CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA 13-06: Alpha Stem Cell Clinics Network-
Alpha Clinic Award

I. Purpose

To accelerate therapeutic development and delivery of stem cell therapies, CIRM is establishing the CIRM Alpha Stem Cell Clinics (CASC) Network. This network will provide a high quality, efficient infrastructure to support clinical research emanating from CIRM's funding pipeline as well as non-CIRM funded investigator- or industry-sponsored trials with stem cell products being developed in California, or those developed worldwide and brought to California.

The CASC Network has the following overarching goals and will be organized as depicted in Figure 1:

Clinical Trials: Develop resources and leverage existing infrastructure to address the unique challenges and needs of testing and delivering conceptually novel investigational stem cell products
Delivery of Therapies: Facilitate the delivery of approved stem cell-based therapies to the clinics
Data and Information: Compile information about stem cell clinical trial experience and outcomes, and support data analysis to inform research, clinical, regulatory and reimbursement decisions
Educating Patients and the Public: Create tools and assemble staff to provide patients and public education, outreach and training regarding legitimate stem cell therapies and trials. Educate and inform the public about the issues of "stem cell tourism" whereby unproven and unregulated interventions and products are sold to patients
Healthcare Economics: Develop an evidence base to support the development of sustainable business models including reimbursement strategies

The CASC Initiative consists of two co-released Requests for Applications (RFAs) that will fund:

a) RFA13-06: Alpha Stem Cell Clinics Sites: Up to five clinical sites located in or affiliated with existing academic centers (Described below)
b) RFA13-07: One Coordinating and Information Management Center (CIMC) (See RFA 13-07)

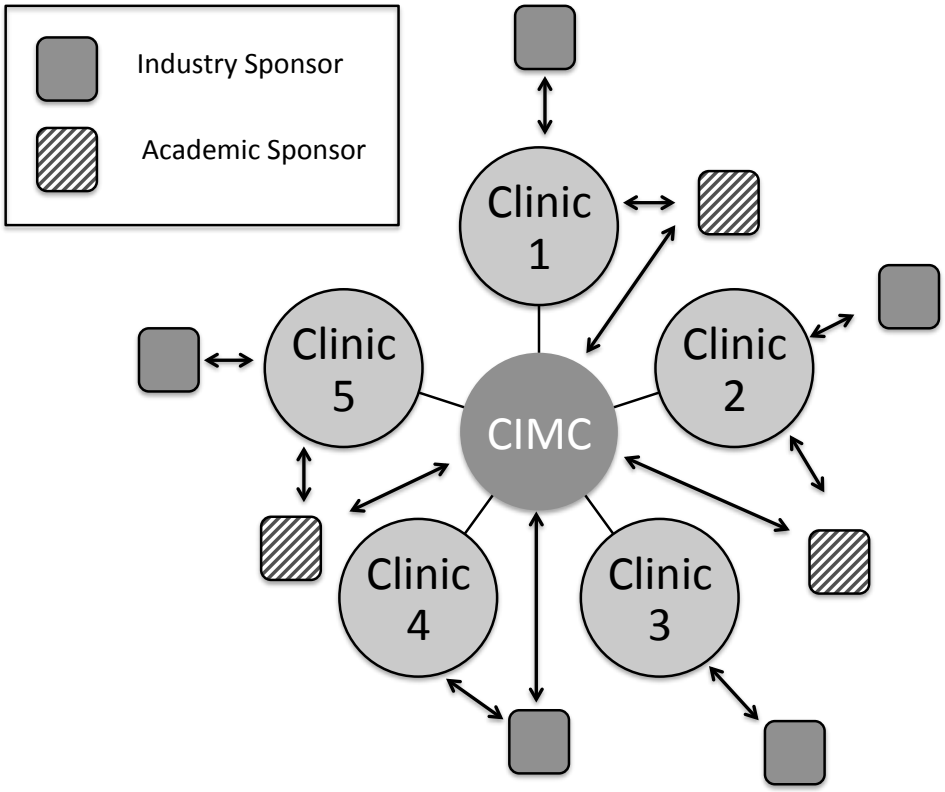

Figure 1. Organizational model for the CASC Network. To accomplish the goals as stated above, the CASC Network will be organized as represented in this schematic diagram. The Network will consist of Alpha Stem Cell Clinics Sites (light grey circles), and the Coordinating and Information Management Center (CIMC; dark grey circle). Network members will collaborate to accelerate clinical trials for stem cell therapies and their delivery into medical practice. The CIMC will also provide a number of services, including the provision of public and patient educational services, data and information management, consulting services, and development of healthcare economics expertise for the Network. Academic sponsors (internal and external to that institution; hatched squares) and industry sponsors (gray squares) of clinical trials testing investigational stem cell-based products will conduct clinical research at the Alpha Stem Cell Clinics and will have access to services and expertise of the CIMC. Sponsors may opt not to use all CIMC services. However, all sponsors using CASC Network resources will contribute to the information and "shared knowledge" capacity of the Network, under the appropriate protections for proprietary or other commercially sensitive information. (See Section VI).

II. Objectives and Scope

Under this RFA, up to five California medical institutions will be funded for up to five years to form and operate an Alpha Stem Cell Clinic within that given institution. These Clinics will provide critical operational support for the conduct of clinical trials for investigational stem cell therapies and will operate as a center of excellence for approved stem cell therapies. These activities would be integrated into the larger CASC network, utilizing efficient and standardized methods to accomplish the goals and activities detailed below.

Funds from this RFA shall be used to leverage already existing assets at the awarded Institution, including expertise, capabilities, infrastructure, resources and assets resident within their state-of-the-art medical centers. The Applicant Institution must be committed to the formation and sustainability of the Alpha Stem Cell Clinic. It should be well positioned to attract and support high quality stem cell clinical activities with a variety of candidate stem cell products, involving a range of disease targets. The Applicant will provide a sustainability plan for the Alpha Stem Cell Clinic to continue to provide for operating expenses beyond the period of CIRM funding support.

