CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Briefing Report for September 17 -18 Meeting of CIRM Medical and Ethical Standards Working Group of The Independent Citizens Oversight Committee To The California Institute For Regenerative Medicine

Organized Pursuant To The California Stem Cell Research And Cures Act

Thursday, September 17, 2009 5:00pm - 9:00pm
Friday, September 18, 2009 9:00am - 5:00pm
Westin San Francisco Market Street
50 Third Street
San Francisco, CA 94103

http://www.cirm.ca.gov/Agenda_9-17-09

Report Contents:

Background & Objectives

This report outlines options for modification of the CIRM Medical and Ethical Standards (MES) regulations. These options have been developed in response to five related policy inputs:

1. Public comments received on proposed amendments to the MES regulations (summary attached);
2. The Guidelines for Human Stem Cell Research promulgated by the California Department of Public Health;
3. The findings of CIRM's stem cell research oversight workshop;
4. The development of federal National Institutes of Health (NIH) policy governing human embryonic stem cell research;
5. Participation in the National Academies Human Embryonic Stem Cell Research Advisory Committee meeting August 7, 2009.

At its August 18 meeting, CIRM's governing board, the Independent Citizens Oversight Committee (ICOC), indicated its desire for CIRM policy to be as compatible as possible with the NIH Guidelines.

Collectively these inputs have informed the development of specific options designed to support the following policy objectives:

1. Align CIRM regulations with NIH and Office of Human Research Protection (OHRP) policy;
2. Address concerns raised during the public comment period and workshop;
3. Enhance the quality and efficiency of CIRM policies.

Statement of Principle

The purpose and intent of Proposition 71 is to:

Assure that the research is conducted safely and ethically by including provisions to require compliance with standards based on national models that protect patient safety, patient rights, and patient privacy.

This commitment is embodied in the *CIRM Scientific Strategic Plan*, which states:

CIRM mission is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.

The Standards Working has continually sought to recommend high standards consistent with national models for research oversight and donor consent.

Summary of Previous SWG Recommendations

The SWG previously recommended modifications to (1) SCRO oversight requirements, (2) payment standards and (3) donor consent requirements at its 12/12/08 and 12/17/09 meetings. SWG recommendations were taken under consideration at the 3/12/09 ICOC meeting.

The changes were approved by the ICOC and were posted for public comment in May 2009. CIRM received a number of comments concerning the proposed amendments to sections 100070 and 100090. Participants at the CIRM SCRO workshop developed a summary statement regarding the proposed amendments.

Summary of NIH Guidelines

In July 2009, the National Institutes of Health issued guidelines human embryonic stem cell research. The NIH guidelines outline criteria the agency will utilize when evaluating whether a hESC line is eligible for NIH funding. The eligibility criteria are substantially similar to CIRM's with two noteworthy differences:

1. NIH imposes no restrictions on the use of embryos provided the embryo was originally created using IVF for reproductive purposes and is no longer needed for this purpose. CIRM restricts the use of some IVF-embryos for which gamete donors were paid.
2. NIH requires consent only from individuals who sought reproductive treatment. CIRM policy requires consent from each gamete donor.

NIH is currently in the process of developing a registry to identify lines that conform to the guidelines and are eligible for use in funded research.

Public Comment & Issues for Policy Consideration

The major policy issues, which have emerged as a result of public comment and the development of NIH guidelines, encompass three general aspects of the CIRM MES regulations:

1. Requirements for SCRO oversight / notification;
2. Use of IVF-embryos and somatic cells for which donors have been paid;
3. Donor consent requirements.

These issues are further summarized in Table 1.

Individuals, institutions and organizations providing written comment on MES regulations include:

- Stanford University Office of Research Compliance
- University of California Irvine, Human Stem Cell Research Oversight Committee
- University of California Los Angeles, Center for Regenerative Medicine and Stem Cell Research
- University of California San Diego Embryonic Stem Cell Research Oversight Committee

Table 1: Summary of Issue for Consideration

Issue	Source	Comment
[1] SCRO Oversight Requirements: • Clarify review and approval requirements for in vitro research • SCRO not necessary for in vitro research involving somatic cells or NIH registry hESCs	SCRO Workshop, CDPH & NIH policy	• No policy change necessary to clarify review and approval requirements. Proposed language strengthens existing policy. • Revising policy for in vitro research involving somatic cells or registry lines consistent with previous SWG recommendation; see Table 2.
[2] Donor Compensation: • CIRM should not restrict use of cells procured under IRB-approved protocols • Restricting use of IVF is inconsistent with CA and national (NAS & NIH) policy	Public Comments, SCRO Workshop CDPH & NIH policy	• Focusing payment restrictions on oocytes "generated specifically for research purposes" would address both points raised and be consistent with NAS and CA state policy.
[3] Donor Consent Requirements: • Clarify disclosure requirement • CIRM and NIH policy vary with regard to embryo donor consent	Public Comments & NIH policy	• No policy change necessary; CIRM should clarify (through regulation or guidance) when disclosure is appropriate.

1. Requirements for SCRO Oversight / Notification

When the original MES regulations were developed, there was an absence of federal policy and general concerns about the use of hESC lines. In response, the SWG recommended and the ICOC approved a package of regulatory requirements that incorporate SCRO oversight based on the NAS Guidelines.

Since the original regulations took effect, the SWG has periodically reevaluated various review and oversight requirements. In March 2009 the ICOC approved the SWG-recommended policy for a more flexible approach, consistent with federal and California state policy, for in vitro research involving the use of human somatic cells. The California Department of Public Health Human Stem Cell Research Advisory Committee (HSCR) recently revised its guidelines to exclude some somatic cell research from SCRO oversight. In addition, during the June / July 2009 SCRO Workshop participants recommended policies consistent with the approach adopted by the HSCR Advisory Committee.

Based on analysis of the California HSCR Advisory Committee Guidelines, NIH Guidelines, NAS Guidelines, public comments on the previous SWG recommendations and

recommendations from the SCRO Workshop, CIRM staff recommends the following amendments to section 100070:

1. Strengthen existing language to ensure all research involving the creation or use of gametes or embryos receives full SCRO review and approval;
2. Revise the SCRO notification standard for iPS derivation to only encompass human subjects research involving identifiable somatic cells;
3. For non-human subjects in vitro research involving (1) somatic cell reprogramming or (2) NIH-approved hESCs, allow the "designated official" to provide a statement of compliance.

The above recommendations are designed to emphasize the need for full SCRO review of in vitro research involving gametes and embryos (in addition to any in vivo research). As written, the revised standard would cover gametes and embryos generated from any source including differentiation from iPS cells. In addition, the recommendations recognize that in vitro research using cell that meet federal standards is not controversial and a statement of compliance is sufficient. The proposed amendments are described in detail in Table 1.

