California Institute for Regenerative Medicine
Strategic Planning Advisory Committee Meeting

Overview of the Clinical Research Process, Clinical Networks, and the Role of Academic Medical Centers
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Introduction

The following document provides a high-level overview of the clinical trials process, of selected clinical trials networks, and the role of the academic medical center (AMC) in clinical trials. It is designed to provide some background for our discussion and is not intended to be comprehensive or exhaustive.

I. Brief Overview of the Clinical Research Process

A. Clinical Research Outlined

a. New therapies require rigorous evaluation through a well-established process that is briefly described below (1):
   i. Phase I clinical trials test a new biomedical intervention in a small group of people for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
   ii. Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
   iii. Phase III studies investigate the efficacy of intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

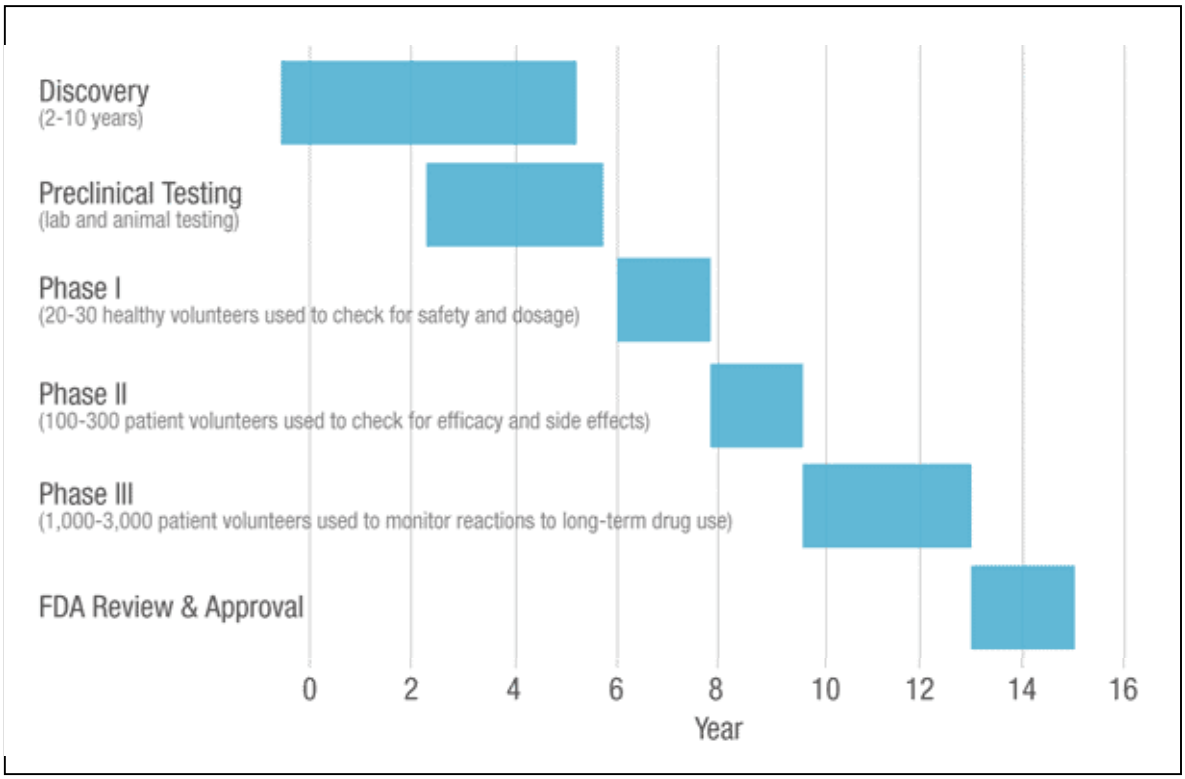
   (Note: These classifications are neither exhaustive nor discrete. For example, each category may have subcategories, such as a Phase IIa trial, and may overlap with other categories, such as a Phase II/III trial.)

b. The development of novel therapeutic procedures, such as a stem cell therapy, where delivery of cells may involve invasive and perhaps surgical interventions, is likely to be more complex than the development of a new drug or monoclonal antibody. Rather than the simple sequence of Phase I, Phase II, and Phase III clinical trials, multiple Phase II studies may be necessary to refine the technical problems associated with a novel therapeutic procedure such as neuronal transplantation for Parkinson's disease. Often, it is investigative groups at AMCs who conduct the initial clinical trials to evaluate and refine these novel types of therapies, in effect readying them for the more focused clinical drug /

cellular development process for product registration and approval that is more typically undertaken by industry.

