Duke University Stem Cell Research Oversight Committee

11/2011

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The Cell Therapy Research Oversight Committee has proposed that a specialized review process be created to improve the quality of review of cellular therapy protocols at Duke University. In the case of embryonic, pluripotent stem cells or human neural progenitor cells such a review is directed by Institute of Medicine Guidelines on Embryonic Stem Cell Research Oversight (ESCRO).

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DUKE UNIVERSITY STEM CELL RESEARCH OVERSIGHT (SCRO) COMMITTEE PURPOSE

This Duke University Committee is organized to provide research oversight and regulatory review for stem cell protocols in conjunction with the University Institutional Review Board (IRB) for the Protection of Human Subjects, the Institutional Biosafety Committee (IBC), and the Institutional Animal Care and Use Committee (IACUC). The SCRO Committee will review protocols using human cells, human embryonic cells (hES), induced pluripotent cells (iPS), or tissue in research and moving toward or involving human clinical trials. Protocols will be identified for review and electronically referred to the committee by answering questions on the electronic IRB, IACUC or IBC applications. Comments, questions and suggestions will be sent back to the investigator by the same electronic route that the review was referred from – IRB, IBC or IACUC. The review will be tiered according to the content of the application, with exempt and more commonly used applications receiving administrative review, and the most novel applications being considered according to the scheme below.

Levels of Review:

The SCRO Committee will employ a multi-tiered review process to provide appropriate review with minimum delay in the protocol approval process.

- **Administrative Review** by a knowledgeable person who confirms that the request for review is appropriate and that all of the required information is supplied. The protocol will then be assigned.
- **Designated Review** by one committee member who performs the review and circulates to the other members so they can read and comment or concur. This level of review is appropriate for previously approved protocols, clinical trials from cooperative trials and studies that have been previously reviewed and approved by other institutions or multi-institutional boards. This can all be done by e-mail.
- **Full SCRO** by conference call. One committee member will be designated as the lead. This will allow discussion but will make scheduling easier. The designated primary reviewer will summarize the protocol and questions to be discussed.
- **Full SCRO** in person with additional personnel added for embryonic cell issues. For this review, the issues will be complex enough; at least early on, that the extended committee with an ethicist, community representatives, and appropriate basic science experts will be invited. Some portion of this group may need to join by teleconference if scheduling requires.

If new hES or iPS cell lines are being established or imported into Duke University, then cell line registration is required. In the electronic application process through the IBC, investigators will be directed to a registration page on the DTMI website, https://duke.qualtrics.com/SE/?SID=SV_3VIw7b1qLwNkNBa

These listings of cell lines will be used to make reports to the University of activities in the field and to keep the principal investigators informed when new guidance or regulation is released. For issues arising in full SCRO review where practices suggested are felt to be out of the current realm of scientific acceptability, the issues will be referred to the School of Medicine Dean for final review.

ROSTER

Joanne Kurtzberg, MD
Committee Chairman
Susan B. Dees Distinguished Professor of Pediatrics and Professor of Pathology
Director, Pediatric Blood and Marrow Transplant Program
Director, Carolinas Cord Blood Bank

Ron Banks (Added 10/20/11)
Staff Veterinarian
Office of Animal Welfare Assurance (IACUC)

Bruce Burnett
Director, Regulatory Affairs
Duke Translational Medicine Institute

Wesley Byerly, Pharm D
Associate Dean
Research Support Services

Nelson J. Chao, MD, MBA
Professor of Medicine and Immunology
Chief, Division of Cellular Therapy/BMT

Victoria Christian
Chief Operating Officer, DTRI
Duke Translational Institute

Robert Cook-Deegan, M.D.
Director, Center for Genome Ethics, Law & Policy
Institute for Genome Sciences & Policy
Sanford Institute of Public Policy

Richard Frothingham, MD
Associate Professor
Department of Microbiology

Christopher Granger, M.D.
Professor Medicine
Cardiology

Laura Hale, M.D., PhD (Added 10/20/11)
Professor
Pathology Research (OLAW)

Brigid Hogan, PhD (Added 11/02/11)
Professor
Cell Biology

Sally Kornbluth, PhD
Vice Dean for Research
Professor
Pharmacology and Cancer Biology

Chay Kuo, MD
Assistant Professor
Cell Biology

Maria Mirotsou, PhD
Assistant Professor
Medicine – Cardiology

Scott Palmer, MD (Added 08/23/11)
Associate Professor
Medical Director, Lung Transplant Program
Pulmonary Medicine

Thomas J. Ribar (Added 08/23/11)
Shared Resource Lab Manager
Cell Biology

John H. Sampson, M.D, Ph.D.
Assistant Deputy Director, Preston Robert Tisch Brain Tumor Center at Duke
Associate Professor of Surgery
Assistant Professor of Pathology

Gregory D. Sempowski, PhD
Associate Professor
Departments of Medicine and Pathology
Director, Laboratory of T Cell Biology and Immune Reconstitution, Duke University Human Vaccine Institute

Keith Sullivan, M.D.
James B Wyngaarden Prof of Medicine
Cellular Therapy Division / BMT

