BROWN

Embryonic Stem Cell Research Oversight (ESCRO) Committee

Policies & Procedures

April 7, 2017

1. Role and Authority of the ESCRO Committee

The ESCRO Committee shall be responsible for ensuring that all human embryonic stem cell (hESC) research conducted at or funded by Brown University is conducted in an ethical manner. The ESCRO Committee shall have the authority to review and approve, disapprove, or require modifications to any project involving the derivation or use of hESCs.

2. Responsibilities

The ESCRO Committee shall be responsible for providing oversight of all issues relating to Brown University derivation and research use of hESC lines, including:

- Reviewing the scientific and ethical merits of all Brown University research activities involving the derivation or use of hESCs (see Section 5 for details).
- Ensuring that the provenance of hESC lines used by Brown University is documented (Section 7).
- Maintaining a registry of Brown University's ongoing hESC research (Section 8.1.)
- Educating Brown University's personnel with respect to existing guidelines, laws, and procedures relating to the derivation and use of hESCs (Section 8.3.).

3. Membership

3.1. ESCRO Chair

3.1.1. Selection & Term

The ESCRO chair shall be a Brown University employee, shall be appointed by The Vice President of Research, and shall serve on an ad hoc basis as review of hESC research arises.

3.1.2. Responsibilities

The chair shall be responsible for, or delegate to an appropriate party, scheduling meetings and planning meeting agendas, taking meeting minutes, identifying and nominating potential members for committee approval, maintaining the registry on ongoing hESC research, and reviewing and categorizing submitted projects.

3.2. ESCRO Committee Membership

3.2.1. Composition & Selection

The ESCRO Committee shall typically include at least five members, to be appointed by the Vice President for Research. At least one voting member of the ESCRO Committee shall be an external member who is not employed by Brown University and does not have any significant financial interest in Brown University (i.e., sponsorship of research, consulting agreement, etc.). The membership of the ESCRO Committee shall typically include the following types of individuals: scientists, ethicists, members of the public, patient advocates, and experts on assisted reproduction.

3.2.2. Responsibilities

Responsibilities of all ESCRO Committee members shall include attending convened ESCRO Committee meetings; serving as the primary reviewer of submitted proposals as requested by the chair; participating in committee deliberations regarding provenance of cell lines; reviewing circulated proposals and raising any concerns with the chair; deliberating and voting on the ethical and scientific merit of proposals; recommending improvements to ESCRO Committee policies and procedures as appropriate; reporting any conflicts of interest and otherwise conducting their duties in an ethically irreproachable manner.

3.3. Voting Members

The voting members of the ESCRO Committee shall include all members except the chair (who shall vote only to break a tie) and any member with a declared conflict of interest in the vote at hand (see Section 4.4.)

3.4. Advisors

The ESCRO Committee and/or its members may request the advice of certain internal or external advisors as necessary for completion of their duties (i.e., clinicians or scientists with expertise in the area of a project under review; ethicists with experience/insights relevant to the issues under consideration; a representative from Brown's Office of General Council). Such advisory roles may consist of attendance at a meeting by an internal/external advisor or consultation with an individual ESCRO Committee member. ESCRO Committee members wishing to consult with an external advisor shall first obtain approval of the chair, and shall work with Brown University's Office of General Council to obtain a completed confidentiality agreement with any outside advisor prior to sharing of any non-public information regarding Brown University projects or processes. Outside advisors shall not have authority to vote on matters under review by the committee.

4. Meeting Procedures

4.1. Meeting Attendance

Members may attend ESCRO Committee meetings in person or via teleconference or videoconference. The chair shall make every effort to schedule meetings at times that are

convenient for the largest number of ESCRO Committee members, however, meetings may be scheduled for any time at which a quorum can be obtained.

4.2. Voting

All matters shall be determined by majority vote of the committee, except as otherwise indicated in this document. Votes shall generally be taken by an informal oral poll at the conclusion of discussion. However, if any member of the ESCRO Committee so requests, any vote may be taken by secret ballot instead. Votes regarding conflict of interest of ESCRO Committee members shall routinely be taken by secret ballot. The chair shall not participate in committee votes, except as required to break a tie.

