CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA 13-07: Alpha Stem Cell Clinics Network Coordinating and Information Management Center

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 linked Requests for Applications (RFAs) that will be co-released:

a) RFA13-06: Alpha Stem Cell Clinics Sites: Up to five clinical sites located in or affiliated with existing academic centers. (See RFA 13-06)
b) RFA13-07: Coordinating and Information Management Center (CIMC): One coordinating center to facilitate the efficiency and effectiveness of the network of clinical sites across California. (See below)

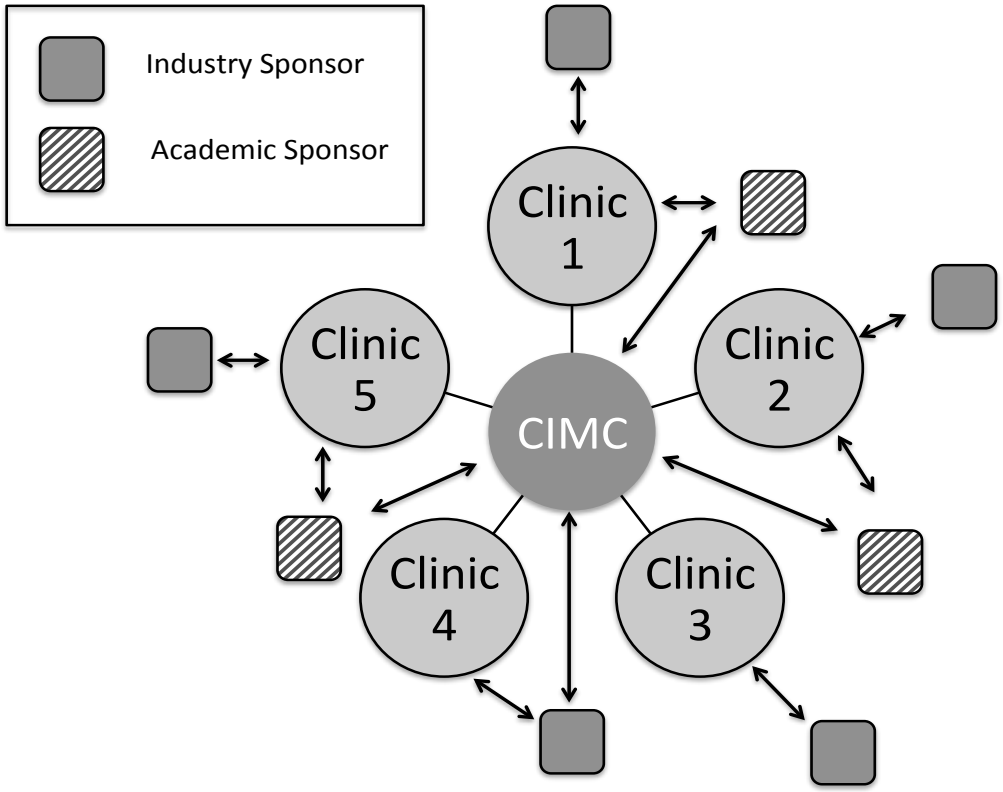

Figure 1. **Organizational model for the CASC Network.** To accomplish the goals as stated above, the CASC Network will be organized as represented in this schematic diagram. The Network will consist of Alpha Stem Cell Clinics Sites (light grey circles), and the Coordinating and Information Management 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 II, Data and information management).

II. Objectives, Scope and Requirements for CIMC Activities

Objectives

Under RFA 13-07, a single Applicant Organization will be funded for up to five years to provide supporting services to the Alpha Stem Cell Clinics (separately funded by RFA 13-06). The CIMC will provide critical inputs to the Alpha Stem Cell Clinics sites on trial design, data and information management, public and patient education and developing an evidence base to help sponsors achieve informed insurance decisions once their investigational therapies become approved. To promote the development of stem cell therapies worldwide, the CIMC will ensure maintenance and accessibility of valuable data and information relating to network clinical trials to the public, patients and the research community.

The CIMC's key activities will be:
1) Clinical trial support
2) Data and information management
3) Outreach, education and training
4) Development of healthcare economics resources

Scope of CIMC Activities

The activities below may be implemented in phases as the CASC Network evolves. However, upon its formation, the CIMC must provide a minimal slate of critical activities to support clinical operations, regulatory interactions, and data management (See Section II, *Requirements for the CIMC*, for further information).