B. The Drug Development Timeline (2)

Below is a graphic depiction of the timeline typically required for drug development indicating (roughly) the time required for each stage. This is a representative timeline and may vary substantially depending upon the disease indication under investigation and the therapeutic modality (e.g., therapies based on cells versus small molecules).



C. Initiators of Clinical Research

1. The responsibility for the conduct of clinical research in accordance with all applicable laws, regulation, and ethical standards lies with the initiator (or sponsor).

    a. Industry-Initiated Clinical Research
        i. Today, most clinical research is initiated by a company that seeks to test and gain approval for a drug, device, etc. Studies estimate that approximately 70% of the funding for clinical drug trials in the United States was provided by industry. (3,4)
        ii. Larger pharmaceutical and biotech companies fund clinical research through their own operations; smaller companies generally fund clinical trials though

other sources, such as the NIH, the venture capital community, or private foundations.

b. Investigator-Initiated Clinical Research (5)
   i. Numerous studies are initiated and conducted by physicians, often in university settings, that receive little direction from the pharmaceutical industry. The purpose of these trials is to evaluate new therapeutic products, expand the approval of products to include the treatment of other diseases, and rigorously investigate the safety and efficacy of products for which FDA approval otherwise is not required.
   ii. The sources of funding for physician-initiated and designed trials span the range of industrial, governmental, and private granting institutions. Pharmaceutical and biotechnology companies often fund small-scale projects that could identify new areas of effective treatment for their already-approved products. The NIH provides a significant amount of funding for physicians to conduct clinical trials and research programs. Funding is also provided by private organizations and disease-based foundations.

D. The Academic Medical Center's Role in Clinical Trials

1. The unique role of the AMC in clinical research spans activities including identifying the causes of diseases, discovering drugs and inventing medical devices, evaluating and testing these discoveries, the early application of these discoveries, advising about and disseminating information on the value of these innovations, and educating the next generation of researchers and clinicians. (6)

2. Over the last decade, the role of the AMC in pharmaceutical drug development has changed dramatically.(3) Previously, industry needed academic clinician-investigators to perform drug trials because they did not have the in-house expertise to design trials themselves. Companies also relied on AMCs to provide patients as subjects for trials and needed the prestige of academic publications and the involvement of academic "thought leaders" to market their products. Now, however, industry employs top level research physicians to design and interpret drug trials. The AMC continues to participate in industry-sponsored drug development through clinician-investigator recruitment of patients to clinical trials and the subsequent conduct of those trials, including drug administration / device implantation, patient monitoring, data collection, and complying with protocol and regulatory guidelines.

3. We have heard concern from some of our interviewees over the shift of the AMC clinician-investigator from an active collaborator in study design and analysis to a service provider. We have also heard concerns from some interviewees that companies, particularly smaller companies, may focus their clinical development strategy on only those studies important for licensure of a therapy and may be less

able to fund those studies or sub-studies that could be or value to understanding better ways to use / assess the therapy for patient benefit.

II. Issues in the Current Environment of Clinical Research

A number of issues face the clinical research community, with two of the key ones being the changing role of the AMC and the challenges associated with obtaining capital to support earlier stage clinical research.

A. The Changing Nature of the AMCs' Role in Conducting Clinical Trials

1. We have heard anecdotally of the increasing difficulty that academic researchers face in obtaining funding for investigator-initiated research, which is due to a number of reasons:
   a. Decreased clinical margins at AMCs resulting in less discretionary funding available for research.
   b. The shrinking of the NIH budget.
   c. The general unwillingness of the pharma / biotech industries and the venture capital community to fund research that does not have direct, obvious commercial applications.

2. In addition, while academics may sometimes believe that clinical research depends on the AMC, non-academics believe that clinical research, to truly thrive, needs to be present in multiple venues of care. (6)
   a. The pharmaceutical industry is seeking more non-academic providers to conduct clinical research, which is creating enormous opportunities for hospitals, physicians, and outpatient providers (7) such as the for-profit contract-research organizations (CROs) and site-management organizations (SROs) to fulfill some of the functions traditionally carried out by AMCs. For example, at the beginning of the decade of the 90's, 80% of industry-sponsored clinical trials were placed in AMCs; by 1999 the number was down to 40%. (6)
   b. One reason given for this shift is the amount of time it takes to gain protocol approval in academic settings: the initial approval process prior to study initiation can take from two to six months in an AMC, compared with one to two months in a private hospital or less than one month in a physician's practice. (6a) In an industry where speed is paramount, and where for each day's delay in gaining FDA approval of a drug the manufacturer loses and average of $1.3 million (3), such delays are problematic, at best.
   c. There has also been a trend in recent years for US pharmaceutical companies to conduct clinical trials outside the US. For example, the number of American sites where clinical trials were underway declined from about 51,000 in 2001 to 48,000 in 2003. During that same period, the number of FDA-approved investigational drug studies in all phases of research rose from about 3,900 to 4,500, but with less research being done at U.S. sites. (8)