4.3. Quorum

For votes to be binding, a quorum of voting members must participate in the vote. A vote shall be deemed to have a quorum so long as votes are cast by at least half of the voting members of the ESCRO Committee.

4.4. Conflict of Interest

ESCRO Committee members will be polled at the beginning of each meeting regarding whether, in their opinion, they have a conflict of interest with respect to any of the items to be discussed on that meeting's agenda. External members shall be considered to have conflict of interest if they have a significant professional or financial interest in a project under consideration (ex. investment in a collaborating company). Upon disclosure of any conflicts of interest (COI), the committee shall take a secret ballot vote with respect to whether the member disclosing a COI should participate in the discussion of such project. Members shall recuse themselves from voting on a project for which they have a COI, but may remain present for the discussion if a majority of ESCRO Committee members believe their presence would be of value to the discussion.

4.5. Meeting Minutes

The chair, or his/her designee, shall keep minutes for each ESCRO Committee meeting. A draft of the minutes shall be provided to all members in attendance at the meeting for review and comment within two weeks of each meeting. Following an opportunity for comment by other members, a copy of the minutes shall be circulated to all committee members in advance of the next ESCRO Committee meeting. At each ESCRO Committee meeting, a vote of committee members will be taken to approve the minutes of the previous meeting. A copy of all approved minutes shall be maintained in the ESCRO Committee files.

5. Project Review Procedures

5.1. Project Submission

All Brown University projects involving human embryonic stem cells must be approved by the Brown University ESCRO Committee. Projects shall be submitted to the ESCRO

chair by the Principal Investigator (PI) using the project review form in Appendix A. Projects may be approved for periods of up to two years, as requested by the PI and at the discretion of the ESCRO Committee. It shall be the responsibility of all senior Brown University scientific staff to ensure that all activities relating the derivation or use of hESCs under their supervision have been approved by the Brown University ESCRO Committee prior to project initiation. Upon submission of the project, the ESCRO chair or another member as designated by the chair ("primary reviewer") shall review the submission and categorize the project to one of the review categories described in Section 5.2.

5.2. Project Review Categories

Category A: Projects requiring minimal ESCRO Committee review

This category shall be comprised of projects consisting entirely of *in vitro* research on: (i) cell lines on the NIH registry, or (ii) cell lines that have been approved as "anonymous lines" by the Brown University ESCRO Committee (see Section 7.2.).

Category B: Projects requiring additional ESCRO Committee review and approval

This category shall be comprised of projects involving any of the following: the derivation of new hESC lines, the introduction of hESCs or their derivatives into humans or non-human animals, and/or the use of hESC lines classified by the ESCRO Committee as "non-anonymous lines" (see Section 7.2.). "Derivatives" shall include any whole cell derived from hESCs, but not proteins, nucleic acids, etc. derived from such cells.

Category B1: Expedited Review

Projects involving the introduction of hESCs or their derivatives into post-pubertal non-human animals shall be eligible for expedited review if the proposed transplant experiments are deemed by the ESCRO chair or primary reviewer to have limited potential to contribute to brain or reproductive function.

Category B2: Standard Review

Projects involving the derivation of new hESC lines, the use of non-anonymous lines, or the introduction of hESCs or their derivatives to humans or pre-pubertal animals shall not be eligible for expedited review. In addition, any project for which the chair believes broader ESCRO Committee consideration is in order may be categorized for standard review.

Category C: Projects not permitted by the ESCRO Committee

This category shall be comprised of projects which involve: the *in vitro* culture of an intact human embryo for more than 12 days or until the primitive streak begins, the introduction of hESCs into human or non-human primate blastocytes, or the breeding (or insufficient control to prevent breeding) of animals into which hESCs have been introduced.

5.3. Project Review Procedures

Category A Projects

For projects deemed by the ESCRO chair or primary reviewer to fall into Category A, the chair (and primary reviewer, if applicable) shall sign the ESCRO Committee review form, as certification of that determination. A copy of the completed project review form shall be provided to each member of the ESCRO Committee. ESCRO Committee members will have up to 3 business days to object to the categorization, after which the project shall be deemed approved to proceed. If, within one week of circulation, at least two committee members request broader project review, the project shall be scheduled for review at a subsequent ESCRO Committee meeting.