Wayne Thomann, PhD
Assistant Professor
OESO Administration

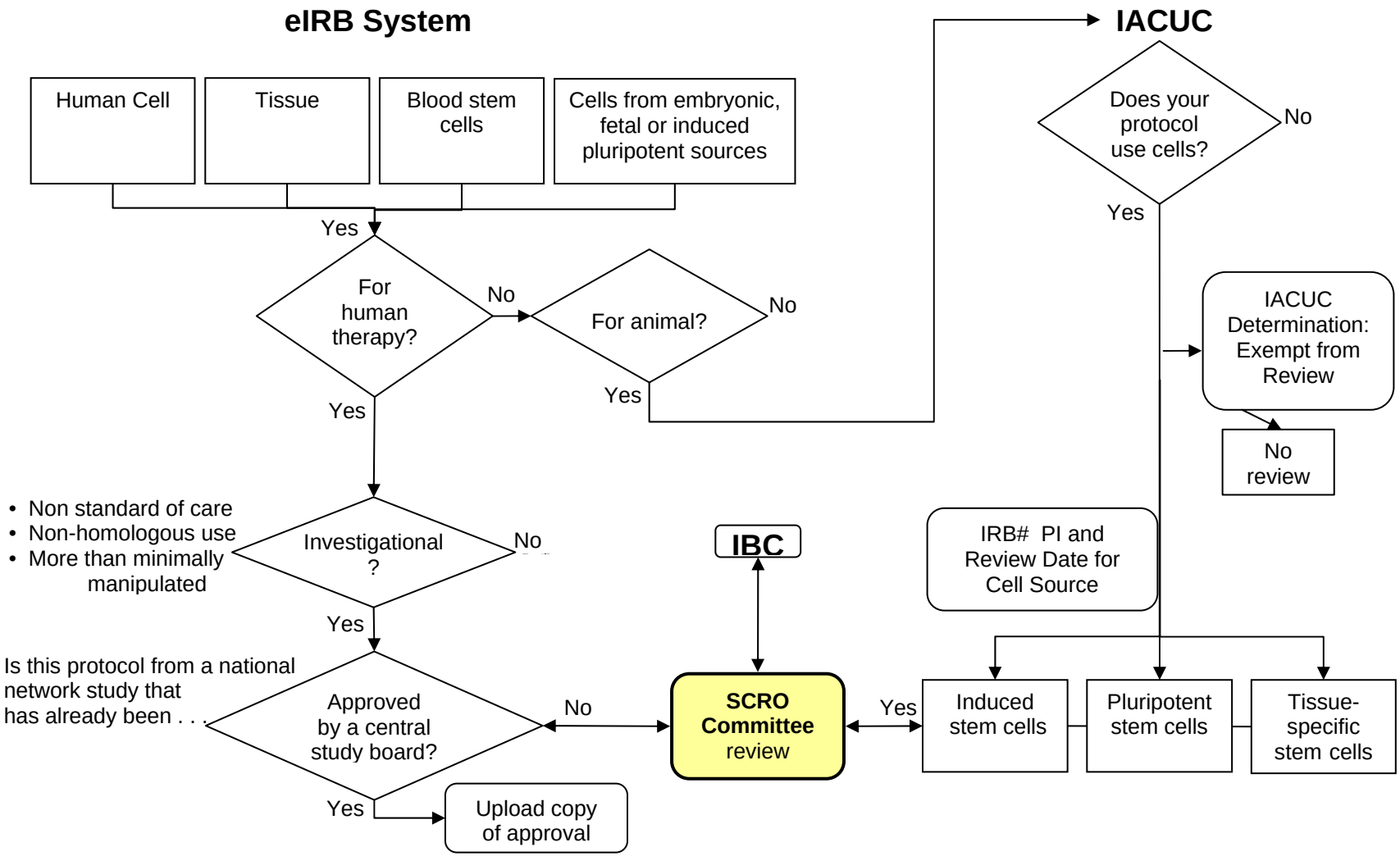
Kent J. Weinhold, Ph.D.
Professor of Surgery and Immunology
Director, Duke Center for AIDS Research (CFAR)

Administrative Manager
Doris M. Coleman, RN, CCRP
Robertson Clinical and Translational Cell Therapy Program (CT2)
Duke Translational Research Institute