This RFA will fund a core Alpha Stem Cell Clinic team for each site, consisting of a Program Director (PD) and staff consisting, at minimum, of a Study Coordinator and a Patient Care Coordinator. To be eligible for this Award, the Alpha Stem Cell Clinic Applicant must provide evidence that at least two Lead Clinical Trials will be conducted at the Alpha Stem Cell Clinic (see Section II, "Lead Clinical Trials" for a full description). The clinical trials themselves will not be funded directly by this RFA; however, the scope, quality and relevance of the proposed Lead Clinical Trials to the CIRM mission will be used as criteria to evaluate the Alpha Stem Cell Clinics application. (See Sections VIII Review Criteria and Section IX B Application Submission Instructions). As described in Section II, the Alpha Stem Cell Clinic will provide focused resources and expertise in clinical research with novel stem cell-based products, and an array of critical clinical operations support and patient care coordination personnel and resources. In addition, as part of the CASC Network, the Alpha Stem Cell Clinic will provide access to CIMC support, including information and data management, consulting services, and independent patient education counselors as described below and in RFA13-07.

To promote accelerated learning and shared knowledge, the Alpha Stem Cell Clinics and the clinical trial investigators/sponsors entering these clinics will contribute to the CIMC informational resources. For a description of the CIMC see RFA 13-07.

A CASC Steering Committee will be formed by CIRM within three months of the award dates for RFA 13-06 and RFA 13-07 and it will be composed of CASC Network PDs, the CIMC PD and a CIRM representative; the Steering Committee will utilize ad hoc advisors for relevant scientific, ethical, regulatory, and clinical development input. By serving on the CASC Steering Committee, the Alpha Stem

Cell Clinics PDs will engage in activities to promote shared knowledge within the CASC network, develop quality standards, and create efficiencies and shared resources for the CASC network in order to achieve the goals as set forth in Section I. This support structure, "shared knowledge" and access to CIMC resources will promote high standards and efficiencies within the Alpha Stem Cell Clinics for their clinical operations, regulatory compliance, data management, and contracts.

The Alpha Stem Cell Clinic will initially support the conduct of clinical trials and approved cell therapies that are within the scope of this RFA, as described below. The Alpha Stem Cell Clinic is also expected to support the conduct of a robust pipeline of clinical trials and activities in the long-term, as the field matures and more products are approved. Therefore applicants will be asked to provide a sustainability plan and propose a pipeline of future clinical activities. The institution should demonstrate the ability to support the Alpha Stem Cell Clinic "scale up" for later stage trials and for the delivery and dissemination of best practices of approved stem cell therapies.

Scope:
The Alpha Stem Cell Clinic Award will provide funding to support personnel and operations directed to supporting the clinical trials and clinical activities carried out in the Alpha Stem Cell Clinic. The award does not directly fund the clinical trials (see Alpha Stem Cell Clinic Activities below for description of costs covered by this RFA). Given the aforementioned parameters, the activities of the Alpha Stem Cell Clinic personnel supported by this RFA include the below activities.

Alpha Stem Cell Clinic Activities:
In-scope activities for the Alpha Stem Cell Clinics include:

- Providing operational support for:
  - Clinical Trials (i.e. providing services such as trial screening and enrollment, clinical trial monitoring support, patient coordination and scheduling)
  - Approved stem cell-based treatments as appropriate and consistent with best practices of medicine
- Providing coordinated care for patients enrolled in a clinical trial at the Alpha Stem Cell Clinic, providing appropriate referrals, communicating with referring physicians and treating specialists, and facilitating access to medical center resources (for the conduct of the study or for associated medical matters, as required).
- Providing resources and facilities in which the CIMC independent patient counselors (funded by the CIMC) will interact with patients and families.
- Collaborating with the CIMC and other CASC Network Alpha Stem Cell Clinics to garner collective know-how and resources in clinical trial operations and regulatory matters and to contribute data and know-how to the robust database, patient registry, and shared knowledge repository.

- Participating in CASC Network activities to promote efficiencies in the IRB review process (including working toward centralized or shared IRB review for stem cell trials).
- Providing capable and active representation to the CASC Steering Committee.
- Initiating at least one Lead Clinical Trial within 12 months of the grant start date that is indicated on the signed Notice of Grant Award (NGA). .

The following activities fall outside the scope of this RFA:
- Construction of new or renovation of existing facilities.
- Research activities including pre-clinical research and IND-enabling studies.
- Process development.
- Cell manufacturing.
- Clinical trial costs (*Note: Services provided by the Alpha Stem Cell Clinic may defray some costs, such as for clinical operations and patient recruitment; however, this RFA will not directly fund any clinical trials or related costs such as procedure costs, in-patient hospital charges, lab tests, pharmacy, radiology investigational product, manufacturing, or salary support for sponsor personnel or clinical investigators*).

Proposed Lead Clinical Trials:
To qualify, Lead Clinical Trials must be limited to the types of investigational products and activities listed below. (*Note, however, that in the Sustainability Plan and Pipeline section (see section IX B Instructions for Full Application), the applicant may propose future clinical activities with stem-cell therapies which may not directly fall into one of the below categories, but these may not be submitted as "Lead Clinical Trials." These future clinical trials will be selected by the Alpha Clinic PD with advice from the CASC Steering Committee.)*

- The investigational candidate for the trial(s) must be a stem/progenitor cell product requiring transplantation or infusion. Proposed Lead Clinical Trials testing small molecule or biologics products are not in scope for this RFA.
- The product candidate must be conceptually novel and shall not be a product of minor modifications to therapies in current medical practice. Note that projects with cell therapies arising from major modifications of standard therapies (e.g. gene-modification of bone marrow or umbilical cord blood cells) are considered within the scope of this RFA.
- Investigations must be conducted under an IND or other relevant U.S. regulatory requirements, and comply with Good Clinical Practices and Common Rule requirements for the protection of human subjects. They must meet regulatory standards of record keeping, allowing monitoring and GCP inspections.
- The clinical study may originate from investigators within the Alpha Stem Cell Clinic institution or it may be brought in from an outside institution. The Alpha Stem Cell Clinic must be a clinical site for the proposed project, even if there are collaborating or satellite trial sites elsewhere.