3. While this has not yet become an issue, one interviewee astutely observed that any groups that hope to do clinical trials in association with AMC hospitals using non-Presidential hESCs lines and derivative differentiated lines will likely have to deal with two complications:
    a. It is currently not possible to obtain federal funding for clinical trials using non-federally approved hESC lines or derivative differentiated lines.
    b. The ban on the use of federal funding for hESC lines that are not federally-approved has created a need to essentially segregate such research from federally funded activities. Given this complication, it may be difficult, if not impossible, to conduct clinical trials using non-approved hESC lines or derivative differentiated lines in AMC hospitals that are supported by federal funds.

B. The Difficult in Securing Capital to Support Early Stage Stem Cell based Clinical Research

1. There has been a trend in recent years for pharmaceutical and larger biotechnology companies to focus their licensing efforts on mid-stage (preclinical, Phase 1) and especially later-stage (Phase II, Phase III) compounds to bolster R&D productivity and growth. (9, 10)
    a. The fraction of the total number of biotechnology outlicensing deals for preclinical and clinical stage therapeutics (as defined above) increased from 26.8% of all deals in 2001 to 41% of all deals in 2005, with earlier stage drug discovery and technology deals showing a corresponding decrease. Outlicenses of later stage (Phase 2 and Phase 3) therapeutics comprised the majority of such preclinical and clinical phase outlicensing deals, and made up 29.3% of all outlicenses in 2005. This illustrates a growing trend for companies to invest in more clinically proven therapies. (10)
    b. In a similar fashion, and as discussed at the CIRM's most recent Scientific Conference, the venture capital community is also looking to invest in later stage products.
2. Given the newness, uncertainties, and challenges associated with cell-based therapeutics, and in particular stem cell therapeutics, funding (either on the form of licensing by the pharmaceutical industry or investment by the venture capital community) is unlikely to be available for such therapies until there is proof of clinical concept; until methods to consistently produce cells are developed; and until the related business models becomes more accepted. This will likely limit the ability of smaller companies to move promising therapeutic approaches into clinical trials and eventually to patients without additional sources of funding.

III. Clinical Networks

Increasingly, organizations including AMCs (3) and disease-targeted foundations are creating clinical networks. AMCs are creating such networks to compete more effectively with CROs and SMOs for industry, public, and foundation clinical study dollars. Foundations and disease based organizations are creating such networks to improve access for patients to trials they

sponsor and, in some cases, that are sponsored by companies. These networks facilitate and increase the efficiency and effectiveness with which promising therapies can be moved out of the laboratory and through clinical development. A selected number of examples of such networks are discussed below.

A. The Cystic Fibrosis Foundation's Therapeutics Development Network (11)

1. Mission / Objectives
   a. The purpose of the Therapeutics Development Network (TDN) is to centralize the development of new therapeutics for cystic fibrosis (CF) and to dramatically decrease the amount of time and money needed to develop a new drug.
   b. The network streamlines the process for initiating and conducting Phase I and II clinical trials and ensures uniform data collection and sharing.

2. Overview / Description
   a. The TDN consists of 18 accredited CF care centers with extensive experience and expertise and in conducting clinical trials, which conduct the high quality, state-of-the-art CF clinical research using coordinated and multidisciplinary approach.
   b. The TDN operates through a Coordinating Center which is responsible for development of: 1) study protocols; 2) statistical analysis plans; 3) laboratory analysis plans; as well as clinical database network development and management. Other network participants conduct clinical protocols. The selection of clinical trials and approval of network protocols is managed through a steering committee including the principle investigator from each of the participating centers as well as executive medical officers of the foundation.
   c. Many of its projects may be done in concert with pharmaceutical and biotechnology interests.