2. Donor Compensation

Payments for Somatic Cells

The CIRM MES regulations contain provisions restricting payments to donors of "gametes, embryos, somatic cells or tissue." – section 100080(a)(2)(B). CIRM applies these restrictions to modest payments ($25-50) for donation of blood, skin cells, tissue, urine, or other minimally invasive donations. It is generally accepted practice based on federal regulations to allow modest IRB-approved payment to these donors. Some clinical studies may ask for volunteers to donate blood, for example, without payment, but this information may not be readily available to researchers using banked cells.

Modification of this standard for somatic cells was considered at the December 12, 2008 SWG meeting. At that time questions were raised regarding the scope of payment restrictions in Proposition 71 section 125290.35, and no action was taken.

Based on analysis of NIH Guidelines, public comments on the previous SWG recommendations and recommendations from the SCRO Workshop, staff recommends the following amendment to section 100080(a)(2)(B):

1. Limit the payment restriction to donation of oocytes provided specifically for research purposes.

The above recommendations would maintain restriction on the payment of donors providing oocytes for research. The payment of oocyte donors (not somatic cell donors) was the primary concern for development of this standard.

Payments for Gametes for Reproductive (IVF) Use

Section 100080(a)(2)(B) also restricts the use of hESC derived from embryos created for reproductive (IVF) use for which the gamete donor was paid. The NIH policy contains no restriction on the use of these hESC lines. As a consequence of this provision, CIRM potentially finds itself in the position of restricting the use of hESC lines that would be available to NIH-funded researchers.

Table 2: Summary of Proposed Modifications to Section 100070 SCRO Committee Review and Notification

Current Section 100070 Oversight Categories	SCRO Requirement	Proposed Revised Section 100070 Oversight Categories	Rationale
(a) research involving the procurement or use of human oocytes	No Change: Review and Approval	(a) research involving the **creation or use** of human gametes	Clarifies creation of gametes from any source, including iPS, requires full SCRO review
(b) research involving human embryos	No Change: Review and Approval	(b) research involving the **creation or use** of human blastocysts or embryos (including SCNT)	Embryo research covered in one section. Previously included in both sections (b) and (c). Creation of blastocysts from any source, including IVF and SCNT, covered.
(c) research with the aim to derive or create a covered stem cell line from human gametes embryos or products of SCNT	Notification Standard Narrowed	(c) **human subjects** research involving the reprogramming of human somatic cells with the aim to derive or created a covered stem cell line	Gamete and embryo research now covered in (a) and (b) above. Section limited to iPS research. SCRO notification requirement narrowed to address consent considerations.
(d) purely in vitro research using covered stem cell lines	Notification or Statement from Designated Official	(d) Notification of SCRO for **in vitro research** involving covered stem cell lines. If the line is de-identifiedd **AND** recognized by an authorized authority, a statement from designated official that compliant cell lines will be utilized is sufficient.*	Addresses issues raised in public comment. Allowing designated institutional official to certify hESC lines and somatic cells are recognized by an authorized authority enhances flexibility for grantee.
(e) research introducing covered stem cell lines to animals	No Change: Review and Approval	No change	No change
(f) research introducing cells from covered stem cell line to humans	No Change: Review and Approval	No change	No change

At its August 19, 2009 meeting, ICOC members articulated the position that CIRM should not be more restrictive than NIH. Based on analysis of NIH Guidelines, public comments on the previous SWG recommendations, recommendations from the SCRO Workshop, and feedback from the ICOC, staff reiterates the previous recommendation for amendment of section 100080(a)(2)(B):

1. Limit the payment restriction to donation of oocytes provided specifically for research purposes.

The above recommendations would maintain restriction on the payment of gametes provided for research. The payment of oocyte donors (not somatic cell donors) was the primary concern for this standard.

3. Donor Consent Requirements

Disclosure of Research Use

The SWG has previously articulated the position that it is acceptable to utilize IVF-embryos in CIRM-funded research where the ooctye donor has been informed that surplus embryos may be donated for research use. Documentation provided by fertility clinics to donors generally contains language that informs the donor that research use is one option among many for final embryo disposition. Since oocyte donation for fertility treatment does not constitute research as defined by 45 CFR Part 46, it may not be accurate to refer to this disclosure as "informed consent." A more accurate term may be "disclosure."

Staff recommends through regulation or guidance documents that CIRM indicate that in the case of third-party donors a "disclosure" of research use is sufficient for embryo use in funded research. Table 2 summarizes how the recommendations outlined in this report would impact the "acceptably derived" standard.

Difference Between NIH and CIRM Consent for Embryos

As described previously, NIH requires consent from individuals who sought reproductive treatment. CIRM policy requires consent from each gamete donor. As noted in the previous section, it may be most accurate to state that CIRM requires consent from or disclosure to each gamete donor.

Currently, the CIRM regulations differ from the NIH Guidelines with regard to this consent provision. Operationally, this difference does not restrict the use of research materials because NIH approved lines are authorized for use by CIRM grantees.

Since the CIRM consent standards exceeds the NIH requirement, it is anticipated that any hESC line derived with CIRM funding would be eligible for NIH registration.

Staff recommends no change at this time.

Table 3 CIRM Acceptably Derived Standard: Current & Proposed Revisions

Current Application of "Acceptably Derived" Standard				
	Consent	No Valuable Consideration	IRB or Equivalent Oversight	No Storage Reimbursement
Research Oocytes	✔	✔	✔	✔
IVF-Embryos	✔	✔	✔	✔
Somatic Cells	✔ or OHRP	✔ or OHRP	✔ or OHRP	✔

Proposed Revision of "Acceptably Derived" Standard				
	Consent	No Valuable Consideration	IRB or Equivalent Oversight	No Storage Reimbursement
Research Oocytes	✔	✔	✔	✔
IVF-Embryos	✔ Disclosure		✔	✔
Somatic Cells	✔ or OHRP	IRB-approved or OHRP	✔ or OHRP	✔

Attachments:

- SCRO Workshop Consensus Statement
- Public comments on sections 100070 and 100090 amendments
- NIH Guidelines for Human Stem Cell Research

Appendix C: Summary Statement

July 6, 2009

Summary Statement From CIRM SCOR Workshop Regarding Amendments to CIRM MES Standards Regulations

Background:

CIRM sponsored a workshop designed to examine institutional approaches for addressing ethical, legal and policy issues related to stem cell research. The workshop was attended by representatives from 13 institutions currently involved in CIRM-funded human pluripotent stem cell research. The workshop included discussion of proposed amendments to the CIRM MES Standards regulations. Considerable discussion emerged during the workshop regarding proposed revisions to section 100090(a)(1). There was consensus among workshop participants that a summary statement should be developed regarding proposed changes to this section.

Major Comment:

There were concerns among the workshop participants over the proposed revisions to section 100090(a)(1) – *for embryos created on or before August 13, 2008, "valuable consideration" does not include payments to gamete donors in excess of "permissible expenses," provided the embryo was originally created for reproductive purposes*. Participants articulated concerns that were both conceptual and policy related.

