Advancing the Field: Institutional Approaches Supporting Ethics in Stem Cell Research

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Workshop Summary
June 30 – July 1 2009
Aviation Museum
San Francisco, California
Published July 21, 2009

CONTENTS

Background:

CIRM's 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 therapies and cures for chronic disease and injury. Pursuant to our obligation to assure that research is conducted safely and ethically, CIRM is committed to the ongoing evaluation and improvement of its Medical and Ethical Standards Regulations through an evidence-based policy development process. Such a process is essential in a rapidly evolving field such as stem cell research.

Numerous national bodies, including the Institute of Medicine, Department of Health and Human Services Office of Inspector General, and Office for Human Research Protection, recommend evaluation to support the development of scientific and ethically responsible research.[1] [2] [3] Evidence-based evaluation can serve to identify challenging compliance issues among the regulated community, refine best practices, promote consistency, and create sustainable feedback mechanisms for policy development. Figure 1 illustrates CIRM's model for evidence-based policy evaluation and development.

In 2007, CIRM published *Advancing Effective Research Oversight: CIRM's Evaluation Initiative*. This report detailed findings from two regional workshops attended by individuals with responsibility for institutional research compliance and stem cell research oversight. The findings from this report were taken into consideration by CIRM's Medical and Ethical Standards Working Group and served as the basis for subsequent policy recommendations.

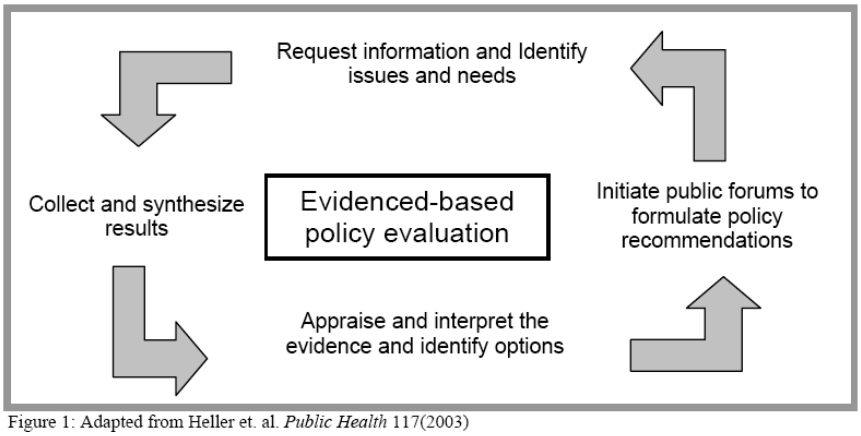


Figure 1: Adapted from Heller et. al. *Public Health* 117(2003)

[1] Responsible Research: A Systems Approach to Protecting Research Participants. Daniel D. Federman, Kathi E. Hanna, and Laura Lyman Rodriguez, Editors Committee on Assessing the System for Protecting Human Research Participants. Institute of Medicine of the National Academies.

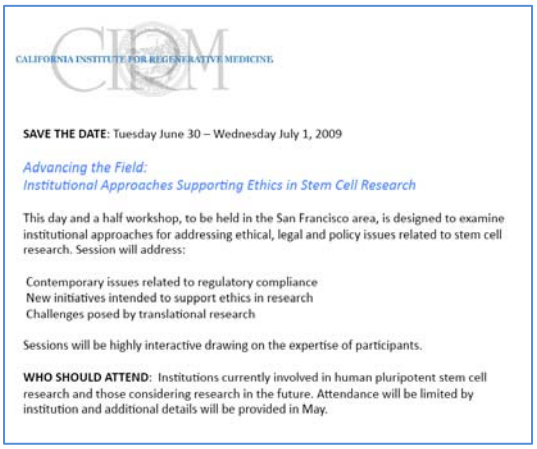
[2] Department of Health and Human Services Office of Inspector General, Institutional Review Boards: A Time for Reform. June 1998, OEI-01-97-00193.

[3] Office for Human Research Protections (OHRP) Division of Assurances and Quality Improvement Objectives and Overview of the OHPR Quality Improvement Program April 15, 2002.

Current Evaluation Activities:

In June 2009, CIRM sponsored *Advancing the Field: Institutional Approaches Supporting Ethics in Stem Cell Research*. This workshop represented a continuation of the CIRM Evaluation Initiative, which is designed to inform the development of Institute policies. The 2009 workshop was focused on the following topics:

- Current state and national issues related to regulatory compliance;
- Initiatives designed to support ethics in stem cell research;
- Potential future challenges posed by translational research.



CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

SAVE THE DATE: Tuesday June 30 – Wednesday July 1, 2009

Advancing the Field:
Institutional Approaches Supporting Ethics in Stem Cell Research

This day and a half workshop, to be held in the San Francisco area, is designed to examine institutional approaches for addressing ethical, legal and policy issues related to stem cell research. Session will address:

Contemporary issues related to regulatory compliance
New initiatives intended to support ethics in research
Challenges posed by translational research

Sessions will be highly interactive drawing on the expertise of participants.

WHO SHOULD ATTEND: Institutions currently involved in human pluripotent stem cell research and those considering research in the future. Attendance will be limited by institution and additional details will be provided in May.

Figure 2: Workshop Announcement

The workshop was divided into seven segments. Each segment addressed specific questions related to oversight policy and implementation (See Appendix A for a complete agenda). In addition, each session included survey questions and an evaluation form. Workshop sessions were designed to be interactive, with the majority of each session dedicated to group discussion. The survey questions were used to inform later sessions by providing a basis for prioritizing issues.

The workshop was attended by representatives from thirteen California research institutions, members of the CIRM Standards Working Group, members of CIRM's governing board ,the Independent Citizens Oversight Committee, and a representative from the California Department of Public Health Human Stem Cell Research Program.

This report summarizes major themes that emerged from each session. Themes were derived from session notes, survey forms and materials provided by presenters. Slides developed for each session are contained in Appendix B. Each session was coordinated by a moderator who reviewed the summary for each session.

Session 1: What is Effective Oversight of Stem Cell Research

Moderator: Susan Stayn JD

Panelists: Celia Molvin IRB Lead Manager Stanford University
Lewellyn Cox PhD SCRO Administrator City of Hope

Summary:

This session included a presentation from two institutions, one with a comparatively large research portfolio (Stanford) and the other with a more modest portfolio (City of Hope). Conceptually, each institution incorporated a similar approach to protocol triage, where the proposed research was assigned a level of review and oversight. Each system of triage tended to mirror the requirements of the CIRM regulations and the CA State Guidelines for Stem Cell Research. In some cases (typically transplantation of non-pluripotent human cells to animals), full SCRO committee review would be provided despite no explicit requirement for such review. [4]

From an operational standpoint, both institutions reported success in constituting oversight committees consistent with CIRM and state standards. The major difference related to infrastructure requirements. Stanford University developed an electronic (eProtocol) system to manage research applications. Such a system was deemed necessary given the large number of protocols managed by the committee at any given time.

