Study Group Working Notes #1: Oversight Standards for Non-CIRM Funded Cell Lines

Study Group: Interstate & International Standards

Background: The Standards Working Group (SWG) believes that all cell lines used in CIRM funded research should be ethically derived. For cell lines derived with CIRM funding, adherence to the SWG's standards for derivation will be a condition for funding. There are, however, existing cell lines and future cell lines that will be derived from non-CIRM funded activities. These cell lines are desirable for use in CIRM funded research. The SWG seeks assurance that there is adequate oversight in other states and countries.

Options:

Existing cell lines, cells and cell-derived test articles: There is a general consensus that NIH approved cell lines and cell lines obtained under license of the Human Fertilization and Embryology Authority (HEFA), have been obtained according to high ethical standards. Thus for certain existing cell lines the Study Group recommends a *presumption standard* where existing lines are presumed to be ethically derived. Under this standard the researcher or institution can use existing lines provided they notify the ESCRO that a given cell line is being used. If ethical concerns regarding the cell lines emerged, the ESCRO would have the authority to consider whether a presumption of ethical derivation is appropriate. If a determination is made that the cell line was not ethically derived then line could no longer be used by the institution.

For other previously derived cell lines, it would be conceptually consistent to apply the same standard applied to outside cell lines derived after the CIRM Regulations take effect. (see below)

Future cell lines: For cell lines derived without CIRM funds after the regulations are in effect, the SWG believes there needs to be a minimum level of assurance that ethical safeguards were in place. Critical safeguards include:

- Oversight by an IRB or equivalent;
- All participants provided voluntary and informed consent;
- Payment, beyond reasonable compensation, was not provided for gametes or blastocysts.

The SWG may want to consider a mechanism where cells lines can be certified a "ethically derived." Once this determination has been made, the specific cell line would be regarded as ethically derived unless demonstrated otherwise. The value of such an approach would be to prevent the need for repeated reviews for the same cell line.

Recommendation and/or Proposed Language:

For human stem cell lines that are to be used in CIRM-funded research that were derived before the effective date of this chapter to be considered ethically derived, the SCRO committee must determine either of the following requirements are satisfied:

(1) The human cell lines have been approved by the National Institutes of Health, deposited in the United Kingdom Stem Cell Bank, or derived by, or approved for use by, a licensee of the Human Fertilisation and Embryology Authority.
(2) The cell lines have been derived in accordance with the requirements (1-3) in the following section.

For covered stem cell lines that are to be used in CIRM-funded research, obtained from human subjects or through the procurement of gametes or blastocysts, without CIRM funding after the effective date of this chapter to be considered ethically derived, the SCRO committee must determine all of the following requirements are satisfied.

(1) Derivation of human covered stem cell lines from human subjects or through the procurement of gametes or blastocysts occurred under the oversight of an IRB (or, in the case of foreign sources, an IRB-equivalent).

(2) Voluntary and informed consent was obtained from all donors of gametes, blastocysts or somatic cells.

(3) The donation of gametes, blastocysts, somatic cells or tissue occurred without payment beyond reasonable compensation for participation. A determination of reasonable compensation shall be performed in accordance with the policies governing the institution involved in derivation activities.

Discussion Items: [1] For existing cell lines should there be any minimum notification standards in regulation?

[2] For outside cell lines derived after effective date the SWG might consider a two-tiered approach – (1) did the derivation meet extant standards in the time and place where it occurred; (2) if so, is there any reason why those extant standards, either substantive or procedural, are inadequate to meet the "substantial equivalence" test? A determination of "substantial equivalence" is always subject to review should new information emerge.

Study Group Working Notes #2: Banking & Sharing of CIRM Funded Cell Lines

Study Group: Banking

Reference: Section 100009

Background: The Standards Working Group and the public have identified the need for cell-lines, cell products, and other materials derived using CIRM funding to be made available. Further, SWG members have expressed concerns over the "commodification" of cell lines. These concerns have been reinforced in public comments where comments have centered on concerns that materials derived with CIRM funds be widely available and not patented for exclusive use or profit-making. In response to this need, the Standards Working Group agreed that CIRM materials should be in public domain and included the following language in section 100009 of the Interim Regulations:

Cell lines derived or modified in any way with CIRM-funds are required to be shared through a well recognized stem cell bank that will make the lines widely available to investigators.

Subsequently, CIRM has received comments that there are technical challenges related to the centralized banking of cell lines. One concern is that the maintenance of cell lines is difficult. Experience suggests that quality tends to be highest when cells are maintained in the laboratories where they were derived. In time, the art of maintaining cells lines may evolve to the point where central banks can achieve an equivalent quality level.