Conceptual Concerns

It is already clear from Proposition 71 and CIRM policy that embryo or gamete donations for research cannot be coerced with excessive compensation. The clear purpose of this policy is to prevent the solicitation of research subjects exposed to research projects that are inherently risky, by means of large financial incentives. However, CIRM wisely clarified that it should not interfere with normal clinical practice where gametes for reproductive purposes are often obtained from compensated donors. Clearly, we should not be suggesting that there is anything less ethical or moral about embryos for reproductive purposes where the sperm or oocyte donor was compensated.

Given that principle, it was difficult for the participants to understand the need for a cutoff date. The cut off date of August 13, 2008 provides no meaningful or useful protections to potential embryo donors or to individuals previously compensated for providing gametes for clinical IVF procedures. The conditions in which the embryos were created after August 13, 2008 are no less ethical than the conditions of creation before that date. It is also improbable that any practicing fertility specialist will explain to the patients the research limitations that might result from the use of compensated gamete donations. In fact, as indicated below, the fertility specialist is obligated to identify research donation as an option under existing law. Thus, several years from now some individuals with stored embryos and with completed families will want to donate the supernumerary embryos for research and will be told it is not possible because of events that happened after an arbitrary date. The participants agreed that such a restrictive policy will not benefit donors, stem cell research, or the state of California and is incompatible with the intent of Proposition 71.

Policy Related Concerns

The participants agreed that CIRM regulations should not enact policies that restrict the research availability of embryos created for reproductive purposes based on the date of the creation of the embryo(s) or based on whether individuals were compensated for providing gametes for clinical purposes. The reasoning supporting their position is as follows:

- Established State Law Requires Donors to be Notified of the Option to Donate Embryos for Research

  Under existing state law IVF physicians have a legal obligation to offer several dispositional options (including donation to research) to all fertility patients. This practice is required regardless of whether the patients used a third-party gamete donor or not. The citation is CA Health & Safety Code sec. 125315 (partial excerpts below). Prop. 71 explicitly states that Sec. 125315 applies to CIRM-funded research (Sec. 125290.35(a)).

  H&S 125315 separately prohibits a person from buying or selling embryonic tissue "for research purposes." But payment to a gamete donor for fertility reasons is legal and routine in the state and is not a purchase/sale for research purposes.

  Given that NIH also does not appear to be distinguishing between IVF embryos created by gamete donors and other IVF embryos, it may be an appropriate time to re-look at this California law, expressly pulled in by Prop. 71. This point was made in connection with CIRM's currently proposed revision about grandfathering paid gamete donors only until Aug. 13, 2008.

  125315. *(a) A physician and surgeon or other health care provider delivering fertility treatment* ***shall*** *provide his or her patient with timely, relevant, and appropriate information to allow the individual to make an informed and voluntary choice regarding the disposition of any human embryos remaining following the fertility treatment. The failure to provide to a patient this information constitutes unprofessional conduct within the meaning of Chapter 5 (commencing with Section 2000) of Division 2 of the Business and Professions Code.*
  (b) Any individual to whom information is provided pursuant to subdivision (a) ***shall be presented*** *with the option of storing any unused embryos, donating them to another individual, discarding the embryos, or* ***donating the remaining embryos for research***. *When providing fertility treatment, a physician and surgeon or other health care provider shall provide a form to the male and female partner, or the individual without a partner, as applicable, that sets forth advanced written directives regarding the disposition of embryos.*

- Established State Stem Cell Law Expressly Exempts Embryos Created for Fertility Treatment from Regulation

  Senate Bill 1260's (2006) intent is to protect research subjects providing oocytes for research. The legislation expressly exempts oocytes donated for fertility treatment.

  The purpose of this act is to create protections for research subjects and it should not be construed to affect any other form of medical care.

- CIRM is Inconsistent with State and National Policy

  Other U.S. states incorporating the NAS Guidelines and the National Institutes of Health Guidelines do not restrict the use of embryos for research provided they were created for reproductive purposes. The NIH Final Stem Cell Guidelines acknowledge and respect the informed consent from "'the individual(s) who sought reproductive treatment' because this/these individual(s) is/are responsible for the creation of the embryo(s) and, therefore, its/their disposition". It seems unusual and counter to the intent of Proposition 71 that CIRM would promulgate regulations that are more restrictive than federal policy without adequate ethical or legal justification.

STANFORD UNIVERSITY
Research Compliance Office
1215 Welch Road, Modular A
Stanford, CA 94305-5401

June 30, 2009

Geoff Lomax, DrPH
Senior Officer for Medical & Ethical Standards
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

Re: Comments in Response to CIRM's Proposed Amendments to Medical and Ethical Standards (MES) Regulations

Dear Dr. Lomax:

Thank you for the opportunity to respond to CIRM's Proposed Regulation Amendments regarding SCRO Committee Review and Special Considerations for CIRM-Funded Derivation which were posted for comment on May 22, 2009. We commend CIRM for its consideration of the need to support iPS research using somatic cells and to tailor oversight requirements to the nature of that research. We have a limited number of comments and recommendations for consideration by CIRM.

Stanford endorses the clarification that the SCRO Committee requires notification for in vitro iPS research. We believe a process could be devised relatively easily that would be similar to the IRB's procedure for the certification of exemption for human subject research.

Stanford also generally concurs with the amendment to Section 100090(a)(1), which allows for the use of embryos created from gametes from which the donors were paid solely for reproductive purposes (IVF). However, we would encourage CIRM not to limit the use of these embryos to those created on or before August 13, 2008. Because the third party's private agreement to serve as a gamete donor for fertility purposes is entirely separate from any decision to donate extra embryos for research, we do not believe that there is any payment for a research donation, and hence no reason to assign an arbitrary date to this section.

Moreover, under state law, IVF physicians are legally required to offer all dispositional options, including research donation, to all fertility patients, not just those who are able to use their own gametes. It seems unfortunate and contrary to the intent of Proposition 71 if patients exercise their state-supported choice to donate embryos to research, but certain patients' embryos are effectively categorically excluded from CIRM-funded research. The NIH's draft guidelines have no such categorical exclusion.

Again, thank you for the opportunity to respond to CIRM's proposed amendments. If you have any questions, please contact me or Celia Molvin (celia.molvin@stanford.edu; 650-723-0082).

Respectfully submitted,

Alice Haskett

Alice Haskett, HRPP Associate Director
(on behalf of the Stanford University SCRO Panel)

Subject: Re: Regulatory Revision (Section 100070)
Date: Sunday, July 5, 2009 12:55 PM
From: Sid Golub <sgolub@uci.edu>
To: CIRM User <glomax@cirm.ca.gov>

I am writing regarding proposed revision to Section 100070, Subdivision (d). This proposed revision was discussed at a recent meeting of the UC Irvine Human Stem Cell Research Oversight Committee. Concern was expressed about the use of the term "notification" for review of projects using induced pluripotent stem cells. The concern is simply that our SCRO has no formal procedure termed "notification" nor are we aware of such a procedure at other comparable committees. We are concerned that investigators may misinterpret this section to indicate that notification procedures are in place and available when they are not.