In general, the presenters and workshop participants indicated no major difficulties meeting SCRO membership requirements. Some participants inquired about strategies for recruiting community members to participate. Institutions indicated that established public outreach programs proved to be a useful link to the community and a mechanism for recruiting.

Presenters and workshop participants indicated that they had developed two or more SCRO review categories to address the levels of review mandated by the CIRM regulations and CA CDPH guidelines. The full committee would be convened for research involving embryos, gametes or transplantation of certain cells to animals. A more limited level of review is typical for *in vitro* research.

[4] Recent revisions to the CDPH Guidelines for Human Stem Cell Research (see: http://www.cdph.ca.gov/services/boards/HSCR/Documents/MO-ProposedAmendmentstoSection5-InTrackChanges.pdf) require review of transplantation *pluripotent cells or cells differentiated from human pluripotent stem cell lines into non-human animals.* Institutional polices to review such transplantation predate this requirement.

Major Themes from Discussion and Surveys:

- Having multiple laws, regulations and guidelines (CA state, CIRM and federal) creates confusion, can increase compliance program costs and may result in some research not being performed. A consistent set of policies would be very helpful.
- It seems odd to have multiple institutional SCROs review the same documents and possibly come to different conclusions about the same lines. It would be fantastic to have a registry of acceptable hESC lines.
- Requiring the SCRO committee to "confirm" all approvals are in place and correspond to the protocol under review is a potential burden. It might be more efficient to allow this responsibility to be delegated to a coordinating office and leave the exact arrangement to the individual institutions.

Figure 3: Workshop participants

Session 2: What is New in the Regulatory / Policy Arena

Panelists: Geoffrey Lomax DrPH
Alta Charo JD

Summary:

This session covered three general policy topics – (1) the revisions to the CIRM regulations, (2) CIRM's approach to regulatory implementation and compliance evaluation and (3) regulatory harmonization in light of NIH's revised stem cell policy.

Revision to CIRM Regulations

Two major themes dominated the discussion of CIRM regulatory revisions. The first was a concern over CIRM requiring SCRO "notification" for certain experiments involving the use of pluripotent stem cells. Participants also indicated that requiring the SCRO to "confirm" all approvals might not be the most efficient approach. They suggested that the exact arrangement be left to the individual institutions. Participants were encouraged to include this point in written comments to CIRM pursuant to the regulatory comment process.

A second concern involved the proposed cut-off date for donation of reproductive embryos for research for which a gamete donor was paid. Participants raised a series of legal, ethical and policy considerations they felt should be addressed prior to a final regulation. CIRM encouraged participants to include their thoughts in the regulatory comment process. In addition, the group felt it was important to develop a consensus statement. CIRM agreed to facilitate communication among participants to enable the drafting of a statement. The final statement is contained in Appendix C.

Regulatory Implementation

This segment discussed what CIRM looks for during compliance evaluations. CIRM commented on the importance of clear operating procedures for SCRO operations. Specifically, CIRM emphasized the need for written policies that indicate when different levels of review are applied (e.g. full committee review vs. administrative or expedited review).

Regulatory Harmonization

This session was framed around the expectation that the final NIH guidelines would accommodate established federal procedures for consent and oversight. Discussion focused on the fact that institutions will face at least three sets of

stem cell policies – CIRM, California CDPH and NIH. Participants expressed hope that federal policy would drive greater harmonization of state policy.

Major Themes from Discussion and Surveys:

- There are a number of ethical, legal and policy concerns with the regulatory revisions, see Appendix C.
- A number of individual institutions are attempting to "peg" their policies to the most "restrictive" standard to create internal procedures that result in compliance with all applicable standards. Some suggested this could change if state regulations are overly burdensome or become more time consuming to implement compared with NIH policy.
- Other institutions reported "pegging" their policies to the specific requirements of the funding agency.
- If a legal requirement (e.g. state regulation) were in conflict with a guideline, then the legal requirement would "generally trump."
- CIRM should provide clear guidance about what is respected with regard to regulatory compliance.

Session 3: Acceptable Derivation and the Evaluation of Cell Lines

Moderator: Sidney Golub PhD

Panelist: Rob Streiffer PhD

This session considered the ethical dimensions of various policies concerning the use of hESC lines. Dr. Golub reviewed the experience of the UC Irvine SCRO in reviewing projects, focusing on issues involving cell lines. Dr. Streiffer made the case for utilizing hESC lines only if the embryo donors provided informed consent. He then explored the consent status of a number of established cell lines. In this analysis, he emphasized two general categories of problems encountered when evaluating cell lines – restrictions and omissions. Restrictions are when the consent process included language that set limitations on research. Omissions occur when the consent form does not completely describe how donor materials will be utilized.

Dr. Streiffer cited surveys where the public was uncomfortable with certain types of biotechnology and biomedical research to suggest why omission was a critical issue. An example where there is public concern is the creation of inter-species chimeras. It was also acknowledged that contextualizing the question of chimeras results in a more positive public response to such issues. In the case of omissions, there was discussion over what one can reasonably anticipate for consent purposes. Participants pointed out that there would always be unforeseen uses for donated research materials.

Major Themes from Discussion and Surveys:

- There will always be challenges in maintaining the confidentiality of embryo donors while obtaining evidence the consent was truly informed.
- There was considerable discussion of the research use of embryos created with anonymous oocytes or sperm.
- Participants expressed concern with potentially needing to apply different provenance standards especially in cases where mixed funding sources are being used.
- There are going to be lines where it will be impossible to track down provenance data; we will likely lose materials.
- This session underscored the need for a list of lines that have been approved and are considered allowable for research from all funding sources.

Session 4: Ethics Training

Moderator: Michael Kalichman PhD

Dr. Kalichman cited various policy statements from the National Academies of Sciences and the CIRM suggesting SCRO committees provide educaton and training regarding stem cell research ethics. In response to these requirements, the San Diego Research Ethics Consortium developed an ethics-training requirement (see summary Appendix D).

The Consortium includes an initial training requirement and a continuing education requirement for all individuals performing human embryonic stem cell research. To date, initial training has been conducted through frequent in person session, but more recently, an online training module has been developed to satisfy the initial training requirement. The goal of the training program is to create a community in which ethical challenges and regulatory responsibilities are know and understood. One challenge for this program is balancing this goal against resistance to imposing additional requirements on researchers.

During discussion Dr. Kalichman indicated the training program has support from leader in the San Diego Consortium. This “high-level” support has served to create a positive attitude among researchers. The program uses a discussion format (rather than lecture) to engage participants. Participating in a discussion seminar often satisfies the continuing education component. Topics tend to focus on contemporary issues in the field of stem cell research.