Further the SWG felt it was not appropriate to include all the specific banking requirements in the existing NA Guidelines, so the following language was included in the Interim Regulations.

Institutions engaged in CIRM-Funded hES derivation or research shall be encouraged at present and possibly mandated in the future to create or participate in central repositories for hES cell lines, including through partnerships or augmentation of existing quality research cell lines repositories, and shall adhere to high ethical, legal, and scientific standards consistent with Section 100009(a) and Section 100007.

Most recently, intellectual property issues related to the banking and distribution of cell lines or cell products emerged. These issues were summarized at the 12/1 SWG meeting and there was consensus that resolution is beyond the expertise and mandate of the SWG. The ICOC has charged a working group to recommend CIRM policies for intellectual property policy with the intention of developing formal CRIM regulations to govern intellectual property.

Options: The Standards Working Group and participants in the public sessions are looking for assurances that CIRM-funded research will result in high quality materials being available in the public domain to support additional research and ultimately effective therapies. A critical question at this juncture is **how can this goal be realized most effectively**?

Three questions have emerged in relation to this goal (1) is a central bank the most effective means of ensuring high quality materials are available (2) what specific steps should be taken to promote sharing, (3) what are the intellectual property issues related to banking and sharing of materials?

Question 1: There is anecdotal evidence to suggest that a central bank may not be feasible in the near term for storing cell lines. Should the SWG consider focusing on the goal of sharing cell lines for primary research without mandating the exact mechanism for sharing?

Question 2: Currently, the interim guidelines *encourage but do not require* a variety of specific steps be taken to support material documentation, exchange and quality control – see section 100009. Specific steps may be included as part of the cooperative agreement between CIRM and its grantee institution(s) rather than detailed in the CIRM regulations.

Question 3: Experts have repeatedly emphasized that Federal law dominates patent policy in research institutions. As a result, any CIRM policy should be compatible with Federal law. The issue of compatibility is being addressed by the IP Task Force. The IP Task Force has identified sharing and dissemination of materials, for research purposes, as a major goal, and will be developing policy options towards this ends.

Recommendation and/or Proposed Language:

Given the range of unresolved issues, it is impossible to determine the most efficient means of achieving the goal of getting materials into the public domain at this time. For the following reasons below, it is recommended that no specific policies be drafted at this time by the SWG. The SWG can return to this issue at a later date if necessary.

Questions 1 & 2:

A rigid standard on banking and/or sharing may be impossible to implement. Absent any intellectual property consideration it is not clear a central bank is feasible at this time. In the near term, CIRM policies should remain flexible. Cooperative agreements developed between CIRM and grantees can best address the SWG's expectations for banking and distribution. The CIRM Science Office will be providing direct oversight of grantee agreements. Therefore, the Science Office, through its agreements with funded institutions, is best positioned to promote sharing and distribution.

The SWG may consider developing a policy statement that promotes sharing, but does not prescribe a bank or banking requirement in regulation. Specifically, the intended desire should be made clear, but the SWG might defers any specific requirements related to material documentation, exchange and quality control to the CIRM. CIRM would be in a position through its grants program to establish requirements related to material documentation, exchange and quality control as such language becomes available. The following language may be appropriate for regulation or could serve as the basis for a policy statement.

Stem cell lines and biomedical materials developed with CIRM funding at academic, commercial research and development organizations should be broadly disseminated. CIRM-funded research institutions shall comply with the CIRM-IP policy intended to ensure data and materials sharing.

Questions 3:

The additional questions remain, to what extent is an open-source bank feasible given existing policies and laws patenting and intellectual property. Given the SWG and IP Task Force share a common objective of making materials widely available for research purposes, the SWG should refrain from policy mandates and await the recommendations of the IP Task Force.

Study Group Working Notes #3: Informed Consent General

Study Group: Donor Recruitment

Background: The interim CIRM Regulations prescribe specific informed consent requirements. In addition, it is suggested that explicit consent be obtained for some controversial issues in the final CIRM Guidelines (see Working Notes #8) adding more prescriptive elements. One challenge in developing regulations in a new and rapidly evolving field, such as stem cell research, is to provide assurance that high standards will be achieved while providing flexibility in achieving such standards. The intent of providing flexibility is to allow standards to evolve in an evidence-driven fashion as the evidence-base is developed. Because regulations require a complex approval process, they may not be sufficiently flexible to provide timely oversight.

Many government organizations (for example, NIH, OHRP) and institutions (IRB policies and guidance) have policies requiring informed consent in research, and they provide guidance through the development of guidance documents and templates. Such guidance supplements the federal regulations governing human subjects research (45 CFT 46). This type of approach often includes identification of "required elements" and "additional elements as appropriate." Often guidance documents will provide model language for conveying complex issues in appropriate language.