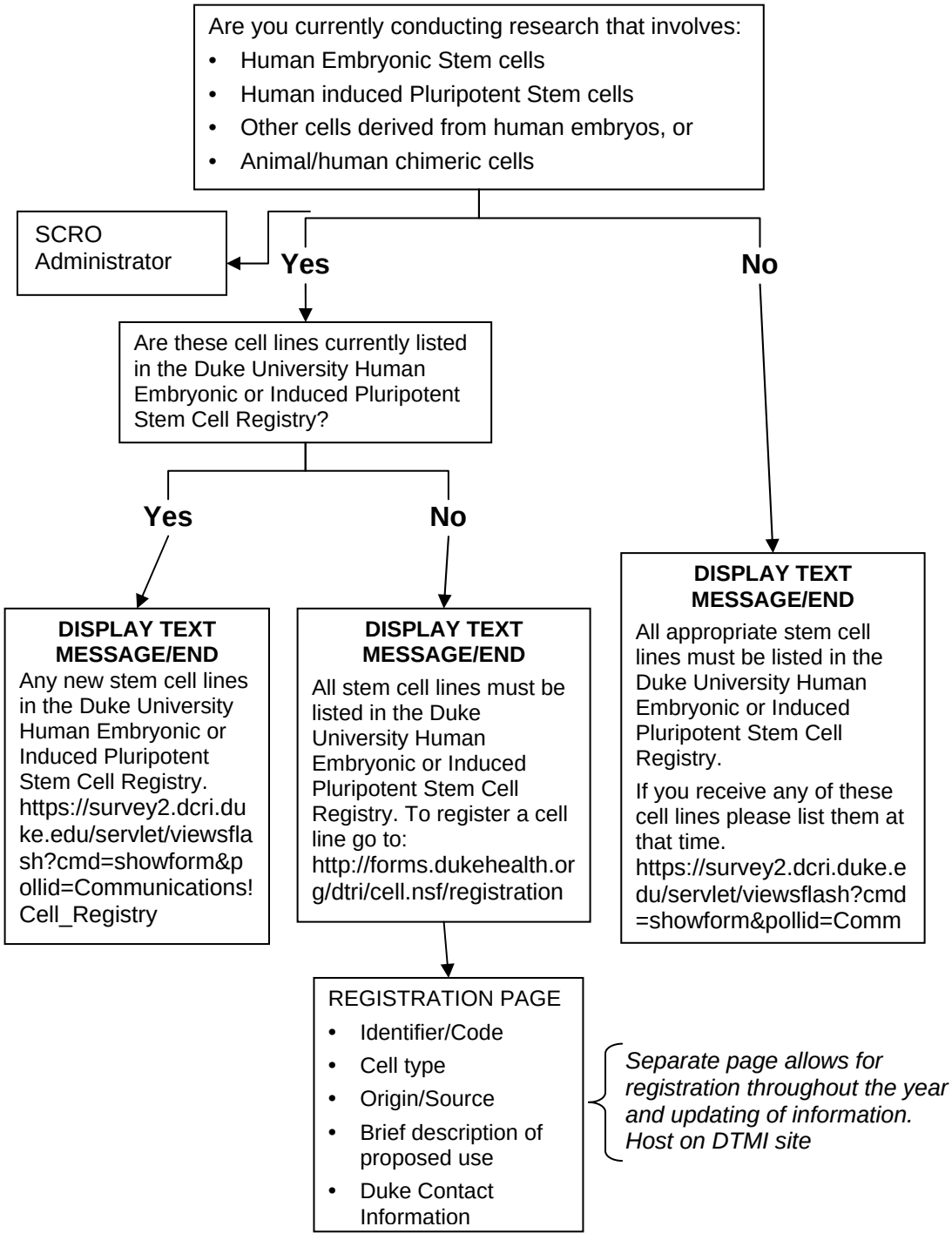
Community Representative(s)

SECTION 1

IRB AND IACUC APPLICANTS WITH REVIEW MAP



STEM CELL LINE REGISTRATION PROCESS



SECTION 2

STEM CELL RESEARCH OVERSIGHT COMMITTEE

This Duke University Committee is organized to provide research oversight and regulatory review for protocols using human cells, human embryonic cells (hES), induced pluripotent cells (iPS or hPS), tissue, genes or genetic material in research and moving towards or involving human clinical trials. The committee will review protocols as part of the University's official review during the Institutional Review Board for the Protection of Human Subjects (IRB) and Institutional Animal Care and Use Committee (IACUC) process of institutional review and approval. The committee will offer this review to each of the Site-Based Research Organizations. The committee will not participate in the business review of the protocols because that remains the responsibility of each departmental Site-Based Research Unit.

Suggested Levels of Review:

When the SCRO committee receives protocols for review, the committee suggested that the process employ levels to all expedited process with appropriate attention to the protocol with a minimum of delay. They recommended:

- **Administrative Review** by a knowledgeable person who confirms that the request for review is appropriate and that all of the required information is supplied. The protocol will then be assigned.
- **Designated Review** by one committee member who performs the review and circulates to the other members so they can read and comment or concur. This level of review is appropriate for previously approved protocols, clinical trials from cooperative trials and studies that have been previously reviewed and approved by other institutions or multi-institutional boards. This can all be done by e-mail.
- **Full SCRO** by conference call. One committee member will be designated as the lead. This will allow discussion but will make scheduling easier. The designated primary reviewer will summarize the protocol and questions to be discussed.
- **Full SCRO** with additional personnel added for embryonic cell issues, in person. For this review the issues will be complex enough, at least early on, that the extended committee with an ethicist, community representatives, and appropriate basic science experts will be invited. Some portion of this group may need to join by teleconference if scheduling requires. A quorum of three clinical and three basic science members from the base committee will be required at a meeting of the full SCRO. Other ad hoc members will be included as necessary and will be documented in the minutes of the meeting.

2.1 Establishment of an Institutional Stem Cell Research Oversight Committee

The committee will oversee the investigational use of cells as cell therapy. It will also provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES research. This committee is organized for oversight of hES and iPSC at Duke University.

2.2 Committee Membership

Persons with expertise in stem cell research, developmental biology, molecular biology, assisted reproduction, ethical and legal issues in stem cell research, and members of the lay community will serve as committee members. The basis of the committee will be the current Cell Therapy Steering Committee and will review the more routine protocols. Additional members will be included as necessary from the disciplines above as required by the protocol under review.

The committee must have suitable scientific, medical and ethical expertise to conduct its own review and the resources needed to coordinate with the management of the various other reviews required for the protocol. The additional paths for clinical protocol reviews are set up and coordinated through the Institutional Review Board for the Protection of Human Subjects. However, much hES cell research does not require IRB review.