Major Themes from Discussion and Surveys:

- Some participant indicated that their institutions have ethics-related training but a majority reported they had no formal training programs.
- There was interest in the on-line training module among participants.
- There was a general sense that training was useful, based on the presenter’s experience and feedback from participants.

Session 5: Emerging Considerations in Human Subjects Research

Moderator: Steve Peckman

This session covered a range of issues related to research oversight including human subjects research. Early discussion concerned the role of the SCRO committee in the context of an institutions overall program of research oversight including assuring the appropriate use of eggs and embryos, described by the NAS as a "precious resource" versus the traditional role of the IRB to ensure the ethical and legal acquisition of somatic cells, such as skin and blood, as well as materials with linked identifiers to living individuals.

The presenter posed questions regarding the "added value" of SCRO committees, specifically in the review of research that is the established domain of the IRB such as prospective collection of human biological materials, such as skin and blood, and clinical stem cell research (clinical trials). He asked the attendees to question what SCROs do, why SCROs do it, and to ensure that SCRO oversight is for a good reason that avoids delaying research, and wasting resources and time through redundant review. The presenter provided the perspective that IRBs are already obligated to address core ethical and regulatory concerns related to human subjects protection. The presenter then posed the question whether a separate committee is necessary.

Discussion of the SCRO role in the context of research oversight generated lively discussion. In discussion and written comments, some participants articulated the view that SCROs play an important role addressing "new" or novel issues related to stem cell research. Examples were raised where duplicative review did "catch" issues not identified by another review body suggesting value in redundancy. One participant pointed out that the existence of SCRO committees to oversee stem cell line derivation was repeatedly cited in Congressional policy deliberations to support expansion of federal funding.

There was general consensus that the oversight process could be streamlined. In some cases overlapping reviews resulted in redundancy without demonstrated benefit. Some participants suggested the SCRO function is best served as an advisory body or sub-committee to the IRB rather than a separate committee. It was also suggested that SCRO committee review be limited to issues not otherwise addressed through existing regulatory oversight. Recent amendments to the California state Guidelines were cited as an example where SCRO review has been narrowed to focus on use of gametes and embryos and the introduction of hESCs to animals.

This session also reviewed issues that emerge in clinical trials. The presenter asked the attendees whether stem cell based clinical research poses

substantively new questions that require SCRO review? Most participants indicated that their IRBs were experienced in the review of cell based clinical research. Considerable focus was given to the existing requirement for IRBs to provide risk/benefit review of human trials. The presenter presented evidence to suggest that the established system of review and safety monitoring has proved effective. One participant suggested the special knowledge gained by SCRO committees could serve to inform risk/benefit considerations in clinical trials. To be most effective, it may be important to consider how expertise can be shared across the state or country. For example, could CIRM convene experts in cell trials to inform future clinical trials?

Major Themes from Discussion and Surveys:

- There is redundancy built into the research oversight and stem cell research specifically. Serious consideration should be given to whether each "layer" of oversight adds value to the research and the protection of the donors and recipients of cells.
- The NAS will be considering similar issues in August 2009. Given that CIRM regulations are based on the NAS Guidelines, consideration should be given to the committee's recommendations.
- It may be helpful to identify mechanisms where experience resulting from the planning and implementation of trials involving cell based therapies can be shared.

Major Recommendations

1. Strive for greater consistency with state and federal guidelines and regulations.

   Most major research institutions are dealing with three sets of rules (CIRM, CDPH and NIH). Some of the proposed amendments to the CIRM regulations actually make the institute policies less compatible with state law and the NIH Guidelines (see Appendix C). CIRM should review these proposed changes in light of the revised state Guidelines and NIH policy.

2. Create or identify of list of compliant hESC lines.

   Redundant review of hESC lines is inefficient. There should be a mechanism for identifying already approved lines. Lines listed in the NIH registry should be available without further review by SCRO committees.

3. Clarify regulatory requirements regarding notification procedures for SCRO committees.

   Requiring the SCRO to “confirm” all approvals are in place and correspond to the protocol under review is a potential burden. It might be more efficient to allow this responsibility to be delegated to a coordinating office. Leave the exact arrangement to the individual institutions.

Appendix A-C

APPENDIX A: FINAL AGENDA

CIRM SCRO Workshop
San Francisco Airport Museum

Tuesday June 30th

9:00am- 9:30am **Breakfast**

9:30am- 9:45am

Welcome and Introduction
Marie Csete, CIRM

9:30am – 11:00am

1. **Panel & Group Discussion: What is effective oversight of stem cell research?**
   Moderator: *Susan Stayn, Stanford*

   - Experience with a SCRO committee from a management, workload and expertise perspective. How committees fulfill their mission: two perspectives
   - How does CIRM view the SCRO role in supporting grants management and compliance?

11:00am –11:15am **Break**

11:15am – 12:15pm

2. **Presentation and Group Discussion: What is new in the regulatory / policy arena?**
   Moderator: *Geoffrey Lomax, CIRM*

   CIRM regulatory update:
   - What the revisions to CIRM regulations mean for SCRO operations
   - New CIRM resources to support compliance
   - How does CIRM evaluate regulatory compliance?

   NIH Guidelines for Human Stem Cell Research:
   - Critical difference(s) between draft NIH Guidelines and CA / CIRM policy
   - How do we move forward to support greater harmonization of research guidelines / regulations?

12:15pm – 1:30pm **Lunch**

1:30pm – 3:00pm

3. **Panel & Group Discussion: Acceptable derivation and the evaluation of research materials**
   Moderator: *Sidney Golub, UC Irvine*

   Keynote: Rob Streiffer, University of Wisconsin
   Retrospective evaluation of established cell lines:
   - What issues emerge in evaluating existing cell lines for provenance?
   - What are the “tough-calls” that SCRO committees encounter?

   Prospective verification of provenance for new cell lines:
   - What has CIRM proposed for provenance verification and why?
   - What is the value of this approach nationally?
   - What is the experience of institutions implementing this approach?

3:00pm – 3:15pm **Break**

Tuesday June 30th

3:15pm – 5:30pm

4. **Presentation and Group Discussion: Ethics training: Required, voluntary, or unnecessary?**
   Moderator: *Michael Kalichman, UCSD*

   - Approaches to ethics training
   - What has been the value of ethics training for institutions?

6:00pm	**Dinner TBD**

Wednesday July 1st

8:30	**Breakfast**

9:00am- 9:45am

5. **What are the participants' thoughts and perceived needs?**
   Moderator: *Geoff Lomax, CIRM*

   - What are the responses to our survey questions?
   - Are there unmet needs with regards to compliance?
   - What state and/or national resources would be valuable?