We suggest a wording change to indicate that existing review procedures such as full committee, expedited or administrative review may be used by the responsible institutional oversight committee, depending on its procedures and the content of the proposed study.

Thank you for the opportunity to comment.

Sidney Golub

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Sidney H. Golub, Ph.D.
Chair, UCI Human Stem Cell Research Oversight Committee
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email: sgolub@uci.edu

Subject: RE: Regulatory Revision
Date: Monday, July 6, 2009 5:56 PM
From: Steve Peckman <SPeckman@mednet.ucla.edu>
To: CIRM User <glomax@cirm.ca.gov>
Cc: Marie Csete <mcsete@cirm.ca.gov>, Amy Cheung <acheung@cirm.ca.gov>

Dear Dr. Lomax,

Please accept my comments regarding the proposed regulatory change.

1. Section 100090: CIRM should authorize use of embryos created for reproductive purposes regardless of the date of the creation of such embryos provided that the individual(s) responsible for the creation of the embryo(s) and, therefore, the disposition of the embryos, provide adequate informed consent for the research donation of the embryos.

As noted by Dr. Sidney Golub (UCI) in a separately submitted comment, the revision is neither necessary, useful, nor practical since the existing regulations prevent excessive payment for research donations of human biological material. CIRM has wisely clarified that it should not interfere with normal clinical practice where gametes for reproductive purposes are often obtained from compensated donations. Clearly, we should not be suggesting that there is anything less ethical or moral about embryos for reproductive purposes where the sperm or oocyte donor was compensated.
The guiding principle should remain the prevention of undue influence of gamete or embryo donors to participate in research. That being said, embryos made for clinical IVF purposes with the assistance of paid donors is a separate clinical issue from payment for research oocytes. The clinical IVF donor is not being paid for research but rather to assist in clinical reproduction. If we can agree on that principle then all restrictive dates are arbitrary and not relevant to the issue of payment for the research donation and possible undue influence on decision making and voluntary

informed consent of gamete providers.

Furthermore, the proposed regulation would be inconsistent with existing CA law (H&S Code 125315).

Therefore, the CIRM regulation should indicate:

For embryos created for clinical purposes, payments to gamete donors in excess of "permissible expenses" are exempt from restriction provided the embryo was originally created for reproductive purposes.

2. 100090(a)(2): The NIH Final Stem Cell Guidelines acknowledge and respect the informed consent from "'the individual(s) who sought reproductive treatment' because this/these individual(s) is/ are responsible for the creation of the embryo(s) and, therefore, its/ their disposition" rather than any third party gamete donors. Consistent with the NIH guidelines, 100090(a)(2) should be omitted.

3. Section 100070(d): The term "notification" for review of projects using induced pluripotent stem cells is unclear and inconsistent with formal practice of similar committees in the regulatory field such as IRB and IACUC. As also noted by Dr. Golub in his submitted comments, investigators may misinterpret this section to indicate that notification procedures are in place and available when they are not. Therefore, I suggest a modification of the proposed rule to indicate that existing review procedures such as full committee, expedited or administrative review may be used by the responsible institutional oversight committee, depending on its procedures and the content of the proposed study.

Thank you for the opportunity to provide comments on the proposed regulations.

Sincerely,

Subject: Recommended wording change
Date: Monday, July 6, 2009 9:24 AM
From: Michael Kalichman <kalichman@ucsd.edu>
Reply-To: <kalichman@ucsd.edu>
To: CIRM User <glomax@cirm.ca.gov>

I am writing to suggest a wording change in the proposed amendments for the CIRM MES section 100070.

Section 100070 (d) provides a useful flagging of research that may not require the same level of scrutiny as other research. However, if I understand the intent of this paragraph, it would be much clearer if re-written along the following lines:

> (d) CIRM-funded research requiring written notification to the designated SCRO committee includes: (i) purely in vitro research with covered stem cell lines; (ii) attempted derivation of covered stem cell lines by reprogramming of human somatic cells; and (iii) assays to evaluate pluripotency in non-human animals. However, the introduction of derived covered stem cell lines in non-human animals shall be reviewed in accordance with subdivision (e) of this regulation.

Please note that this suggestion for wording does not resolve the question raised by others about the potential for misunderstanding of the meaning of "written notification."

Michael Kalichman
Director, UC San Diego Research Ethics Program
Co-Chair, UC San Diego ESCRO Committee
kalichman@ucsd.edu
858-822-2027

and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute on Alcohol Abuse and Alcoholism. Special Emphasis Panel Alcohol Pharmacotherapy and the Treatment and Prevention of HIV/AIDS. (RFA AA 09 007/008) and Other AIDS Related Research.

Date: August 6, 2009.

Time: 8 a.m. to 11 a.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 5635 Fishers Lane, Bethesda, MD 20892. (Telephone Conference Call).

Contact Person: Katrina L Foster, PhD, Scientific Review Officer, National Inst on Alcohol Abuse & Alcoholism, National Institutes of Health, 5635 Fishers Lane, Rm. 2019, Rockville, MD 20852. 301–443–4032. *katrina@mail.nih.gov*.

(Catalogue of Federal Domestic Assistance Program Nos. 93.271, Alcohol Research Career Development Awards for Scientists and Clinicians; 93.272, Alcohol National Research Service Awards for Research Training; 93.273, Alcohol Research Programs; 93.891, Alcohol Research Center Grants; 93.701, ARRA Related Biomedical Research and Research Support Awards, National Institutes of Health, HHS)

Dated: June 29, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–15847 Filed 7–6–09; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of General Medical Sciences; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel Minority Biomedical Research Support.

Date: July 19–20, 2009.

Time: 7 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Hyatt Regency Bethesda, One Bethesda Metro Center, Bethesda, MD 20814.

Contact Person: Margaret J. Weidman, PhD, Scientific Review Officer, Office of Scientific Review, National Institute of General Medical Sciences, National Institutes of Health, 45 Center Drive, Room 3AN18B, Bethesda, MD 20892. 301–594–3663. *weidmanma@nigms.nih.gov.*

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel MBRS Score.

Date: July 20–21, 2009.

Time: 8 a.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Hyatt Regency Bethesda, One Bethesda Metro Center, Bethesda, MD 20814.

Contact Person: Lisa Dunbar, PhD, Scientific Review Officer, Office of Scientific Review, National Institute of General Medical Sciences, National Institutes of Health, 45 Center Drive, Room 3AN12, Bethesda, MD 20892. 301–594–2849. *dunbarl@mail.nih.gov.*

Name of Committee: National Institute of General Medical Sciences. Special Emphasis Panel New Innovator Awards.

Date: July 21, 2009.

Time: 1 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Natcher Building, 45 Center Drive, Bethesda, MD 20892. (Telephone Conference Call).