2.3 Duties of the Committee

The SCRO's duties when considering embryonic or pluripotent cells uses are to:

1. Provide oversight over all issues related to derivation and use of hES cell lines.
2. Review and approve the scientific merit of the protocols.
3. Review compliance of all in-house hES cell research within all relevant regulations and the Institute of Medicine ESCRO guidelines.
4. Maintain registries of all hES research conducted at the institution and hES cell lines derived or imported by Duke investigators. Imported cell lines must have documentation that they were acceptably derived: a) that the donation was made under a protocol was approved by an IRB or equivalent body for donations taking place outside the US; b) consent to donate was voluntary and informed; c) donation was made under reimbursement policies consistent with the IOM ESCRO guidelines; d) donation and derivation complied with legal requirements of the relevant jurisdiction.
    a. Information on registries of this research should be made available to the public in a forum such as a website.
    b. Examples include: project abstracts, sources of funding
5. Facilitate education of investigators involved in hES research
6. Provide oversight on issues related to the investigational use of fetal, cord blood and adult stem and progenitor cells in clinical trials involving cell therapy including tissue repair and regeneration applications.

2.4 Audits

The ESCRO should be audited periodically to verify that it is carrying out its responsibilities appropriately. Auditable records include documentation of decisions regarding the acceptability of research protocols and verification that cell lines in use at Duke University were acceptably derived.

The results of these audits should be made available to the public.

SECTION 3

REVIEW OF CLINICAL RESEARCH USING STEM AND PROGENITOR CELLS DERIVED FROM FETAL, CORD BLOOD AND ADULT TISSUES FOR HUMAN STUDIES

The Duke University SCRO Committee will review research protocols involving these cell sources for clinical research when indicated by positive responses in the eIRB screening process for investigational human studies in **SECTION 1.** This area of clinical research is active at Duke University and will receive the majority of protocols referred to the committee for review. The following areas of the protocol will be reviewed:

3.1 Manufacturing and release criteria for clinical products must meet cGMP requirements appropriate for the phase of the intended study.

3.2 Consent of the donor needs to include the intended uses and kinds of testing done on the donated material. For other than autologous donors infectious disease screening and testing is specified in 21 CFR 1271. Guidances are also issued regularly as new infectious diseases that may affect allogeneic donors are recognized. Genetic testing required of the donor may have implications for both the donor and his/her family members. Consent also needs to include the information that certain positive tests are required by law to be reported to public health officials.

3.3 Each protocol will be reviewed for method and appropriateness of the derivation of source material for the study.

3.4 The protocol will be evaluated for safety data for administration of the product proposed for use.

3.5 Most protocols will require filing of an Investigational New Drug application with the US Food and Drug Administration. Some autologous or novel use of approved products may only require IRB review. The SCRO will issue guidance on these issues when needed.

3.6 Safety monitoring proposed for each protocol will be reviewed for appropriateness and compliance with federal regulations.

3.7 Efficacy endpoints will be reviewed if appropriate. Some Phase I studies will have safety only as their endpoint.

3.8 Protocols will be reviewed to assure that they do not contain deviations from maintenance of standard of care.

SECTION 4

PROCUREMENT OF GAMETES, BLASTOCYSTS OR CELLS FOR hES GENERATION

4.1 The Duke University IRB, as described in federal regulations at 45 CFR 46.107, will review all new procurements of all gametes, blastocysts, or somatic cells for the purpose of generating new hES or hPS cell lines. This includes the procurement of blastocysts in excess of clinical need from infertility clinics, blastocysts made through IVF specifically for research purposes, and oocytes, sperm, and somatic cells donated for development of hES cell lines derived through nuclear transfer (NT) or by parthenogenesis or androgenesis; and hPS cells derived by any means that require human subjects review.

4.2 Consent for donation will be obtained from each donor at the time of donation. Even people who have given prior indication of their intent to donate to research any blastocysts that remain after clinical care should nonetheless give informed consent at the time of donation. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

4.3 When donor gametes have been used in the IVF process, resulting blastocysts may not be used for research without consent of all gamete donors.

4.4 Payment and Reimbursement

a. No payments, cash or in-kind, may be provided for donating blastocysts in excess of clinical need for research purposes. People who elect to donate stored blastocysts for research should not be reimbursed for the costs of storage prior to the decision to donate.
b. Women who undergo hormonal induction to generate oocytes specifically for research purposes (such as for NT) should be reimbursed only for direct expenses incurred as a result of the procedure, as determined by an IRB. Direct expenses may include costs associated with travel, housing, child care, medical care, health insurance, and actual lost wages. No payments beyond reimbursements, cash or in-kind, should be provided for donating oocytes for research purposes. Similarly, no payments beyond reimbursements should be made for donations of sperm for research purposes or of somatic cells for use in NT.

4.5 To facilitate autonomous choice, decisions related to the creation of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.