Informed consent is a particularly important issue with regard to donation of materials for the derivation of new hESC lines because (1) blastocysts are destroyed in derivation procedures, (2) there is controversy surrounding some types of hESC research (e.g. chimeras and human transplantation) and (3) concerns have been raised that women undergoing oocyte retrieval solely for research need to understand the medical risks of the procedure. As more experience is gained with consent from donors of oocytes specifically for research, unanticipated issues and best practices are likely to emerge, which may go beyond the NAS regulations. An important question becomes, <u>which requirements for consent should be placed in the draft final regulations and which should be placed in other guidance</u>?

Options:

The CIRM Regulations could establish a baseline for human subjects protection by referencing the Common Rule. The Common Rule is a widely accepted and utilized model for informed consent, so institutions will have policies in place for compliance. The CA Health and Safety Code also reinforces may of the requirements of the Common Rule and could also be referenced.

Unfortunately CIRM cannot utilize guidance documents in the same manner OHRP does. Requirements in addition to those in the Common Rule and H&S Code would need to be spelled out in regulation. Since the ethically significant areas appear to be in the area of donation of materials for cell line derivation, additional requirements could be limited to consent for derivation activities.

Current Standards:

The existing regulations cite 45 CFR 46, CA Health and Safety Code 24173 and, in addition, indicate informed consent from egg donors must include at least 10 specific statements for donors of materials to derive cell lines. A summary of the CFR and H & S Code requirements is attached.

Discussion Items:

The Working Group should consider the adequacy of the proposed regulations that currently cite the Common Rule and the CA Health and Safety Code.

California Health & Safety Code 24173 (Experimental Subjects Bill of Rights) vs. 45 CFR 46 (Federal Common Rule)

Consent Element	CA H&S Code	Reference	Common Rule	Reference
Explanation of procedure	X	24173(c)(1)	X	46.116(a)(1)
Description of any risk	X	24173(c)(2)	X	46.116(a)(2)
Statement procedure may involve unforeseen risk			X	46.116(b)(1)
Explanation of any benefit	X	24173(c)(3)	X	46.116(a)(3)
Disclosure of any advantageous alternative procedures	X	24173(c)(4)	X	46.116(a)(4)
Estimate of expected recovery time	X	24173(c)(5)		
Statement of confidentiality of records			X	46.116(a)(5)
Explanation whether compensation for injury is available			X	46.116(a)(6)
Offer to answer inquiries	X	24173(c)(6)	X	46.116(a)(7)
Free to withdraw consent without prejudice	X	24173(c)(7)	X	46.116(a)(8)
Name and institutional affiliation of researcher	X	24173(c)(8)		
Name of sponsor or funding source	X	24173(c)(9)		
Name and contact for impartial third party to address complaints	X	24173(c)(10)		
Material or financial stake or interest if any for researcher or institution	X	24173(c)(11)		
Consent is signed and dated by person who can attest requirements have been satisfied	X	24173(d)		
Consent is voluntary and freely given	X	24173(e)	X	46.116(a)(8)
Anticipated circumstances which participation may be terminated			X	46.116(b)(2)
Any cost that may result from participation			X	46.116(b)(3)
Consequence of decision to withdraw			X	46.116(b)(4)
Significant new findings developed during course of research which may relate to willingness to continue will be provided			X	46.116(b)(5)
Approximate number of subjects in study			X	46.116(b)(6)

Study Group Working Notes #4: ESCRO Efficiency, Authority, Membership and Function & Operation

Study Group: Oversight Mechanisms

Reference: Section 100004

Background: Comments from the public and Working Group members have been received regarding the issues of ESCRO efficiency, authority, membership and function and operation.

ESCRO Efficiency: Commentators have suggested that implementing the NA recommendation – namely, establishing an ESCRO committee having the expertise in stem cell research issues – would be difficult and very expensive; it also may be unrealistic to imagine that each institution would be able to find the necessary scientists, personnel and members of the public with sufficient expertise.

ESCRO Authority: There may be research performed in collaboration with two or more institutions where each institution has established an ESCRO. In such cases, should there be a lead ESCRO that has primary responsibility for research oversight? This is both an efficiency issue and an accountability issue where it may be helpful for researchers to have a single point of contact for oversight.

ESCRO Membership: In the current draft of the guidelines, the ESCRO provides two primary functions scientific and ethical review of proposed research. Since the ESCRO's primary role is scientific / ethical review, it is suggested that a member of the public be included to reduce the perception of a conflict-of-interest.