Contact Person: Richard T. Okita, PhD, Program Director, Pharmacological and Physiological Sciences Branch, National Institute of General Medical Sciences, National Institutes of Health, Natcher Building, Room 2A5–49, Bethesda, MD 20892. 301–594–4469. *okitar@nigms.nih.gov*.

(Catalogue of Federal Domestic Assistance Program Nos. 93.375, Minority Biomedical Research Support; 93.821, Cell Biology and Biophysics Research; 93.859, Pharmacology, Physiology, and Biological Chemistry Research; 93.862, Genetics and Developmental Biology Research; 93.88, Minority Access to Research Careers; 93.96, Special Minority Initiatives, National Institutes of Health, HHS)

Dated: June 29, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–15846 Filed 7–6–09; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Human Stem Cell Research

SUMMARY: The National Institutes of Health (NIH) is hereby publishing final ''National Institutes of Health Guidelines for Human Stem Cell Research'' (Guidelines).

On March 9, 2009, President Barack H. Obama issued Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells.* The Executive Order states that the Secretary of Health and Human Services, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell (hESC) research, to the extent permitted by law.

These Guidelines implement Executive Order 13505, as it pertains to extramural NIH-funded stem cell research, establish policy and procedures under which the NIH will fund such research, and helps ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. Internal NIH policies and procedures, consistent with Executive Order 13505 and these Guidelines, will govern the conduct of intramural NIH stem cell research.

DATES: *Effective Date:* These Guidelines are effective on July 7, 2009.

Summary of Public Comments on Draft Guidelines: On April 23, 2009 the NIH published draft Guidelines for research involving hESCs in the **Federal Register** for public comment, 74 FR 18578 (April 23, 2009). The comment period ended on May 26, 2009.

The NIH received approximately 49,000 comments from patient advocacy groups, scientists and scientific societies, academic institutions, medical organizations, religious organizations, and private citizens. The NIH also received comments from members of Congress. This Notice presents the final Guidelines together with the NIH response to public comments that addressed provisions of the Guidelines.

Title of the Guidelines, Terminology, and Background

Respondents felt the title of the NIH draft guidelines was misleading, in that it is entitled ''National Institutes of Health Guidelines for Human Stem Cell Research,'' yet addresses only one type of human stem cell. The NIH notes that although the Guidelines pertain primarily to the donation of embryos for the derivation of hESCs, one Section also applies to certain uses of both hESCs and human induced pluripotent stem cells. Also, the Guidelines discuss applicable regulatory standards when research involving human adult stem cells or induced pluripotent stem cells constitutes human subject research.

Therefore, the title of the Guidelines was not changed.

Respondents also disagreed with the definition of human embryonic stem cells in the draft Guidelines, and asked that the NIH define them as originating from the inner cell mass of the blastocyst. The NIH modified the definition to say that human embryonic stem cells ''are cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.''

Financial Gain

Respondents expressed concern that derivers of stem cells might profit from the development of hESCs. Others noted that because the stem cells eligible for use in research using NIH funding under the draft Guidelines are those cells that are subject to existing patents, there will be insufficient competition in the licensing of such rights. These respondents suggested that this could inhibit research, as well as increase the cost of any future clinical benefits. The Guidelines do not address the distribution of stem cell research material. It is, however, the NIH's expectation that stem cell research materials developed with NIH funds, as well as associated intellectual property and data, will be distributed in accordance with the NIH's existing policies and guidance, including ''Sharing Biomedical Research Resources, Principles and Guidelines for Recipients of NIH Grants and Contracts'' and ''Best Practices for the Licensing of Genomic Inventions.'' *http://ott.od.nih.gov/policy/Reports.html* Even where such policies are not directly applicable, the NIH encourages others to refrain from imposing on the transfer of research tools, such as stem cells, any conditions that hinder further biomedical research. In addition, the Guidelines were revised to state that there should be documentation that ''no payments, cash or in kind, were offered for the donated embryos.''

Respondents were concerned that donor(s) be clearly ''apprised up front by any researchers that financial gain may come from the donation and that the donor(s) should know up front if he/she will share in the financial gain.'' The Guidelines address this concern by asking that donor(s) was/were informed during the consent process that the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the stem cells, such as who may be the recipients of cell transplants. The Guidelines also require that the donor(s) receive(s) information that the research was not intended to provide direct medical benefit to the donor(s); that the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development.

IRB Review Under the Common Rule

Respondents suggested that the current regulatory structure of IRB review under the Common Rule (45 CFR Part 46, Subpart A) addresses the core ethical principles needed for appropriate oversight of hESC derivation. They noted that IRB review includes a full review of the informed consent process, as well as a determination of whether individuals were coerced to participate in the research and whether any undue inducements were offered to secure their participation. These respondents urged the NIH to replace the specific standards to assure voluntary and informed consent in the draft Guidelines with a requirement that hESC research be reviewed and approved by an IRB, in conformance with 45 CFR Part 46, Subpart A, as a prerequisite to NIH funding. Respondents also requested that the NIH create a registry of eligible hESC lines to avoid burdensome and repetitive assurances from multiple funding applicants. The NIH agrees that the IRB system of review under the Common Rule provides a comprehensive framework for the review of the donation of identifiable human biological materials for research. However, in the last several years, guidelines on hESC research have been issued by a number of different organizations and governments, and different practices have arisen around the country and worldwide, resulting in a patchwork of standards. The NIH concluded that employing the IRB review system for the donation of embryos would not ameliorate stated concerns about variations in standards for hESC research and would preclude the establishment of an NIH registry of hESCs eligible for NIH funding, because there would be no NIH approval of particular hESCs. To this end and in response to comments, these Guidelines articulate policies and procedures that will allow the NIH to create a Registry. These Guidelines also provide scientists who apply for NIH funding with a specific set of standards reflecting currently recognized ethical principles and practices specific to embryo donation that took place on or after the issuance of the Guidelines, while also establishing procedures for the review of donations that took place before the effective date of the Guidelines.

Federal Funding Eligibility of Human Pluripotent Cells From Other Sources

Respondents suggested that the allowable sources of hESCs potentially available for Federal funding be expanded to include hESC lines from embryos created expressly for research purposes, and lines created, or pluripotent cells derived, following parthenogenesis or somatic cell nuclear transfer (SCNT). The Guidelines allow for funding of research using hESCs derived from embryos created using in vitro fertilization (IVF) for reproductive purposes and no longer needed for these purposes, assuming the research has scientific merit and the embryos were donated after proper informed consent was obtained from the donor(s). The Guidelines reflect the broad public support for Federal funding of research using hESCs created from such embryos based on wide and diverse debate on the topic in Congress and elsewhere. The use of additional sources of human pluripotent stem cells proposed by the respondents involve complex ethical and scientific issues on which a similar consensus has not emerged. For example, the embryo-like entities created by parthenogenesis and SCNT require women to donate oocytes, a procedure that has health and ethical implications, including the health risk to the donor from the course of hormonal treatments needed to induce oocyte production.