1. Assist the Alpha Stem Cell Clinics with Clinical Trials

- Provide regulatory support for
  - FDA interactions and submissions
  - IRBs (e.g. supporting the Alpha Stem Cell Clinics Sites in moving towards a shared/centralized IRB resource for the network)
  - Coordination of Data Safety Monitoring Boards (DSMBs)
- Clinical operations and clinical trial support for a wide range of trial designs, from early to late stage. This support will include:
  - clinical trial enrollment
  - clinical trial monitoring
  - information tracking (e.g. site initiation visits, investigator meetings, and pharmacy visits)
- Creating efficiencies such as establishing standing master trial agreements with "pre-negotiation of recurring issues".

2. Data and information management

- Clinical Data
  - Coordinate the development of a clinical data management system. The system should complement established data protocols to address information needs of clinical trial sponsors within the CASC Network and should use high quality industry-wide data standards and interchanges (such as Clinical Data Information Standards (CDISC) format).
  - Provide biostatistical analysis support.
  - Provide services for creation of high quality presentations and reports for the FDA, DSMBs, technology transfer offices and investors.
  - Establish clinical trial data repositories with efficiencies and standardized methods for data collection and analysis. Functionalities should include Case Report Form (CRF) collection, long-term warehousing and management of data from clinical trials and long-term follow-up studies.
- Web-based resources for CIMC's Outreach, Education and Training (OET) Division
  - Provide platforms for collection and online dissemination of information supporting OET activities (see Section II, Activity 3 for description of OET).
- Knowledge sharing for the CASC Network
  - Create resources for accelerated learning and shared knowledge for the CASC Network. Examples of shared knowledge to improve efficiencies in clinical trial design and execution include:
    - yearly summaries of clinical trial activities, patient enrollment, updates on number of clinical sites involved in each trial and number of enrolled subjects
    - clinical research templates (e.g. CRFs, informed consent guidance, monitoring logs, subject recruitment logs)
    - experience with surrogate markers (e.g., biomarkers and imaging assessment)
  - Provide secure and tiered access that will achieve the dual aims of promoting an accelerated shared learning environment for the network, while at the same time maintaining confidentiality of proprietary information. This system must take into consideration the minimum requirements for data sharing for the CASC Network (see Section XII, *Notification Regarding Disclosure of Information*).
  - Leverage existing local and national registries and information resources.

3. Coordinate outreach, education, and training (OET)

- Create communication tools for disseminating uniform and current information for people interested in a variety of treatments and clinical trials for a wide range of diseases and injuries, using a variety of targeted media, technology, and language, and including people from different demographic groups, including populations that are under-represented in clinical trials.
- Compile information about stem cell-based therapies and clinical trials taking place locally and internationally through staff research and collaboration with other entities such as the International Society for Stem Cell Research (ISSCR), the Alliance for Regenerative Medicine (ARM), disease foundations, transplant societies and existing registries. Participate in efforts to educate and inform the public about dangers associated with stem cell tourism.
- Work with community-based advocacy groups to create an interactive dialogue addressing a range of issues including information about stem cell-based clinical trials, payment policy and other healthcare infrastructure needs related to stem cell therapies and investigational products.
- Organize workshops and meetings for CASC Network Participants, including patient/trial subject support groups, as well as with non-CIRM sponsored participants and investigators when appropriate.
- Deploy trained OET counselors to be available at the Alpha Stem Cell Clinics Sites. These counselors will be objective, will not be associated with the activities of individual clinical trials (e.g. subject recruitment, informed consent), and their management and compensation will emanate from the CIMC. Although these counselors are independent of the clinical trial activities, they will work with the Alpha Stem Cell Clinics Sites to deliver the best-informed and relevant information, resources and referrals for the patients and their families. CIRM will work with the **CIMC post-award, on the OET councelor resource.**
- OET counselors will provide objective information to patients, their families, and the public on:
  - stem cell clinical trials within the CASC Network and worldwide.
  - general education about clinical trials and what it means to be a clinical trial participant.
  - risks associated with stem cell tourism.

