CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

M E M O R A N D U M

DATE **July 19, 2014**

From: **C. Randal Mills, Ph.D. – President and CEO**

To: **INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE**

Subject: **CIMC Portion of the Alpha Clinics Concept Plan**

Dear Members of the Board,

As the new President of CIRM, I am personally driven by our mission of accelerating stem cell therapies to patients in need. For me, all other interests are subordinate to finding treatments and cures for the people of California. And like many other endeavors of historic proportion, this one too will require laser like focus if we are to be successful.

It is for this reason that I share with you my honest assessment of the Alpha Clinics Concept Plan as currently approved by the Board. While all of the aims of the concept plan are individually laudable, it is my firm belief that the proposal as written is too broad and overly complex to be successful. In a word, it lacks focus. As a result of its overly wide-ranging scope, I also believe that there is a real possibility of incurring significant duplicative costs. Following a thorough review and conversations with senior members of the CIRM team, it is my opinion that the $70 million price tag is not clearly justified in terms of the benefits it will deliver to the people of California.

Therefore, I am asking the Board to reconsider the Concept Plan as originally approved. Specifically, I am asking the Board to consider rescinding the CIMC portion of the Concept Plan. As currently crafted, this CIMC proposal attempts to merge disparate functions, such as clinical operations, data sharing, health care reimbursement modeling, and education regarding stem cell tourism into a single, and in my view, unwieldy program. In place of the existing CIMC concept proposal, I offer an amended revised Concept Plan with a focus on early stage clinical operations – those efforts directly related to high quality stem cell clinical trials. The other topics contemplated in the original Concept Plan can be better addressed in separate, more focused proposals if the Board so directs the Agency.

I am not advocating any modification to the Alpha Stem Cell Clinic Sites portion of the Concept Plan. Accordingly, we are preparing for a Grants Working Group review of submitted applications in September. I do, however, recommend a staged approach to funding, where we evaluate with proper metrics, the effectiveness of the program in a limited number of sites before expanding.

I realize that making this recommendation after the submission of applications for the CIMC is not optimal. However, given the magnitude of the spending proposed, not sharing this critical assessment with the Board would be a greater disservice. I believe that these recommendations are not only fiscally responsible, but more importantly, give the program the greatest chance of success to accomplish our mission of getting stem cell treatments to patients in need.

Alpha Stem Cell Clinics Concept Statement

~~7/15/13~~ 7/19/2014

Background

CIRM's mission is to advance stem cell research and regenerative medicine. Currently, the Institute's therapeutic development pipeline is focused on stem cell-based technologies that will require clinical infrastructure optimized for safe and effective testing and delivery of novel stem cell-based products. It is expected that within the next decade, human healthcare will be greatly improved by successful implementation of some of these technologies.

To accelerate therapeutic development and delivery of stem cell therapies, CIRM proposes establishing the CIRM Alpha Stem Cell Clinics Network (CASC Network). The network will be designed to support projects emanating from CIRM's funding pipeline, as well as scientifically outstanding stem cell products being developed worldwide and brought to California. Conceptually, the CASC Network is intended to be a sustainable infrastructure designed to support academic- and industry-initiated clinical trials, and delivery of therapies proven safe and effective.

We propose two RFAs that will encompass major gaps identified by discussions with stakeholders, including scientists, clinicians, cell manufacturers, clinical trial and regulatory experts, members of biotechnology and pharmaceutical industries, investors and funding agencies, patient advocates, and experts on health care economics and reimbursement.

The major thrusts will be:

- Development of clinical capacity and associated resources designed to support the effective implementation and execution of clinical trials and delivery of registered stem cell therapies
- ~~Compilation of data and information concerning clinical trial experience and therapy outcomes to further inform the research, regulatory, and general community about status of investigational stem cell interventions and long-term outcomes~~
- ~~Dissemination of information to the public and counseling of patients and potential trial subjects about therapeutic options and clinical trials involving stem cells in the network and elsewhere~~

These capacities should be built into a network that is scalable, and which leverages existing strengths in academic and other clinical centers. The network should ensure that ~~data~~, information, and protocols are continuously maintained as community resources, far beyond the longevity of individual trials.

Scope

The scope of the Alpha Stem Cell Clinics will be to accelerate testing and delivery of

- Investigational procedures and cell products that are conceptually novel as opposed to modifications of therapies in current medical practice
- Procedures that require transplantation or infusion of cells, as opposed to small molecules or biologics.

Organization

To develop this infrastructure, CIRM proposes funding a network comprising the key elements depicted in Figure 1, namely:

a. A robust network of clinical sites located in or affiliated with existing academic centers, with internal expertise in targeted disease areas. These sites would have a track record of successful execution of clinical trials and would provide experienced investigators; clinical staff; imaging, surgical and diagnostic technologies; and high patient volumes for given disease indications which could be accessed for recruitment into stem cell-based clinical trials and delivery of treatments. Each site would agree to work closely and collaborate with the other Alpha Stem Cell Clinics and with the Coordinating and Information Management Center (CIMC).

b. A coordinating center to facilitate the clinical efficiency and effectiveness of the network of sites across California. A single entry point for enabling distribution of critical inputs on quality standards, reimbursement negotiation, patient registry, patient education ~~and outreach resources~~, and access to consolidated IRB approvals, and clinical trial and regulatory servicesadvice. ~~It would also have a data management component that would be HIPAA compliant and ensure maintenance and accessibility of valuable data and information about clinical trials to the public, patients and the research community, as appropriate.~~

The network structure is depicted below in Figure 1.

