CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Advancing Effective Research Oversight: CIRM's Evaluation Initiative Regional Workshop Summary Report

Introduction

CIRM's mission is to support and advance stem cell research and regenerative medicine under the highest medical and ethical standards for the discovery and development of therapies and cures. 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. This policy development process is described in *Advancing Effective Research Oversight: CIRM's Evaluation Initiative*. This document describes the results from two regional workshops.

CIRM sponsored two regional workshops to create a peer learning environment where representatives of nonprofit research institutions could discuss their experiences implementing the Medical and Ethical Standards (MES) regulations and identify any issues that may have emerged. The first workshop was held at Stanford University on February 9, 2007 and the second on April 6, 2007 at the Burnham Institute for Medical Research. Each three hour workshop started with a short overview of the CIRM evaluation initiative followed by facilitated discussion. The discussion was divided into four segments corresponding to major requirements of the MES regulations – (1) scientific and ethical review / SCRO committee requirement, (2) verification of acceptable research materials, (3) informed consent and (4) protections for research donors.

General Observations

Twenty one institutions (11 at Stanford and 10 at Burnham) attended the workshops. Participants were predominantly individuals with administrative responsibility for research oversight and IRB/SCRO committee members. Additional participants included stem cell scientists and other researchers. In general, discussion focused on practical issues related to implementation of the MES regulations. Institutional representatives frequently described the means by which they had achieved compliance with specific regulatory provisions.

At times, discussion involved compliance issues unrelated to the CIRM MES regulations. For example, institutional officials described their efforts to comply with existing California regulations and law governing stem cell research. Officials expressed hope that there would be harmonization of regulations to allow research to advance under a consistent set of requirements. Federal regulations governing human subjects protection and patient privacy (e.g. the Common Rule and HIPAA) were also discussed in the context of stem cell research. Frequently, institutions with more extensive experience and expertise implementing Federal regulations were able to offer insights to colleagues seeking to identify practical means of compliance.

SCRO Committee Requirement

This segment focused on the general requirements for establishing SCRO committees. All participating institutions had established or were in the process of establishing a stem cell research oversight committee consistent with the requirements of the CIRM MES regulations. Participants indicated that the technical expertise was easily available, but one institution indicated having a problem finding an ethicist for the committee.

There were issues raised concerning outside members and patient advocates. One concern centered on the prohibition on remuneration for outside members. The commenter indicated the institution strives for a uniform policy for all committee members as a matter of fairness and equity. Further, it is common practice to provide stipends to individuals who participate on review and oversight committees. There is no similar restriction in state or Federal law governing IRBs and no evidence to suggest that stipends undermine the efficacy of the review process. The practical consequence is that the regulations result in a differential standard for members based on affiliation.

There were questions from participants on whether there was a definition for a "patient advocate." We responded by indicating that the regulations did not define this term, but the SCRO advocate should be able to effectively represent the interest of the patient community. Further, a number of institutional representatives described how they had gone about identifying patient advocates. One participant suggested utilizing existing patient support networks indicating that from their experience there was strong interest by members in participating in SCRO committees. One participant inquired whether a patient advocate was required if the institution was not performing clinical research; we responded by indicating the patient advocate was still required for compliance with the SCRO committee requirement.

There were also questions regarding voting status and quorum requirements. Clarification was requested regarding the voting status of the patient advocate and outside member. We indicated that the outside member and patient advocate must be full members of the committee with voting authority on committee approvals. We also indicated that there was no specific quorum requirement in the regulations. Rather, it is the institutions obligation to addressed voting requirements in their procedures and polices.