Respondents noted that many embryos undergo Pre-implantation Genetic Diagnosis (PGD). This may result in the identification of chromosomal abnormalities that would make the embryos medically unsuitable for clinical use. In addition, the IVF process may also produce embryos that are not transferred into the uterus of a woman because they are determined to be not appropriate for clinical use. Respondents suggested that hESCs derived from such embryos may be extremely valuable for scientific study, and should be considered embryos that were created for reproductive purposes and were no longer needed for this purpose. The NIH agrees with these comments. As in the draft, the final Guidelines allow for the donation of embryos that have undergone PGD.

Donation and Informed Consent

Respondents commented in numerous ways that the draft Guidelines are too procedurally proscriptive in articulating the elements of appropriate informed consent documentation. This over-

reliance on the specific details and format of the informed consent document, respondents argued, coupled with the retroactive application of the Guidelines to embryos already donated for research, would result in a framework that fails to appreciate the full range of factors contributing to the complexity of the informed consent process. For example, respondents pointed to several factors that were precluded from consideration by the proposed Guidelines, such as contextual evidence of the consent process, other established governmental frameworks (representing local and community influences), and the changing standards for informed consent in this area of research over time. Respondents argued that the Guidelines should be revised to allow for a fuller array of factors to be considered in determining whether the underlying ethical principle of voluntary informed consent had been met. In addition to these general issues, many respondents made the specific recommendation that all hESCs derived before the final Guidelines were issued be automatically eligible for Federal funding without further review, especially those eligible under prior Presidential policy, i.e., ''grandfathered.'' The final Guidelines seek to implement the Executive Order by issuing clear guidance to assist this field of science to advance and reach its full potential while ensuring adherence to strict ethical standards. To this end, the NIH is establishing a set of conditions that will maximize ethical oversight, while ensuring that the greatest number of ethically derived hESCs are eligible for Federal funding. Specifically, for embryos donated in the U.S. on or after the effective date of the Guidelines, the only way to establish eligibility will be to either use hESCs listed on the NIH Registry, or demonstrate compliance with the specific procedural requirements of the Guidelines by submitting an assurance with supporting information for administrative review by the NIH. Thus, for future embryo donations in the United States, the Guidelines articulate one set of procedural requirements. This responds to concerns regarding the patchwork of requirements and guidelines that currently exist.

However, the NIH is also cognizant that in the more than a decade between the discovery of hESCs and today, many lines were derived consistent with ethical standards and/or guidelines developed by various states, countries, and other entities such as the International Society for Stem Cell Research (ISSCR) and the National Academy of Sciences (NAS). These various policies have many common features, rely on a consistent ethical base, and require an informed consent process, but they differ in details of implementation. For example, some require specific wording in a written informed consent document, while others do not. It is important to recognize that the principles of ethical research, *e.g.*, voluntary informed consent to participation, have not varied in this time period, but the requirements for implementation and procedural safeguards employed to demonstrate compliance have evolved. In response to these concerns, the Guidelines state that applicant institutions wishing to use hESCs derived from embryos donated prior to the effective date of the Guidelines may either comply with Section II (A) of the Guidelines or undergo review by a Working Group of the Advisory Committee to the Director (ACD). The ACD, which is a chartered Federal Advisory Committee Act (FACA) committee, will advise NIH on whether the core ethical principles and procedures used in the process for obtaining informed consent for the donation of the embryo were such that the cell line should be eligible for NIH funding. This Working Group will not undertake a *de novo* evaluation of ethical standards, but will consider the materials submitted in light of the principles and points to consider in the Guidelines, as well as 45 CFR Part 46 Subpart A. Rather than ''grandfathering,'' ACD Working Group review will enable pre-existing hESCs derived in a responsible manner to be eligible for use in NIH funded research.

In addition, for embryos donated outside the United States prior to the effective date of these Guidelines, applicants may comply with either Section II (A) or (B). For embryos donated outside of the United States on or after the effective date of the Guidelines, applicants seeking to determine eligibility for NIH research funding may submit an assurance that the hESCs fully comply with Section II (A) or submit an assurance along with supporting information, that the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent to those provided by Section II (A) of these Guidelines. These materials will be reviewed by the NIH ACD Working Group, which will recommend to the ACD whether such equivalence exists. Final decisions will be made by the NIH Director. This special consideration for embryos donated outside the United States is needed because donation of embryos in foreign countries is governed by the laws and policies of the respective governments of those nations. Although such donations may be responsibly conducted, such governments may not or cannot change their national donation requirements to precisely comply with the NIH Guidelines. The NIH believes it is reasonable to provide a means for reviewing such hESCs because ethically derived foreign hESCs constitute an important scientific asset for the U.S.

Respondents expressed concern that it might be difficult in some cases to provide assurance that there was a ''clear separation'' between the prospective donor(s)' decision to create embryos for reproductive purposes and the donor(s)' decision to donate the embryos for research purposes. These respondents noted that policies vary at IVF clinics, especially with respect to the degree to which connections with researchers exist. Respondents noted that a particular clinic's role may be limited to the provision of contact information for researchers. A clinic that does not have any particular connection with research would not necessarily have in place a written policy articulating the separation contemplated by the Guidelines. Other respondents noted that embryos that are determined not to be suitable for medical purposes, either because of genetic defects or other concerns, may be donated prior to being frozen. In these cases, it is possible that the informed consent process for the donation might be concurrent with the consent process for IVF treatment. Respondents also noted that the initial consent for IVF may contain a general authorization for donating embryos in excess of clinical need, even though a more detailed consent is provided at the actual time of donation. The NIH notes that the Guidelines specifically state that consent should have been obtained at the time of donation, even if the potential donor(s) had given prior indication of a general intent to donate embryos in excess of clinical need for the purposes of research. Accordingly, a general authorization for research donation when consenting for reproductive treatment would comply with the Guidelines, so long as specific consent for the donation is obtained at the time of donation. In response to comments regarding documentation necessary to establish a separation between clinical and research decisions, the NIH has changed the language of the Guidelines to permit applicant institutions to submit consent forms,

written policies or other documentation to demonstrate compliance with the provisions of the Guidelines. This change should provide the flexibility to accommodate a range of practices, while adhering to the ethical principles intended.

Some respondents want to require that the IVF physician and the hESC researcher should be different individuals, to prevent conflict of interest. Others say they should be the same person, because people in both roles need to have detailed knowledge of both areas (IVF treatment and hESC research). There is also a concern that the IVF doctor will create extra embryos if he/she is also the researcher. As a general matter, the NIH believes that the doctor and the researcher seeking donation should be different individuals. However, this is not always possible, nor is it required, in the NIH's view, for ethical donation.

Some respondents want explicit language (in the Guidelines and/or in the consent) stating that the embryo will be destroyed when the inner cell mass is removed. In the process of developing guidelines, the NIH reviewed a variety of consent forms that have been used in responsible derivations. Several had extensive descriptions of the process and the research to be done, going well beyond the minimum expected, yet they did not use these exact words. Given the wide variety and diversity of forms, as well as the various policy, statutory and regulatory obligations individual institutions face, the NIH declines to provide exact wording for consent forms, and instead endorses a robust informed consent process where all necessary details are explained and understood in an ongoing, trusting relationship between the clinic and the donor(s).

