DRAFT: Summary 2013 CIRM ESCRO Workshop

CIRM routinely sponsors workshops to create a peer-learning environment where representatives of grantee institutions discuss their experiences implementing programs for stem cell research oversight. These interactive workshops include invited speakers, institutional representatives, the California Department of Public Health and CIRM staff. Workshops are designed to address issues pertinent to the effective implementation of oversight programs. Recommendations emanating from the workshops inform CIRM policy deliberations. Previous science policy workshop summaries may be found here: http://www.cirm.ca.gov/our-funding/publications-cirm-meetings-and-workshop.

The most recent workshop was held June 26, 2013 in San Francisco. The 2013 workshop focused on (1) the ongoing development of Embryonic Stem Cell Research Oversight (ESCRO) Committees, (2) the major activities performed by ESCRO committees and (3) models for clinical research oversight involving stem cell therapies. The following section captures the main points from the discussions of the workshop presenters and participants.

The Development of ESCRO Committees

Participants, comprised predominantly of ESCRO coordinators and members, described their oversight procedures and policies as "matured." Program characteristics include:

- Defined procedures for administrative review and full ESCRO committee review of research protocols;
- Development of information systems and other recordkeeping procedures to document compliance with CIRM and other applicable regulatory requirements;
- Ongoing "streamlining" of processes for incorporating ESCRO oversight into the institutions' broader program of research compliance. For example, combined IRB/ESCRO review of protocols to improve efficiency and knowledge sharing and to provide consistent feedback to investigators.

CIRM also reiterated the value of ESCRO committees for providing a point of contact at grantee institutions for compliance-related inquiries. CIRM frequently contacts ESCRO administrators to confirm the compliance status of awards.

A participant from the University of Connecticut ESCRO provided a perspective from another state where ESCRO requirements are in place. She expressed the view that ongoing gamete and embryo research at her institution benefited from ESCRO oversight.

Major Activities of ESCRO Committees

Participants reported administrative reviews to confirm the provenance of cell lines was a major ESCRO activity. Full reviews predominantly involved protocols where pluripotent or pluripotent-derived cell lines were transplanted to animals.

There were differing views among attendees about the value of ESCRO reviews. For example, one participant suggest that policy questions regarding the effects of pluripotent cells in nonhuman animals have been resolved and questioned the need for ongoing review. Another participant suggested animal studies at his institution were sufficiently different to warrant ESCRO consideration. As a matter of policy, this institutional ESCRO reviews all stem cell studies involving stem cell transplantation to animals regardless of the CIRM-specific regulatory requirement. It was suggested that this policy serves to educate the ESCRO members of the evolving nature of the field.

Models for Clinical Research Oversight

CIRM provided an overview of the Alpha Stem Cell Clinics Initiative. Attention was given to the proposed development of a coordinating center for the Alpha Clinic Network. The coordinating center responsibilities would include compiling and analyzing objective data to support IRBs review of clinical trials involving cell-based therapies. Participants were asked to describe challenges encountered in the review of existing trials and reflect on how a coordinating center could support future trials.

The majority of institutions with medical centers (4/5) reported performing either (1) a joint ESCRO-IRB reviews or (2) having participation by ESCRO members at the IRB review for clinical research involving cell-based therapies. One center was in the process of developing procedures for joint reviews. Based on clinical experience with a comparatively small number of trials involving cell-based therapies, participants offered the following observations:

- The IRB has a fundamental responsibility to review and approve clinical trial protocols and subsequent modifications.
- Some Phase 1 research will likely begin in populations with advanced or end-stage disease. Preliminary safety data from initial subjects may encourage sponsors and investigators to move quickly to patients with earlier stages of disease. Protocol modifications involving such rapid changes in study population (e.g. treating at an early disease stage) may present ethical and regulatory (e.g., minors) challenges for sponsors, investigators, and IRBs.
- IRBs are required to ensure there is adequate expertise to determine the research risks to patients are reasonable in relation to potential benefits. When necessary, IRBs should bring in experts, including but not limited to ESCRO members, to consult during the review process for cell-based therapies.
- Complete, unedited Data and Safety Monitoring Board (DSMB) reports should be made available without delay to the responsible compliance committees in order to support their responsibility to effectively monitor the on-going progress and safety of the clinical trial.
- The goal of the Alpha Clinics Program to compile and share data to support IRB review should be lauded. One participant reported considering developing an IRB dedicated to cell-transplantation trials, but the number of trials planned was insufficient to justify a separate committee at the time.
- A program dedicated specifically to advancing the testing, delivery, evaluation and dissemination of stem cell-based therapies would serve to address important challenges in clinical research.

One historic concern for clinical research oversight has been the potential for duplication of responsibilities between the ESCRO and IRBs. Distinct regulations required the ESCRO and IRB to review stem cell based clinical trials in California. Such duplication of effort may delay the review and approval process. The point of overlap is where the investigator is required to provide evidence to the ESCRO that would also be required for FDA and IRB approval – specifically (1) an acceptable scientific rationale for introducing stem cell based products to patients and (2) an evaluation of the probable effects of cell integration.

Under state and federal regulations the responsibility for assessing the rationale for the proposed research intervention and determining a favorable risk and benefit assessment falls to the IRB. There was consensus that it would be beneficial if the CIRM regulations reflected existing state and federal requirements with regard to delegation of responsibility and avoid unnecessary duplication of effort, such as the IRB responsibility for the risk and benefit assessment.

This delineation of responsibility would not preclude a role for the ESCRO. The ESCRO should continue to confirm cells have been acceptably derived and regulatory assurances are in place. Further, the CIRM Alpha Clinic program will develop capacity to compile and analyze objective data to support IRBs review of clinical trials. This capacity with be available to CIRM-sponsored trials and trials conducted within the Alpha Clinic network.

CIRM Staff Recommendations

- CIRM's existing regulatory requirements for notification, review and approval of basic and pre-clinical research appear effective at this time without creating undue burdens. In fact, mature systems appear to be in place to efficiently incorporate ESCRO operations into institutional compliance programs.
- CIRM's regulatory requirements for clinical research should be modified to avoid duplication of IRB's responsibility for review and approval of clinical trials.