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Based on the provisions of Prop 71 Section 125290.35, it would appear that there are certain topics for which standards must be issued. This handout offers some specific questions that ought to be answered in the course of developing those standards. In some cases, the text of Prop 71 is sufficiently specific, or state and federal law are sufficiently comprehensive, to permit the standard to be written in direct response to the mandate.

There are, of course, some other topics that might benefit from the development of standards, and these topics are listed as an addendum to this handout.

Human Subjects Protection Rules

Federal research regulations apply to some but not all settings in which biological materials are donated for the derivation of hES cell lines. When federal funding is not a factor, federal protections are only triggered when (a) the research is aimed at producing a product for FDA approval or (b) an institution has voluntarily decided to apply the protections. In addition, even where the protections are triggered, the work can be exempt from IRB review (although not from common-law based consent requirements) when the donation consists of nothing more than relinquishing custody of existing embryos and the resulting cell lines are rendered effectively anonymous, e.g. by using codes to obscure donor identities while still retaining key medical information from the donors.

1. Should IRB review be required for all procurement of surplus embryos, even where not required by federal regulation (as is the case with procurement of embryos that will be anonymized)?

2. Shall there be any rules concerning whether the attending physician responsible for the fertility treatment and the investigator deriving and/or proposing to use hES cells may be one and the same person?

3. In the case of collaborations, shall the CIRM-funded investigators be permitted to have their proposals reviewed by the collaborator's institution (whether in another state or another country)? Will it be CIRM or the individual California institutions who assess whether the procedures prescribed by the foreign institution afford protections consistent with those in California?

Informed Consent

Given the controversial nature of some forms of stem cell research, much attention has been paid to the process for obtaining informed consent from those who donate embryos (e.g. surplus IVF embryos) or gametes (e.g. to make IVF embryos solely for research) or somatic cells (e.g. to do somatic cell nuclear transfer research). The consent process not only ensures informed, voluntary decisions; it also offers a venue for laying out substantive policies designed to avoid undue incentives for donation, to ensure the participation of all affected persons, and to anticipate dilemmas that might arise should future research on the cell lines reveal something of possible interest to the original donors.

1. Should consent be required from all potentially relevant parties? This might include anonymous sperm and egg donors as well as the persons who had the embryo made for their own reproductive uses.

2. In the context of donation of gametes or embryos for hES cell research, shall the informed consent process require:

a. information about possible clinical uses in the future?

b. restrictions on directed donation?

c. notice of the kind of information that will be retained about the donors and any methods that will be used to maintain their confidentiality?

d. any choice on the part of the donors as to whether they will ever be recontacted, should research with the cell lines provide unexpected information about themselves? If so, how will the decision to recontact and the process for recontact be managed?

e. information about the range of research uses, including those that might appear to be alarming (e.g. genetic manipulation of the cells or the mixing of human and non-human cells in animal models);

f. restrictions on the right of donors to receive financial or any other benefits from any such future commercial development;

3. Will all CIRM-funded research use standard consent processes and forms, or will institutions be permitted to insist upon local variations? For example, given the lack of uniformity among IRBs nationwide with regard to compensation for injuries incurred due to research participation (e.g. a possible injury to an egg donor), will there be uniform policies or local variation?

4. Shall fertility clinic personnel who have a conscientious objection to hES cell research be permitted to recuse themselves from the consent and procurement process?

Prohibition on Compensation

Prop 71 includes a prohibition on compensation to research donors and participants, a clause that would appear to apply equally to embryo, egg, sperm and somatic cell donation, regardless of the differences in the degree of risk or discomfort associated with these varying forms of donation. The clause does, however, permit reimbursement for expenses. Reimbursement can be understood to encompass only out-of-pocket costs, such as taxi fare to a donation site, or to encompass opportunity costs as well, such as lost time at work. Note that reimbursement for opportunity costs might result in different donors receiving different levels of reimbursement, depending upon their hourly wage at work.

1. Should reimbursement be limited to out-of-pocket expenses? If so, will there be reimbursement for all out-of-pocket expenses or only those deemed (by someone) to be "reasonable"?
2. Should reimbursement include payment for lost time at work or other opportunity costs? If so, shall it be a standard payment or one that correlates with the actual lost wages or opportunities?
3. Shall the prohibition on compensation be understood to include non-monetary transactions, such as discounts for infertility services?

Patient Privacy Laws

Prop 71 asks you to set standards that assure compliance with state and federal patient privacy laws.

The primary source of federal patient privacy protection comes from the combination of research subject protections (discussed above) and the Health Insurance Portability and Accountability Act. Except in certain exceptional situations, the HIPAA Privacy Rule prohibits disclosure of medical information by many kinds of health care workers or institutions, absent an authorization from the patient or a waiver of this requirement by an IRB or specially constituted Privacy Board.

For new hES cell line derivations, medical information about donors will often be collected at the same time as the gamete or embryo donation. The primary purpose of collecting such information is to permit a coded link to be maintained between the resulting hES cell lines and information about the genetic or infectious disease status of the donors. This could facilitate certain types of research (e.g., genetics research) or it might be needed in the future to comply with FDA donor suitability rules prior to using them for tissue transplantation.

The manner in which such donor information is collected and managed can affect whether the human subjects and HIPAA privacy protections apply. A key determinant is whether the resulting cell lines will be managed in a way that makes the donors' identities readily ascertainable to investigators. If so, then both sets of protections apply.