Respondents asked for clarification regarding the people who must give informed consent for the donation of embryos for research. Some commenters suggested that NIH should require consent from the gamete donors, in cases where those individuals may be different than the individuals seeking reproductive treatment. The NIH requests consent from ''the individual(s) who sought reproductive treatment'' because this/these individual(s) is/are responsible for the creation of the embryo(s) and, therefore, its/their disposition. With regard to gamete donation, the risks are associated with privacy and, as such, are governed by requirements of the Common Rule, where applicable.

Respondents also requested clarification on the statement in the draft Guidelines noting that ''although human embryonic stem cells are derived from embryos, such stem cells are not themselves human embryos.'' For the purpose of NIH funding, an embryo is defined by Section 509, Omnibus Appropriations Act, 2009, Public Law 111–8, 3/11/09, otherwise known as the Dickey Amendment, as any organism not protected as a human subject under 45 CFR Part 46 that is derived by fertilization, parthenogenesis, cloning or any other means from one or more human gametes or human diploid cells. Since 1999, the Department of Health and Human Services (HHS) has consistently interpreted this provision as not applicable to research using hESCs, because hESCs are not embryos as defined by Section 509. This long-standing interpretation has been left unchanged by Congress, which has annually reenacted the Dickey Amendment with full knowledge that HHS has been funding hESC research since 2001. These guidelines therefore recognize the distinction, accepted by Congress, between the derivation of stem cells from an embryo that results in the embryo's destruction, for which Federal funding is prohibited, and research involving hESCs that does not involve an embryo nor result in an embryo's destruction, for which Federal funding is permitted.

Some respondents wanted to ensure that potential donor(s) are either required to put their ''extra'' embryos up for adoption before donating them for research, or are at least offered this option. The Guidelines require that all the options available in the health care facility where treatment was sought pertaining to the use of embryos no longer needed for reproductive purposes were explained to the potential donor(s). Since not all IVF clinics offer the same services, the healthcare facility is only required to explain the options available to the donor(s) at that particular facility.

Commenters asked that donor(s) be made aware of the point at which their donation decision becomes irrevocable. This is necessary because if the embryo is de-identified, it may be impossible to stop its use beyond a certain point. The NIH agrees with these comments and revised the Guidelines to require that donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

Medical Benefits of Donation

Regarding medical benefit, respondents were concerned that the language of the Guidelines should not somehow eliminate a donor's chances of benefitting from results of stem cell research. Respondents noted that although hESCs are not currently being used clinically, it is possible that in the future such cells might be used for the medical benefit of the person donating them. The Guidelines are meant to preclude individuals from donating embryos strictly for use in treating themselves only or from donating but identifying individuals or groups they do or do not want to potentially benefit from medical intervention using their donated cells. While treatment with hESCs is one of the goals of this research, in practice, years of experimental work must still be done before such treatment might become routinely available. The Guidelines are designed to make it clear that immediate medical benefit from a donation is highly unlikely at this time. Importantly, it is critical to note that the Guidelines in no way disqualify a donor from benefitting from the medical outcomes of stem cell research and treatments that may be developed in the future.

Monitoring and Enforcement Actions

Respondents have expressed concern about the monitoring of funded research and the invocation of possible penalties for researchers who do not follow the Guidelines. A grantee's failure to comply with the terms and conditions of award, including confirmed instances of research misconduct, may cause the NIH to take one or more enforcement actions, depending on the severity and duration of the non-compliance. For example, the following actions may be taken by the NIH when there is a failure to comply with the terms and conditions of any award: (1) Under 45 CFR 74.14, the NIH can impose special conditions on an award, including but not limited to increased oversight/monitoring/reporting requirements for an institution, project, or investigator; and (2) under 45 CFR 74.62 the NIH may impose enforcement actions, including but not limited to withholding funds pending correction of the problem, disallowing all or part of the costs of the activity that was not in compliance, withholding further awards for the project, or suspending or terminating all or part of the funding for the project. Individuals and institutions may be debarred from eligibility for all Federal financial assistance and contracts under 2 CFR part 376 and 48

CFR subpart 9.4, respectively. The NIH will undertake all enforcement actions in accordance with applicable statutes, regulations, and policies.

National Institutes of Health Guidelines for Research Using Human Stem Cells

I. Scope of the Guidelines

These Guidelines apply to the expenditure of National Institutes of Health (NIH) funds for research using human embryonic stem cells (hESCs) and certain uses of induced pluripotent stem cells (See Section IV). The Guidelines implement Executive Order 13505.

Long-standing HHS regulations for Protection of Human Subjects, 45 CFR part 46, subpart A establish safeguards for individuals who are the sources of many human tissues used in research, including non-embryonic human adult stem cells and human induced pluripotent stem cells. When research involving human adult stem cells or induced pluripotent stem cells constitutes human subject research, Institutional Review Board review may be required and informed consent may need to be obtained per the requirements detailed in 45 CFR part 46, subpart A. Applicants should consult *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm*.

It is also important to note that the HHS regulation, *Protection of Human Subjects*, 45 CFR part 46, subpart A, may apply to certain research using hESCs. This regulation applies, among other things, to research involving individually identifiable private information about a living individual, 45 CFR 46.102(f). The HHS Office for Human Research Protections (OHRP) considers biological material, such as cells derived from human embryos, to be individually identifiable when they can be linked to specific living individuals by the investigators either directly or indirectly through coding systems. Thus, in certain circumstances, IRB review may be required, in addition to compliance with these Guidelines. Applicant institutions are urged to consult OHRP guidances at *http://www.hhs.gov/ohrp/policy/index.html#topics*.

To ensure that the greatest number of responsibly derived hESCs are eligible for research using NIH funding, these Guidelines are divided into several sections, which apply specifically to embryos donated in the U.S. and foreign countries, both before and on or after the effective date of these Guidelines. Section II (A) and (B) describe the conditions and review processes for determining hESC eligibility for NIH funds. Further information on these review processes may be found at *http://www.NIH.gov*. Sections IV and V describe research that is not eligible for NIH funding.

These guidelines are based on the following principles:

1. Responsible research with hESCs has the potential to improve our understanding of human health and illness and discover new ways to prevent and/or treat illness.

2. Individuals donating embryos for research purposes should do so freely, with voluntary and informed consent.

As directed by Executive Order 13505, the NIH shall review and update these Guidelines periodically, as appropriate.

