RFA 10-03: CIRM TARGETED CLINICAL DEVELOPMENT AWARDS

I. Purpose

Stem cells offer the potential to restore tissues damaged by injury or disease. The rapid expansion of stem cell research over the past few years suggests that there are candidate cell therapies ready for clinical development. While there is great therapeutic potential for stem cell derived cell therapies, there are also significant challenges to clinical development, particularly when cell therapies are derived from pluripotent cells. These cells, due to their high replication potential and ability to differentiate into all cells in the body, offer the greatest potential to be the starting cells for cell therapies that broadly benefit patients with disease or injury but, owing to these same properties, also pose significant risk. CIRM, given its mission, will facilitate those innovators who are willing to lead the field in conducting clinical development of these highly innovative products. The purpose of this CIRM Targeted Clinical Development Award RFA is to enable the development of novel cell therapies derived from pluripotent stem cells that may offer unique benefit with well-considered risk to persons with disease or serious injury. For purposes of this RFA, pluripotent stem cells are defined as human embryonic stem cells or human induced pluripotent stem cells.

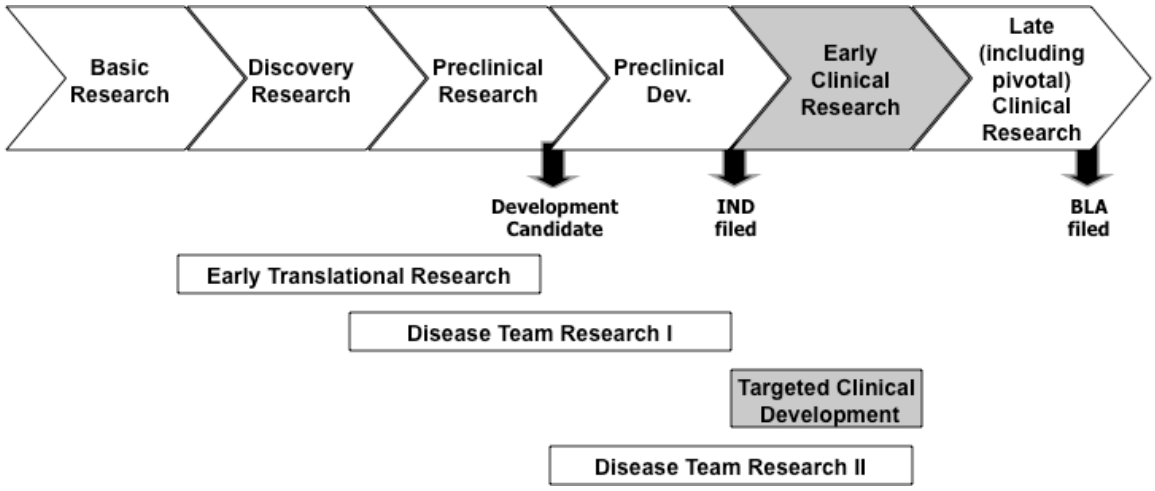
II. Objectives

The key objectives of the CIRM Targeted Clinical Development Award RFA are the completion of early stage clinical trial(s) for a cell therapy derived from human pluripotent stem cells, that will within three years: 1) evaluate preliminary safety in humans, and 2) provide evidence of mechanism in humans as well as preliminary evidence of clinical efficacy that could lead to more definitive efficacy studies.

For applications to be responsive to this RFA, applicants must have filed an Investigational New Drug application (IND) for the human pluripotent stem cell-derived therapy proposed for CIRM funding. The IND must be filed (as evidenced by FDA acknowledgement of receipt and/or assignment of IND number) by the application deadline.

The diagram below shows where the research covered by this RFA falls along the research spectrum, and in the context of our recurring Early Translational and Disease Team RFA initiatives. These translational RFAs are core to our mission to

enable stem cell-based therapies, diagnostics and cures for the benefit of persons with disease and injury.



This award will support activities commensurate with the objectives of this RFA including:

- The conduct of early clinical trials (e.g. Phase 1, Ph 1/2 and/or Phase 2a) that will be completed within three years and will: 1) evaluate preliminary safety in humans and 2) provide evidence of relevant mechanistic activity in humans (proof of principle) as well as preliminary evidence of clinical efficacy.

- Supporting activities that will enable the proposed clinical studies such as cGMP production, testing and release of candidate therapeutic product for the proposed trial(s) and/or further qualification/validation of relevant assays such as potency assays or specialized clinical assays.

The proof of principle/early efficacy studies may employ physiological (which can include imaging), molecular or biochemical endpoints as well as the definitive clinical endpoints generally required for market approval. The application should reflect careful thought given to clinical endpoints. Such endpoints could include evaluation of efficacy measure(s) that may be useful in the planning of more definitive efficacy studies.