ESCRO Function and Operations: For regulatory clarity, the primary ESCRO committee functions should be technical and ethical review of research.

Current Standards:

ESCRO Efficiency: draft standards allow *the establishment of a joint ESCRO committee that would assume oversight responsibilities for two or more research institutions, provided the ESCRO has oversight authority for each institution consistent with the requirements of* the regulations.

ESCRO Authority: Two or more institutions could designate a single ESCRO to provide oversight for collaborative research based on joint ESCRO standard cited above.

ESCRO Membership: *An ESCRO shall have at least five members including representatives of the public, persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research.*

ESCRO Function and Operation: Existing language is substantially similar to the proposed language below.

Options Recommendation & Proposed Language:

ESCRO Efficiency: No need to change language.

ESCRO Authority: Could provide clarifying language, but may not be essential, for example:

If two or more institutions are involved in CIRM-funded collaborative research and each intuition has an established ESCRO, a single lead ESCRO may be designated for the purpose of providing oversight for the CIRM-funded collaborative. The lead ESCRO shall have responsibility for maintaining all necessary documentation pursuant to this chapter.

ESCRO Membership Option 1: Consistent with NA Guidelines

The committee shall, at a minimum, include a representative of the public, a member with expertise in ethical and legal issues surrounding hES cell research, and such persons as necessary with expertise in developmental biology, stem cell research, molecular biology, and assisted reproduction.

Note, the Office of Administrative Law favors regulations that provide a specific minimum standard for regulations such as these, so the regulations may need to include language like: *the committee shall be comprised of no less that 5 members including…*

ESCRO Membership Option 2: Could focus on expertise required.

An ESCRO shall have at least five members including representatives with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in stem cell research.

ESCRO Function and Operation:

Function and operation: The designated SCROC [note ESCRO changed to SCROC in current draft] shall provide expertise to support the scientific and ethical review of CIRM-funded research consistent with the requirements of Section 100006, and other applicable CIRM requirements. The SCROC shall facilitate education of investigators with applicable requirements of this chapter.

Study Group Working Notes #5: HIPAA & Banking Donor Recontact

Study Group: Banking / Recruitment and Donation

Background: There may be a need to re-contact cell donors for additional screening and/or health information. Re-contacting donors raises (1) informed consent and (2) HIPAA privacy rule issues. The informed consent issues are relative straightforward involving the need to ascertain specific information from the donor at time of consent. The HIPAA issues are more complex and resolution is beyond the scope of the current guidelines.

Options: Informed Consent: Greely has indicated that it must be ascertained during informed consents whether a subject generally wishes or does not wish to be re-contacted. He suggests a positive indication of intent using signature, initials, or a checked box. Greely also indicates whatever option is chosen, the person must be told that, if the researchers believe such information has very important consequences for the person, they may seek IRB permission to recontact the person to discuss such information without regard to the person's expressed wishes.

HIPAA Privacy Rule: Under HIPAA authorization is required for research uses and disclosures of any personal identifiable health information. A strict interpretation of HIPAA requirements would suggest an authorization is needed for each disclosure of protected information. This rule may necessitate the regulations authorization the bank to disclose and identifiable information to a researcher if they needed to re-contact a donor. In practice, it may be more efficient for the bank to contact the individual directly. Resolution of HIPAA issues will require further deliberations about stem cell banking. For the purpose of standards development these issues do not require resolution at this time.

Current Standards:

Regarding re-contact: Existing guidelines require the following to be disclosed during the informed consent process:

Whether the identity(ies) of the donor(s) will be ascertainable to those who work with the resulting cells or cell products. If the identities of the donor(s) are retained (even coded), CIRM-funded researchers must discuss any plans for recontact of donors of materials used to derive cell lines and obtain consent for recontact. This requirement includes both recontacting donors to provide information about research findings and recontacting donors to ask for additional health information. Donors may be recontacted in the future only if they consent to contact at the time of donation.

Recommendation and/or Proposed Language:

Consent to recontact donors is implied in the existing language but may want to clarify that donors can be recontacted both to (1) obtain consent for some research activities and to (2) obtain information on research findings. In addition, explicit consent for re-contact should be obtained.

Study Group Working Notes #6: Diversity

Study Group: NA

Background: There is agreement in principle among members of the Standards Working Group that diversity of cell lines is essential. In addition, California is the nation's most ethnically diverse state, so stem cell research intended to serve the people of California should reflect this diversity. Some commentators have suggested CIRM establish *diversity criteria* for distribution of funds and that *diversity be embodied in the policies and practices of the Institute*.