9:30am – 11:00am

6. **Presentation and Group Discussion: Emerging considerations in human subjects research**
   Moderator: *Steve Peckman, UCLA*

   - The use of identifiable cells and cell lines in clinical research: new issues
   - Tracking patients

11:00am –11:15am Break

11:15am – 12:15pm

7. **Group discussion, what are the key themes and/or specific needs CIRM or other organizations should consider in future policy development?**
   Moderator: *Marie Csete, CIRM*

   - What are the needs for California?
   - What are the needs nationally?
   - What are the needs internationally?

12:15pm –1:00pm LUNCH

California Institute for Regenerative Medicine (CIRM) Workshop

Oversight of Stem Cell Research:

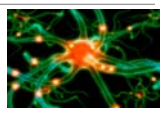
Practical Considerations

Celia Molvin
Sr. IRB Lead Manager
Stanford University
June 30, 2009

Introduction

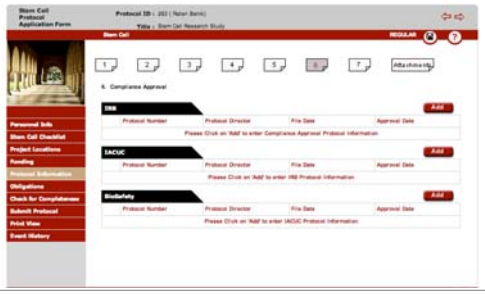
- A short list of topics
  - Documentation of Compliance
  - Reviewer System and Review Type
  - SCRO Membership Considerations
  - eProtocol as a Tool

Documentation of Compliance



1. Documentation of Compliance of Other Mandated Review Bodies
   IACUC, IRB, Biosafety
   a. Parallel Review
   b. Cross-Panel memberships
   c. Approval: Necessary but not sufficient
   d. eProtocol

eProtocol Tracking



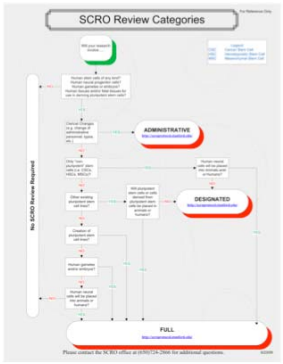
4

Review Types

- Changing Regulations means Changing SOPs
- Regulations in flux
  - NIH, CIRM, CDPH
- Flow Chart Guidance

5

Flow Chart



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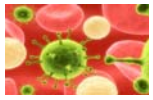
Reviewer Systems

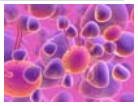


- New Full (Convened) Review
  - 3 Reviewers; 1 Presenter
- New Designated (Nonconvened) Review
  - 1 Reviewer
- Renewal Review – Full
  - 1 Reviewer / Presenter
- Renewal Review – Designated
  - 1 Reviewer
- Revision Review – Full or Designated
- Administrative Review
  - Staff

Written Notification?

7

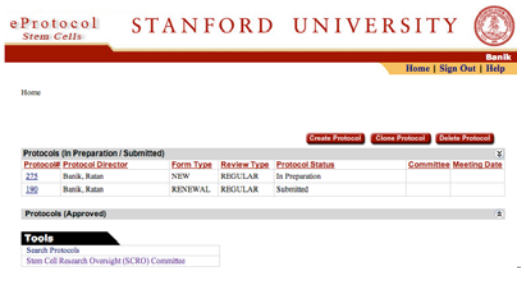
Membership Considerations



- Scientific Expertise
  - Neurosurgery, Psychiatry, Dermatology, Cardiology, Neurology
- Expertise in Assisted Reproduction
  - OB-GYN
- Expertise in Ethical Issues
  - Law, Biomedical Ethics
- Nonscientist Member of the Public
- Patient Advocate
- Stanford's Team Approach & Quorum

8

eProtocol Submission – Researcher Home Page



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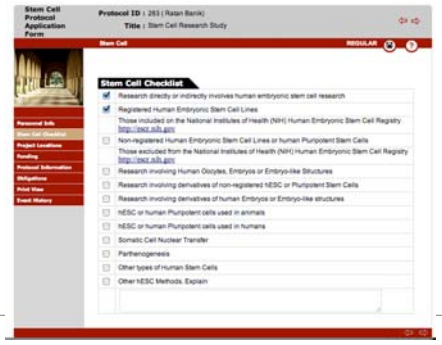
Stem Cell Checklist – Protocol Application



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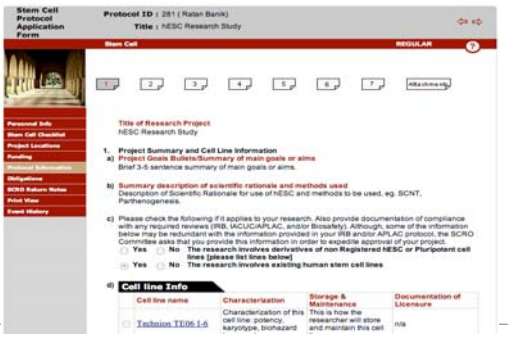
Funding – eProtocol Application

11

Protocol Information



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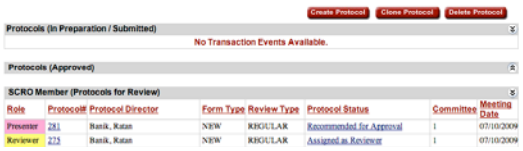
Reviewer Roles – Reviewer Home Page



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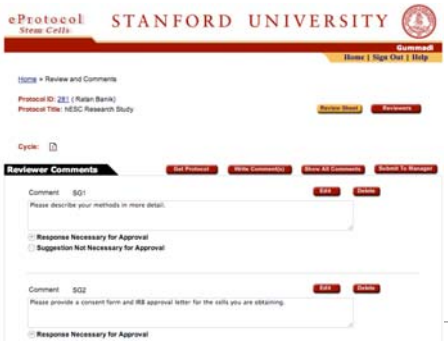
eProtocol Review – Reviewer/Staff View



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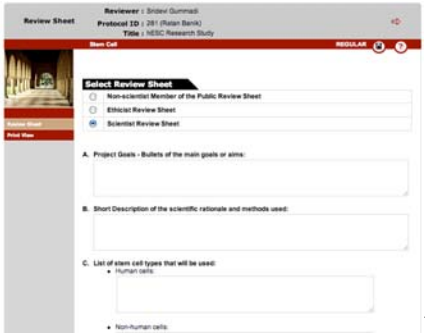
Review Sheets – Reviewer View



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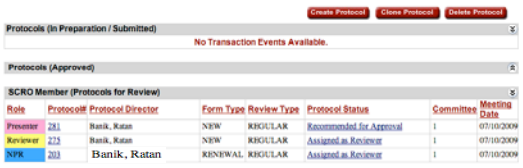
Non-Primary Reviewer Access – Reviewer Home Page



Agenda List – Staff view

Questions?