- Projects must have a committed a sponsor (i.e. IND holder) and funding source (as supported by an executed Clinical Trial Agreement or a confirmatory letter of intent from the funding source for the given clinical trial(s)). These could include the following: clinical trials funded by CIRM Disease Team or Strategic Partnership grants; clinical trials funded by non-CIRM sources, such as investigator-sponsored trials (with corporate, private or grant funding) and industry-sponsored trials.

Priorities:

- Proposals with Lead Clinical Trials that include study endpoints that, if met, would provide proof of concept efficacy data in addition to safety data.
- Alpha Stem Cell Clinic applicants with a California-based sponsor (i.e., a sponsor with established operations within California) for at least one of the proposed Lead Clinical Trials.

III. Award Information and Mechanism

Under this RFA, CIRM intends to commit up to $55 million to support up to five awards for a funding period of up to five years. Given the urgency of CIRM's mission, all approved applications are expected to be initiated within three months of a grant start date that is indicated on a signed Notice of Grant Award (NGA) and must be initiated within six months of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizen's Oversight Committee (ICOC), CIRM's Governing Board.

For all awards, CIRM reserves the right to negotiate funded project activities, milestones (both technical and financial), success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA), subject to renegotiation annually and/or based on progress. CIRM may also wish to review (for compliance with CIRM's policies and regulations) key contract/agreements that are critical to the success of the project.

Due to the interdependence of activities performed under RFA 13-06 with those under RFA 13-07, CIRM will monitor the coordination of activities of the CIMC with those of the Alpha Stem Cell Clinics. As stated in Section II, the Alpha Stem Cell Clinic PD will be required to participate in a CASC Network Steering Committee which will serve to guide CASC Network activities and processes to accomplish its overall objectives, as described in both RFA 13-06 and RFA 13-07.

Grant Terms: Grantees will submit quarterly progress reports which will include updates related to the Milestones set forth in the Notice of Grant Award (NGA) and will receive grant funding in quarterly disbursements, and be subject to all terms of CIRM's applicable regulations. Notwithstanding the forgoing it should be noted that CIRM is in the process of amending its Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.) so that they are consistent with the goals and objectives of this RFA.

Applicants are encouraged to participate in the rulemaking proceedings associated with such revisions. CIRM's full set of regulations can be found at: http://www.cirm.ca.gov/our-funding/stem-cell-regulations-governing-cirm-grants.

The grantee is required to serve on the CASC Steering Committee (see description of its composition and purpose in Section II). CIRM will have representation on this Committee during the five-year award period. The first CASC Steering Committee meeting will be convened by CIRM within three months of the CASC and CIMC Award. The PDs of the Alpha Stem Cell Clinics and the CIMC, along with CIRM, will develop a charter to define provisions for the frequency of CASC Steering Committee meetings and responsibilities of the Steering Committee. At a minimum, these responsibilities will include: (1) promoting communication among the CASC Network PDs (e.g., discuss issues such as standards and criteria for clinical trials entering the Network) (2) promoting consensus-driven initiatives (e.g., how to effectively provide guidance to the CIMC regarding prioritization of database needs), and (3) supporting the overall mission of the CASC (e.g., identify and provide advice/assistance for logistical issues that may hinder the operations of the CIMC, Alpha Stem Cell Clinics or OET program).

IV. Eligibility

A. Institutional Eligibility

Both non-profit and for-profit organizations are eligible to apply. At the time of the application deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a leased or owned location in California). At the time of application, the applicant organization must be affiliated with an academic medical center and must have the appropriate hospital/clinics and facilities accreditations and operational medical facilities in California. If these requirements are not met, CIRM may terminate all further action on the application.

"Non-profit organization" means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.
"For-profit organization" means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as "commercial organizations".

CIRM encourages collaborative endeavors between non-profit and for-profit organizations.

Each institution may submit only one application in response to this RFA. However, institutions submitting an application for RFA 13-07 (CIMC) are also eligible to submit an application for this RFA. PDs listed for RFA13-07 (CIMC) may not be an

applicant PD for RFA 13-06 (Alpha Stem Cell Clinic). The applications for RFA13-07 and RFA13-06 will be reviewed independently and they should not incorporate conditional interdependencies between the two applications.

B. Program Director (PD) Eligibility

The PD must have an M.D. or an equivalent medical degree and must be authorized by the applicant institution to manage a clinic at that institution and to manage the conduct of the Alpha Stem Cell Clinic activities as described in Section II. By the application deadline, the PD must:

- Be authorized by the Institution's Authorized Executive Officer (AEO; defined in section VIIA) (in the Letter of Intent) to apply for this RFA;
- Be an independent investigator in California at a non-profit or for-profit applicant institution; and
- Have an active California medical license and hospital privileges at the applicant institution's medical center.

C. Project Eligibility – Lead Clinical Trials

- The Alpha Stem Cell Clinics applicant must propose a minimum of two Lead Clinical Trials.
- The investigational product(s) of the clinical studies must be within the scope of this RFA as defined in Section II.
- An IND or alternate regulatory designation must have been submitted for at least one of the Lead Clinical Trials at the time of application submission.
- There must be a committed source of funding in place for the proposed Lead Clinical Trials at the time of application submission.
- At the time of LOI submission, there must be certification from the applicant institution that it has, in place, clinical trial agreements and/or letters of intent to enter a clinical trial agreement with the clinical trial sponsors of the lead clinical trials.
- At least one of the proposed Lead Clinical Trials has either already been initiated before the grant start date (indicated on the NGA) or will be initiated within 12 months of the award date (award date is defined in Section III).