Current Standards:

The California Health Research Fairness Act (Health and Safety Code, Sections 439.900-439.906) requires state agencies to adopt policies on women and minorities as subjects of research carried on or funded by such agencies based on a 1990 NIH policy. The Fairness Act also requires state agencies to transmit such policies to the Legislature, provide opportunities for funding research where women and minorities have been underrepresented, report on the use of state funds for research on medical issues of particular concern to women and minorities, collect data on data from such research and incorporate such data into existing reports required by law.

The California Inclusions of Women and Minorities in Clinical Research Act applies these same standards to women and minority groups are included as research subjects in clinical trails.

It appears that neither the Fairness Act nor the Inclusions of Women and Minorities in Clinical Research Act apply to CIRM by virtue of the California Stem Cell Research and Cures Act (Health and Safety Code Section 125290.10 et seq.):

[T]he institute will develop its own scientific and medical standards to carry out the specific controls and intent of the act, notwithstanding . . . any other current or future state laws or regulations dealing with the study and research of pluripotent stem cells and/or progenitor cells, or other vital research opportunities, except Section 125315. The ICOC, its working committees, and its grantees shall be governed solely by the provisions of this act in the establishment of standards, the award of grants, and the conduct of grants awarded pursuant to this act. (emphasis added).
Source: Health and Safety Code, Section 125290.35(a)

Recommendation and/or Proposed Language:

CIRM Grants Policy includes the following statement in applications:

Because of the diversity of the California population, CIRM is particularly interested in training a diverse pool of investigators. We encourage institutions to make special efforts, consistent with the law, to recruit and retain individuals

from many backgrounds, including under-represented minorities, as trainees and as mentors.

In addition, the Grants Working Group is developing reporting requirements to support the CIRM requirements for diversity. These requirements could be cited in the regulations developed by the SWG.

The Grants or Standards Working Group could also develop a declaration of intent drawing from California Health Research Fairness Act or cite the act in its policy statements.

The following language is recommended for a diversity section:

Fairness and Diversity in Research

It is the intent of CIRM to ensure that women and members of minority groups are appropriately included as subjects of health research projects carried out by CIRM-funded institutions. CIRM endorses the objectives of California Health Research Fairness Act (Health and Safety Code, Sections 439.900-439.906) and Inclusions of Women and Minorities in Clinical Research Act (Health and Safety Code, Sections 100237-100239). All CIRM-funded research shall conform to the reporting requirements in the CIRM Grants Administration Policy pursuant to the objectives of these policies.

The Grants Working Group is developing reporting requirements pursuant to this policy statement, and this policy should be referenced. If a reference is not available at the time of OAL submission, then the regulations will require revision at a later date to reflect this policy.

Study Group Working Notes #7: Scope of Regulations / Definition of "Stem Cells"

Study Group: NA

Background: Definitions can serve to define the scope of regulations and make them consistent and effective. Proposition 71 and existing California regulations apply to a broader scope of materials than the National Academies Guidelines.

The National Academies Guidelines address human embryonic stem cells. CIRM-funded research applies to a broader range of materials including but not limited to adult stem cells, fetal tissue and placenta derived cells. Proposition 71 includes definitions of "adult stem cells," "pluripotent cells," "stem cells," (see below) in addition existing language in the CA Health and Safety Code applies to a broader range of materials (see below). A key question is: what is the most appropriate definition for the Draft CIRM Regulations? This question is explored further below; also, Working Notes 10 examines how definitions effect ESCRO review.

Current P71 Definitions:

"Adult stem cell" means an undifferentiated cell found in a differentiated tissue in an adult organism that can renew itself and may, with certain limitations, differentiate to yield all the specialized cell types of the tissue from which it originated.

"Pluripotent cells" means cells that are capable of self renewal, and have broad potential to differentiate into multiple adult cell types. Pluripotent stem cells may be derived from somatic cell nuclear transfer or from surplus products of in vitro fertilization treatments when such products are donated under appropriate informed consent procedures. These excess cells from in vitro fertilization treatments would otherwise be intended to be discarded if not utilized for medical research.

"Stem cells" mean non-specialized cells that have the capacity to divide in culture and to differentiate into more mature cells with specialized functions.

Current CA Health and Safety Code:

California Health and Safety Code Section 125300(a) applies to the range of materials described in Proposition 71.

***125300**. The policy of the State of California shall be as follows:*

(a) That research involving the derivation and use of human embryonic stem cells, human embryonic germ cells, and human adult stem cells from any source, including somatic cell nuclear [transfer] transplantation, shall be permitted and that full consideration of the ethical and medical implications of this research be given.