Oversight of Stem Cell Research:
Practical Considerations

Llewellyn Cox PhD
SCRO Administrator
City of Hope
June 30th, 2009

CIRM SCRO Workshop

Stem Cells @ City of Hope

11 PIs

7 "Presidential" hESC lines

2 "non-Presidential" hESC lines

1 NSC line (for in vivo study)

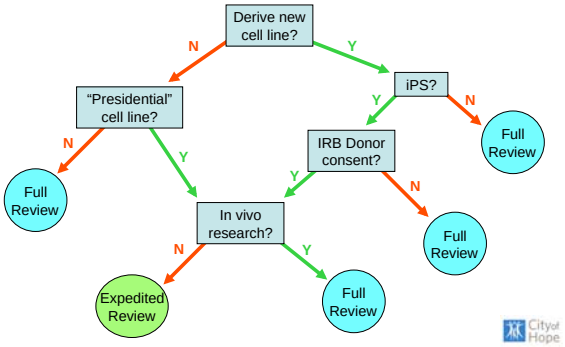
3 iPS lines

SCRO Committee

Full (Voting) Members (9):
- Research Faculty (6, including Chair)
- Bioethicist (Chair; Ethics Committee)
- Patient Advocate
- Community Member

Associate (Non-Voting) Members:
- SCRO Administrator
- Director, Research Subj. Protection
- General Counsel
- Biological Safety Officer
- Chair, OSBC
- VP Basic Research

SCRO Proposal Triage



Full v. Expedited Review

Full Review:
- Full committee (voting & non-voting members) meets quarterly
- Ethical Issues
- Subjects Protections
- Appropriateness of research
- Permissions obtained/sought from other reg. committees
- Vote is by simple majority of quorum

Expedited Review:
- Voting members are sent proposal electronically
- In vitro work only with proven provenance lines
- Approves protocol, or refers to full review (no denials)
- One vote to refer to full review is sufficient

City of Hope

Session 2:

CIRM regulatory update:

What the revisions to CIRM regulations mean for SCRO operations
New CIRM resources to support compliance
How does CIRM evaluate regulatory compliance?

NIH Guidelines for Human Stem Cell Research:

Critical difference(s) between draft NIH Guidelines and CA / CIRM policy
How do we move forward to support greater harmonization of research guidelines / regulations?

Proposed Revisions to CIRM MES Regulations June 2009

Section 100070	SCRO	IRB	IACUC
(a) procurement or use of oocytes	Full review	Full review	
(b) use of human embryos	Full review	Possible	
(c) use of gametes or embryos to derive a covered stem cell line	Full review	Possible	
(d) in vitro research with covered stem cell line or reprogramming (iPS)	Notification*		
(e) introduce covered stem cell line to animals	Full review		Yes

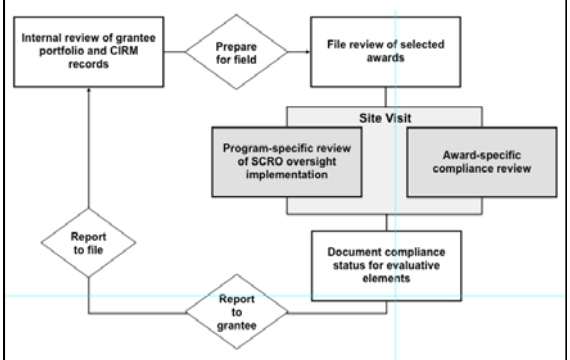
* Subsequent introduction of pluripotent cell line to animals should have full review (e)

Proposed Revisions to CIRM MES Regulations June 2009

Section 100090	Comment
(a)(1) Embryos created prior to 8/13/08, for which the gamete donor was paid, may be used in CIRM research	Designed to enable use of IVF embryos created from paid oocyte donors
(a)(2) Oocyte donor consent acceptable for embryos created prior to 11/22/06	Recognizes that consent from each gamete donor may not have been standard of care prior to CIRM / NAS regulations and guidelines
(c) For somatic cells procured after 11/22/06 and research is designed to develop a transplantation product, consent for human transplantation required	

New CIRM Resources to Support Compliance

How Does CIRM Evaluate Regulatory Compliance



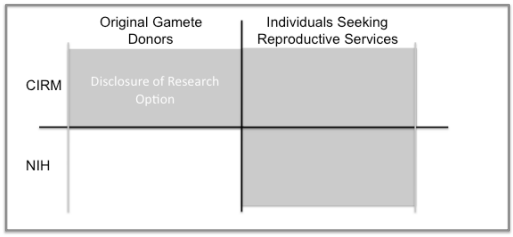
How Does CIRM Evaluate Regulatory Compliance

Exceptional	Adequate	Opportunities to Enhance
• Committee constituted according to guidelines / regulations • Well documented procedures and policies (e.g. expedited vs. full review) • Systematic "intake" process for investigators • Documentation / minutes reflect "core" considerations relevant to protocol • Approval letters correspond to minutes / agendas • Documentation of interaction between ESCRO and investigator in "tough" cases; evidence of protocol modification • Committee members share anecdotes concerning protocols under review	• Committee constituted according to guidelines / regulations • Procedures and policies, but may be inconsistent with approval letters (e.g. expedited vs. full review) • Approval letters correspond to minutes / agendas • Minutes exist for specific protocol	• Committee constituted according to guidelines / regulations • No clear procedures and policies or policies vague / not specific to ESCRO process • Disorganized minutes or agendas inconsistent with approval letters • General indicators that committee is unaware of research activities

Critical Difference(s) Between draft NIH Guidelines and CA / CIRM Policy

CA/CIRM: Donors of gametes, embryos, somatic cells or human tissue gave voluntary and informed consent

NIH: Written informed consent was obtained from individual(s) who sought reproductive services



UCI hSCRO: Human Stem Cell Research Oversight Committee

Sidney H. Golub, Ph.D.
CIRM Workshop
June 30, 2009

UCIrvine

UCI hSCRO Mandate

- Scientific review – Is this a study that will advance science and medicine?
- Policy review – Is this a study that ought to be done at UCI?
- Coordinate with IRB review of human subject issues and consent process
- Coordinate with IACUC, IBS, COI and other regulatory functions
- Educational role

UCIrvine

hSCRO Anticipated Issues

- Nuclear transfer technology raises the possibility of human reproductive cloning.
- Research use of human-animal 'chimeras' might alter our definition of 'human'.
- Defining the consent process and the rights of the donors of the genetic material.
- Pluripotent cells *in vivo*
- Compliance with CA/CIRM regulations

UCIrvine

The Investigator's View of a SCRO

The Experiments that the SCRO Suspects the Investigator Really Wants To Do

UCI hSCRO

- Started October, 2005
- 10 members appointed by VC Research for 3 year terms
- Stem cell science (3)
- Clinical investigation, ART (2)
- Ethics (1)
- Community representatives (3)
  - Patient advocates (2)
  - Moral philosophy/theology
- Science policy, IRB liaison (Chair)
- Alternates (3: ethics, 2 clinical)