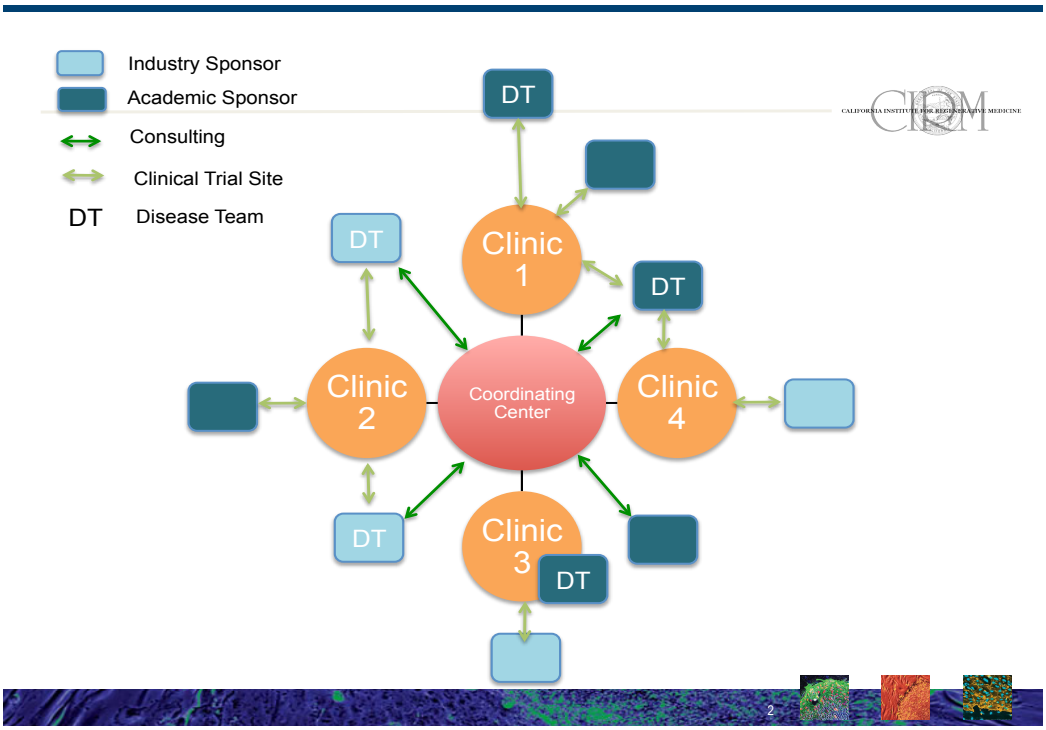

Figure 1 Organizational model for the Alpha Stem Cell Clinics Network. The Alpha Stem Cell Clinics Network would consist of up to five Alpha Stem Cell Clinics Sites (orange circles), and a Coordinating and Information Management Center (CIMC) (red circle). They would work together to bi-directionally share information and expertise to enhance efficiencies and accelerate clinical trials for stem cell therapies, and delivery of approved therapies. They would also work to improve public understanding of stem cell clinical trials and therapies. Academic and corporate sponsors of stem cell clinical trials (blue squares) would contract with the CIMC, and choose from a menu of consulting services that would streamline and provide economies of scale for clinical, data management, and regulatory processes.

~~**Education, Outreach and Training (OET)**~~

~~The Alpha Stem Cell Clinics workshop participants pointed out a serious gap in navigational resources available to patients seeking stem cell based treatments, or to enroll in clinical trials. On the web, there is a mix of information coming from credible sources, with information from dubious clinics offering untested, unregulated products. Many of these could be ineffective, potentially harmful, and do not provide long term follow-up treatment and assessment for the patient. The CASC Network would assemble a means of concentrating useful data and know-how that would inform the public, potential patients seeking stem cell therapies for the various disease targets, and people interested in enrolling in clinical trials for investigational stem cell products.~~

~~The CIMC would create an Education, Outreach, and Training (OET) component, which would develop educational resources and programs to educate clinical staff and the public. This team would create webinars, visual aids such as computer "apps",~~

~~animations, and videos, that would address cultural differences and provide simplified and accurate information. They would leverage international efforts to improve patient resources, and create training programs for physicians interested in stem cell-based therapies. There would be a designated staff member at the CIMC and a team of public health educators/counselors working at the Alpha Clinics Sites to develop uniform and high quality information for patients. This unique team would address a profound gap in quality information available to the public. The OET would accomplish this be drawing from various registries that currently exist (i.e. from the NIH, transplant networks, various disease networks and foundations), and the centralized CIMC database as it develops.~~