4.6 In the context of donation of gametes, blastocysts, or somatic cells for hES cell research or for hPS cell research that requires human subjects review, the informed-consent process, will, at a minimum, provide the following information.

a. A statement that the blastocysts, gametes, or somatic cells will be used to derive hES or hPS cells for research that may include research on human transplantation
b. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation
c. A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES or hPS cell lines
d. If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines
e. An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of stem cells (Traceable information, however, must be secured to ensure confidentiality.)
f. A statement that derived hES or hPS cells and/or cell lines might be kept for many years
g. A statement that the hES or hPS cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models
h. Disclosure of the possibility that the results of study of the hES or hPS cells may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development
i. A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation
j. A statement that embryos will be destroyed in the process of deriving hES cells
k. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.
l. A statement of the risks involved to the donor
m. A statement that donor screening for infectious and genetic diseases will be conducted in accordance with federal regulations and guidances and that positive results will be reported to the donor and to the appropriate public health authorities as required by law

In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored. Investigators and stem cell banks are, of course, free to choose which cell lines to accept, and are not obligated to accept cell lines for which maintaining information about specific research use prohibitions would be unduly burdensome.

New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original donations were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes,

blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply.

4.7 Clinical personnel who have a conscientious objection to hES cell research should not be required to participate in providing donor information or securing donor consent for research use of gametes or blastocysts. The institution should ensure that where hES research is available, organizational structures are in place that ensure potential donors have access to the information and process needed to make informed decisions about embryo donation. Where clinical personnel object to participation, processes should be in place that ensure potential donors have access to non-objecting personnel who can provide donor information or secure donor consent for research use of gametes and blastocysts. The privilege of conscience-based refusals should not extend to the care of a donor or recipient.

4.8 Researchers may not ask members of the infertility treatment team to generate more oocytes than necessary for the optimal chance of reproductive success or provide incentives for them to do so. An infertility clinic or other third party responsible for obtaining consent or collecting materials should not be able to pay for or be paid for the material obtained (any payment must be limited to specifically defined cost-based reimbursements and payments for professional services).

SECTION 5

DERIVATION OF hES CELL LINES

Requests to the SCRO committee for permission to attempt derivation of new hES cell lines from donated embryos or blastocysts must include evidence of IRB approval of the procurement process (see Section 4.0 above).

5.1 The scientific rationale for the need to generate new hES cell lines, by whatever means, must be clearly presented, and the basis for the numbers of embryos and blastocysts needed should be justified.

5.2 Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES cells before permission to derive new lines is given.

5.3 When NT experiments involving either human or nonhuman oocytes are proposed as a route to generation of ES cells, the protocol must have a strong scientific rationale. Proposals that include studies to find alternatives to donated oocytes in this research should be encouraged.

5.4 Neither blastocysts made using NT (whether produced with human or nonhuman oocytes) nor parthenogenetic or androgenetic human embryos may be transferred to a human or nonhuman uterus or cultured as intact embryos *in vitro* for longer than 14 days or until formation of the primitive streak, whichever occurs first.

5.5 Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines and how they will maintain the confidentiality of any coded or identifiable information associated with the lines (see Section 5.0 below). Investigators are encouraged to apply the same procedures and standards for characterization, validation, storage, and distribution to hPS cell lines

SECTION 6

BANKING AND DISTRIBUTION OF hES CELL LINES

Duke University's hES research should seek mechanisms for establishing central repositories for hES cell lines – through partnerships or augmentation of existing quality research cell line repositories and should adhere to high ethical, legal, and scientific standards. At a minimum, an institutional registry of stem cell lines should be maintained. Institutions are encouraged to consider the use of the same procedures for banking and distribution of hPS cell lines.

6.1 In order to bank or in planning to bank hES cell lines, Duke University will establish uniform guidelines to ensure that donors of material give informed consent through a process approved by an IRB and that meticulous records are maintained about all aspects of cell culture. Uniform tracking systems and common guidelines for distribution of cells should be established.

6.2 The University, in obtaining and storing hES cell lines, will consider the following standards:

a. Creation of a committee for policy and oversight purposes and creation of clear and standardized protocols for banking and withdrawals.
b. Documentation requirements for investigators and sites that deposit cell lines, including
    (i) A copy of the donor consent form
    (ii) Proof of Institutional Review Board approval of the procurement process
    (iii) Available medical information on the donors, including results of infectious disease screening
    (iv) Available clinical, observational, or diagnostic information about the donor(s)
    (v) Critical information about culture conditions (such as media, cell passage, and safety information)
    (vi) Available cell line characterization (such as karyotype and genetic markers). A repository has the right of refusal if prior culture conditions or other items do not meet its standards
c. A secure system for protecting the privacy of donors when materials retain codes or identifiable information, including but not limited to
    (i) A schema for maintaining confidentiality (such as a coding system)
    (ii) A system for a secure audit trail from primary cell lines to those submitted to the repository
    (iii) A policy governing whether and how to deliver clinically significant information back to donors
d. The following standard practices:
    (i) Assignment of a unique identifier to each sample
    (ii) A process for characterizing cell lines
    (iii) A process for expanding, maintaining, and storing cell lines
    (iv) A system for quality assurance and control
    (v) A website that contains scientific descriptions and data related to the cell lines available
    (vi) A procedure for reviewing applications for cell lines

(vii) When shipped (such as number of passages)
(viii) A system for auditing compliance
(ix) A schedule of charges
(x) A statement of intellectual property policies
(xi) When appropriate, creation of a clear Material Transfer Agreement or user agreement
(xii) A liability statement
(xiii) A system for disposal of material

e. Clear criteria for distribution of cell lines, including but not limited to evidence of approval of the research by an embryonic stem cell research oversight committee or equivalent body at the recipient institution.