D. Percent Effort Requirements

CIRM, mindful of the urgency of its mission, will only fund PDs who are able to devote substantial, focused attention to the project. Therefore for this RFA, PDs must commit a minimum 30% effort at the initiation of the award (grant start date), with the expectation that this commitment would increase to 100% if needed. In addition, the applicant will either identify existing personnel or commit to a plan to hire, at a minimum, the following personnel upon initiation of the award: a 1.0 FTE Alpha Stem Cell Clinics Study Coordinator and a 1.0 FTE Alpha Stem Cell Clinics

Patient Care Coordinator. This RFA does not allow designation of a Co-Program Director (Co-PD).

E. Extraordinary Exceptions

The President of CIRM has the discretion to permit exceptions to any eligibility requirement specified in this Section IV. The President may permit an exception if he determines, in his individual discretion, that the applicant has demonstrated that the exception would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must be consistent with the objectives of this RFA and the requirements of Proposition 71 as well as California state regulations, including the Grants Administration Policy (see Section XIII of this RFA).

Applicants who will need an exception are strongly encouraged to request it at least 30 days before the relevant application deadline. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section XII.

V. Collaborative Funding Partners

CIRM has established a Collaborative Funding Partner (CFP) program with several other agencies that fund stem cell and regenerative medicine research. (For a description, please see http://www.cirm.ca.gov/our-funding/stem-cell-research-collaborative-funding-agreements.) CIRM is the only funder for this RFA, so CASC Network and CIMC awards will not include CFP-sponsored collaborations. CIRM and its CFPs will continue to support collaborative clinical research, and it is likely that some of those projects will conduct clinical trials at Alpha Stem Cell Clinics as trial sponsors. CIRM also intends to explore opportunities for the CASC Network to work with similar initiatives around the world, particularly initiatives associated with CIRM's CFPs.

VI. Notification Regarding Disclosure of Information

In order to use the Alpha Stem Cell Clinics, clinical trial sponsors will be required to disclose and make publicly available certain information to be determined by the CIMC Steering Committee in consultation with CIRM. As discussed in Sections II and III, the CIMC Steering Committee will include Alpha Stem Cell Clinics PDs and will arrive at decisions regarding disclosure on a consensus basis. CIRM expects that, at a minimum, trial sponsors will be required to disclose and make public all information and data elements reported through ClinicalTrials.gov pursuant to Section 801 of the federal Food and Drug Administration Amendments Act of 2007 (FDAAA). CIRM also expects the CIMC to establish a shared knowledge repository for collecting and disseminating (on a voluntary basis) information within the CASC Network, as described in Section II of this RFA.

VII. Application and Evaluation Process

Prior to submitting an application, an applicant must submit a Letter of Intent (LOI). If the applicant meets the eligibility criteria (as defined in Section V) based on information provided in the LOI, the applicant will be notified by CIRM that it is eligible to submit an application.

A. Letter of Intent (LOI)

The PD must submit a letter of intent, which identifies the PD, all key personnel, the two Lead Clinical Trials, and the applicant institution. In addition to the Authorized Organizational Official (AOO) authorization, the LOI must be signed by an Authorized Executive Officer (AEO) who is an organizational official (e.g. Vice Chancellor, Dean, etc.) with the authority, or delegated authority, to nominate the institution's sole candidate for this award and to commit the Applicant Institution's resources to support the activities of the PD and the Alpha Stem Cell Clinic. The AOO and AEO providing supporting signatures for the LOI and Application may not be members or alternate members of the ICOC.

In the LOI, the applicant must confirm that the Applicant Institution has an accredited medical center in California and that the PD meets the eligibility criteria (including an active California medical license, an appointment at that institution and hospital privileges for that medical center). The PD will be asked to certify that, if awarded, he or she will commit to active participation in the CASC Steering Committee (see description in Section II) and will interact with the CIMC (see RFA 13-07).

The applicant will be asked to provide a summary description of the Lead Clinical Trial activities with their respective stem cell products/product candidates. The applicant must confirm the following: the proposed Lead Clinical Trials are testing cell products that are within the scope of this RFA; for at least one of the Lead Clinical Trials, the sponsors of the proposed clinical study have submitted an IND; and there is a commitment from a defined funding source to initiate the clinical activities within one year of grant award date indicated on the NGA for this RFA.

The LOI will be evaluated to determine the eligibility of the applicant PD and institution and the scope of the Lead Clinical Trials, as described in Section IV.C. If the PD and Applicant Institution meet the eligibility criteria based on the LOI, the PD will be notified by CIRM that an application may be submitted (see instructions below).

B. Application

Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The list of some of the scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/GrantsWkgGrpMembers and, due to the nature of this RFA, additional expert reviewers, including but not limited to, medical specialists, clinical operations and regulatory experts, and healthcare economists may be added to the GWG. The fifteen expert reviewers on the GWG will review the applications and score them according to scientific and technical merit applying the review criteria described in Section VIII below. The entire GWG will make funding recommendations based on scientific merit. The Board's Application Review Subcommittee will make funding decisions based on the GWG recommendations, any staff recommendations and a programmatic review. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff, and external reviewers (Per Gov. Code §6254.5(e). Non-public records may be disclosed to government agencies under confidentiality agreements.)

VIII. Review Criteria

Applications will be evaluated for scientific merit by the GWG in the following key areas: (1) Responsiveness to the RFA; (2) Institutional Support and Sustainability Plan; (3) Alpha Stem Cell Clinic Team; (4) Implementation and Operational Plan; and (5) Alpha Stem Cell Clinic Lead Clinical Trials. The specific criteria for review of applications are based on the CIRM Grants Administration Policy (GAP, see Section XIII of this RFA).