Options & Analysis:

The CIRM regulations could be limited initially to hES and then expanded over time. Ultimately they will need to cover the range of materials described in Proposition 71. Some Working Group members have suggested starting initially with hES and then expanding to scope over time to cover the range of materials. The value of this approach is that it would initially result in regulations substantially equivalent to the NA Guidelines.

Expanding the definition of stem cells would have the benefit of making the regulations comprehensive in scope and consistent with existing language in the Health and Safety Code. Recent research has included efforts to derive stem cell lines from non-emborynic sources.

The CIRM Grants Team was consulted to consider what the scope of materials might be used in by institutions in the Training Grant Program. Since this will be the first set of grants funded by CIRM, it would be prudent that our regulations cover the scope of activity reasonably anticipated under this program. The Grants Team indicated that they expect some trainees to be working with materials other than embryonic stem cells.

At the December 1 SWG meeting the following definition of human stem cells was considered:

Stem cells refer to cells that are capable of self-renewal, and have potential to differentiate into multiple cell types.

Research institutions submitted comments indicating that this definition may be overly expansive and result in regulations the cover research never intended to be reviewed by an ESCRO. The intent should not be to cover all research activities that might incidentally involve stem cells. For example, the transplantation of human tumor tissue, that may contain incidental stem cells, into mice. This practice is common in cancer research and should not require review by an ESCRO. Conceptually, the issue of concern is stem cell lines not incidental stem cells.

Scientists on the SWG were asked to consider these issues and suggest a definition that captured the activities of interest for the purpose of the CIRM Regulations. The follow was recommended.

Recommendation and/or Proposed Language:

Suggested Definitions:

Covered stem cell line: A culture-derived, self renewing human cell population that thought to be capable of tri-lineage differentiation potential into tissues of the endoderm, ectoderm and mesoderm. This definition includes both embryonic and non embryonic human stem cell lines regardless of the original tissue of origin.

Or

This definition has been modified based on comments from the Grants Working Group to read:

Covered stem cell line: A culture-derived, human stem cell population which may: 1) be propagated indefinitely in culture, 2) differentiate along multiple germ layer lineages, and 3) give rise to daughter cells with equivalent developmental potential (i.e., self-renewing). This definition includes both embryonic and non-embryonic human stem cell lines regardless of the original tissue of origin.

The above definitions are consistent with the language in Proposition 71 because they incorporate language consistent with the definition of *"adult stem cell," "pluripotent cells,"* and *"stem cells."* The focus on cell lines in culture alleviates concerns that scope of regulation is overly expansive.

Study Group Working Notes #8: Informed Consent for Controversial Issues

Study Group: Donor Recruitment

Background: Some uses of stem cells may be controversial and it has been suggested that such uses merit explicit permission. Controversial uses include but are not limited to chimeras, SCNT and human transplantation. The Common Rule already requires disclosure of the "purpose" and "procedures" of research. Further recommendations for informing participants of the potential for controversial uses, particularly when they are not known, are provided.

Options: One option is to obtain explicit consent for "controversial" types of research. This requirement is embedded in the Common Rule (incorporated in the CIRM Regulations by reference) and additional requirements could be spelled out in regulation.

Current Standards:

Regarding controversial uses: The Interim CIRM regulations and NAS guidelines indicate the informed consent must include the following:

A statement that the hES 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.

The consent process shall ascertain whether donors have objections to any specific forms of research to ensure that their wishes are honored, and donors shall be offered the option of agreeing to some forms of hES cell research but not others.

Recommendation & Proposed Language:

If the proposed research anticipates uses of materials in an experiment consider ethically controversial, the explicit consent could be obtained for such use. The Common Rule (referenced in the CIRM Regulations) requires an "explanation of the purposes" and "any procedures." The CIRM Regulations go further to require the following:

In addition to the general requirements for informed consent, for donation of materials to derive human stem cell lines, researchers must disclose, [when applicable]:

(1) Derived cells or cell products may be used in research involving genetic manipulation.
(2) Derived cells or cell products may be transplanted into humans or animals.

Study Group Working Notes #9: Other Informed Consent Issues

Study Group: Donor Recruitment

Background: There are additional informed consent issues that should be considered; they include the following:

- Permission for Unforeseen Future Research

People who were willing to donate materials for certain types of research may not agree (if asked) to have their materials used in other types of research. On the other hand, it may not be possible to predict all uses of a stem cell line. Also if a donor doesn't agree to unforeseen uses of a stem cell line derived from his or her materials, researchers might have to go back to derive a new line. Is blanket consent for "all future uses of the stem cell line derived from my materials, provided the research is approved by the institutional ESCRO," ethically valid?