3. Sites / Funding
   a. The Network is comprised of 18 CF care centers from the CF Foundation’s existing network of more than 115 accredited care centers.
   b. The Network's primary funding source is the Cystic Fibrosis Foundation. Other funding sources include the NIH / NCRR, non-profit organztaions, and for-profit or commercial enterprises

B. The Immune Tolerance Network (ITN) (12)

1. Mission / Objectives
   a. The mission of the ITN is to advance the clinical application of immune tolerance by performing high quality clinical trials of emerging therapeutics integrated with mechanism-based research. In particular, the ITN aims to:
      i. Establish new tolerance therapeutics

ii. Develop a better understanding of the mechanisms of immune function and disease pathogenesis
iii. Identify new biomarkers of tolerance and disease

2. Overview / Description
   a. Research supported by the ITN comes from a year-round, open call for proposals from tolerance researchers around the world awarded through an interactive peer-review process.
   b. In addition to providing research funds, the ITN provides key tools to help investigators get the most from their research, whether it is academic or industry-initiated, a clinical trial or an tolerance assay, such as:
      i. Assistance identifying potential collaborators and clinical sites,
      ii. Access to an in house "CRO-style" Clinical Trials Group for trial planning, development, monitoring, and analysis,
      iii. Access to cutting-edge biological assays and equipment
      iv. Assistance in procuring vital agents and equipment.
   c. All clinical trials supported by the Immune Tolerance Network are augmented by a series of studies designed to uncover the basic biological features of clinical tolerance. To support such efforts, the ITN operates a number of core facilities to provide investigators with cutting-edge technologies.
      i. The Clinical Trials Group offers scientific, technical, and administrative support, including trial development and regulatory assistance, as well as monitoring staff and experts and tools for data analysis.
      ii. The Tolerance Assay Group assists investigators with the development, data acquisition and analysis for mechanistic and marker studies associated with every trial.

3. Sites / Funding
   a. The ITN is funded by the National Institute for Allergy and Infectious Diseases, the National Institute for Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Foundation who, together, have provided over $140 million dollars over 7 years.

C. Spinal Cord Injury - The Christopher Reeve Foundation's (CRF) North American Clinical Trials Network (NACTN) (13)

1. Mission / Objectives
   a. The mission of the North American Clinical Trials Network (NACTN) for the Treatment of Spinal Cord Injury is to bring promising therapies into clinical trials in a manner that provides evidence of effectiveness and safety.
   b. The North American group will collaborate with a similar network in Europe to provide the foundation for a global network to speed therapeutic development.

2. Overview / Description
    a. NACTN has brought together six leading clinical research centers to create a network; it is hoped the NACTN will create a framework for clinical trial design and analysis for researchers worldwide and provide an opportunity for researchers and clinicians in different countries to communicate and collaborate.

3. Sites / Funding
    a. The NACTN is based at six sites in the U.S. and Canada; five focus on clinical investigations while the sixth is responsible for data analysis and management.

D. Parkinson Disease - Parkinson Study Group (PSG) (14)

1. Mission / Objectives
    a. The PSG aims to advance knowledge about the cause(s), disease progression and treatment of PD and related disorders and is committed to:
        i. Open communication within the scientific community;
        ii. Ensuring research is reviewed by other health care providers prior to publication to make certain all results (good and bad) are available to the public;
        iii. Revealing all potential conflicts of interest of the group and each PSG member and;
        iv. Democratic governance of its organizations and activities.

2. Overview / Description
    a. The PSG is a non-profit, cooperative group of Parkinson's disease experts from medical centers in the US and Canada who are dedicated to improving treatment for persons affected by Parkinson's disease.
    b. The PSG has carried out cooperative therapeutic research since 1986, beginning with an NIH-sponsored clinical trial

3. Sites / Funding
    a. The core resource of the PSG is a network of experienced investigators, coordinators, and consultants from academic / research institutions in the US and Canada.
    b. The PSG now includes more than 350 active investigators, coordinators, and scientists from approximately 85 PSG sites.

IV. Potential Roles for CIRM - Questions for Discussion

A. Do you see a role for academic physician–initiated (sponsored) clinical research as well as industry initiated clinical research in a new therapeutic modality such as stem cell therapy?

B. Should CIRM play a role in facilitating investigator initiated and / or industry initiated clinical studies? What would that role entail (e.g., supporting "pilot studies" to allow the development of pre-clinical data, funding Phase I clinical trials, etc.)?

C. What model should CIRM use for decision making and oversight on clinical trials

D. What specific services or networks might CIRM establish to facilitate stem cell-based clinical investigation that would be of value to physician initiated and / or industry initiated clinical research?

E. Is there a need for CIRM to support training in clinical trial design and related statistical analysis for clinical-investigators?

F. How can CIRM help solve the difficulties that may arise in conducting clinical trials using non-approved lines in AMCs that receive federal funding?

G. What role should CIRM play in supporting effort to educate both the patient and physician community about the benefits and risks of clinical trials related to stem cell based or derived therapies?

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