The GWG will be asked to give special consideration to CIRM's priorities for this RFA (see Section II).

The following criteria will be evaluated in the application.

1. **Responsiveness to the RFA.** Whether, and to what extent, the proposed Alpha Stem Cell Clinic proposal adequately and appropriately addresses the goals and objectives of the RFA.

2. **Institutional Support and Sustainability Plan:** The proposed Alpha Stem Cell Clinic will be evaluated based on its ability to attract stem cell clinical trials and activities. The Institution will be expected to provide substantial facilities and other infrastructure support and will be evaluated based on the following components:
   - **Infrastructure**
     - The extent, to which the Institution houses state-of-the-art medical facilities, has a track record in clinical care with a broad array of in-house medical expertise and resources (e.g. electronic medical records, specialized research pharmacy, specialized radiology, blood bank and histocompatibility lab, and patient support services) and conducts relevant high quality clinical research of FDA regulated investigational products.
     - The strength of the applicant's plan for leveraging these resources and assets to establish and operate an Alpha Stem Cell Clinic.
     - Evidence for a clear and executable plan for integrating the Alpha Stem Cell Clinic into the existing administrative structure for that medical center/institution, while at the same time, maintaining its ability to execute the specific scope of Alpha Stem Cell Clinic activities (as described in Section II of the RFA).

   - **Patient Base**
     - The extent to which the Applicant Institution has sufficient clinical volume and patient-referral base to support the proposed Lead Clinical Trials as well as activities proposed in the Sustainability and Pipeline Plan.
     - The demonstrated strength of the Applicant Institution's medical center in recruiting patients into early and late phase clinical trials in the intended therapeutic areas for the lead clinical trials, and in other therapeutic areas.

   - **Commitment and Support**
     - The extent to which the Applicant Institution's "in kind" and other forms of support for the proposed Alpha Stem Cell Clinic Site would promote its success in achieving the objectives of this RFA, as described in Sections I and II.
     - The strength of the Applicant's proposal for how institutional resources would be made available to the Alpha Stem Cell Clinic, and how the Applicant Institution would leverage its assets to facilitate the success of the Alpha Stem Cell Clinic in its objectives within the CASC Network (see description, Section I).
     - Commitment to supporting the PD in his/her role in the integrated activities of the CASC Network, including responsibilities involving the Steering Committee, the CIMC, other CASC Alpha Stem Clinics, and the clinical trials sponsors for CASC Network trials.

- **Sustainability**
  - The extent to which the sustainability plan presents a feasible and compelling business/ fundraising proposal, and the likelihood that implementation of the plan would support the Alpha Stem Cell Clinics beyond the 5-year funding provided by this RFA.
  - The feasibility and strength of the proposed pipeline of future clinical activities.

3. **Alpha Stem Cell Clinic Team:** The strength of the team should be evaluated based on the following considerations:

   - The strength of the PD's track record in clinical research in carrying out FDA regulated trials, and his/her administrative and clinical experience.
   - Based on track record and the PD's position within the Applicant Institution, the likelihood that the PD will be successful in accomplishing the goals and activities as described in Section II of the RFA.
   - The experience of the proposed team in subject recruitment, clinical trial operations and involvement and experience in clinical research networks.
   - The strength of the proposed team's experience with stem cell clinical trials and/or in the therapeutic areas that are proposed in the projects described in the application.

4. **Alpha Stem Cell Clinic Structure and Operational Plan:**
   - The strength of the proposed structure (i.e. space, personnel, proposed activities and sequencing and prioritization of the activities) and operational plan.
   - The likelihood and extent to which this Alpha Stem Cell Clinic would accomplish the goals and activities as outlined in Section II (i.e. clinical operations, data safety monitoring, patient coordination, shared knowledge and data sharing with the CASC Network participants, communication plan and efficient integration with network functions such as the Steering Committee, and the CASC Network Outreach, Education and Training program).
   - The alignment of proposed activities with the budget justification and the appropriateness of the budget.
   - The likelihood of a timely set up and implementation of the Alpha Stem Cell Clinic operations and the feasibility of the proposed timeline, given the existing institutional infrastructure and resources that the applicant plans to leverage for this project.
   - The strength of the applicant's plan for managing multi-center trials in a manner that would maintain the objectives of the CASC network, i.e., Sponsor access to CASC resources, maintenance of standards and efficiencies, and "shared knowledge" objectives (as described in Section II). The strength and feasibility of the PD's proposal for participation in working toward a centralized (or shared) IRB review process within the Network.

5. **Lead Clinical Trials for the Alpha Stem Cell Clinic**
   The initial projects entering the Alpha Stem Cell Clinic (so-called "Lead Clinical Trials") must have a submitted or approved IND (or equivalent regulatory designation) for at least one of the Lead Clinical Trials and both must have committed funding sources. For the purposes of this RFA, the below criteria, related to the Lead Clinical Trials, will be used to evaluate the strength of the Alpha Stem Cell Clinics application:
   - The extent to which the proposed Lead Clinical Trials meet the scope and priorities of this RFA (Section II), in particular, the strength of the proposed clinical endpoints to provide early proof of concept data on efficacy, as well as safety, for each of the proposed trials.
   - The "fit" between the Alpha Stem Cell Clinic Team and the proposed Lead Clinical Trials (as described in Section 3 above, "Alpha Stem Cell Clinic Team"), i.e., does the team possess specific expertise that would favorably position them to provide clinical trial support for the proposed Lead Clinical Trials?
   - The extent to which the proposed Lead Clinical Trials address important unmet need(s) in medicine. The likelihood that the therapeutic candidate(s) would have a significant impact on the management of the target disease/injury and/or would offer tangible advantages over current therapies or those in development.
   - The rigor of the process by which these Lead Clinical Trials were evaluated for funding (i.e. by CIRM, NIH or other funding organizations, corporate due diligence, other evaluation processes).
   - The status of the IND or equivalent regulatory designation (based on, for instance, regulatory correspondence, meeting minutes, clinical holds or other outstanding regulatory issues), and the likelihood that there is at least one Lead Clinical Trial that will be initiated within the 12-month period from the grant award date indicated on the NGA.