UCI hSCRO: Summary June, 2009

- Total: 126 Reviews
  - 91 Full Committee, 35 Expedited*
- 39 New Protocols reviewed
  - 28 Full, 11 Expedited
- 50 Continuing Protocols
  - 34 Full, 16 Expedited
- 37 Protocol Modifications
  - 29 Full, 8 Expedited

UCIrvine

*Expedited -- *in vitro* studies with cell lines of approved provenance or minor modifcations

Cell Types Used

- 32 using already established cell lines
  - 2 lines of doubtful provenance
  - 2 sets of lines of foreign origin required translated documents
  - 1 group of lines from parthenotes
- 7 derivations using adult cells
  - 3 with iPS
  - 4 other adult or fetal cells
- 3 derivation of new embryonic cell lines
  - 2 from blastocysts
  - Oocytes for SCNT or parthenogenesis

UCIrvine

hSCRO Issues Encountered

- The consent process and the rights of the donors of genetic material
- Provenance of cell lines
- Compliance with CA/CIRM regulations
- Pluripotent cells *in vivo*

UCIrvine

Informed Consent and the NIH Registered Cell Lines

Advancing the Field:
Institutional Approaches Supporting Ethics in Stem Cell Research
June 30 – July 1, 2009
California Institute for Regenerative Medicine
San Francisco, California

Robert Streiffer, Ph. D.
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Overview

- Review of the Problems
  - Update on BresaGen Lines
  - Update on Cellartis Lines
  - Update on WARF Lines
- The Persistent Problem

Review of the Problems

- Streiffer, Robert. 2008. "Informed Consent and Federal Funding for Stem Cell Research." *Hastings Center Report* 38(3): 40-47
- Streiffer, Robert. 2008. "Response to Robertson, Hyun, and Cohen." *The Hastings Center Report* 38(6): 5.

Some Ethical Starting Points

- The Weaker Retrospective Thesis: Other things equal, performing research with existing hESC lines derived with higher quality consent is ethically preferable to using existing hESC lines derived with lower quality consent.
- The Stronger Retrospective Thesis: It is ethically permissible to perform research using an existing hESC line only if the embryo donors provided informed consent.
- The Prospective Thesis: It is ethically permissible to derive a new hESC line from an embryo only if the embryo donors provided informed consent.

CIRM and the Ethical Theses

§100080 Acceptable Research Materials: All covered stem cell lines used in CIRM-funded research must be "acceptably derived"

a) To be "acceptably derived," the stem cell line must meet one of the following criteria:
   1) Recognized by an authorized authority
      A. NIH (Bush): The Stronger Retrospective Thesis
      B. UK Stem Cell Bank: The Stronger Retrospective Thesis
      C. UK Human Fertilization and Embryology Authority (HFEA): The Prospective Thesis
      D. Canadian Institutes of Health Research (CIHR) Guidelines: The Prospective Thesis and the Stronger Retrospective Thesis
      E. Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells: The Prospective Thesis and the Stronger Retrospective Thesis
      F. §100090 Additional Requirements for CIRM-Funded Derivation: The Prospective Thesis
   2) The stem cell line *is* derived from human … embryos … under the following conditions:
      A. Donors of human … embryos … *gave* voluntary and informed consent.

The Stronger Retrospective Thesis

- Bush's 2001 Policy
- Clinton's 2000 NIH Guidelines
- Castle-DeGette Bill
- Obama's NIH Draft Guidelines

Two Kinds of Problems

- Restrictions: The consent process included language that set limitations on the research in which the cell lines can be used.
- Omissions: The consent process failed to disclose important information about the research in which the cell lines would be used.
- The ethical basis of informed consent provides ethical reasons for limiting the use of the NIH lines to research that respects the restrictions imposed by the consent forms and that falls within areas about which donors were adequately informed.

Two Kinds of Problems

- Restrictions: The consent process included language that set limitations on research in which the cell lines can be used.

  §100100 Informed Consent Requirements: "when CIRM funded research involves the donation of human … embryos … for derivation of new covered cell lines … CIRM-funds may not be used for research that violates the documented preferences of donors with regard to the use of donated materials."

  – Why only for lines derived under CIRM funds?
  – Is a signed consent form with an explicit restriction treated as a documentation of a preference?

Problematic Omissions

1. The nature of the research, esp. with regard to activities that donors could find morally objectionable
2. That the cells will be cultured indefinitely and shared with other researchers
3. The voluntary nature of donation, esp. that medical care will not be affected either way
4. That the embryos will be destroyed in the research
5. Risks of regret and breach of confidentiality

Omissions: BresaGen

- "if fertilization occurs with too many sperm or if embryos form but are not developing or living, scientific study of these may be undertaken."
- Omits:
  1. The nature of the research, esp. with regard to activities that donors could reasonably find morally objectionable
  2. The duration of the research and whether the materials will be shared with other researchers
  3. The voluntary nature of donation, esp. that medical care will not be affected either way
  4. That the embryos will be destroyed in the research
  5. Risks of regret and breach of confidentiality

BresaGen's Response

- "The original IVF consent form clearly stated that discarded embryos could be used for research. Because the embryos were used without cryopreservation there was not an opportunity to obtain a second specific consent to use these embryos for derivation of human ES cells. We discussed this with the IVF clinic and they did not want to obtain a second consent while their patient was undergoing an IVF process as they felt this could add undue stress. …. The embryos used by us had the IVF consent in place with permission to use embryos of insufficient quality for research. The embryos had no identifiers so it is not possible to go back and obtain consent after the fact." Wisconsin State Journal, September 22, 2008

Omissions: Embryo Destruction

- UCSF only: "The embryos will not survive the stem cell derivation process"

  The other forms did not clearly state that the embryo would be destroyed.

Omissions: Risks

- UCSF and UW only: Loss of privacy if confidentiality of subjects' records is breached
- All the forms omit to mention the possibility of regret if a donor changes his or her mind after the embryo is destroyed

Omissions: Chimeras

- All of the forms omit to tell donors that cells derived from their embryos might be used to make human/nonhuman chimeras
- No direct, systematic data on donor attitudes, but:
  - General negative tenor of public discussion
  - Systematic data on attitudes towards species-mixing in other contexts (transgenic plants and animals) indicates significant moral discomfort

Omissions: Chimeras

Source	Plants	Animals
OTA (1987)	6.6 (out of 10) average acceptability with genetically modifying plant cells	5.3 with animal cells
Hoban et al. (1992)	23% opposed plant GE	53% opposed animal GE
Rutgers Food Policy Institute (2002)	37% disapproved strongly or somewhat of GE plants; 22% said it was wrong	68% disapproved strongly or somewhat of GE animals; 55% said it was wrong
Pew (2003)	6.08 mean comfort level	2.81 mean comfort level
Pew (2003)	81% said that producing more affordable pharmaceuticals was a good reason to genetically modify plants; 14% said it was a bad reason	49% said that it was a good reason; 42% said it was a bad reason

Restrictions: Cellartis

- "In this current project we only wish to develop a technique for longer-term cultivation of those cells which otherwise had been rejected. …. After the studies are completed all cells will be destroyed."
  - August 9, 2001: Placed on the NIH Registry
  - October 2003: Received permission to send cells to Canada without reconsenting
  - April 2004: Received permission to reconsent donors regarding sharing of cells (1 couple withdrew)
  - 2nd FOIA: NIH never received, much less reviewed, the form used to reconsent the donors.