On the other hand, both the research regulations and the Privacy Rule permit personal health information obtained by the researcher to be "de-identified" (e.g., aggregate statistical data or data stripped of individual identifiers) in order to be used or disclosed without restriction. In the alternative, a researcher can ask an IRB or Privacy Board to grant a waiver, based on a showing that the personal health information is coded to obscure personal identities and is protected by a plan to guard against unauthorized disclosure, so that there is no more than "minimal risk" to the privacy of individuals.

Not mentioned in Prop 71, but relevant to investigators working with European collaborators, are the provisions of the various European data privacy directives, which forbid the transmittal of medical data to those outside Europe absent adequate assurances that the data will remain confidential. Important to note is that the U.S., despite its research regulations and HIPAA, is not deemed to have yet achieved a satisfactory level of privacy protection, so individual investigators will need to be attentive to any requirements for an individualized plan for compliance.

1. Shall CIRM add any additional privacy protections beyond those already required by federal law?
2. What documentation, if any, must investigators provide to CIRM to assure their compliance with federal or international privacy protections prior to the release of CIRM funding for their projects.
3. If CIRM were to develop a physical or virtual stem cell bank, what procedures would be used to ensure that cell lines were maintained and distributed in a fashion that complies with federal law?

Time Limits for Obtaining Cells

Prop 71 sets a limit of 8 - 12 days for the maintenance of fresh or thawed extrauterine embryos. Internationally the limit has tended to be set at 14 days or when the primitive streak begins to appear, whichever occurs first. In practice, 8 to 12 days already exceeds the likely time for which such embryos can or need to be maintained in culture.

1. Shall CIRM consider shortening the permissible culture period to less than 8 days?
2. Shall CIRM set an absolute limit of 8, 9, 10, 11, or 12 days? In the alternative, shall institutions be permitted to set their own limits, within the constraints of California law and the conditions for CIRM funding?

OTHER TOPICS FOR FUTURE CONSIDERATION AND POSSIBLE STANDARD-SETTING

In addition to the topics identified in Prop 71, there are other topics for which some decisions or standards might be helpful, prior to releasing research funding. These include:

Scope:
For procurement and derivation, the controversy is focused primarily on hES cells, although the practices surrounding hEG cells have some commonalities (and are already governed by federal law). For research uses, many of the controversial issues raised by hES cells are raised by the use of so-called adult stem cells as well.

1. For hES cells, will your standards cover derivation? procurement? banking?

2. Are your standards designed to cover surplus embryos from IVF clinics? embryos made by IVF solely for research? somatic cell nuclear transfer? parthenogenesis? research using stem cells derived from non-human animals? research using human adult stem cells? research using fetal stem cells or embryonic germ cells derived from fetal tissue? (Note that such research is covered by federal statutory restrictions at 42 U.S.C. 289g-2(a) and federal regulations at 45 CFR 46.210.)

Establishment of an Additional Oversight Committee
While most institutions have the committees required by federal law for currently mandated reviews (including IRBs for human subjects protections; Privacy Boards for HIPAA protections; IBCs for recombinant DNA research; IACUCs for animal research) few have any committee specially created to monitor and coordinate compliance with these mandates by hES cell researchers. Nor do many have a special committee to register the level of activity at the institution, to offer investigator training in stem cell research ethics, or to serve as a venue for discussion, review or even approval of potentially problematic forms of the research. A key question, then, is whether CIRM wishes to encourage or require institutions to create such committees, or whether it plans to have CIRM provide one centrally for all CIRM-funded research. In the alternative, this question could be left entirely to the discretion of individual institutions, who could set up such committees, designate existing committees to expand their functions to incorporate some of these tasks, or simply do without such added oversight entirely.

Banking and Distribution of Hes Cell Lines
Forming a physical or virtual stem cell bank could be of great value to the community of researchers in California (and indeed, the nation and the world). Facilitating the task of documenting the ethical standards under which lines were derived will help collaborators to work more efficiently, given the variations in national and international research rules in this field. In addition, a cell bank could set standards for the quality of the characterizations and the accompanying medical information associated with the lines.

1. Will CIRM start or participate in a stem cell banking effort? If so, what will be the standards for characterizing, expanding, storing, and releasing cell lines? What protections will be available to ensure the confidentiality of donor identities? What means will be used to document the provenance of cell lines, and to track their subsequent delivery to investigators? Shall the bank have criteria for

distribution of cell lines, including but not limited to evidence of approval of the research by an appropriate body at the recipient institution.

Research Use of hES Cell Lines

As noted above, there is tremendous variation among states and nations with respect to the ethics of hES cell research. Some governments prohibit the use of lines derived from oocytes activated by somatic cell nuclear transfer. Others prohibit certain forms of research. Setting standards for CIRM-funded research puts investigators and potential collaborators in other states and countries on notice as to the extant standards in California.

1. Should institutions insist upon receiving documentation about the provenance of all cell lines brought into the institution for research use? Must the provenance comport with the ethical standards of the institution or is it sufficient that the lines were derived in a manner that met the legal and ethical standards of the institution, state or country where they were derived?

2. Are there forms of research that ought to be prohibited? For example:
– research that involves combining human and nonhuman primate ES cells and blastocysts?
– research that involves breeding animals into which hES cells have been introduced?

3. Are there forms of research that ought to subjected to special review for safety, ethical acceptability, and scientific rationale? For example, research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development? If so, what should be the key factors in the review? Would they include the predicted pattern and extent of integration of the hES cells into the animal embryo, fetus or live-born? Does the stage of the animal's development affect this assessment? Whether the animal will be developed to birth? In which cases will prior experiments using primate ES cells be required before working with hES cells?