IX. Application Procedure

Applicants must follow these instructions for submission of an LOI and, if accepted, a formal application for RFA13-06. Applications will only be accepted from applicants who 1) meet the Scope (Section II) and Eligibility Criteria (Section IV) for this RFA, 2) have submitted an LOI to CIRM and 3) have been notified by CIRM that they are eligible to submit a formal application (this notification will occur within four weeks of the LOI submission date).

A. Letter of Intent (LOI) Forms

LOIs must be submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov. A PD may only submit one LOI for this RFA and the LOI must be received by CIRM no later than 5:00 pm (PST) on December 16, 2013. Only one LOI will be accepted from each Institution for this RFA and this must be

accompanied by signed authorization from an AOO and AEO from the institution. Instructions for the LOI are in Section VII.

B. Application Submission Instructions

The electronic copy of all applicable parts of the CASC-Alpha Stem Cell Clinics RFA 13-06 **application** must be submitted online no later than 5:00 PM (PDT) on March 14, 2014, with PD and AEO signatures, as instructed on the CIRM Grants Management Portal (**https://grants.cirm.ca.gov**). **It is the Applicant's responsibility to meet this deadline; no exceptions will be made.**

The application for this RFA consists of the following Parts:

Part A: Application Information Form (Web-based form) Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, Budget, Budget Justification and Related Business Entities Disclosure (See Instructions for Part A, 1−6 below).

Part B: Alpha Stem Cell Clinic Proposal (MS Word template) Part B includes: (1) Institutional Attributes and Commitment (2) Program Director (PD), Alpha Stem Cell Clinic team and Leadership Plan (3) Implementation and Operational Plan (4) Lead Clinical Trials (5) Sustainability Plan and Pipeline (6) Intellectual Property, Licenses and Agreements and (7) References (see Instructions for Part B, 1-7 below).

Part C: Biographical Sketches for Key Personnel (MS Word template) and letters of collaboration and/or institutional support.

Part D: Activity Based Budget (Web-based form). Detailed budget based on the activities proposed in the Application (i.e. Implementation and Operational Plan).

Part E: Documentation. Key regulatory correspondence for proposed Lead Clinical Trials; letters of intent from the Lead Clinical Trial Sponsors, copies of clinical trial agreement(s) (if in place) and letters of intent for committed funding for the proposed Lead Clinical Trials; Hospital Accreditation; PD Medical License.

Part F: Licenses and agreements. If you have licenses or agreements, which relate to the conduct of the scope of services required under this RFA, submit copies.

Instructions for Part A:

1. Abstract (6000 characters) Project Description: Briefly describe the hosting institution and proposed Alpha Stem Cell Clinic. Describe institutional assets and infrastructure that will be leveraged into the establishment of the clinic.

Lead Clinical Trials: Describe the product candidates, clinical indications and proposed endpoints for each of the lead clinical trials. Explain the rationale for the choice of proposed Lead Clinical Trials.

Overview of operational and sustainability plans: Summarize the proposed operational plan and provide a high level timeline for Alpha Stem Cell Clinic launch.

2. Public Abstract (up to 3000 characters) In lay language; briefly discuss how the proposed Institution and team is well suited for the establishment of an Alpha Stem Cell Clinic. Explain the choice of Lead Clinical Trials and how these proposed therapeutic approaches will advance treatment of disease or serious injury in humans. This Public Abstract will become public information and will be available online. Therefore, do not include proprietary or confidential information. Do not disclose the name of the applicant or of the Sponsors.

3. Statement of Benefit to California (up to 3000 characters) Describe in a few sentences how the proposed Alpha Stem Cell Clinic and the Lead Clinical Trials will benefit the State of California and its citizens. This Statement of Benefit will become public information and will be available online; therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., name or location of PD and Applicant Institution.)

4. Key Personnel (included in Parts A and C) List all key personnel and their roles on the project in the relevant sections of Part A. Key personnel are defined as individuals who would contribute to the leadership and operations of the Alpha Stem Cell Clinic in a substantive way, whether or not they receive salaries or compensation under the grant. Key personnel may include any staff, collaborators, or consultants who meet this definition. Key personnel who are not part of the applicant institution should be listed in the subcontract section of the application.

Personnel that are not considered "key personnel", such as technical support staff, may be supported by award funds but need not be listed. The PD is required to commit a minimum of thirty percent (30%) effort, and the Clinical Trial Coordinator and Patient Care Coordinator are each required to commit 100% effort. A minimum of one percent effort is required for other key personnel.

For each key person listed, provide a two-page biographical sketch using the template provided under Part C. The biographical sketch should highlight relevant experience with, in particular, clinical experience, conduct of clinical trials, including experience in data safety monitoring, data reporting and clinical network experience. Following the biosketch for the PD, provide biosketches for the other Alpha Stem Cell Clinic key personnel.

5. Budget (included in Parts A and D) Provide all budget information requested in the budget section of Part A and in Part D. Specify and provide well-justified budgets for subcontracts and consultants in the appropriate section in Part A. In the activities-based budget spreadsheet (Part D), detail key activities and associated costs.

