CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Meeting Goals / Objectives
June 10, 2011 Standards Working Group

Background:

Proposition 71 directs the Standards Working Group to make recommendations to the ICOC for standards for the medical, socioeconomic, and financial aspects of clinical trials. On May 4, 2011 ICOC approved an award to support the first FDA-approved clinical trial based on cells derived from human embryonic stem cells. Prior to finding this award the ICOC has requested to SWG to consider the statutory and regulatory oversight of FDA-approved clinical trials.

SWG Statutory and Regulatory Considerations:

The attached *Resolution on U.S. Clinical Trials* identifies selected statutory and regulatory requirements relating to the safety of therapies, protocol review and oversight, monitoring. In addition, selected CIRM-specific requirements relating to reporting and access to therapies are identified. Appendix A provides additional detail regarding applicable statutory and regulatory requirements.

Meeting Goal:

The goal of this meeting is to consider the resolution for recommendation to the ICOC.

Draft
Resolution on U.S. Clinical Trials:

CIRM is committed to the development of safe and effective cell-based therapies under the highest medical and ethical standards to relieve disease and injury. By this Resolution, the CIRM Scientific and Medical Accountability Standards Working Group (the "Standards Working Group") recommends standards for clinical trials and therapy delivery to patients in the United States as follows:

Whereas the Standards Working Group recognizes that clinical trials conducted in the United States are subject to robust oversight which includes state and federal statutes, regulatory requirements, and oversight by Institutional Review Boards (IRBs) and, potentially, data safety monitoring boards (DSMBs) and further that except in limited circumstances, the United States Food and Drug Administration (FDA) has jurisdiction over clinical trials and requires each investigational therapy to have an Investigational New Drug (IND) issued before commencement of such clinical trial.

Safety Requirements for Cell-Based Therapies

Whereas FDA's regulations include a comprehensive framework for ensuring adherence to the principles of Good Clinical Practices (GCP) and insuring adequate protection of participants including compliance with: (i) the requirement to have an Investigational New Drug (IND) issued before commencement of clinical trials in the United States (except in limited circumstances); (ii) current Good Manufacturing Practices (cGMP); (iii) Good Laboratory Practice and (iv) current good tissue practice for establishments that manufacture human cell, tissue, and cellular and tissue-based products (HCT/Ps), establishment registrations required by the FDA, HCT/P listing, donor screening and donor testing requirements, requirements for current good tissue practice all of which increase the safety of HCT/Ps

Institutional Review and Oversight and Informed Consent

Whereas existing CIRM regulations require all human subjects research to be conducted in accordance with the Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects). These regulations adopted by the Department of Health and Human Services establish a common framework for the review and oversight of research; require the informed consent of human participants in research, as well as approval and ongoing monitoring of the study by an Institutional Review Board (IRB).

Whereas existing regulations require the clinical trial to be registered on ClinicalTrials.gov and the IRB(s) overseeing providing review to be registered with the federal Office for Human Research Protection. In addition, the Food and Drug Administration has established standards governing the composition, operation, and responsibility of institutional review boards (IRBs).

Monitoring Plans

Whereas CIRM requires that Investigators submit a general description of the data and safety monitoring plan as part of the research application. For phase I and II clinical trials, a detailed monitoring plan must be included as part of the protocol and submitted to the local IRB and reviewed and approved before the trial begins.

Reporting of Results

Whereas CIRM will perform ongoing monitoring of trials for scientific progress, and upon completion of any CIRM-funded trial, CIRM has the expectation that results will be submitted for publication in a timely manner.

Access Requirements

Whereas CIRM regulations require a plan to provide access to uninsured Californians when trials result in effective therapies.

Advancing the Field

Whereas the CIRM Medical and Ethical Standards Working Group has recommended policies to enhance the responsible conduct of CIRM-sponsored research. For research in clinical settings, CIRM is committed to working with trial sponsors to evaluate and advance effective approaches for supporting participant safety and autonomy.

Resolution

Based On The Forgoing, It Is Hereby Resolved B**y The CIRM Medical And Ethical Standards Working Group that:** existing statutory and regulatory oversight of clinical trials conducted in the United States, including the privacy protections in the Health Information and Portability Act (HIPAA), FDA regulations, and existing CIRM regulations provide the robust oversight for clinical trials that meet the high standards required by the CIRM Medical and Ethical Standards Working Group for conducting clinical trials.