The proposed clinical trials may include supporting studies performed in the context of the clinical trial, designed to provide critical additional data to better inform decisions on continued clinical testing. Examples of such studies include: measurement of additional pharmacodynamic parameters to improve decisions on dosing; evaluation of relevant biomarkers; use of additional clinical, biological, immunological, imaging or efficacy measures to enhance/correlate data on the mechanism of action or efficacy of the proposed cell therapy. Applicants will be expected to justify how such supporting studies will specifically inform the trial

results and contribute to decision making on continued clinical testing of the proposed cell therapy.
CIRM expects clinical trials that it funds to include women and members of minority groups unless a clear and compelling rationale and justification establishes to the satisfaction of CIRM that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

Research activities that fall outside the scope of this RFA include the following examples:

- Activities designed to lift a clinical hold prior to issuance of Notice of Award.
- Pivotal clinical efficacy studies designed to be submitted for marketing approval.
- Non-interventional clinical studies (e.g. biomarker discovery; clinical studies that do not involve administration of the proposed cell therapy; or studies using samples not from subjects of the proposed clinical studies)
- Process scale-up or production for clinical studies other than those proposed as part of this project.
- Development and qualification of a medical device for the delivery of the product if needed.

III. Award Information

CIRM proposes to fund one or two projects. CIRM will fund the lesser of $25 million or 50% of the total costs of a proposed project for up to three years. The amount and timing of funds disbursed will be based on a jointly agreed to activity-based project budget. CIRM proposes to commit up to $50 million under this RFA.

CIRM will require matching funding (1:1 ratio) from applicants for the proposed project. Additional funding over and above the required match may be provided by the applicant if necessary. Matching and additional funds can be used to fund jointly agreed-to project costs such as activities conducted outside of California and long-term follow-up studies on test subjects (see section XIV.D). CIRM's and the applicant's funding contributions are to be reasonably distributed over the award period. Applicants will be expected to address status and sources for matching funds (and any additional funding) required for achievement of RFA objectives prior to award issuance during pre-funding administrative review.

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) or Notice of Loan Award (NLA), 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 (e.g. with Contract Research Organizations, CROs or Contract Manufacturing Organizations, CMOs) that are critical to the success of the project.

The award recipient must have an IND that is in effect (i.e. not subject to clinical hold) for the novel cell therapy proposed for CIRM funding before issuance of Notice of Award. Before CIRM will release funding, successful applicants will be required to provide evidence that the IND is in effect.

Mindful of the urgency of its mission, CIRM requires that a Notice of Grant (or Loan) Award for approved applications be executed and that the project commences no later than six months after the Independent Citizens Oversight Committee (the "Governing Board") approval and/or authorization for funding, unless CIRM's President grants an extension based upon compelling justification of the need for additional time.

IV. Award Mechanism

CIRM expects to fund approved proposals from non-profit and for-profit institutions (separately or in collaborations), through grants or loans.

For an **investigator-sponsored IND**, the investigator-sponsor must be the Principal Investigator (PI) on the CIRM application.

For an **organization-sponsored IND**, the organization sponsor must be the applicant organization on the CIRM application, and the PI must be an employee of that organization.

The following outlines the applicable award mechanism:

- Loan, if a for-profit organization holds (sponsors) the IND and is the applicant organization. The loan holder will be responsible for the entire award from CIRM, even if a Co-PI is from a non-profit organization. Loan terms are described in section XVII. Appendix C.

- Grant, if PI holds the IND and is from a non-profit organization

Grant Terms: Non-profit institutions or a PI at a non-profit organization that holds (sponsors) the IND will receive grant funding in quarterly disbursements, and be subject to all terms of CIRM's Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.).

Loan Terms: The terms of the Loans are set forth in detail in section XVII, Appendix C to this RFA. Loan recipients shall be governed by the CIRM Loan Administration Policy that is in effect as of the date of the execution of the Notice of Loan Award.

Approved for-profit applicants who accept a loan will pay for loan administration costs out of indirect costs included in the award.

Loan applicants will be required to submit financial information. For information on the loan program, consult the Interim CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/cirm-operations/Regulations

V. Eligibility Information

A. Project Eligibility

Under this RFA, CIRM will not limit the number of applications from each eligible institution. However, CIRM will only accept a Letter of Intent (LOI) for a project that meets the following Eligibility Criteria.

1. The project must be a cell therapy derived from human pluripotent stem cells (either from human embryonic stem cells or human induced pluripotent stem cells) where an IND has been or will be filed with FDA by the application deadline (as evidenced by FDA acknowledgement letter and/or assignment of IND number).