SECTION 7

RESEARCH USE OF hES CELL LINES

Once hES cell lines have been derived, Duke University investigators, through the SCRO committee and other relevant committees (such as an IACUC, an IBC, or a radiation safety committee) should monitor their use in research.

7.1 Duke University will require documentation of the provenance of all hES cell lines, whether the cells were imported into the institution or generated locally. The institution should obtain evidence of IRB-approval of the procurement process and of adherence to basic ethical and legal principles of procurement as described in Sections 3 and 4. In the case of lines imported from another institution, documentation that these criteria were met at the time of derivation will suffice.

7.2 *In vitro* experiments involving the use of already derived and coded hES cell lines will not need review beyond the review described in Section 6.2 and 8.1.

7.3 Each institution should maintain a registry of its investigators who are conducting hES cell research and ensure that all registered users are kept up to date with changes in guidelines and regulations regarding the use of hES cells.

7.4 All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals must be submitted to the Duke University IACUC for review of animal welfare issues and to the Duke University SCRO committee for consideration of the consequences of the human contributions to the resulting chimeras.

7.5 Transplantation of differentiated derivatives of hES cells or even hES cells themselves into adult animals will not require extensive ESCRO committee review. If there is a possibility that the human cells could contribute in a major organized way to the brain of the recipient animal, however, the scientific justification for the experiments must be strong, and proof of principle using nonhuman (preferably primate) cells, is desirable.

7.6 Experiments in which hES cells, their derivatives, or other pluripotent cells, are introduced into nonhuman fetuses and allowed to develop into adult chimeras need more careful consideration because the extent of human contribution to the resulting animal may be higher. Consideration of any major functional contributions to the brain should be a main focus of review. (See also Section 8.3(c) concerning breeding of chimeras.)

7.7 Introduction of hES cells into nonhuman mammalian blastocysts should be considered only under circumstances in which no other experiment can provide the information needed. (See also Section 8.3(c)(ii) concerning restrictions on breeding of chimeras and production of chimeras with nonhuman primate blastocysts.)

7.8 Research use of existing hES cells does not require IRB review unless the research involves introduction of the hES cells or their derivatives into patients or the possibility that the identity of the donors of the blastocysts, gametes, or somatic cells is readily ascertainable or might become known to the investigator.

SECTION 8

RECOMMENDATIONS FOR NON-CLINICAL RESEARCH USE OF NON-EMBRYO-DERIVED HUMAN PLURIPOTENT STEM CELLS (hPS CELLS)

8.1 Derivation

Because non-embryo-derived hPS cells are derived from human material, their derivation is covered by existing IRB regulations concerning review and informed consent. No SCRO committee review is necessary, although the IRB may always seek the advice of an SCRO committee if this seems desirable. The IRB review should consider proper consent for use of the derived hPS cells. Some of the recommendations for informed consent that apply to hES cells also apply to hPS cells (see Section 3.6), including informed consent to genetic manipulation of resulting pluripotent stem cells and their use for transplantation into animals and humans and potentially in future commercial development.

8.2 Use in *in Vitro* Experiments

Use of hPS cells in purely *in vitro* experiments need not be subject to any review beyond that necessary for any human cell line except that any experiments designed or expected to yield gametes (oocytes or sperm) should be subject to ESCRO committee review.

8.3 Use in Experiments Involving Transplantation of hPS Cells into Animals at any Stage of Development or Maturity

a. Research involving transplantation of pluripotent human cells derived from non-embryonic sources into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by SCRO committees and IACUCs, as are similar experiments that use hES cells.
b. SCRO committees should review the provenance of the hPS cells as they review the provenance of hES cells (see section 1.6) to ensure that the cell lines were derived according to ethical procedures of informed consent as monitored by an IRB or equivalent oversight body.
c. Proposals for use of hPS cells in animals should be considered in one of the following categories:

   (i) Permissible after currently mandated reviews and proper documentation [see Section 2: experiments that are exempt from full ESCRO committee review but not IACUC review (experiments that involve only transplantation into postnatal animals with no likelihood of contributing to the central nervous system or germ line).

   (ii) Permissible after additional review by a SCRO committee, as described in Section 2.2 of the guidelines: experiments in which there is a significant possibility that the implanted hPS cells could give rise to neural or gametic cells and tissues. Such experiments need full ESCRO committee and IACUC review and would include generation of all preimplantation chimeras as well as neural transplantation into embryos or perinatal animals. Particular attention should be paid to at least three factors:

- Extent to which the implanted cells colonize and integrate into the animal tissue;
- Degree of differentiation of the implanted cells;
- Possible effects of the implanted cells on the function of the animal tissue;

(iii) Should not be conducted at this time.

(1) Experiments that involve transplantation of hPS cells into human blastocysts.
(2) Research in which hPS cells are introduced into nonhuman primate embryos, pending further research that will clarify the potential of such introduced cells to contribute to neural tissue or to the germ line.

8.4 Multipotent Neural Stem Cells

It is also relevant to note that neural stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals. ESCRO committees should decide whether they wish to review and monitor such experiments with neural stem cells in a similar fashion.

8.5 Prohibition on Breeding

No animal into which hPS cells have been introduced such that they could contribute to the germ line should be allowed to breed.