4. Development of healthcare economics resources

- Provide expertise such that healthcare economics is taken into consideration during CASC Network clinical trial design and decisions.
- Carry out activities relating to healthcare economics, such as forging partnerships with Accountable Care Organizations and industry groups.
- Leverage CASC Network information to gain support for coverage decisions and for development of sustainable business models for stem cell therapies (i.e. provide data and economic analyses to support reimbursement strategies).

Requirements for the CIMC

Provide Minimal Slate of "Non-Fee Based Activities" for Clinical Trial Support
As described in RFA13-06, the Alpha Stem Cell Clinics within the CASC Network will each provide clinical operations including data management support for the conduct of their Lead Clinical Trials (two per center) and additional trials that will enter the network once formed. Pursuant to this RFA 13-07, the CIMC must provide a "minimum slate " of services to support the two Lead Clinical Trials per Alpha Stem Cell Clinic. This support will be without charge to the sponsors of the Lead Clinical Trials (hereafter referred to as "Non-Fee Based Activities"). This minimum slate of services will be proposed by the CIMC applicant (See Section VIII, *Part B*) and, subject to post-award negotiations with CIRM, will be defined in the Notice of Grant Award (NGA).

In addition, the CIMC is required to provide a certain level of support for other clinical trials and activities conducted in California (referred to herein as "Fee- Based Activities") that will advance the overarching goals of the CASC Network initiative (see above Section I, *Purpose*). For these additional activities, CIMC may charge reasonable, but competitive, fees to ensure support for as wide a range of activities as possible, and to support increases in staff and capacity of service. These could include services for later stage clinical trials.

OET and Healthcare Economics are Non-Fee Based Activities, and must be implemented by the CIMC to support patient and public education, and sustainability of the initiative.

Participation in CASC Network Steering Committee
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 CIMC PD will work with other Steering Committee members to establish guidelines 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.

III. Award Information

Under this RFA for the Coordination and Information Management Center, CIRM intends to commit up to $15 million to support one award over five years. Given the urgency of CIRM's mission, an approved application is expected to be initiated within three months of a grant start date that is indicated on a signed Notice of Grant Award, 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. Timely progress on this award is important to CIRM. In addition to the annual progress report that is required by the CIRM Grants Administration Policy (GAP, Section XI A), CIRM will require a quarterly written progress report.

The PD is required to serve on the CASC Steering Committee (see description of its composition and purpose in Section II). CIRM will have a representative on this Committee during the five-year award period. The first CASC Steering Committee meeting will be convened by CIRM within 3 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. Within this charter, there will be provisions for the frequency of CASC Steering Committee meetings and for the responsibilities of the Steering Committee. These responsibilities 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 the priorities, needs for the database); 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. Award Mechanism

CIRM expects to fund one approved proposal from a non-profit or for-profit organization, through a grant.

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 will 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.

V. Eligibility

A. Organizational Eligibility

Both non-profit and for-profit organizations are eligible to apply.

"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".

The minimum requirements for Applicant Organization eligibility at the LOI stage are:

- Continuous experience in the five years preceding the application deadline in providing clinical trial services and data and information management services, listed in Section II, *Activities 1* and *2*, respectively. (A completed "LOI Track Record Template 1" must be submitted with the LOI.)
- Existing infrastructure and staffing to support clinical operations and data management services.

At the time of the application submission, the Applicant Organization does not have to be located in California. In order to be eligible for this award, at the time of submission of an application, the Applicant Organization must have either (i) a location in California from which it will engage in activities critical to the project, as evidenced by a lease or purchase agreement or (ii) submit a letter of intent to enter into such a lease or purchase agreement for a location from which it will operate.

The facility shall be the primary place of business from which key personnel (identified in the application) operate and shall be equipped and operational, including information and data management capacity, before issuance of the NGA.

An organization may submit only one application in response to this RFA. However, organizations submitting an application for an Alpha Stem Cell Clinics Site in response to RFA13-06 may also submit an application for RFA13-07. However PDs listed for the Alpha Stem Cell Clinics may not be listed as a PD for the CIMC. The applications for RFA13-06 and RFA13-07 will be reviewed and awarded independently. Therefore, applications submitted under each RFA should stand alone, and should not include contingencies or conditional terms that assume CIRM approval of any other application submitted by the same organization.