There are Extensive Federal Regulatory Protections for Human Subjects in Clinical Trials

- Food & Drug Administration (FDA) – research related to getting a product approved
  - 21 C.F.R. Part 312 (Investigational New Drugs)
  - 21 C.F.R. Part 56 (Institutional Review Boards)
  - 21 C.F.R. Part 50 (Informed Consent)
  - 21 C.F.R. Part 1271 (Good Tissue Practices)

- National Institutes of Health (NIH) – research conducted by NIH grantees
  - Enforced by the Office for Human Research Protection (45 C.F.R. Part 46)

- The Securities and Exchange Commission (SEC) – Rules governing disclosure of adverse events in clinical trials
  - § 10(b) of the Securities Exchange Act of 1934 and SEC Rule 10b(5)

Food and Drug Administration

- 21 C.F.R. Part 312 (Investigational New Drug (IND) Rules) – Disclosure of safety concerns with experimental products in clinical trials. An approved IND is required prior to beginning clinical trials (21 C.F.R. § 312.20(a)).
  - New (March 2011) FDA regulation significantly expands and clarifies reporting requirements for trial sponsors and investigators
  - Requires investigators to immediately report to the sponsor any serious adverse event, whether or not considered drug related
  - Requires sponsors to report to FDA fatal or life-threatening suspected adverse reactions as soon as the sponsor receives that information
  - Requires sponsors to report to FDA potential serious risks to patients, including serious and unexpected suspected adverse reactions and findings from other human or animal studies
  - Requires sponsors to review all information relevant to the safety of the drug on a regular basis (e.g., other studies, reports in the scientific literature, unpublished scientific papers, and information presented at professional meetings) and report risks to FDA if necessary
- 21 C.F.R. § 312.42 -- Allows FDA to order a clinical hold or halt any clinical trial if patients are at risk

Food and Drug Administration

- 21 C.F.R. Part 56 (Institutional Review Boards) – Independent oversight of the clinical trial to ensure safety of research subjects
  - Any clinical investigation under an IND must be reviewed and approved by, and is subject to continuing review by, an independent IRB registered with FDA
  - IRBs must follow written procedures for conducting oversight responsibilities and for ensuring prompt reporting of any unanticipated problems involving risk to human subjects, as well as any noncompliance with FDA or IRB regulations
  - IRBs must oversee/require documentation of the informed consent of human subjects
  - IRBs have the authority to suspend or terminate their approval of research that is not being conducted properly or is associated with unexpected serious harm to subjects. If approval is terminated, IRBs must report that to FDA, which has the power to impose a clinical hold or shut the trial down
  - IRBs must maintain detailed records that are available for FDA inspection, including copies of all research proposals and reports, IRB votes and meeting minutes, all correspondence with investigators, and required written procedures
  - FDA may inspect IRBs and may withhold approval of new studies or terminate ongoing studies if it finds noncompliance

Food and Drug Administration

- 21 C.F.R. Part 50 (Informed Consent) – Voluntary informed consent from research subjects is an important safety feature of the regulations
  - No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject
  - In seeking informed consent, the investigator must provide to the subject, among other things:
    - A statement regarding the purposes of the research, the expected duration of the subject's participation, and a description of the procedures to be followed
    - A description of any foreseeable risk or discomfort
    - Notice that the subject can withdraw from the trial at any time for any reason
    - Contact information in the event of research-related injury
  - Additional safeguards apply for subjects who are children
  - Documentation of informed consent is required and must be signed and dated by the subject

FDA Good Tissue Practices Promote Patient Safety for Cell, Gene Therapy/Tissue-Based Products

- 21 C.F.R. Part 1271 (Good Tissue Practices) - FDA regulates human cells or tissue intended for "implantation, transplantation, infusion, or transfer into a human recipient" to help ensure safety
  - FDA requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cell, tissue, and cellular and tissue-based products, including but not limited to all steps in recovery (collection), donor screening, donor testing, processing, storage, labeling, packaging, and distribution
  - FDA rules require tissue establishments to register and list their products with the agency, screen and test donors to reduce the transmission of infectious diseases, prepare and follow written procedures for the prevention of the spread of communicable disease, and maintain records
  - If the product contains cells or tissue that have been more than minimally manipulated and is not for homologous use, FDA rules governing INDs (noted earlier) apply also