~~To be objective, these counselors will work independently from the Alpha Clinics' clinical trial activities. They would not be involved in subject recruitment, informed consent or any trial activities and their management and directives will emanate from the CIMC. However, though independent of the Alpha Clinics core staff, they would nonetheless work with the staff, draw from their expertise, and leverage institutional resources (i.e. from existing infrastructure such as CTSA and public outreach programs) to deliver the best-informed and relevant information, resources and referrals for the patients and their families. By providing this resource, the public and potential patients would be better educated and informed, whether or not they should opt to enroll in clinical trials or approved treatments at any of the Alpha Clinics.~~

RFA 1. CIRM – Alpha Stem Cell Clinics Sites

Description:

There would be funding for up to 5 Institutions for the formation of an Alpha Stem Cell Clinic within that institution. The awarded Institution would have existing expertise, infrastructure and resources that would be leveraged to form a clinic that would focus on the operational support of stem cell based therapeutics and studies in a variety of disease targets. As described below, the Institution would propose up to 2 lead projects and demonstrate the potential to bring in a pipeline of additional stem cell-based therapeutic trials as well as future funding streams to sustain the clinic.

The Institution hosting the Alpha Clinic would be expected to provide substantial facilities and other infrastructure support. The proposed Alpha Clinics sites would be evaluated in their ability to create a positive "brand" that would attract clinical trials. Considerations include:

- The ability to provide state-of-the-art clinical facilities and staff for conducting clinical trials and delivering approved therapies

- The prestige and excellence of the individual investigators and managers associated with the clinics
- Demonstrated ability to enroll patients
- Capacity to integrate with the Coordination and Information Management Center, which would streamline administrative requirements, and provide efficiencies, clinical trial information, and quality control.

The Alpha Clinics have an initial priority for first in human clinical trials phase 1 and 2 studies; these seed capacities could eventually be scaled up for later-stage trials and for delivery of FDA-approved treatments as they become available.

The alpha clinic funding would not include preclinical/ product development or manufacturing for each given project. The clinic would provide operational support for the conduct of the clinical trial, and through its relationship with the CIMC and other participating alpha clinics and their individual networks would garner collective know-how, data management, clinical operations and regulatory support. In addition, the clinic would have an independent education counselor who would interact with the CIMC and the other Alpha Clinics within the network to provide high quality, updated information, referrals and educational material related to stem-cell based therapies and alternative therapies for the patient's given condition(s).

The long-term vision is for the Alpha Clinics to expand and accommodate a broad array of stem cell-based clinical trials for the given disease target, including IND, NDA, post-marketing, as well as investigator initiated INDs and clinical trials performed without an IND under "practice of medicine" where appropriate and where the trial meets the scientific, clinical trial design and ethical standards set forth by the Alpha Clinics Network. In the first instance, however, the Alpha Clinic would lead off with clinical trials conducted under an IND. This RFA is not intended to fund the Clinical Trial(s). Sponsors of funded trials would be eligible to utilize the Alpha Clinic for services, operational support and other resources needed for trial implementation.

Eligibility:

To ensure an efficient launch of the Alpha Clinic program, each applicant would be required to show that it is ready to initiate a clinical trial within 12 months of the award. Applicable regulatory requirements (i.e., IND) for the trial would have to be met, and any necessary collaboration and clinical trial agreements would have to be in place, by the application submission deadline. Per CIRM's usual practice, the President would have authority to make exceptions to the eligibility requirements in exceptional cases.

Applicants would be judged based on the strength of the PI/Institution, ability to deliver on the components outlined below, and the strength of the proposed clinical trial(s) to be conducted at the clinic. Priority would be given to applicants able to show that at least

two additional trials with a committed funding stream would be ready for initiation by Year 2 of the award.

The CIRM Alpha Clinics Network Awards will fund a Principal Investigators (PI) with an M.D. for each Alpha Clinic. The PI would demonstrate administrative and clinical research expertise and have the necessary clinical privileges and certification to manage a clinic at the given non-profit or for-profit institution. The PI must devote a minimum of 30 percent effort exclusively to the administration of the Alpha Clinic, with an expectation that this commitment will increase commensurate with the Alpha Clinic's activities. This Alpha Clinic PI is distinct from the PI (s) for each given project or clinical study. As this RFA would not fund the actual clinical investigation/project, it will not cover salary for the PI(s) on the given projects.

In addition to the PI, the clinic would be staffed with a full time clinical trial coordinator, a full time patient care coordinator, and a full time patient education liaison/ counselor. Each of these personnel would interact with the institution's clinical team but the responsibilities and reporting structure would be within the Alpha Clinic and/or the CIMC.

The PI institutions in which the Alpha Clinics would be established are clinical centers with a robust patient referral base and established expertise for the given Alpha Clinic Disease(s) targets. These centers must have a demonstrated track record for clinical research, clinical staff with expertise in the given disease target as well as a complete array of specialists and services available for the conduct of the study(ies), delivery of approved therapies, and, where needed, for the care of the study subjects (i.e. critical care, infectious disease, cardiology, pulmonary, surgery, radiology). The PI/institution must have existing clinic space, offices and full access to the institution's inpatient facilities and the infrastructure to support a wide scope of clinical trial designs and intervention, i.e. operating rooms and personnel, interventional radiology suites and specialists and specialized imaging capabilities (i.e. nuclear medicine, MRI).