8.6 Guidance for Banking and Distribution

Institutions should consider the value of banking and distributing hPS cells using the guidance and rules that are already in place for hES cells and the value of including hPS cell lines in their registries.

GLOSSARY

Adult stem cell – An undifferentiated cell found in a differentiated tissue that can renew itself and (with limitations) differentiate to yield the specialized cell types of the tissue from which it originated.

Androgenesis – Development in which the embryo contains only paternal chromosomes.

Autologous transplant – Transplanted tissue derived from the intended recipient of the transplant. Such a transplant helps to avoid complications of immune rejection.

Blastocoel – The cavity in the center of a blastocyst.

Blastocyst – A preimplantation embryo of 50–250 cells depending on age. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

Blastomere – A single cell from a morula or early blastocyst, before the differentiation into trophectoderm and inner cell mass.

Bone marrow – The soft, living tissue that fills most bone cavities and contains hematopoietic stem cells, from which all red and white blood cells evolve. The bone marrow also contains mesenchymal stem cells from which a number of cell types arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

Chimera – An organism composed of cells derived from at least two genetically different cell types. The cells could be from the same or separate species.

Differentiation – The process whereby an unspecialized early embryonic cell acquires the features of a specialized cell, such as a heart, liver, or muscle cell.

DNA – Deoxyribonucleic acid, a chemical found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.

Ectoderm – The outermost of the three primitive germ layers of the embryo; it gives rise to skin, nerves, and brain.

Egg cylinder – An asymmetric embryonic structure that helps to determine the body plan of the mouse

Electroporation – Method of introducing DNA into a cell.

Embryo – An animal in the early stages of growth and differentiation that are characterized by cleavage, laying down of fundamental tissues, and the formation of primitive organs and organ systems ; *especially* the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a fetus.*

Embryoid bodies (EBs) – Clumps of cellular structures that arise when embryonic stem cells are cultured. Embryoid bodies contain tissue from all three germ layers: endoderm, mesoderm, and ectoderm. Embryoid bodies are not part of normal development and occur only in vitro.

Embryonic disk – A group of cells derived from the inner cell mass of the blastocyst, which later develops into an embryo. The disk consists of three germ layers known as the endoderm, mesoderm, and ectoderm.

Embryonic germ (EG) cells – Cells found in a specific part of the embryo or fetus called the gonadal ridge that normally develop into mature gametes. The germ cells differentiate into the gametes (oocytes or sperm).

Embryonic stem (ES) cells – Primitive (undifferentiated) cells derived from the early embryo that have the potential to become a wide variety of specialized cell types.

Endoderm – Innermost of the three primitive germ layers of the embryo; it later gives rise to the lungs, liver, and digestive organs.

Enucleated cell – A cell whose nucleus has been removed.

Epidermis – The outer cell layers of the skin.

Epigenetic – Refers to modifications in gene expression that are controlled by heritable but potentially reversible changes in DNA methylation or chromatin structure without involving alteration of the DNA sequence.

Epithelium – Layers of cells in various organs, such as the epidermis of the skin or the lining of the gut. These cells serve the general functions of protection, absorption, and secretion, and play a specialized role in moving substances through tissue layers. Their ability to regenerate is excellent; the cells of an epithelium may replace themselves as frequently as every 24 hours from the pools of specialized stem cells.

Feeder cell layer – Cells that are used in culture to maintain pluripotent stem cells Feeder cells usually consist of mouse embryonic fibroblasts.

Fertilization – The process whereby male and female gametes unite to form a zygote (fertilized egg).

Fibroblasts – Cells from many organs that give rise to connective tissue.

Gamete – A mature male or female germ cell, that is, sperm or oocyte, respectively.

Gastrulation – The procedure by which an animal embryo at an early stage of development produces the three primary germ layers: ectoderm, mesoderm, and endoderm.

Gene – A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene usually directs the formation of an enzyme or other protein.

Gene targeting – A procedure used to produce a mutation in a specific gene

Genital ridge – Anatomic site in the early fetus where primordial germ cells are formed

Genome – The complete genetic material of an organism.

Genotype – Genetic constitution of an individual.

Germ cell – A sperm or egg or a cell that can become a sperm or egg All other body cells are called somatic cells.

Germ layer – In early development, the embryo differentiates into three distinct germ layers (ectoderm, endoderm, and mesoderm), each of which gives rise to different parts of the developing organism.

Germ line – The cell lineage from which the oocyte and sperm are derived

Gonadal ridge – Anatomic site in the early fetus where primordial germ cells (PGCs) are formed.

Gonads – The sex glands - testis and ovary

Hematopoietic – Blood-forming.

Hematopoietic stem cell (HSC) – A stem cell from which all red and white blood cells evolve and that may be isolated from bone marrow or umbilical cord blood for use in transplants.

Hepatocyte – Liver cell.

Heterologous – From genetically different individuals

hES cell – Human embryonic stem cell; a type of pluripotent stem cell.

Histocompatibility antigens – Glycoproteins on the surface membranes of cells that enable the body's immune system to recognize a cell as native or foreign and that are determined by the major histocompatibility complex

Homologous recombination – Recombining of two like DNA molecules, a process by which gene targeting produces a mutation in a specific gene.

hPS cells – Human pluripotent stem cells derived from non-embryonic sources.