Scientific & Ethical Review

This segment focused on the requirements for review of CIRM-funded research. Participants indicated that the precise scope of the CIRM MES regulations was important for providing regulatory clarity and avoiding duplicative reviews. SCRO review of CIRM-funded research is triggered by three types of research activity (1) procurement and use of human oocytes, (2) use of human embryos, and (3) derivation and certain uses of covered stem cell lines. Participants indicated that the definition of "covered stem cell line" was useful because the scope was limited to human pluripotent stem cell lines. In contrast, existing state regulations covering non-CIRM-funded research require IRBs to review research involving embryonic and adult stem cells from "any source." This broad scope is a source of confusion potentially requiring duplicative reviews. For example, one participant interpreted existing state regulations to require review of bone marrow transplants and inquired whether the CIRM regulations also require review by a SCRO. We indicated that the CIRM MES regulations do not because bone marrow does not fall within the definition of a covered stem cell line. We did not offer an opinion on existing state regulations and indicated that these existing regulations were not within CIRM's authority. Optimism was expressed that recent state legislation requiring stem cell research oversight for non-CIRM-funded research in "substantial accordance" with the National Academies' Guidelines and the CIRM MES regulations would result in consistent and compatible standards.

Because there is overlap between SCRO committee and IRB review, a number of institutional representatives indicated they were in the process of determining the best way for these committees to interact. No inherent problems in the regulations were identified. The major issues appear to be related to institutional culture where the overall review and oversight process must be adapted to accommodate an additional review body. We acknowledged the regulations were flexible with regard to the exact timing of SCRO/IRB approvals but emphasized the SCRO committee requirements for tracking and verification of necessary reviews and approvals.

Questions were raised about what constitutes SCRO committee "notification" – the regulations require the SCRO to be "notified" of all in vitro research utilizing coverend stem cell lines. We indicated that the intent of this provision was to ensure there was an active mechanism to for tracking all CIRM-funded research occurring at the institution involving use of covered stem cell lines, oocytes or embryos. Notification is a mechanism for insuring the SCRO is aware of stem cell research that it does not need to formally review and approve. One institution described a web-based system that allowed the researcher to document for the SCRO committee the stem cell lines being utilized in vitro research. This approach represents an efficient means of achieving compliance with the "notification" requirement.

Finally, in the written evaluation, one participant suggested that the CIRM sponsor a class modeled after IRB training. In the same vein, another participant indicated that it would be valuable to develop a training mechanism that focused on very practical implementation issues. The thinking is that some institutions have more experience and others are just

starting out. There was perceived benefit of having a training mechanism that focused on lessons learned.

Verification of Acceptable Research Materials

This segment focused on institutional requirements to verify that materials have been "acceptably derived" as defined by the regulations. Participants described their efforts to verify appropriate consent was provided for the derivation. The greatest challenge in this regard was verification of consent from lines derived outside the United States. Issues such as the translation of consent forms and obtaining a reasonable understanding of the consent process were identified. Participants indicated that this issue was not unique to stem cell research, and they had developed procedures to verify the consent process. Given the time and effort required to verify that lines have been "acceptably derived," however, institutional officials indicated that it would be of tremendous value to the field to maintain some type of web-based registry system to identify cell lines that are known to comply or not comply with CIRM standards, so duplicative reviews were not performed. We suggested that CIRM's focus on funding the derivation of new cell lines combined with plans to develop a cell bank could serve to expand to inventory of "acceptably derived" lines.

Participants also indicated that the regulatory provisions authorizing use of stem cell lines approved by the NIH or other jurisdictional authorities (e.g. the UK Stem Cell Bank, UK HFEA, or the CIHR – spell out) was desirable because they serve to streamline the review process. Participants noted that it would be useful to expand this approach to other states and nations as future policies become codified. Participants expressed optimism that an international consensus might be reached for cell lines. We indicated our commitment to work with other states, nations and international bodies to facilitate collaboration and exchange.

Informed Consent

This segment focused on the consent requirements of the MES regulations on embryo donation. Participants indicated that the consent requirements were clear and easily implemented from a strict compliance perspective. Further, one participant indicated in their experience couples interested in donating embryos to research are well informed because of their knowledge from the IVF experience. This knowledge brings them to the decision to donate embryos to research. Rather than focus on compliance per se, there was considerable exchange about methods of providing quality information to research participants. For example, participants talked among themselves about sharing educational materials and consent documents. Participants thought it would be useful to create a clearinghouse of materials and that future studies of embryo donors' experiences could be useful to enhancing the consent process. For example, in the written evaluation, one participant suggested providing examples of protocol review forms used at various institutions. To date, donation of oocytes for research has been limited to failed-to-fertilize oocytes from fertility clinics (discussed in the next section).