A letter of support indicating that the Institution would work with the Alpha Clinics PI and the CIMC on financial/reimbursement plans would be considered a major strength. The Institution should demonstrate financial sustainability and strength to be able to support the Alpha Clinic.

Eligibility criteria for the Alpha Clinic would also include the "Alpha Clinic Attributes and Core Competencies" listed below. Also Alpha Clinics must be able to accommodate the "Activities within the Alpha Clinics " as listed below.

Alpha Clinic Attributes & Core Competencies:

a) Established excellence in clinical care

b) Full Accreditation (TJC, JCI, DNV or equivalent) with an accredited blood bank (FACT, AABB or equivalent); HIPAA compliant and established electronic medical records
c) Established successful track record with clinical trials of investigational regulated products
d) On site core facilities for imaging, diagnostics, and biomarkers
e) In-patient and out-patient resources
f) Clinical laboratory with capacity to ship to specialized laboratories as required by the given clinical study
g) Central pharmacy with quality systems, tracking and record keeping that would be compatible with clinical trial conduct and investigational product handling & release.
h) Full complement of medical services with wide array of expertise and personnel available for consultation if required for care of clinical trial subjects (e.g. critical care, disease, cardiology, pulmonary, surgery radiology)
i) Social Services
j) Financial Counselors – i.e. to assist with billing and insurance processes
k) Rehabilitation facilities or established partner/referral facilities

Activities within Alpha Clinics Site:

a) Work with CIMC to develop tools and processes for patient outreach, education and counseling, and provide counseling services to patients on site
b) The Alpha Clinic PI would work with CIMC to provide the best negotiated patient charges at the Institution.
c) Conduct clinical trials (GCP compliance, training & other requirements of clinical trial sponsors)
d) Site data management and deposit into CIMC database
e) Assist project Sponsors in the efficient timely submission, timed review, and management of IRB applications and other regulatory requirements and ensure compliance with IRB and Regulatory requirements.
f) Coordinate medical care and referrals for clinical trial subjects

g) Active participation in the bidirectional flow of information and feedback to CIMC, with the aim of improving efficiencies to the benefit of the Alpha Clinics Network and for advancing stem cell therapies worldwide
h) For multi-center trials, provide a lead PI who will carry out trial in collaboration with CIMC, the trial sponsor, and clinical staff at other sites

Budget:

CIRM would fund the Alpha Stem Cell Clinics Network start up phase with 5 years of support up to approximately $11M, total, for each Alpha Clinic and up to 5 Alpha Clinics will be funded in this RFA.

RFA 2. CIRM – Coordinating and Information Management Center

Description

The Alpha Stem Cell Clinics CIMC would share many attributes of contract research organizations that provide consultation services for clinical trial sponsors and investigators, and as coordination centers for clinical trial consortiums. The goal would be to create a centralized resource that would interact with Alpha Clinics Sites and with clinical trial sponsors outside the network, to aid a large number of researchers throughout the state.

The aim will be to streamline clinical trial design ~~and~~ execution, and regulatory processes~~, and to provide high quality educational materials and develop online resources to educate the public, patients, and clinicians about stem cell therapies and clinical trials, through an Outreach, Education, and Training (OET) program that would coordinate with a staff of up to five counselors working at the Alpha Clinics Sites~~.

~~An Information Management Center would be an integral part of the CIMC, and would provide a variety of services to aid the efficient, secure, and appropriate management of clinical trial information and monitoring of long-term outcomes for investigators, clinicians, patients, and the public.~~

The main activities of the CIMC would be:

1) Services for clinical trial design and execution

Active participation ***accelerating the development of stem cell therapies*** ~~***in the bidirectional flow of information and feedback to***~~***through*** ***Alpha Stem Cell Clinics*** ~~***sites, with the aim of improving efficiencies to the benefit of the networks and accelerating development of stem cell therapies worldwide***~~

a) Form steering committee comprising network PIs, and staff from CIMC and CIRM, to discuss key issues of importance such as attributes for prioritizing projects.

~~a)~~b) Provide the infrastructure necessary to, on a contractual basis; offer standard clinical operations services with an emphasis on conducting early stage stem cell clinical trials.

~~b) Assemble and staff the OET team to provide patient education and counseling about clinical trials taking place within the network and elsewhere, as well as non-registered unscientific options marketed on the internet and elsewhere~~

c) Advise investigators on regulatory issues, statistics, project management, and other cross-cutting needs common to clinical trial development and execution
d) Provide resources for creation of high quality reports and presentations for Data and Safety Monitoring Board (DSMB) and other purposes
e) Establish expertise to provide IRB consultation and work to improve efficiency of regulatory matters
f) Establish standing master trial agreements with "pre-negotiation of recurring issues"
g) Compile information on quality systems and Standard Operating Procedures (SOPs)
h) Establish and maintain links with existing infrastructure such as specialized clinical networks, academic translational centers, NCATS and CTSAs
i) Provide training to clinical staff on Good Clinical Practices in cell therapies
~~j) Build expertise in healthcare economics, partnerships with Accountable Care Organizations, and participate in initiatives for gathering evidence for informing coverage and payment decisions~~
~~k)~~j) Provide patient referrals and recruitment for clinical trials at other sites