B. Program Director (PD) Eligibility

The CIRM Alpha Stem Cell Clinics Network Awards will support a single Program Director (PD) for the CIMC. Highly qualified individuals with the skills, knowledge and resources to act as PD for the CIMC, and with the leadership and management experience that would enable him/her to effectively coordinate activities and build efficiencies across the CASC Network, are invited to work with their organization to submit a LOI and, if notified by CIRM that they are eligible, a formal application (See Section VIII).

By the application deadline the PD must:

- Be an employee at the Applicant Organization, and either be an organizational official, or report directly to an organizational official with broad trans-organizational authority.
- Have documented commitment from the Applicant Organization to staff, and to secure office space and equipment, to carry out the proposed activities in California.
- Have continuous experience in the five years preceding the application deadline in providing clinical trial services and data and information management services, listed in Section II, *Activities 1* and *2*, respectively. (The applicant must submit a completed "LOI Track Record Template 2" with the LOI.)

C. Co-Program Director (Co-PD) Eligibility

This RFA does not allow designation of a Co-PD.

D. Percent Effort Requirements

CIRM, mindful of the urgency of its mission, will only fund PDs who are willing to devote substantial, focused attention to the project. For this RFA, the PD must be willing and able to commit a minimum 30% effort in California by the grant start date (issued and signed NGA) and the expectation is that this level of commitment will increase over the five-year grant period.

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 XI of this RFA).

If CIRM determines that an application does not meet the eligibility requirements, CIRM may terminate all further action on the application. 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 X.

VI. 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.

Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific and clinical research experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The list of 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 participating scientists on the GWG will review the applications and score them applying the review criteria described in Section VII below. The entire GWG will make funding recommendations based on scientific and technical merit to CIRM's governing board, the ICOC. 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 other government agencies under confidentiality agreements.)

VII. Review Criteria

A. Letter of Intent (LOI)

LOIs will be evaluated to determine the eligibility of the Applicant Organization and PD, as described in Section V of this RFA.

B. Full Application

Applications will be evaluated based on
1) Organizational strength, assets, commitment and sustainability plan;
2) qualifications and track record of the applicant PD and team;
3) implementation plan;
4) responsiveness to the RFA; and
5) appropriateness of the budget.

1. Organizational Strength, Asset, Commitment and Sustainability Plan

- Whether and to what extent existing assets will be leveraged for know-how, facilities and equipment.
- Financial strength of the organization based on the documents submitted in *Part F*.
- Depth of experience with clinical trials and with cell therapies in the FDA-regulated space based on the documents submitted in *Part D*.
- Appropriateness, scalability and likely effectiveness of staffing plan to carry out slate of Non-Fee Based Activities through the five-year funding period (i.e. services to support 10 Lead Clinical Trials to be conducted at Alpha Stem Cell Clinics Sites).
- Likely feasibility and effectiveness of business model, staffing plan and fee schedule necessary to create a sustainable business that will support Fee-Based Activities that fall within the scope of this initiative, which will maximize both the beneficial impact and the financial viability of the CIMC and the CASC Network initiative as a whole.

- Extent to which sustainability plan will encourage access and use by network participants, stakeholders from outside of the network, and will ultimately benefit the development of stem cell-based therapies in California and worldwide. Likely effectiveness of their proposed strategies to attract a funding stream (e.g. revenue, investors, philanthropy) beyond the five-year CIRM funding period.
- The ability of the Applicant Organization to set up minimal slate of services and clinical data management support by the award start date (NGA).
- Based on the Applicant Organization's track record and background, its ability to establish, maintain, and sustain a CIMC with high standards of excellence in all its requisite activities, and to effectively and efficiently coordinate activities of CASC Network.
- Likely effectiveness of strategies to attract investors and philanthropists to support clinical and educational activities within the CASC Network.

2. Qualifications and Track Record of the PD and team

- The extent to which the PD applicant has the necessary training and experience to carry out proposed activities, including management of staff and clinical operations, clinical networks, data and information, and establishment of innovative programs.
- The extent to which the applicant PD will have the authority and influence necessary to create an effective new clinical network.
- The likely ability of the PD to have daily involvement with the activities of the CIMC and the CASC Network.
- For the team, the relevance and quality of their demonstrated experience in activities relevant to the proposed CIMC construct.
- The extent to which the percent time commitments of key staff is consistent with the CIMC mission to create a "brain trust" that can be drawn upon to advance stem cell therapies, and that is sustainable and scalable.