Protections for Research Donors

This segment focused primarily on donation of failed-to-fertilize oocytes from fertility clinics for research. None of the participants had experience with oocyte donation solely for research. A representative from UCSF described the protocol used by the embryo bank to ensure donation to research does not compromise the reproductive success of the woman in IVF treatment. The embryo bank achieves this objective by remaining independent of the research team and implementing a set of procedures to ensure that individuals evaluating oocytes for reproductive purposes remain unaware (e.g. blinding protocols) of the woman's decision to donate for research. A second institution described a different protocol that accomplished the same outcome.

In the written evaluation, one participant indicated a need for further review of the risk of ovarian stimulation. The participant acknowledged that the IOM/NRC report was available at the meeting but was interested in more detailed conclusions.

Summary of Major Themes

The following major themes emerged from the workshops:

- Institutions have established SCRO committees consistent with the CIRM MES regulations.
- Specific SCRO committee requirements regarding payments to outside members may conflict with established institutional review committees such as IRBs and IACUCs.
- The defined scope of the CIRM MES regulations, particularly the definition of "covered stem cell line," contributes to regulatory clarity.
- Research review and oversight would be greatly enhanced by a registry that characterized cell lines as "acceptably derived" or not acceptably derived.
- Research and the development of educational materials to support informed consent could enhance the quality and consistency of the process.
- Protocols and mechanisms exist to enable donation of failed-to-fertilize oocytes without compromising the optimal reproductive success of women undergoing IVF.

Evaluation

All participants were asked to complete a workshop evaluation form. The evaluation included questions about the topics covered and the materials provided in addition to offering the opportunity for open-ended comments. The open-ended comments relating to specific topic areas have been incorporated into the summary above. In addition, there was a general comment indicating the need for more discussion of the key topics as experience with implementation is gained. This comment was echoed during informal discussion and, as noted previously, some participants felt more formal trainings may have value.

Thirteen completed evaluation forms were received from participants. Participants were asked to consider whether the advance materials made the workshop goals and objectives clear. Eleven respondents indicated they had reviewed the materials and they made the goals and objectives clear, the remaining 2 respondents did not review the advance materials. All 13 respondents found the topics relevant and indicated they had acquired new information. As noted previously, a number of participants indicated during the workshop and in informal conversation that more detailed materials and discussion regarding the range of compliance issues would be helpful in the future.

A number of participants provided comments via e-mail after the meeting. One noteworthy comment below describes how the workshop provided the foundation for collaboration between institutions to enable SCRO cooperation. CIRM is aware of three-way collaboration between funded institutions to share expertise and perform required reviews.

- *The workshop was very helpful, both for clarification as described in your workshop summary, and because it gave us a chance to speak directly to colleagues involved in stem cell research oversight at other universities.*

- *I just wanted to add that we are a small non-profit independent research institution and through the contacts I made at the Stanford workshop were helpful. We asked [a larger institution] to have their SCRO Committee review the one CIRM grant that we have. Thankfully, they agreed and reviewed the grant for us. Therefore we did not have to build an entire SCRO Committee to review only one grant. I hope other larger CIRM recipients would extend that level of cooperation to smaller institutions such as ours.*

- *I think it was quite successful from all standpoints. There was certainly animated discussion among the participants! In addition to your obtaining feedback for the CIRM, an valuable part of the discussion was hearing how the rules came about, and why not having them specify exactly how things should be done (which can initially can be frustrating) is the best approach. Another important aspect of such a meeting is the community building among those of us involved in overseeing adherence to the CIRM MES. To that end, we look forward to getting the list of attendees, which will help in following up on our discussion of best practices. Finally, I look forward to additional discussion on how to streamline the determination that hESC lines have been acceptably derived.*

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