Under this RFA, the budget will not include clinical trial costs such as patient hospital charges, pharmacy, radiology, clinical laboratory, patient travel or housing, among other costs. It will not include out-of-scope activities. CIRM-funded allowable costs include the following:

- **Salaries for Key Personnel and other Support Staff**
  Salaries for personnel may include the Program Director, Alpha Stem Cell Clinics personnel and key technical or other support staff, each that must perform the subject work in California, based on percent of full time effort commensurate with the established salary structure of the applicant institution. The independent OET counselors and patient education and outreach activities will be funded by the CIMC (see RFA 13-07) and will not be supported under this RFA. The OET counselors, however, will perform their activities in an integrated manner with the Alpha Stem Cells Clinic personnel and will meet with and advise patients and potential trial subjects at the Alpha Stem Cell Clinics facilities. The total salary requested must be based on a full-time, 12-month staff appointment or the full time annual salary for employees of a for-profit institution. Administrative support salaries for financial administration can be budgeted as direct project costs if adequately justified.

- **Supplies**
  Grant funds will support supplies for the Alpha Stem Cell Clinic operations. Minor equipment purchases (less than $5,000 per item) are considered supplies and may be included as direct costs in the budget.

- **Travel**
  Recipients (PDs) of a CIRM CASC-Alpha Stem Cell Clinics Award are instructed to include, in their annual travel budget, travel costs to attend CIRM meetings, which includes CASC Steering Committee meetings and at least one additional CIRM-sponsored meeting. Travel costs associated with collaborations necessary to the grant are allowable. Planned travel should be consistent with the proposal and the budget justification. Details of allowable travel costs can be found in the GAP (see Section IX A of this RFA).

- **Equipment**
  Major equipment (more than $5,000 per item) necessary for conducting activities at the Alpha Stem Cell Clinics should be itemized and justified. Under this RFA, no more than 5% of total direct project costs can be used for equipment. Under special circumstances, with sufficient rationale, CIRM may allow a higher percentage of direct project costs for equipment.

- **Consultants/Subcontracts**
  Grantees that subcontract CIRM-funded work should note that CIRM-funded research must generally be conducted in California. Aside from small consulting contracts, Grantees may not use CIRM funds to contract for services to be performed outside of California. Consulting contracts for out-of-state research are limited to $15,000 per year for a single contract, and $25,000 per year in aggregate. (CIRM may allow modest increases to these limits in exceptional circumstances.)

- **Facilities Costs**
  Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for for-profit applicant organizations are limited to 35%. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees and subcontract amounts in excess of $25,000. Applicants may use lower Facilities rates, and use up to 100% of the awarded funds for direct research purposes. The Facilities cost rate budgeted is to be applied to the entire award project period.

- **Indirect Costs**
  Indirect Costs are not funded by grants under this RFA.

B. Instructions for Part B

1. Institutional Attributes and Commitment (up to 6 pages)
Provide a description of the applicant institution's medical center and describe how the Institution would provide facilities and infrastructure support to establish this Alpha Stem Cell Clinic. Provide a brief description of the facilities, environment(s), core services, and resources available for conducting the proposed activities proposed in the "Implementation and Operational plan" of this application. Discuss how the proposed Alpha Stem Cell Clinic will benefit from unique features of these resources. Specifically, describe the institutional assets in terms of operational strengths, health care services, clinical delivery networks, patient and referral base, and unique technologies or specialties. Highlight particular features of the institution that would attract stem cell clinical trials and activities. Include a description of resources available for on-site data storage and data management. Provide quantitative details of inpatient and outpatient capacities (e.g. number of inpatient beds, number of short-stay unit beds, number of annual hospital admissions by department). Provide a summary of clinical trials conducted at your Institution over the past five years, with details such as Phase of trial, disease areas and number of subjects per trial and the Clinical Trials.gov summary (if available). Outline the Institution's commitment and support to the successful operation of the Alpha Stem Cell Clinic during the 5-year funding period, and to the sustainability plan as outlined below (Sustainability Plan & Pipeline).

2. Program Director (PD), Alpha Stem Cell Clinic Team and Leadership Plan
(Up to 4 pages)
Describe the leadership plan and organizational structure of the proposed Alpha Stem Cell Clinic team. List the key members (including consultants) and indicate their role. Highlight specific skillsets and experience in the context of the proposed activities below (deposit PD and Key Personnel Biosketches, Part C). Indicate which team member(s) will have responsibility for patient care coordination, clinical operations support, regulatory support, safety monitoring, data collection, interaction with the CIMC and other network Clinics. Describe the communication plan that will facilitate efficient and optimal interactions between the Alpha Stem Cell Clinic personnel with the following: (i) other Alpha Stem Cell Clinic team members, at the Applicant Institution (ii) the medical center's healthcare, administrative and ancillary staff (iii) referring physicians/organizations (iv) team members at other CASC Network Alpha Stem Cell Clinics Sites and (v) the CIMC, including OET staff (see Section Figure 1 and CASC RFA 13-07 for a description of the Alpha Stem Cell Clinics CIMC relationship). Describe proposed oversight for these activities. Indicate the process for project decision-making and for resolution of potential issues or conflicts that may arise.
If there have been instances where the PD has been out of compliance with FDA regulations, this must be disclosed in the application and relevant documentation as to the resolution of these instances must be provided in *Part E*.