Restrictions: Technion-Israel

- Consent form: "I am free to stop my participation in the experiment at all times."
- MTA: "Upon termination of the Research Program, the Recipient and the Recipient Scientist shall return all Material to the Provider, or upon the Provider's request, destroy the material and advise the Provider in writing of such destruction."

Restrictions: WARF

- "Because of these embryonic properties, certain experiments which would be controversial for whole human embryos would be controversial for these cell lines. In particular, two experiments that will not be performed with embryonic cell lines derived from this study are: (i) Intermixing of human embryonic cells with an intact embryo, either human or nonhuman…."

Restrictions: WARF

- "Embryonic cell line": refers to source rather than pluripotency

Restrictions: WARF

- "Embryo"
  - Scott Gilbert, *Developmental Biology: "the* study of animal development has traditionally been called embryology, referring to the fact that between fertilization and birth the developing organism is known as an embryo."
  - Merriam-Webster's: "a vertebrate at any stage of development prior to birth or hatching"
  - OED On-Line Dictionary: ""The offspring of an animal before its birth (or its emergence from the egg) "

Restrictions: WARF

- "Embryo"
  - Merriam Webster's: "an animal in the early stages of growth and differentiation that are characterized by cleavage, the laying down of fundamental tissues, and the formation of primitive organs and organ systems"
- UW SCRO
  - No introductions of WARF's original lines through Carnegie Stage 23 (mice E16; rats E17.5; chicks E10; pigs E32.5)
  - Preference for performing introductions through Carnegie Stage 23 only using lines derived under consent forms that informed donors of this possibility (such as WA15 and WA16), when doing so does not hinder the research objectives.

The Relativity of "Informed Consent"

- Consent can be informed vis-à-vis one research project but not informed vis-à-vis another.
  - E.g., Cellartis, prior to reconsenting; WARF lines for introduction into an embryo
- Any ethical reason for preferring or requiring that research using already existing hESC lines be performed with lines derived with informed consent from embryo donors is really a reason for preferring or requiring that research be performed with lines derived with informed consent *for that research.*

The Persistent Problem

- The Even Stronger Retrospective Thesis: It is ethically permissible to perform research using an existing hESC line only if the embryo donors provided informed consent *for that research*.
  - Pluripotent cells obtained from embryos → informed consent
  - Already existing, anonymized cell lines → generic consent or no consent
- Significant conceptual tension in trying to obtain informed consent for unanticipated, unspecified future uses
  - Informed waiver of informed consent

Arguments for Waiving Retrospective Requirement for Informed Consent

1. Until the National Academies' Guidelines were published in 2005, no one had thought about informed consent in the context of procuring embryos for research.

- Objections
  - HERP (1994)
  - ASRM (1997)
  - NBAC (1999)

  HERP (1994): "These concerns [about consent to embryo donation] parallel concerns addressed by well-established ethical guidelines for all human research."

Arguments for Waiving Retrospective Requirement for Informed Consent

2. All legitimate research uses of already existing anonymized cell lines are exempt from the federal human subjects regulations altogether (2004 OHRP Guidance on Research Involving Coded Private Information or Biological Specimens)

- Objections
  - Regulatory compliance is not, in general, sufficient for ethical permissibility
  - Overly narrow view of people's rights and interests in even their run-of-the-mill donated human biological materials
    - Washington Post this morning: "Some Samples Are Stored and Used For Research Without Parents' Consent"
  - Especially narrow view of people's rights and interests in the disposition of their embryos
  - Goes much farther than people are (rightly) willing to (publicly) go; poses significant threat to public trust in the scientific research enterprise
  - Still would not be in compliance with guidelines and policies that implement the Stronger Retroactive Ethical Thesis

Arguments for Waiving Retrospective Requirement for Informed Consent

3. All legitimate research uses of already existing anonymized cell lines satisfy the conditions for 45 CFR 46.116(d).
   - No more than minimal risk
   - Waiver will not adversely affect the rights and welfare of the subjects
   - The research could not practicably be carried out without the waiver
   - Whenever appropriate, the subjects will be provided with additional pertinent information after participation

Arguments for Waiving Retrospective Requirement for Informed Consent

3. All legitimate research uses of already existing anonymized cell lines satisfy the conditions for 45 CFR 46.116(d).

- Objections:
  - Regulatory compliance is not, in general, sufficient for ethical permissibility
  - Overly narrow view of people's rights and interests in even their run-of-the-mill donated human biological materials
  - Especially narrow view of people's rights and interests in the disposition of their embryos
  - Consent form language can generate rights, both in terms of explicit restrictions and in terms of inferences donors might make about the scope of research based on omissions
  - Still would not be in compliance with guidelines and policies that implement the Stronger Retroactive Ethical Thesis

Embryos Are Not Viewed as Analogous to Residual Blood Spots

- Wendler (2006): In 4 out of 5 studies reviewed, 93-99% of people expressed a willingness to donate leftover samples for research; in the other 83% did
- Syrop et al. (1995): 9% chose to donate surplus embryos for research; 44% chose discard over donate to research
- McMahon et al. (2003): 10% probable, 34% possible that they would donate their surplus embryos for research
- Bangsbøll et al. (2004): 57% expressed willingness to donate surplus embryos for hESC
- Lyerly and Faden (2007): 50% of couples with cryopreserved embryos would be willing to donate surplus embryos for hESC research
- Costs of a false positive are vastly different

Upshot

- Those involved in the hESC research enterprise—providers, distributors, intellectual property holders, researchers, IRBs, and ESCRO committees—should consider whether their commitment to informed consent requires limiting the use of some of the hESC lines on the NH registry, and should not presume that the consent processes have been adequately reviewed either by the NIH or by the NAS.
- Use of the BresaGen lines is incompatible with a commitment to only using hESC lines derived with informed consent from the embryo donors.
- Use of the WARF lines should exclude the introduction of those lines, in their pluripotent or more specialized forms, into embryonic animals.
- Some of the consent problems are easy to resolve as we go forward with improved consent processes, but there is a larger issue arising from the tension between the desire for informed consent in the context of hESC research and the desire for generic or no consent in the context of already existing, anonymized cell lines. Informed waiver of informed consent is a promising strategy for relieving this tension in the future.