II. Eligibility of Human Embryonic Stem Cells for Research With NIH Funding

For the purpose of these Guidelines, ''human embryonic stem cells (hESCs)'' are cells that are derived from the inner cell mass of blastocyst stage human embryos, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although hESCs are derived from embryos, such stem cells are not themselves human embryos. All of the processes and procedures for review of the eligibility of hESCs will be centralized at the NIH as follows:

A. Applicant institutions proposing research using hESCs derived from embryos donated in the U.S. on or after the effective date of these Guidelines may use hESCs that are posted on the new NIH Registry or they may establish eligibility for NIH funding by submitting an assurance of compliance with Section II (A) of the Guidelines, along with supporting information demonstrating compliance for administrative review by the NIH. For the purposes of this Section II (A), hESCs should have been derived from human embryos:

1. That were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose;

2. That were donated by individuals who sought reproductive treatment (hereafter referred to as ''donor(s)'') and who gave voluntary written consent for the human embryos to be used for research purposes; and

3. For which all of the following can be assured and documentation provided, such as consent forms, written policies, or other documentation, provided:

a. All options available in the health care facility where treatment was sought pertaining to the embryos no longer needed for reproductive purposes were explained to the individual(s) who sought reproductive treatment.

b. No payments, cash or in kind, were offered for the donated embryos.

c. Policies and/or procedures were in place at the health care facility where the embryos were donated that neither consenting nor refusing to donate embryos for research would affect the quality of care provided to potential donor(s).

d. There was a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes. Specifically:

i. Decisions related to the creation of human embryos for reproductive purposes should have been made free from the influence of researchers proposing to derive or utilize hESCs in research. The attending physician responsible for reproductive clinical care and the researcher deriving and/or proposing to utilize hESCs should not have been the same person unless separation was not practicable.

ii. At the time of donation, consent for that donation should have been obtained from the individual(s) who had sought reproductive treatment. That is, even if potential donor(s) had given prior indication of their intent to donate to research any embryos that remained after reproductive treatment, consent for the donation for research purposes should have been given at the time of the donation.

iii. Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.

e. During the consent process, the donor(s) were informed of the following:

i. That the embryos would be used to derive hESCs for research;

ii. What would happen to the embryos in the derivation of hESCs for research;

iii. That hESCs derived from the embryos might be kept for many years;

iv. That the donation was made without any restriction or direction regarding the individual(s) who may receive medical benefit from the use of the hESCs, such as who may be the recipients of cell transplants;

v. That the research was not intended to provide direct medical benefit to the donor(s);

vi. That the results of research using the hESCs may have commercial potential, and that the donor(s) would not receive financial or any other benefits from any such commercial development;

vii. Whether information that could identify the donor(s) would be available to researchers.

B. Applicant institutions proposing research using hESCs derived from embryos donated in the U.S. before the effective date of these Guidelines may use hESCs that are posted on the new NIH Registry or they may establish eligibility for NIH funding in one of two ways:

1. By complying with Section II (A) of the Guidelines; or

2. By submitting materials to a Working Group of the Advisory Committee to the Director (ACD), which will make recommendations regarding eligibility for NIH funding to its parent group, the ACD. The ACD will make recommendations to the NIH Director, who will make final decisions about eligibility for NIH funding.

The materials submitted must demonstrate that the hESCs were derived from human embryos: (1) That were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose; and (2) that were donated by donor(s) who gave voluntary written consent for the human embryos to be used for research purposes.

The Working Group will review submitted materials, *e.g.*, consent forms, written policies or other documentation, taking into account the principles articulated in Section II (A), 45 CFR part 46, subpart A, and the following additional points to consider. That is, during the informed consent process, including written or oral communications, whether the donor(s) were: (1) Informed of other available options pertaining to the use of the embryos; (2) offered any inducements for the donation of the embryos; and (3) informed about what would happen to the embryos after the donation for research.

C. For embryos donated outside the United States before the effective date of these Guidelines, applicants may comply with either Section II (A) or (B). For embryos donated outside of the United States on or after the effective date of the Guidelines, applicants seeking to determine eligibility for NIH research funding may submit an assurance that the hESCs fully comply with Section II (A) or submit an assurance along with supporting information, that the alternative procedural standards of the foreign country where the embryo was donated provide protections at least equivalent to those provided by Section II (A) of these Guidelines. These materials will be reviewed by the NIH ACD Working Group, which will recommend to the ACD whether such equivalence exists. Final decisions will be made by the NIH Director.

D. NIH will establish a new Registry listing hESCs eligible for use in NIH funded research. All hESCs that have been reviewed and deemed eligible by the NIH in accordance with these Guidelines will be posted on the new NIH Registry.

III. Use of NIH Funds

Prior to the use of NIH funds, funding recipients should provide assurances, when endorsing applications and progress reports submitted to NIH for projects using hESCs, that the hESCs are listed on the NIH registry.

IV. Research Using hESCs and/or Human Induced Pluripotent Stem Cells That, Although the Cells May Come From Eligible Sources, Is Nevertheless Ineligible for NIH Funding

This section governs research using hESCs and human induced pluripotent stem cells, *i.e.*, human cells that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers. Although the cells may come from eligible sources, the following uses of these cells are nevertheless ineligible for NIH funding, as follows:

A. Research in which hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells are introduced into non-human primate blastocysts.

B. Research involving the breeding of animals where the introduction of hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells may contribute to the germ line.

V. Other Research Not Eligible for NIH Funding

A. NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research (Section 509, Omnibus Appropriations Act, 2009, Pub. L. 111–8, 3/11/09), otherwise known as the Dickey Amendment.

B. Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.

Dated: June 30, 2009.

Raynard S. Kington,

Acting Director, NIH.

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BILLING CODE 4140–01–P

DEPARTMENT OF HOMELAND SECURITY

U.S. Customs and Border Protection

Agency Information Collection Activities: Importer's ID Input Record

AGENCY: U.S. Customs and Border Protection, Department of Homeland Security.

ACTION: 30-Day notice and request for comments; Extension of an existing information collection: 1651–0064.

SUMMARY: U.S. Customs and Border Protection (CBP) of the Department of Homeland Security has submitted the following information collection request to the Office of Management and Budget (OMB) for review and approval in accordance with the Paperwork Reduction Act: Importer's ID Input Record (Form 5106). This is a proposed extension of an information collection that was previously approved. CBP is proposing that this information collection be extended with no change to the burden hours. This document is published to obtain comments from the public and affected agencies. This proposed information collection was previously published in the **Federal Register** (74 FR 16226) on April 9, 2009, allowing for a 60-day comment period. This notice allows for an additional 30 days for public comments. This process is conducted in accordance with 5 CFR 1320.10.

DATES: Written comments should be received on or before August 6, 2009.

ADDRESSES: Interested persons are invited to submit written comments on the proposed information collection to the Office of Information and Regulatory Affairs, Office of Management and Budget. Comments should be addressed to the OMB Desk Officer for Customs and Border Protection, Department of Homeland Security, and sent via electronic mail to *oira_submission@omb.eop.gov* or faxed to (202) 395–5806.

SUPPLEMENTARY INFORMATION: U.S. Customs and Border Protection (CBP) encourages the general public and affected Federal agencies to submit written comments and suggestions on