~~**2) Outreach, Education, and Training (OET)**~~

~~a) Create uniform "branded" information for people interested in a variety of treatments and clinical trials for a wide range of diseases and injuries~~
~~b) OET counselors will be active at the Alpha Clinics Sites to advise patients and potential trial subjects on active clinical trials, registered treatments, and what constitutes a safe and effective *bona fide* stem cell therapy. These activities will counteract the negative impact of unproven procedures currently advertised on the internet and elsewhere~~
~~c) Create community-based advocacy platforms to address range of issues including information about clinical trials, consent, payment policy and other infrastructure needs~~
~~d) Create CME programs to educate physicians about stem cell treatments and what is available for their patients~~
~~e) Create templates for informed consent to improve consistency, efficiency, and compliance~~
~~f) Organize workshops and teleconferences for Alpha Stem Cell Clinic Network Participants, including patient/trial subject support groups, as well as with non-CIRM sponsored participants and investigators when appropriate~~

~~**3) Information Management Center**~~

~~a) Provide data and information for all stakeholders who are developing stem cell therapies, to help accelerate the implementation of efficient and excellent practices worldwide~~
~~b) Support for OET and clinical trial registries~~

c) Coordinate with CIRM to provide data and information for prioritization and decision-making for funding and assisting grantees
d) HIPAA-compliant data and Clinical Report Form (CRF) collection, long-term warehousing and management of data from clinical trials and long-term follow-up studies
e) Harmonization of data platforms and data collection protocols
f) Statistical design and analysis on consultation basis
g) Searchable database of standard operating procedures, forms and de-identified data

4) Business development

a) Build expertise in healthcare economics, partnerships with Accountable Care Organizations, and participate in initiatives for informing coverage and payment decisions
b) Design strategies to attract investors and philanthropists
c) Create successful business plans, and marketing and branding strategies for the Alpha Clinics Sites and the CIMC

Eligibility

Applicants for the CIMC would be funded by CIRM through a competitive RFA process. To reduce costs and capitalize on existing infrastructure, the successful applicant institution would be an existing profit or non-profit CRO-like entity, with appropriate organization, management, and general expertise, and an excellent track record in seeing clinical trials in biomedical research through fruition with successful outcomes. Their staff should be composed of management and support staff with appropriate clinical, scientific, regulatory, and business skills to creatively meet the challenges of introducing novel therapeutic modalities in a rapidly changing health economics environment, and to provide maximal benefit to the public interested in learning about stem cell therapies and engaging in clinical trials, where appropriate for their conditions.

The CIRM Alpha Clinics Network Awards will fund one PI for the CIMC. The PI would have appropriate management experience to provide leadership for CIMC staff, as well as across the network to facilitate network activities. The PI must devote 100 percent effort to administration of the CIMC.

Ideally, the applicant organization should have experience in cell therapies at the time of application, however, this expertise could be augmented by CIRM funding to employ, as needed, staff with this specific expertise, with scalability and flexibility to meet the demands of a growing pipeline of clinical trials. The applicant organization should also have demonstrated excellence in scientific outreach, data and information management, data packaging and presentation to the FDA, IRBs, DSMBs, and the investment

community, and a strong potential to sustain their activities in the stem cell therapy arena well beyond the initial investment of CIRM. The applicant should be based in California, or establish a California-based branch with demonstrated potential to operate their CIRM-funded activities within California at the start of the funding period, and as a long term priority for their organization.

Budget

CIRM would fund the Coordination and Information Management Center for 5 years with~~of~~ approximately ~~up to~~ $105M.

~~**Provisional timetable for RFAs**~~

- ~~Concept proposal - July 24, 2013~~
- ~~Release of RFAs - Oct 2013~~
- ~~Letters of Intent due – Dec 2013~~
- ~~Applications due - March 2014~~
- ~~GWG Review – May 2014~~
- ~~ICOC approval – July 2014~~

Clean Version

Alpha Stem Cell Clinics Concept Statement

7/19/2014

Background

CIRM's mission is to advance stem cell research and regenerative medicine. Currently, the Institute's therapeutic development pipeline is focused on stem cell-based technologies that will require clinical infrastructure optimized for safe and effective testing and delivery of novel stem cell-based products. It is expected that within the next decade, human healthcare will be greatly improved by successful implementation of some of these technologies.

To accelerate therapeutic development and delivery of stem cell therapies, CIRM proposes establishing the CIRM Alpha Stem Cell Clinics Network (CASC Network). The network will be designed to support projects emanating from CIRM's funding pipeline, as well as scientifically outstanding stem cell products being developed worldwide and brought to California. Conceptually, the CASC Network is intended to be a sustainable infrastructure designed to support academic- and industry-initiated clinical trials, and delivery of therapies proven safe and effective.