- Withdrawal

It is argued that research participants must be notified that they have the right to withdraw at any time from the specific research and the right to withdraw permission for unforeseen future research uses, either in general or with respect to specific research topics. The researchers or banking entity would need contact information for either kind of withdrawal raising HIPAA concerns.

- Time Limits

Should time limits exist for how long the researchers can keep materials collected and to have them available for unforeseen future research? Commentators suggest a finite time for keeping materials.

Options: Unforeseen Future Uses: There are precedents for "tiered" consent forms, where subjects can agree for use of stored tissues in various types of future research. Subjects should be notified prior to donation that donated materials are intended for future research.

Withdrawal: SWG members and individuals providing public comment indicated it generally is not feasible to track donated materials on an ongoing basis to enable a withdrawal. A blanket consent for research approved by a institutional review committee is recommended. Materials not achieving this level of consent should not be disseminated for other research use. As a means of overcoming the problem of tracking donated materials (for consent purposes), it is reasonable to allow researcher to limit participation in derivation research to those individuals willing to consent to all future uses.

Time Limits: In general, donors of gametes for creation of cell lines should be informed that the intent is to utilize the cell lines indefinitely. An initial request for an indefinite lifetime for the research should be approved by an IRB. Any extension of the lifetime for research use of the information or materials collected

beyond the period set out in the initial consent or permission may also be approved by an IRB.

Recommendation & Proposed Language:

Unforeseen Future Uses: In the informed consent process donors should be informed:
Researchers may use cell lines for future studies, which cannot be described at this time.

Withdrawal: Researchers should attempt to ascertain in advance if the donor has specific preferences. Given the practical difficulties tracking the use of donate materials, researchers should consider only choosing donors who agree to all future uses.

CIRM-funded research may not violate expressed donor preferences. If it is not be feasible to ensure how donated materials will be used, researchers may choose to use only donors who agree to all future uses that are approved by appropriate science and ethics review panels.

Time Limits: In the informed consent process donors should be informed:
Derived cells or cell products may be kept for many years.

Study Group Working Notes #12: Triggers for ESCRO Review

Study Group: Oversight Mechanisms

Reference: Section 100006

Background:

The SWG has received comments requesting clarification of what CIRM-funded research activities trigger a requirement for ESCRO review. Concerns were raised that the requirements in the 12/1 draft are broader in scope than the NA Guidelines. The 12/1 draft requires ESCRO review when attempting to derive human stem cell lines or attempting to introduce human stem cells into animals.

The designated ESCRO shall review and have authority to approve, require modification in, or disapprove in writing all funded research attempting to derive human stem cells.

The designated ESCRO shall review and have authority to approve, require modification in, or disapprove in writing all funded research attempting to introduce human stem cells into nonhuman animals at any state of embryonic, fetal, or postnatal development.

Two specific points of concern were raised:

1. Research attempting to isolate stem cells from tissue samples or biological specimens, such as cord blood, fetal tissue or tumor biopsy, is already adequately regulated should not require additional review.
2. The overly broad definition of human stem cells [*undifferentiated cells that have the capacity to self-renew and, to differentiate into mature cells with specialized functions*] may result in ESCROs being asked to review routine research where tissue (that may contain incidental stem cells) is injected into animals. For example, injecting human tumor biopsies into mice in cancer research.

Concern #1 raises a fundamental question of where additional oversight is needed. The National Academies stated the following:

One particularly important aspect of regulatory compliance for hES cell research deals with protection of donors of blastocysts and gametes. Laboratory research that uses hES cells is generally not subject to federal regulations governing research with human subjects unless it involves personally identifiable information about the cell line's progenitors…

…The second role of ESCRO committees is to review research proposals that involve particularly sensitive kinds of research, including all proposals to generate additional hES cell lines by any means.

One interpretation of the National Academies report, is that **any** research use of oocytes or blastocysts should trigger ESCRO review. However, in their written recommendation the committee focused on using oocytes or blastocysts to **derive** cell lines.

Recommendation 3(b): The ESCRO committee should evaluate all requests for permission to attempt derivation of new hES cell lines from donated blastocysts, from in vitro fertilized oocytes, or by nuclear transfer.

Interviews with NA committee members indicate that the committee felt it was necessary to review activities that would result in the destruction of blastocysts and oocytes. If the SWG adopts the NA committee position, then the current requirement in the draft CIRM Regulations could be narrowed to derivation activities that involve the destruction of blastocysts and oocytes. Options for narrowing the scope are presented in the next section. However, it is important to be mindful that the SWG has also indicated that attempting to derive a new stem cell line is an appropriate activity for ESCRO review.