3. Implementation Plan

- The quality and design of the planned data and information management systems, including the ability to achieve the dual aims of protecting confidentiality of proprietary information while implementing and sustaining a robust accelerated learning environment through appropriate sharing of information.
- The strength of their plans to establish all CIMC activities listed in Section II including those that they do not currently have as part of their operations.
- The extent to which the organization's business plans for operations (both for Non-Fee Based services for initial cohort of 10 Lead Clinical Trials under grant budget, and for Fee-Based Activities) are feasible and maximize the likelihood of the long-term sustainability of the CASC network.

- The feasibility of establishing operations of the proposed CIMC construct within the proposed timelines, and the strength and appropriateness of the proposed milestones (See Application *Part B*, Section 3).
- The likelihood that staff, with the requisite expertise to carry out activities listed in Section II, can be assembled in a timely fashion from in-house, external recruitment or sub-contracts.

4. Responsiveness to the RFA

- Whether and to what extent the proposed research project or activity adequately and appropriately addresses the goals and objectives of the RFA.

5. Appropriateness of Budget

- The strength of the proposed "minimal slate" of services for the Alpha Stem Cell Clinics that would be covered by the Budget under this RFA.
- The competitiveness (by comparison to market standards) and appropriateness of the fee structure for other services beneficial to the CASC Network that fall outside of the "minimal slate" of services.
- The appropriateness of budget and the clarity of alignment between the proposed activities and plans and the proposed budget.
- The strength of the budget justification for the Activities-Based Budget.

VIII. Application Procedure

A. Letter of Intent (LOI) Forms

Applicants must follow these instructions for submission of an LOI and, if accepted, a formal application for RFA13-07. Applications will only be accepted from applicants who 1) meet the Eligibility Criteria (Section V) 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).

B. LOI Instructions

A PD may submit only a single LOI for this RFA using the forms and instructions provided in the Grants Management Portal at http://www.cirm.ca.gov/RFAs. The completed LOI must be submitted online using the Grants Management Portal and must be received by CIRM no later than 5:00 pm (PST) on December 16, 2013.

The PD must submit a summary of the proposed CIMC plan, indicating the location of the Applicant Organization, the California location (or planned location), the name of the PD, the team composition (if not by name, then by description of the positions).

The PD must certify that the Applicant Organization has:

- Continuous experience in the five years preceding the application deadline in providing clinical trial services and data and information management services, listed in Section II, *Activities 1* and *2*, respectively. (A completed "LOI Track Record Template 1" must be submitted with the LOI.)
- Existing infrastructure and staffing to support clinical operations and data management services.

The Applicant Organization must demonstrate, at a minimum, a cash flow neutral financial status over the past year. Such evidence will require submission of supporting documentation, including recent financial statements and pro-forma for any concurrent investment based on the last twelve months (LTM). Specific documents that should be provided include:

- Financial statements prepared in accordance with US GAAP for the quarters ended September 30, 2012 and September 30, 2013, as well as year ended December 31, 2012.
- Relevant financial notes and disclosures related to all financial statements.

The PD must certify that they have continuous experience in the five years preceding the application deadline in providing clinical trial services and data and information management services, listed in Section II, *Activities 1* and *2*, respectively. (The applicant must submit a completed "LOI Track Record Template 2" with the LOI.)

C. Application Forms

CIRM will only accept Applications from applicants who submitted an LOI that was accepted by CIRM. The application must have the same PD listed in the LOI, or it will be deemed ineligible. Application forms will be available via the Grants Management Portal at https://grants.cirm.ca.gov on December 16, 2013 and, if an application is submitted, it must be submitted no later than 5PM (PST) on March 14, 2014.