We propose two RFAs that will encompass major gaps identified by discussions with stakeholders, including scientists, clinicians, cell manufacturers, clinical trial and regulatory experts, members of biotechnology and pharmaceutical industries, investors and funding agencies, patient advocates, and experts on health care economics and reimbursement.

The major thrusts will be:

- Development of clinical capacity and associated resources designed to support the effective implementation and execution of clinical trials and delivery of registered stem cell therapies

These capacities should be built into a network that is scalable, and which leverages existing strengths in academic and other clinical centers. The network should ensure that, information, and protocols are continuously maintained as community resources, far beyond the longevity of individual trials.

Scope

The scope of the Alpha Stem Cell Clinics will be to accelerate testing and delivery of

- Investigational procedures and cell products that are conceptually novel as opposed to modifications of therapies in current medical practice
- Procedures that require transplantation or infusion of cells, as opposed to small molecules or biologics.

Organization

To develop this infrastructure, CIRM proposes funding a network comprising the key elements depicted in Figure 1, namely:

a. A robust network of clinical sites located in or affiliated with existing academic centers, with internal expertise in targeted disease areas. These sites would have a track record of successful execution of clinical trials and would provide experienced investigators; clinical staff; imaging, surgical and diagnostic technologies; and high patient volumes for given disease indications which could be accessed for recruitment into stem cell-based clinical trials and delivery of treatments. Each site would agree to work closely and collaborate with the other Alpha Stem Cell Clinics and with the Coordinating and Information Management Center (CIMC).

b. A coordinating center to facilitate the clinical efficiency and effectiveness of the network of sites across California. A single entry point for enabling distribution of critical inputs on quality standards, reimbursement negotiation, patient registry, patient education, and access to consolidated IRB approvals, and clinical trial and regulatory services.

The network structure is depicted below in Figure 1.

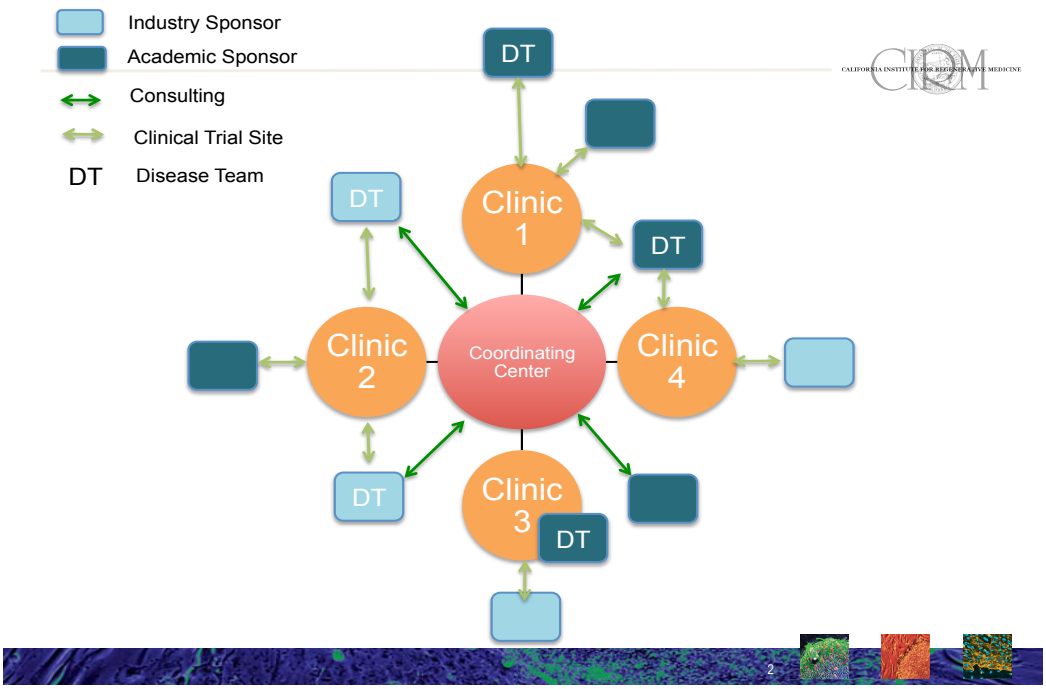

Figure 1 Organizational model for the Alpha Stem Cell Clinics Network. The Alpha Stem Cell Clinics Network would consist of up to five Alpha Stem Cell Clinics Sites (orange circles), and a Coordinating and Information Management Center (CIMC) (red circle). They would work together to bi-directionally share information and expertise to enhance efficiencies and accelerate clinical trials for stem cell therapies, and delivery of approved therapies. They would also work to improve public understanding of stem cell clinical trials and therapies. Academic and corporate sponsors of stem cell clinical trials (blue squares) would contract with the CIMC, and choose from a menu of consulting services that would streamline and provide economies of scale for clinical, data management, and regulatory processes.

RFA 1. CIRM – Alpha Stem Cell Clinics Sites

Description:

There would be funding for up to 5 Institutions for the formation of an Alpha Stem Cell Clinic within that institution. The awarded Institution would have existing expertise, infrastructure and resources that would be leveraged to form a clinic that would focus on the operational support of stem cell based therapeutics and studies in a variety of disease targets. As described below, the Institution would propose up to 2 lead projects and demonstrate the potential to bring in a pipeline of additional stem cell-based therapeutic trials as well as future funding streams to sustain the clinic.