Concern #2 is effectively an issue of clarification. Neither the NA committee or the Standards Working Group felt it was necessary to regulate the use of pathological or diagnostic specimens. This can be made clear in the regulations by developing a more concise definition of "stem cell," creating exemptions for materials not subject to regulation or a combination of both options. Options for definitions and exclusionary language are presented in the next section.

Options Recommendation & Proposed Language:

Definition of Stem Cell:

Covered stem cell line: A culture-derived, self renewing human cell population that thought to be capable of tri-lineage differentiation potential into tissues of the endoderm, ectoderm and mesoderm. This definition includes both embryonic and non embryonic human stem cell lines regardless of the original tissue of origin.

or

Covered stem cell line: A culture-derived, human stem cell population which may: 1) be propagated indefinitely in culture, 2) differentiate along multiple germ layer lineages, and 3) give rise to daughter cells with equivalent developmental potential (i.e., self-renewing). This definition includes both embryonic and non-embryonic human stem cell lines regardless of the original tissue of origin.

Either of these definitions would serve the purpose of focusing the regulations on the derivation of purified stem cell lines; thus alleviating concerns that the presence of incidental stem cells would trigger additional review.

ESCRO Review for Derivation:

Option 1:
The designated SCROC shall review and approve in writing all CIRM-funded research attempting to derive covered stem cell lines from oocytes or blastocysts including the use of SCNT. CIRM-funded research involving derivation of covered stem cell lines using oocytes, blastocysts or SCNT cannot commence without SCROC approval..

Option 2:
The designated SCRO committee shall review and approve in writing all CIRM-funded research attempting to derive covered stem cell lines or research which otherwise involves the use of human oocytes or blastocysts. This requirement includes, but is not limited to, attempted derivation of new stem cell lines from donated blastocysts, oocytes, sperm, somatic cells or by SCNT...

Option 1 is consistent with the NA Guidelines; option 2 represent an extension of the NA Guidelines to include all derivation activities and all uses of oocytes and blastocysts. Each is limited to the derivation of a pure stem cell line, and thus alleviates the problems associated with the previously broad definition of human stem cells.

ESCRO Review for Introduction to Human or Animals:

The designated SCROC shall review and approve in writing all CIRM-funded research attempting to introduce covered stem cell lines into human or non-human animals at any state of embryonic, fetal, or postnatal development. CIRM-funded research involving the introduction of covered stem cell lines cannot commence without SCROC approval. The designated SCROC can require that modification be made to proposed research or documentation of compliance with the requirements of 100006(b)(3) as a condition of granting its approval. At a minimum, the SCROC shall require the investigator to:

Optional language for clarification:

This requirement shall not apply to research involving the introduction of human tissue derived from pathological or diagnostic specimens, [for which patient has provided prior consent for specimens to be used for research] or [if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.]

This language indicates that the introduction of all human stem cells to humans or animals requires ESCRO review. This optional language is not necessary give the definition of "covered stem cell line." However, such language might be considered in a regulatory guidance document.

Study Group Working Notes #11: Reimbursement

Study Group: NA

Background: SWG members have asked for an interpretation of what Proposition 71 allows with regard to reimbursement to research donors for participation in CIRM funded research. The relevant language with regard to reimbursement has been incorporated into the California Health and Safety Code section 125290.35.

H&S Code section 125290.35, subdivision (b)(3), states:

The ICOC shall establish standards as follows:

Prohibition on Compensation:
Standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses.

Options & Analysis:

A central issue is the definition of *expenses*. Since there is not a definition of expenses in Proposition 71, the scope of what may be compensated for remains undefined. Further, it is not be satisfactory to suggest there was an intended meaning unless the intended meaning is extensively described in campaign materials that would be readily available to the voters.

Recommendation and/or Proposed Language:

Since the term *expenses* remains undefined and the term is use in the CIRM Regulations, the SWG should consider a definition of either the term *expenses* or *necessary and reasonable costs*. Options are presented below.

Option A:

Pursuant to Health and Safety Code section 125290.35, subdivision (b)(3), research donors or participants may be reimbursed for *necessary and reasonable costs* directly incurred or expended as a result of their donation or participation in research activities.

Option B:

Pursuant to Health and Safety Code section 125290.35, subdivision (b)(3), a research donor or participant may be reimbursed for necessary and reasonable costs, as determined by the IRB, directly incurred or expended as a result of his or her donation or participation in research activities.

Option: Definition to be appended to either "A" or "B" above

"Necessary and reasonable costs" [**a:** include but are not limited to **b:** that are reimbursable are the following: 1) out-of-pocket expenses associated with transportation and lodging (including meals) required to be undertaken in connection with the donation or participation; 2) costs of child care [with time limitation?]; medical expenses…..