Ethics training: Required, Voluntary, or Unnecessary?

Michael Kalichman
SCRO Workshop
June 30 – July 1, 2009

Is ethics education required?

National Academy Guidelines:
ESCRO Committees are charged with facilitating education of investigators

"To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution should have activities involving hES cells overseen by an Embryonic Stem Cell Research Oversight (ESCRO) committee."

National Academies' Guidelines for Human Embryonic Stem Cell Research, 2008 Amendments

Is ethics education required?

CIRM MES Regulations:
SCRO Committees are charged with providing an "ethical" review.

"The designated SCRO committee shall provide scientific and ethical review of CIRM-funded research consistent with the requirements of Section 100070 and other applicable CIRM requirements."

Title 17 California Code of Regulations Section 100060(c)

Is ethics education useful?

Challenges
- Scrutiny, Risk of missteps
- New compliance responsibilities
- Scientific Integrity

Goal
- Create community in which ethical challenges and regulatory responsibilities are known and understood.

Barrier
- However, this has to be balanced with potential resistance to imposing additional requirements.

What do we do in San Diego?

San Diego Research Ethics Consortium:
Burnham, Salk, and Scripps, plus UC San Diego

Shared resources: ethics education, outreach and review

Audience: Community, not individual

Goals: Sensitivity, positive attitude, awareness of review requirements

Education requirement

1. Initial training
2. Continuing education
3. Exemption

Discussion Questions

What are other institutions doing?

Is it useful?

Do the benefits outweigh the costs?

Voluntary or required?

Identifiable cells, cell lines, and clinical trials: IRB/SCRO

Yorgos Nikas, MD, National Geographic: 2005

July 1, 2009

Steven Peckman
University of California, Los Angeles
Eli & Edythe Broad Center of Regenerative Medicine and Stem Cell Research

Human Subjects Research: Have SCROs Outlived Their Utility?

The Christian Science Monitor Bennett

What is the intent of SCRO review in the context of research interactions and interventions with human subjects?

Oversight Committees

- Institutional Review Board (IRB)
- Institutional Animal Care & Use Committee (IACUC)
- Institutional Biosafety Committee (IBC)
- Medical Radiation Safety Committee (MRSC)
- Scientific Peer Review Committee (SPRC)
- Gene Medicine Committee
- Data & Safety Monitoring Board (DSMB)
- Conflict of Interest (COI)
- Stem Cell Research Oversight Committee (SCRO)

What expertise does SCRO provide that is relevant to and absent from IRB review?

Is a separate committee necessary?

IRB Review: Membership & Expertise

- Sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel and safeguard the rights and welfare of human subjects
- Professional competence to review and assess the research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice.

45 CFR 46.107 & 21 CFR 56.107

Comparison of SCRO and IRB Membership and Duties as Defined by CIRM and Federal Regulations

	SCRO	IRB	Scientific Peer Review
MEMBERSHIP			
Scientific expertise	Yes	Yes	Yes
Medical clinical trial expertise	No	Yes	Yes
Ethics expertise	Yes	Implied	No
Community (non-scientist)	Yes	Yes	No
Diversity of membership (race, gender, culture)	Not required	Yes	No
Biostatistics	No	Often but not required	Yes
Pharmacist	No	Often but not required	Yes
RN	No	Often but not required	Yes
DUTIES			
Scientific evaluation	Yes	Yes	Yes
Ethics	Yes	Yes	No
Risk:Benefit analysis	Yes	Yes	Yes
Informed consent	Yes	Yes	No
Accrual	No	Yes	Yes
Education	Yes	Yes	Yes

Novel Challenges?

- New ethical & regulatory issues in the obtaining of cells from living individuals and creating new cell lines?
  - Collection of somatic cells, gametes, or embryos
  - Collection & use of somatic cells for iPSC research

August 7, 2006

February 9, 2009

Cell Based Clinical Trials

- Risks: the novelty and unpredictability of early stem cell based clinical research
  - Known toxicities from similar research or relevant animal models
    - May not accurately reflect human disease or predict toxicities
    - May not provide full prediction of immune or other biologic responses in humans
    - = Unknown toxicities
  - Inability to control proliferation of cells
  - Differentiation potential (unipotent v. pluripotent)
    - Integration of cells into unintended tissue
    - Act on several different targets with both detrimental and beneficial effects
    - Risk of tumor formation
    - Transplants persisting for many years with actions that are irreversible necessitating careful subject monitoring and long-term follow-up
  - Worsening condition or disability

IRB Protocol Review

- Risk/Benefit Calculation
  - Donor suitability
  - Clinical Protocol & Investigator's Brochure
    - Basic and pre-clinical animal research
    - Mechanism, route and dose of administration
    - Toxicology
    - Other data
- Respect for persons
  - Recruitment of subjects
  - Informed consent process & document
- Equitable selection of subjects
- Continuing review

Risk/Benefit Assessment

- Subject selection
  - Patients v. non-patients
  - Patient v. patient
    - Older v. younger
    - Adult v. minor
    - Earlier v. later disease
    - Standard of care v. Treatment naïve
- Initial and Continuing Protocol Review
- Long Term Follow-up

Post-Approval Monitoring

- Continuing Review: "An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year" *45 CFR 46.109(e)*
  - IRB continuing review responsibilities include reviewing reports of adverse reactions and unexpected events involving risks to subjects
  - Information that may impact on risk/benefit ratio should be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the subjects. Based on such information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

David Lepay, MD FDA: 2001

Post-Approval Monitoring

- On-going monitoring: "When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects." *45 CFR 46.111(a)(6)*
- Adverse event review
- Data and Safety Monitoring Plans
  - Appropriate analysis of the progress of the research and adverse event reports
  - Real time or delayed monitoring and recommendations
    - Enrollment
    - Study procedures
    - Data quality
    - Adherence to protocol
    - Toxicity
  - May suspend or recommend early termination of the research
    - Due to safety concerns
    - Inadequate performance or accrual
    - Research objectives attained or unattainable

Long Term Follow-up

- Cell based research may need long term follow-up of subjects to ensure safety of current and future recipients of the product and maximize generalizable knowledge:
  - Life time follow-up in gene transfer research
  - Quality of life
  - ISSCR: Transplants persisting for many years with actions that are irreversible necessitating careful subject monitoring and long-term follow-up

Role of SCRO v. IRB

- In the current human research context…
- What value is added by SCRO review of clinical research?
- Is SCRO review redundant?
  - If so, does redundant oversight provide added value in ensuring ethical and scientifically valid research?
  - What is the cost and benefit?

Steven Peckman
Eli & Edythe Broad Center of Regenerative Medicine and 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.