reconsidered.

D. Protocols Reconsidered or Not Approved

If the UM ESCRO committee decides to reconsider or disapprove the proposed research, the principal investigator will be provided:

1. The primary reason(s) for the committee's decision to reconsider or withhold approval of the research;

2. A listing of additional problems or deficiencies identified by the committee;

3. Instructions regarding resubmission of the research for review by the committee including a requirement to address the statements and concerns emanating from the initial review;

4. Notification that s/he may appear in person at the meeting of the committee wherein the research will be reconsidered, to address any additional questions or concerns of the committee; and

5. Notification that s/he must respond to the committee's request for revisions within six (6) weeks of the date of the notification, and that failure to respond within this six (6) week period may result in termination of the respective research submission.

X. UM ESCRO Committee Meetings

The minutes of the UM ESCRO committee meetings shall include but not be limited to the following items: record of attendance, declared conflicts of interest, protocols reviewed (including controverted issues), documentation of approval intervals (if applicable), any expedited/designated review approvals (if applicable) and committee votes.

Documentation shall include UM ESCRO committee members voting for and against the action taken and the number of members abstaining from the vote (e.g.,7-for, 1-against, 1-abstain), including the name(s) of any voting member(s) who abstained from the vote due to conflict-of-interest or other considerations.

The minutes shall be reviewed and accepted by the UM ESCRO committee chairman prior to generating investigator correspondence.

The minutes shall be distributed to UM ESCRO committee members. At each meeting, a vote of shall be taken to approve the minutes of the previous meeting. The minutes may be modified as necessary to obtain approval of the UM ESCRO committee.

Portions of this document were derived from:

The Policies and Procedures of the Johns Hopkins University School of Medicine ESCRO Committee http://www.hopkinsmedicine.org/Research/escro/Pol icies/PoliciesProcedures.html

University of Pittsburgh *UMESCRO Committee Policies and Procedures Manual* http://www.rcco.pitt.edu/UM ESCRO committee/pol icy 053106.pdf ,and from the

National Academy of Sciences *Guidelines for Human Embryonic Stem Cell Research* http://darwin.nap.edu/books/0309096537 /html