The application for RFA13-07 consists of **seven 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*: CIMC Proposal** (MS Word template). *Part B* includes:
(1) Proposed CIMC Construct; (2) Financial and Sustainability Plan; (3) Applicant Organization Experience, Attributes and Assets; (4) Applicant PD and Team Experience; and (5) References (See instructions for *Part B*, 1- 5 below)

***Part C*: Biographical Sketches for Key Personnel** (MS Word template)

***Part D:* Documentation (including Track Record templates)**

***Part E:* Activity-Based Budget and Fee Schedules**

***Part F*: Supporting Financial Documents**

***Part G*: Licenses and Agreements**

Instructions for Part A:

1. Abstract (up to 3000 characters in Part A)
State the goals of the proposal. Summarize the overall plans for the CIMC and how these will meet the stated objectives of the RFA.

2. Public Abstract (up to 3000 characters in Part A)
In lay language, briefly describe the proposed CIMC and how it will contribute to the advancement of regenerative medicine. This Public Abstract will become public information and will be posted on the CIRM website; therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., PD name, Applicant Organization name or location).

3. Statement of Benefit to California (up to 3000 characters in Part A)
Describe in a few sentences how the proposed CIMC will benefit the State of California and its citizens. This Statement of Benefit will become public information and will be posted on the CIRM website; therefore, do not include proprietary or confidential information or information that could identify applicant (e.g., PD name, Applicant Organization name or location).

4. Key Personnel (included in Parts A and C)
List all key personnel and their roles on the project, and proposed percent time commitments. Key personnel are defined as individuals who contribute to the development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any technical staff, collaborators, or consultants who meet this definition.

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. 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 sketch should highlight relevant experience, accomplishments and/or special skills related to the proposed CIMC activities.

5. Budget (included in Parts A and D)
Provide all 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*), list key activities and associated costs. For Fee-Based Activities, not included within Activities-Based Budget (to support activities beyond 10 Lead Clinical Projects), provide fee schedule for services.

Under RFA 1307, CIRM-funded allowable costs include the following:

• Salaries for Key Personnel
Salaries for Key Personnel may include the Program Director and support staff to perform activities outlined in Section II. Salaries must support a staff of independent counselors (expectation of five) who will work at each of the Alpha Stem Cell Clinics Sites, but will be managed through the CIMC OET, and will participate in carrying out OET counselor activities and responsibilities. Each staff member must perform the subject work in California, based on percent of full time effort commensurate with the established salary structure of the Applicant Organization. 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 organization.

• ***Supplies***
Grant funds will support supplies. 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 CIRM RFA13-07 are encouraged to attend a CIRM-organized grantee meeting in California and should include travel costs for this meeting in the budget. Other allowable costs include travel for OET counselors to report to Alpha Stem Cell Clinics Sites. Details of allowable travel costs can be found in the GAP (see Section XI A of this RFA).

• ***Equipment***
Major equipment (more than $5,000 per item) necessary for conducting the proposed project at the Applicant Organization 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 research 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.)

For activities other than research, Grantees may subcontract outside California, but must make a good faith effort to use California suppliers for more than half of their contracts and purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502). Examples of such activities include data storage, consulting, and training.

• ***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 under this RFA.

Further information on allowable costs for research funded by CIRM is detailed in the CIRM Grants Administration Policy (GAP, see Section XI A of this RFA).

Instructions for *Part B*

1. Proposed CIMC Construct (refer to CIMC Activities, Section II, and Review Criteria, Section VII)

• ***Organization and Operational Plan*** *(up to 4 pages in Part B)*
If a California address is not available at the time of application, the PD must provide, from an authorized organizational official, a letter of intent to locate operations within California should there be successful funding from this RFA and/or an agreed-to term sheet for a lease/purchase of a site for operations in California. In both cases, a summary timeline for establishing operations in California must be provided with the application.

Provide concise, but detailed description of staffing, equipment and facilities, including sub-contractors, proposed to carry out each of the CIMC activities (Section II; *Activities*). Describe staff expertise and depth of experience with cell-based therapies, strategy for recruitment to assemble teams who will carry out each activity, and overall strategy for achieving specialized expertise in stem cell therapies. Describe the leadership plan and organizational structure of the proposed CIMC team.

Describe how staffing will be scaled appropriately over the course of the five year term of the award, to support Non-Fee Based Activities within the CASC Network (i.e. 10 Lead Clinical Trials) as well as Fee-Based Activities within and beyond the CASC Network. Describe the minimal activities the Applicant Organization will provide to support the Alpha Stem Cell Clinics Sites and their 10 Lead Clinical Trials (Non-Fee Based Activities), and the plan for supporting clinical trials and activities *beyond* the 10 Lead Clinical Trials (Fee-Based Activities).