Category B Projects

Category B1: Expedited Review

For projects deemed eligible for expedited review, the ESCRO chair shall circulate the project submission form to ESCRO Committee members via electronic mail together with a statement indicating that the project has been deemed to require minimal review. If, within 3 business days of circulation, at least one committee member requests broader project review, the project shall be scheduled for review at a subsequent ESCRO Committee meeting. Otherwise, the project shall be deemed approved by the committee. Documentation of approval of expedited review projects shall require signature on the project review form by all committee members.

Category B2: Standard Review

For Category B2 projects, the project champion (or other relevant individual) shall be asked to present the project for review at a subsequent ESCRO Committee meeting. For projects including both Category A and Category B activities, the PI's presentation need focus only on the Category B activities, but the project submission form should include description of all major anticipated project activities during the project period, regardless of category. Approval of projects containing Category B2 activities shall require a vote for approval by a majority of ESCRO Committee members present at the meeting in which the project is reviewed, including at least one external member. Approval shall be

documented by the signatures of approving members on the project review form, as well as by the ESCRO chair as certification that the above procedure was followed.

Category C Projects

A project may be categorized to Category C by either the ESCRO chair (upon initial review and categorization of the submitted project), or by the full committee (by vote or a majority of members present at the project review meeting). In either case, the project shall not be eligible for ESCRO Committee approval. The project champion shall be informed of the reasons for the decision, and asked to resubmit the project with modifications to remove or modify the objectionable aspects of the proposal.

5.4. Resubmissions

Requested Changes

Projects for which the ESCRO Committee has requested revisions may be resubmitted to the committee upon completion of the requested changes. Resubmitted projects deemed by the ESCRO chair or primary reviewer to have addressed the concerns of the committee shall be eligible for expedited review at the discretion of the chair/primary reviewer.

Project Modifications

If an approved project undergoes additions or changes from the ESCRO Committee approved project description that are substantial enough to require an IACUC resubmission, it shall also be resubmitted to the ESCRO Committee. Such projects shall be eligible for expedited review at the discretion of the chair or primary reviewer. For projects undergoing more moderate revisions such as those that would require only protocol amendment, the PI shall notify the ESCRO chair, who shall determine whether a resubmission is warranted. Minor project changes that, in the judgment of the project champion are unlikely to impact brain or reproductive function of transplanted animals (ex. minor changes to differentiation protocols), shall not require ESCRO Committee notification. An agenda item at each meeting shall be an update from the chair regarding any project modifications of which (s)he has been notified.

Appeals

ESCRO Committee decisions may be appealed by the following procedure:

i. The matter shall be submitted to the Brown University ESCRO Committee for consideration of whether an appeal is warranted.
ii. If the matter is deemed worth of appeal by the Brown University ESCRO Committee, the project may be submitted to an external ESCRO

Committee for their review. The decision of the external ESCRO Committee shall be considered in the matter.

6. Relationship with other Committees

6.1. Submission Order

It is recommended that project champions submit projects to the ESCRO Committee prior to submission to the Institutional Animal Care and Use Committee (IACUC), Institutional Review Board (IRB), and Institutional Biosafety Committee (IBC). However, submission may be performed in any order to expedite review timelines, so long as all required approvals are obtained prior to initiation of the research.

6.2. Role of ESCRO Committee in animal studies

For projects involving the transplantation of hESCs or derivatives into non-human animals, the ESCRO Committee shall be responsible for consideration of matters relating to the scientific and ethical merits of the proposed experiments. Matters of particular consideration shall include: the likelihood of contribution to the transplanted cell population to brain or reproductive function, and the rationale for use of hESCs versus another cell type. Matters relating to animal welfare shall be deferred to the IACUC for consideration in accordance with normal IACUC procedures.