3. Implementation and Operational Plan (up to 6 pages)
Describe how the Alpha Stem Cell Clinic PD's and the team's background, expertise and experience would enable them to accomplish the goals of the Alpha Stem Cell Clinic as outlined in Sections I & II of this RFA. Describe the leadership, reporting structure and operational plan within the Alpha Stem Cell Clinic and within the institution. Describe how this planned structure will be facilitated by communications plan as described above (PD, Alpha Stem Cell Clinic Team and Leadership Plan). Describe the clinical operations support plan (including, but not limited to, assisting with timely IRB submissions and reporting, patient recruitment, screening and enrollment, and clinical monitoring). Provide a detailed staffing plan to support the proposed Lead Clinical Trials and indicate the capacity for the proposed team (i.e. how many phase I trials with a given number of subjects per trial could be supported by the team). Indicate how the proposed clinic would support later stage, larger trials and multi-center trials in a manner compatible with the objectives of the CASC Network (i.e., data and knowledge sharing). Indicate the PD's willingness to work with their Institutional IRB and the CIMC and other Alpha Stem Clinics PDs to work toward a centralized (or shared) IRB process to increase efficiency and optimize the review process (i.e. by including experts in the Stem Cell field). Elaborate on a plan for contributing to this goal and indicate any existing institutional initiatives or resources related to this goal (i.e., if the IRB already is involved in shared IRBs). Indicate the maximum capacity of the current team and budget provided by this RFA. Refer and align this information with the Activity-Based Budget provided in Part D. Propose a plan for future scale-up of the Alpha Stem Cell Clinic for later stage trials and approved therapies, and describe what resources and systems are

in place, or would be implemented, for scale-up to occur. Propose a plan for future training and dissemination of knowledge and skills related to the therapeutic candidates and propose a plan for how the Alpha Stem Cell Clinic would promote wider clinical adoption and safe application of these approved therapies. Describe how the Alpha Stem Cell Clinic team would integrate and support the activities of OET counselors based at their Alpha Stem Cell Clinics site.

Provide a timeline and associated milestones for the formation of the clinic and for the proposed clinical trials. Include a description of key gating items and deliverables for these events/milestones. Provide a description of potential gating items/issues and mitigations for these potential issues.

4. Lead Clinical Trials (up to 10 pages per Clinical Study)
Provide a description of the Lead Clinical Trials and how the therapeutic candidate(s) in these studies would have a significant impact on the management of the target disease/injury and how it would offer tangible advantages over current therapies. Based on the clinical trial design and endpoints, describe how the trials could yield a clinical proof-of-concept. Describe how success in these projects will move the field of stem cell therapy forward. Provide a product Target Product Profile (TPP), Clinical Trial Synopsis and brief overview of the manufacturing plan for the investigational or therapeutic product for each Lead Clinical Trial. Templates will be provided for the aforementioned components with the application form.
Provide a summary of how the clinical trials were evaluated for funding (i.e. grants, corporate sponsors, due diligence activity). Provide a broad overview of the clinical study budget and documentation for financial support for this budget (Part E).
Provide clinical study timelines and describe where this fits within the Alpha Stem Cell Clinics Implementation timeline proposed in section 3 of Part B.

5. Regulatory and Clinical Trial Agreement (up to 3 pages)
Provide a summary of the regulatory interactions and communications and confirm that the Lead Clinical Trials will be conducted in the regulated space. Summarize any IND discussions and other interactions with the pertinent section(s) of the FDA regarding the proposed clinical study. Describe any clinical hold issues and explain how they were/will be resolved. If there are clinical hold issues, the sponsor's plan (accompanied by a timeline) for addressing these issues must be submitted at the time of application. If any amendments to the active IND are planned/required for the proposed project, provide evidence that studies supporting such amendments have been completed. Provide copies of FDA correspondence and relevant regulatory documents in Part E.

6. Sustainability Plan & Pipeline (up to 4 pages)
Describe a sustainability plan for the Alpha Stem Cell Clinic, including potential revenue streams, funding and fundraising proposals. Briefly summarize the framework for a sustainability plan and a description of potential pipeline for future projects (in addition to the lead project(s)) that will be brought to that Alpha Stem Cell Clinic during the five-year funding period and beyond. The applicant may propose a pipeline of trials and/or activities, which may or may not fall within the

"scope" of this RFA as stipulated in Section II. Provide Letters of Support and/or Letters of Intent from clinicians/investigators/sponsors for these proposed "pipeline" trials and activities (Part E).

7. Intellectual Property, Licenses and Agreements (up to 2 pages)
With respect to the Lead Clinical Trials, describe intellectual property assets (patent applications, patents), including any challenges and pending litigation relating to same and any licenses or rights important to the provision of services required by this RFA.

8. References (up to 2 pages)
List all references used in the body of the proposal.

XI. Schedule of Deadlines and Reviews

Letter of Intent due	December 16, 2013
Notifications to Applicants regarding Eligibility to Submit Applications sent out by CIRM	January 13, 2014
Applications due	March 14, 2014
Review of Applications by Grants Working Group (GWG)	Spring 2014
Review and Approval by ICOC	Summer 2014
Earliest Funding of Awards	Fall 2014

XII. Contacts

For information about the review process for this RFA:

Gilberto R. Sambrano, Ph.D.
Associate Director of Review
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

For information about this RFA:

Maria T. Millan, M.D.
Medical Officer
California Institute for Regenerative Medicine
Email: mmillan@cirm.ca.gov
Phone: (415) 396-9801

XIII. CIRM Regulations

Grant awards made through this RFA will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/our-funding/stem-cell-regulations-governing-cirm-grants

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP

B. Intellectual Property Regulations

CIRM has adopted intellectual property and revenue sharing regulations for non-profit and for-profit organizations. Notwithstanding the forgoing it should be noted that CIRM is in the process of amending its Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.) so that they are consistent with the goals and objectives of this RFA. Applicants are encouraged to participate in the rulemaking proceedings associated with such revisions. By accepting a CIRM Grant, the Grantee agrees to comply with all such applicable regulations.

C. Human Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110 available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#standards). All research conducted under this award will be expected to comply with these standards. This information can be found on the CIRM website.

D. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant and loan recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title17, California Code of Regulations, section 100502). Grant and loan recipients are required to comply with this standard.

E. Clinical Trial Registration

CIRM requires that any clinical trial funded under any of its funding programs be listed on http://clinicaltrials.gov/. CIRM will also require awardees to share the results, at the completion of their studies for the benefit of the field as per Section VI.