The Institution hosting the Alpha Clinic would be expected to provide substantial facilities and other infrastructure support. The proposed Alpha Clinics sites would be evaluated in their ability to create a positive "brand" that would attract clinical trials. Considerations include:

- The ability to provide state-of-the-art clinical facilities and staff for conducting clinical trials and delivering approved therapies
- The prestige and excellence of the individual investigators and managers associated with the clinics
- Demonstrated ability to enroll patients
- Capacity to integrate with the Coordination and Information Management Center, which would streamline administrative requirements, and provide efficiencies, clinical trial information, and quality control.

The Alpha Clinics have an initial priority for first in human clinical trials phase 1 and 2 studies; these seed capacities could eventually be scaled up for later-stage trials and for delivery of FDA-approved treatments as they become available.

The alpha clinic funding would not include preclinical/ product development or manufacturing for each given project. The clinic would provide operational support for the conduct of the clinical trial, and through its relationship with the CIMC and other participating alpha clinics and their individual networks would garner collective know-how, data management, clinical operations and regulatory support. In addition, the clinic would have an independent education counselor who would interact with the CIMC and the other Alpha Clinics within the network to provide high quality, updated information, referrals and educational material related to stem-cell based therapies and alternative therapies for the patient's given condition(s).

The long-term vision is for the Alpha Clinics to expand and accommodate a broad array of stem cell-based clinical trials for the given disease target, including IND, NDA, post-marketing, as well as investigator initiated INDs and clinical trials performed without an IND under "practice of medicine" where appropriate and where the trial meets the scientific, clinical trial design and ethical standards set forth by the Alpha Clinics Network. In the first instance, however, the Alpha Clinic would lead off with clinical trials conducted under an IND. This RFA is not intended to fund the Clinical Trial(s). Sponsors of funded trials would be eligible to utilize the Alpha Clinic for services, operational support and other resources needed for trial implementation.

Eligibility:

To ensure an efficient launch of the Alpha Clinic program, each applicant would be required to show that it is ready to initiate a clinical trial within 12 months of the award. Applicable regulatory requirements (i.e., IND) for the trial would have to be met, and any necessary collaboration and clinical trial agreements would have to be in place, by the application submission deadline. Per CIRM's usual practice, the President would have authority to make exceptions to the eligibility requirements in exceptional cases.

Applicants would be judged based on the strength of the PI/Institution, ability to deliver on the components outlined below, and the strength of the proposed clinical trial(s) to be conducted at the clinic. Priority would be given to applicants able to show that at least two additional trials with a committed funding stream would be ready for initiation by Year 2 of the award.

The CIRM Alpha Clinics Network Awards will fund a Principal Investigators (PI) with an M.D. for each Alpha Clinic. The PI would demonstrate administrative and clinical research expertise and have the necessary clinical privileges and certification to manage a clinic at the given non-profit or for-profit institution. The PI must devote a minimum of 30 percent effort exclusively to the administration of the Alpha Clinic, with an expectation that this commitment will increase commensurate with the Alpha Clinic's activities. This Alpha Clinic PI is distinct from the PI (s) for each given project or clinical study. As this RFA would not fund the actual clinical investigation/project, it will not cover salary for the PI(s) on the given projects.

In addition to the PI, the clinic would be staffed with a full time clinical trial coordinator, a full time patient care coordinator, and a full time patient education liaison/ counselor. Each of these personnel would interact with the institution's clinical team but the responsibilities and reporting structure would be within the Alpha Clinic and/or the CIMC.

The PI institutions in which the Alpha Clinics would be established are clinical centers with a robust patient referral base and established expertise for the given Alpha Clinic Disease(s) targets. These centers must have a demonstrated track record for clinical research, clinical staff with expertise in the given disease target as well as a complete array of specialists and services available for the conduct of the study(ies), delivery of approved therapies, and, where needed, for the care of the study subjects (i.e. critical care, infectious disease, cardiology, pulmonary, surgery, radiology). The PI/institution must have existing clinic space, offices and full access to the institution's inpatient facilities and the infrastructure to support a wide scope of clinical trial designs and intervention, i.e. operating rooms and personnel, interventional radiology suites and specialists and specialized imaging capabilities (i.e. nuclear medicine, MRI).

A letter of support indicating that the Institution would work with the Alpha Clinics PI and the CIMC on financial/reimbursement plans would be considered a major strength. The Institution should demonstrate financial sustainability and strength to be able to support the Alpha Clinic.

Eligibility criteria for the Alpha Clinic would also include the "Alpha Clinic Attributes and Core Competencies" listed below. Also Alpha Clinics must be able to accommodate the "Activities within the Alpha Clinics " as listed below.