Describe a plan for efficient and effective interactions of CIMC staff with Steering Committee, with network participants at the Alpha Stem Cell Clinics, and with clinical trial sponsors.

Using a working assumption that the CIMC will provide a “minimum slate of services” on a non-fee basis for 10 early phase clinical trials (each with less than 200 patients) within the CASC network, describe the “Minimum Slate” of Services and provide timelines and milestones for the components listed below. Additionally, provide a more complete description of services that would be offered on a fee-based schedule (see below) for the components listed below.

• ***CIMC clinical trial services*** *(up to 4 pages in Part B)*
Describe strategies for streamlining clinical trial design and execution, and how the CIMC will build efficiencies, such as working with Alpha Stem Cell Clinics Sites to develop shared/centralized IRBs for the CASC Network, and coordination of DSMBs. Describe services that CIMC will provide to facilitate introduction of approved stem cell therapies into the clinics, as the field evolves. Describe how the staff will support processes such as patient referrals and recruitment for clinical trials at the Alpha Stem Cell Clinics.

• ***Data and Information Management*** *(up to 4 pages in Part B)*
Describe the previous experience of the leadership and operational team in clinical data management systems. Elaborate on the minimum set of data management services that would be provided within the "minimum set of services" proposed by the applicant. Discuss strategies for achieving data interoperability in compliance with industry standards and regulatory requirements. Describe plans for leveraging of existing infrastructure, including data sharing platforms and protocols, and facilities for data warehousing. Discuss potential approaches for data sharing, tiered access, and systems administration. Propose a plan that will be brought to Steering Committee for achieving the CIMC mission of creating a shared learning environment, while simultaneously ensuring the confidentiality of proprietary information owned by clinical trial sponsors who will engage with the CASC Network. (See Section XII for CASC Network guidelines for data sharing.)

• ***OET*** *(up to 3 pages in Part B)*
Describe previous experience of staff, management or proposed collaborators in OET activities. Include plans to recruit and build OET team, including counselors who will be available to the Alpha Stem Cell Clinics. Consider a process for assessing the needs of patients and potential clinical trial subjects. Describe how existing OET modules at professional societies, companies, and institutions may be utilized to support participant and public education. Describe how the CIMC OET will inform different groups interested in stem cell therapies, including potential clinical trial subjects, patients seeking treatments, clinical practitioners, and the general public. Describe how counselors will be trained, how their objectivity will be ensured, and how they will interface with Alpha Stem Cell Clinics staff and the CIMC (See Section II, Activity 3, Bullet 5).
Describe how existing databases and registries on clinical trials will be used and what type of resources will be built by the CIMC. Discuss other programs and innovations that will improve the effectiveness of the OET and fulfill the mission of the CIMC and CIRM.

• ***Healthcare Economics*** *(up to 3 pages in Part B)*
Describe previous experience of leadership and operation team in these areas, and strategies for recruiting expertise if needed. Describe strategies for building relationships with organizations and consortiums such as the CMS and Accountable Care Organizations, to leverage the CASC Network base of evidence to inform coverage decisions.

2. Financial and Sustainability Plan (up to 4 pages in Part B)

Describe a business model, budget forecast and staffing plan to provide Non-Fee Based Activities (see Section II) to support the Alpha Stem Cell Clinics Sites in their conduct of 10 early phase Lead Clinical Trials. Also build on this Non-Fee plan by describing a business model, budget forecast, staffing plan and fee schedule to create a Fee-Based sustainable business entity that will support in-scope clinical trials and activities beyond these 10 Lead Clinical Trials. These activities may emanate from Alpha Stem Cell Clinics sites (for clinical trials beyond the 10 Lead Clinical Trials), or external to the CASC Network (this may include clients from outside of California).

Describe plan for maximizing access and use of the CIMC by network participants, and plans for incentivizing engagement of stakeholders from outside of the network.

Provide a Sustainability Plan for the CIMC's support of stem cell clinical trials beyond the five-year funding period. Provide a business and strategic plan to attract a funding stream (i.e. revenue, investors) to support the Sustainability Plan.