Hybrid – An organism that results from a cross between gametes of two different genotypes.

Immune system cells – White blood cells, or leukocytes, that originate in the bone marrow. They include antigen-presenting cells, such as dendritic cells, T and B lymphocytes, macrophages, and neutrophils, among many others.

Immunodeficient mice – Genetically altered mice used in transplantation experiments because they usually do not reject transplanted tissue.

Immunogenic – Related to or producing an immune response.

Immunosuppressive – Suppressing a natural immune response.

Implantation – The process in which a blastocyst implants into the uterine wall, where a placenta forms to nurture the growing fetus.

Inner cell mass – The cluster of cells inside the blastocyst that give rise to the embryonic disk of the later embryo and, ultimately, the fetus

Interspecific – Between species

In utero – In the uterus

In vitro – Literally, "in glass," in a laboratory dish or test tube; in an artificial environment

***In vitro* fertilization (IVF)** – An assisted reproductive technique in which fertilization is accomplished outside the body

In vivo – In the living subject; in a natural environment

Karyotype – The full set of chromosomes of a cell arranged with respect to size, shape, and number.

Leukemia inhibitory factor (LIF) – A growth factor necessary for maintaining mouse embryonic stem cells in a proliferative, undifferentiated state

Mesenchymal stem cells – Stem cells found in bone marrow and elsewhere from which a number of cell types can arise, including chondrocytes, which produce cartilage, and fibroblasts, which produce connective tissue.

Mesoderm – The middle layer of the embryonic disk, which consists of a group of cells derived from the inner cell mass of the blastocyst; it is formed at gastrulation and is the precursor to bone, muscle, and connective tissue.

Morula – A solid mass of 16 – 32 cells that resembles a mulberry and results from the cleavage (cell division without growth) of a zygote (fertilized egg).

Mouse embryonic fibroblast (MEF) – Cells used as feeder cells in culturing pluripotent stem cells.

Multipotent – Capable of differentiation into a limited spectrum of differentiated cell types.

Neural stem cell (NSC) – A stem cell found in adult neural tissue that can give rise to neurons, astrocytes, and oligodendrocytes.

Nuclear transfer (NT) – Replacing the nucleus of one cell with the nucleus of another cell.

Oocyte – Developing egg; usually a large and immobile cell.

Ovariectomy – Surgical removal of an ovary.

Parthenogenesis – Development in which the embryo contains only maternal chromosomes.

Passage – A round of cell growth and proliferation in culture.

Phenotype – Visible properties of an organism produced by interaction of genotype and environment.

Placenta – The oval or discoid spongy structure in the uterus from which the fetus derives its nourishment and oxygen.

Pluripotent cell – A cell that has the capability of developing into cells of all germ layers (endoderm, ectoderm, and mesoderm)

Precursor cells – In fetal or adult tissues, partly differentiated cells that divide and give rise to differentiated cells. Also known as progenitor cells.

Preimplantation genetic diagnosis (PGD) – A procedure applied to IVF embryos to determine which ones carry deleterious mutations predisposing to hereditary diseases.

Primary germ layers – The three initial embryonic germ layers – endoderm, mesoderm, and ectoderm – from which all other somatic tissue types develop.

Primordial germ cell – A cell appearing during early development that is a precursor to a germ cell

Primitive streak – The initial band of cells from which the embryo begins to develop. The primitive streak establishes and reveals the embryo's head-tail and left-right orientations.

Pseudopregnant – Refers to a female primed with hormones to accept a blastocyst for implantation

Somatic cells – Any cell of a plant or animal other than a germ cell or germ cell precursor.

Somatic cell nuclear transfer (SCNT) – The transfer of a cell nucleus from a somatic cell into an egg (oocyte) whose nucleus has been removed

Stem cell – A cell that has the ability to divide for indefinite periods *in vivo* or in culture and to give rise to specialized cells

Teratoma – A tumor composed of tissues from the three embryonic germ layers. Usually found in ovary or testis. Produced experimentally in animals by injecting pluripotent stem cells to determine the stem cells' abilities to differentiate into various types of tissues

Tissue culture – Growth of tissue *in vitro* on an artificial medium for experimental research

Transfection – A method by which experimental DNA may be put into a cultured cell.

Transgene – A gene that has been incorporated into a cell or organism and passed on to successive generations

Transplantation – Removal of tissue from one part of the body or from one individual and its implantation or insertion into another, especially by surgery.

Trophectoderm – The outer layer of the developing blastocyst that will ultimately form the embryonic side of the placenta

Trophoblast – The extra embryonic tissue responsible for negotiating implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Undifferentiated – Not having changed to become a specialized cell type.

Xenograft or xenotransplant – A graft or transplant of cells, tissues, or organs taken from a donor of one species and grafted into a recipient of another species.

Zygote – A cell formed by the union of male and female germ cells (sperm and egg, respectively).

http://www.nlm.nih.gov/medlineplus/mplusdictionary.html. In common parlance, “embryo” is used more loosely and variably to refer to all stages of development from fertilization until some ill-defined stage when it is called a fetus. There are strictly defined scientific terms such as “zygote,” “morula,” and “blastocyst” that refer to specific stages of preimplantation development (see Chapter 2). In this report, we have used the more precise scientific terms where relevant but have used the term “embryo” where more precision seemed likely to confuse rather than clarify.