Alpha Clinic Attributes & Core Competencies:

a) Established excellence in clinical care

b) Full Accreditation (TJC, JCI, DNV or equivalent) with an accredited blood bank (FACT, AABB or equivalent); HIPAA compliant and established electronic medical records
c) Established successful track record with clinical trials of investigational regulated products
d) On site core facilities for imaging, diagnostics, and biomarkers
e) In-patient and out-patient resources
f) Clinical laboratory with capacity to ship to specialized laboratories as required by the given clinical study
g) Central pharmacy with quality systems, tracking and record keeping that would be compatible with clinical trial conduct and investigational product handling & release.

h) Full complement of medical services with wide array of expertise and personnel available for consultation if required for care of clinical trial subjects (e.g. critical care, disease, cardiology, pulmonary, surgery radiology)
i) Social Services
j) Financial Counselors – i.e. to assist with billing and insurance processes
k) Rehabilitation facilities or established partner/referral facilities

Activities within Alpha Clinics Site:

a) Work with CIMC to develop tools and processes for patient outreach, education and counseling, and provide counseling services to patients on site
b) The Alpha Clinic PI would work with CIMC to provide the best negotiated patient charges at the Institution.
c) Conduct clinical trials (GCP compliance, training & other requirements of clinical trial sponsors)
d) Site data management and deposit into CIMC database
e) Assist project Sponsors in the efficient timely submission, timed review, and management of IRB applications and other regulatory requirements and ensure compliance with IRB and Regulatory requirements.
f) Coordinate medical care and referrals for clinical trial subjects

g) Active participation in the bidirectional flow of information and feedback to CIMC, with the aim of improving efficiencies to the benefit of the Alpha Clinics Network and for advancing stem cell therapies worldwide
h) For multi-center trials, provide a lead PI who will carry out trial in collaboration with CIMC, the trial sponsor, and clinical staff at other sites

Budget:

CIRM would fund the Alpha Stem Cell Clinics Network start up phase with 5 years of support up to approximately $11M, total, for each Alpha Clinic and up to 5 Alpha Clinics will be funded in this RFA.

RFA 2. CIRM – Coordinating and Information Management Center

Description

The Alpha Stem Cell Clinics CIMC would share many attributes of contract research organizations that provide consultation services for clinical trial sponsors and investigators, and as coordination centers for clinical trial consortiums. The goal would be to create a centralized resource that would interact with Alpha Clinics Sites and with

clinical trial sponsors outside the network, to aid a large number of researchers throughout the state.

The aim will be to streamline clinical trial design execution, and regulatory processes..

The main activities of the CIMC would be:

1) Services for clinical trial design and execution

Active participation accelerating the development of stem cell therapies through Alpha Stem Cell Clinics

a) Form steering committee comprising network PIs, and staff from CIMC and CIRM, to discuss key issues of importance such as attributes for prioritizing projects.
b) Provide the infrastructure necessary to, on a contractual basis; offer standard clinical operations services with an emphasis on conducting early stage stem cell clinical trials.
c) Advise investigators on regulatory issues, statistics, project management, and other cross-cutting needs common to clinical trial development and execution
d) Provide resources for creation of high quality reports and presentations for Data and Safety Monitoring Board (DSMB) and other purposes
e) Establish expertise to provide IRB consultation and work to improve efficiency of regulatory matters
f) Establish standing master trial agreements with "pre-negotiation of recurring issues"
g) Compile information on quality systems and Standard Operating Procedures (SOPs)
h) Establish and maintain links with existing infrastructure such as specialized clinical networks, academic translational centers, NCATS and CTSAs
i) Provide training to clinical staff on Good Clinical Practices in cell therapies
j) Provide patient referrals and recruitment for clinical trials at other sites

Eligibility

Applicants for the CIMC would be funded by CIRM through a competitive RFA process. To reduce costs and capitalize on existing infrastructure, the successful applicant institution would be an existing profit or non-profit CRO-like entity, with appropriate organization, management, and general expertise, and an excellent track record in seeing clinical trials in biomedical research through fruition with successful outcomes. Their staff should be composed of management and support staff with appropriate clinical,

scientific, regulatory, and business skills to creatively meet the challenges of introducing novel therapeutic modalities in a rapidly changing health economics environment, and to provide maximal benefit to the public interested in learning about stem cell therapies and engaging in clinical trials, where appropriate for their conditions.

The CIRM Alpha Clinics Network Awards will fund one PI for the CIMC. The PI would have appropriate management experience to provide leadership for CIMC staff, as well as across the network to facilitate network activities. The PI must devote 100 percent effort to administration of the CIMC.

Ideally, the applicant organization should have experience in cell therapies at the time of application, however, this expertise could be augmented by CIRM funding to employ, as needed, staff with this specific expertise, with scalability and flexibility to meet the demands of a growing pipeline of clinical trials. The applicant organization should also have demonstrated excellence in scientific outreach, data and information management, data packaging and presentation to the FDA, IRBs, DSMBs, and the investment community, and a strong potential to sustain their activities in the stem cell therapy arena well beyond the initial investment of CIRM. The applicant should be based in California, or establish a California-based branch with demonstrated potential to operate their CIRM-funded activities within California at the start of the funding period, and as a long term priority for their organization.

Budget

CIRM would fund the Coordination and Information Management Center for 5 years with approximately $10M.