3. Applicant Organization Experience, Attributes and Assets *(up to 6 pages)*

Describe the organization's assets in terms of operational strengths, services, information and management infrastructure, and specialized expertise. Include a description of resources available for data storage and data management.

Describe the facilities and infrastructure the Applicant Organization will provide to establish and maintain the CIMC. Specifically, provide a brief description of the facilities, environment(s), core services, and resources available for conducting the proposed activities as outlined in Section II of this RFA. Explain how and to what extent existing assets will be leveraged to form and operate this CIMC. Demonstrate organizational commitment for this effort and provide a letter of support from an appropriate organizational official (if other than the PD) (see *Part D*). The organizational official may not be a member or alternate member of the ICOC.

Discuss how the proposed CIMC will benefit from unique features of these resources. Describe the nature of services provided to the clients who have provided Letters of Reference (see *Part C*).

Describe the capacity of the Applicant Organization as it currently stands to establish operations to carry out all activities in a timeframe consistent with the urgency of CIRM's mission.

Provide a narrative highlighting the organization's track record in clinical research in FDA regulated trials, and provision of services relating to managing and operating clinical trials, information and data management, and involvement in clinical research networks (as summarized in *Part D*, Track Record Template 1).

4. *Applicant PD and Team Experience* *(Up to 6 pages)*

List the key members (including consultants) and indicate their role. Highlight specific skill sets and experience in the context of the proposed activities below (deposit PD and Key Personnel Biosketches, *Part C*). Describe services provided to the clients who have provided letters of support (see *Part C*).

For the applicant PD, provide details of track record in clinical research. Describe experience in leadership roles and management of organizations, networks and staff. Describe specific experience in the following areas: project management; regulatory affairs; protocol development; investigator meetings; patient recruitment; study monitoring & site management; safety monitoring; data management; biostatistics; clinical study report or manuscript preparation; and other. Fill out Track Record Template 2 in *Part B* of the application.

5. References *(up to 2 pages in Part B)*
List all references used in the body of the proposal.

Part C. **Biographical Sketches for Key Personnel (MS Word template)**

Part D. **Documentation (**(MS Word template).
Submit Letters of Organizational Support, 3 Letters of Reference from Clients, Track Record Templates 1 and 2, and if sub-contractors will be engaged, Letters of Intent describing their services and credentials (if relevant), Documentation of California address or Letter of Intent or agreed-to term sheet to enter into lease or purchase agreement for a California location.

Part E. **Activity-Based Budget and Fee Schedules**
Provide a detailed budget with line items that align with the activities described in *Part B*.

Part F. **Supporting Financial Documents**

Submit specific documents to demonstrate the organization's financial strength and the strength of the proposed sustainability plan and fee structure, specifically:

- Financial statements prepared in accordance with US GAAP for the quarters ended September 30, 2012 and September 30, 2013, as well as year ended December 31, 2012.
- Relevant financial notes and disclosures related to all financial statements.
- Submit budget forecasts, market analysis, evidence of relevant financial incentive programs, and other supporting documents for business and sustainability plan.

***Part G*: Licenses and agreements.**

Submit copies of any licenses or agreements required to conduct services required under this RFA.

C. Application Submission Instructions

Applications will only be accepted from applicants who 1) submitted an LOI and 2) are notified by CIRM that they are eligible to apply.

All applicable parts of the application must be submitted to CIRM no later than 5:00 PM PDT on March 14, 2014, via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions to this deadline will be made.

IX. Schedule of Deadlines and Reviews

Letters of Intent due	December 16, 2013
Invitations for Applications sent out by CIRM	January13, 2014
Applications due	March14, 2014
Review of Applications by Grants Working Group (GWG)	Spring 2014
Review and Approval by ICOC	Summer 2014
Earliest Funding of Awards	Fall 2014

X. Contacts

For information about this RFA or the review process:

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

For information about this RFA:

Natalie DeWitt, Ph.D.
Special Projects Officer
California Institute for Regenerative Medicine
Email: ndewitt@cirm.ca.gov
Phone: (415) 396-9305

XI. 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. 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.

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 (Title 17,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.

XII. 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 be composed of Alpha Clinics PDs, the CIMC PD and CIRM representation 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.