6.3. Role of ESCRO Committee in informed consent process for embryo, gamete or somatic cell donors

For projects contemplating the donation of human-sourced materials for hESC derivation, the ESCRO Committee shall review and approve the informed consent document with respect to its consistency with the NAS guidelines. Such review shall be in addition to IRB review and approval of the informed consent process. It is recommended that ESCRO Committee review precede IRB review, as the IRB will have final approval authority. The ESCRO chair or another member as designated by the chair may also serve in an advisory capacity to an IRB with respect to hESC-specific considerations for the informed consent process as requested by the IRB.

6.4. Role of ESCRO Committee in human clinical research

For projects involving the transplantation of hESCs or derivatives into humans, the ESCRO Committee shall review the proposed clinical protocol for it scientific and ethical merits, especially as it relates to the use of hESCs versus another cell type, and the appropriate mention of hESC-specific items in the informed consent document. The ESCRO chair or another member as designated by the chair may also serve in an advisory capacity to the PI with respect to hESC-specific considerations during the IRB process. It is recommended that ESCRO Committee review precede IRB review, as the IRB will have final approval authority with respect to the clinical protocol and informed consent process. Similarly, the ESCRO Committee shall have no responsibility for the

review of patient safety considerations, in which it shall defer to the FDA (or similar regulatory authority).

7. Review of provenance of lines

7.1. Lines listed on the NIH Human Embryonic Stem Cell Registry

In accordance with NAS Guidelines, presence of a cell line on the NIH Human Embryonic Stem Cell Registry shall be considered adequate documentation of their provenance as an "anonymous cell line." The ESCRO Committee reserves the right to set policy that varies from NAS Guidelines when doing so is determined to be advisable by the committee members.

7.2. Other lines

For lines not listed on the NIH Human Embryonic Stem Cell Registry, the ESCRO Committee shall determine whether provenance of the line was sufficiently documented in accordance with the criteria of the NAS Guidelines. The ESCRO Committee reserves the right to set policy that varies from NAS Guidelines when doing so is determined to be advisable by the committee members. Considerations include:

- The procurement process was IRB approved.
- Informed consent was obtained from all gamete donors and addressed all elements listed in the NAS Guidelines.
- The anonymity of donors was suitably protected or appropriate authorizations were obtained from donors with respect to the transmission of their confidential health information.
- Decisions relating to the production of embryos for infertility treatment were free from influence by researchers planning to derive hESC lines from excess embryos.
- No cash or in-kind payments were provided for donation of blastocysts, oocytes, or gametes (oocyte donors may be reimbursed for direct expenses relating to donation).
- Informed consent was obtained at the time of donation and donors were given the opportunity to withdraw consent at any time up to destruction of the embryo.
- Appropriate steps were taken to ensure that consent or refusal to donate did not affect quality of care.
- Clinical personnel having a conscientious objection were not required to participate in the donation process.

The ESCRO Committee shall vote with respect to whether provenance of a given hESC line is sufficiently documented. Approval of a line for use at Brown University shall

require approval by a majority of ESCRO Committee members, including at least one external member. Approved lines shall be further categorized by the ESCRO Committee into "anonymous lines" and "non-anonymous lines." The review and approval process shall be documented through completion of the "provenance review form" in Appendix B.

Once a line is approved for use at Brown University, it shall be subject to periodic re-review. If it comes to light that information considered by the ESCRO Committee during the approval process was incorrect, and ESCRO Committee member may request reconsideration of the approval of such line by the committee. Such re-review shall be undertaken if at least two additional ESCRO Committee members second the motion for re-review.

8. Additional Responsibilities of the ESCRO Committee

8.1. Maintenance of Registries

The ESCRO chair, or his/her designee, shall be responsible for maintaining a registry of ongoing hESC research and of hESC lines approved for use at Brown University. This registry shall include a signed copy of each project review form and provenance review form approved by the committee.

8.2. Education of Investigators

The ESCRO Committee shall be responsible for ensuring that Brown University scientists engaged in hESC research are aware of the NAS Guidelines, and of the need to submit hESC research projects to the ESCRO Committee for review.

9. Revision of this Charter

This charter and any revisions thereto must be approved by the Vice President for Research, and a majority of the ESCRO Committee membership, to be effective.