2. All aims of the proposed project must address the clinical development of the cell therapy derived from human pluripotent stem cells that is the subject of the IND filing. The proposed project objectives must directly address:

a) The completion within three years of early stage clinical trial(s) (e.g. Phase 1, Phase 2a) for a cell therapy derived from human pluripotent stem cells that will:

1) evaluate preliminary safety in humans, and

2) provide evidence of mechanism in humans as well as preliminary evidence of clinical efficacy that could lead to more definitive efficacy studies.

CIRM requires that any clinical trial that is part of the proposed project include at least one clinical trial site in California, subject to section V.E. To the maximum extent reasonably possible, matching funds should be used to pay for clinical trial execution that is conducted out-of-state.

CIRM expects clinical trials that it funds to include women and members of minority groups where feasible.

b) Supporting activities that will enable the proposed clinical studies, such as cGMP production, testing and release of candidate therapeutic

product for the proposed trial(s) and/or further qualification/validation of relevant assays such as potency assays or specialized clinical assays.

B. Institutional Eligibility

Principal Investigators may apply from non-profit and for-profit research organizations that are located in California and are actively conducting or managing research at a site in California at the time of Application deadline. Non-profit and for-profit institutions sponsoring Co-Principal Investigators (Section VII.B, Co-Principal Investigators) are subject to the same eligibility requirements as applicant institutions.

"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 are also referred to as "commercial organizations".

C. Investigator Eligibility

Principal Investigator

CIRM requires that a single Principal Investigator (PI) and a single applicant institution (the PI's institution) be designated in each application. The PI is the designated point of contact for CIRM and is the person responsible and accountable to CIRM for scientific performance on the project. The applicant institution is the designated contact institution for all financial and other administrative considerations.

A Principal Investigator (PI) may submit only one application under this RFA. An investigator who is a PI or a Co-PI on a Disease Team Research Award (RFA 09-01) is not eligible to submit a Letter of Intent (LOI) as a PI or Co-PI under this RFA. The PI must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed project. By the Application deadline for this RFA, the PI must:

- be an independent investigator at a non-profit applicant institution in California, or have an equivalent position and be an employee (at least 50-percent time) of a for-profit institution in California;

- have documented authority from the applicant institution to staff the proposed project; and

- have documented commitment from the applicant institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

Co-Principal Investigator(s)
In order to encourage multidisciplinary team-based research, CIRM will allow for a single CIRM-funded Co-Principal Investigator (Co-PI). The Co-PI must have an M.D., Ph.D. or equivalent degree and must be sponsored by the institution at which the Co-PI will conduct the proposed project. By the Application deadline, the Co-PI must:

- be an independent investigator at the sponsoring non-profit applicant institution in California, or have an equivalent position and be an employee (at least 50-percent time) of the for-profit institution in California;

- have documented authority from the sponsoring institution to staff the proposed project; and

- have documented commitment from the sponsoring institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

Designating a Co-PI is not a requirement of this award. The decision of whether to include a Co-PI should be guided by the goals of the project. All applications will require a leadership plan as outlined below (Section IX.B.14). When considering a Co-PI, please be aware that the reviewers will consider the structure and governance of the development team as well as the knowledge, skills and experience of the individual PI and Co-PI. The Co-PI is responsible and accountable to the grantee organization.

D. Percent Effort Requirements

CIRM will only fund PIs and Co-PIs who are willing to devote substantial, focused attention to the project. For this RFA, PIs must be willing and able to commit a minimum 30% effort, and for Co-PIs, 20%.

E. Extraordinary Exceptions

In extraordinary circumstances, the President of CIRM shall have the discretion to permit exceptions to requirements specified in this section V. of the RFA (except for the requirement for a cell therapy derived from human pluripotent stem cells) if the President determines, in his sole 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 XIV of this RFA) and the Loan Administration Policy (see section XVII, Appendix C of this RFA), or they will not be considered. Such exceptions **must** be requested by September 29th, 2010 (see contact information, section XIII of this RFA) to allow the President of CIRM adequate time to review and to approve or deny the request prior to December 1st, 2010, the deadline for submission of applications.

VI. Award Administration and Project Management

A clinical development project is inherently multidisciplinary, involving a team of professionals with diverse expertise who may be from for-profit or non-profit institutions. CIRM will require for this project a team leader (Principal Investigator, PI) and a project management professional (Project Manager), the latter with relevant experience in managing clinical development programs and who is able to devote an appropriate percentage effort (≥50%). The proposed project may also include a Co-Principal Investigator (Co-PI) (section V.C). These individuals will be responsible for keeping the team focused, achieving expectations and milestones, and providing ongoing communication with CIRM.

The PI is the designated point of contact for CIRM, provides overall vision and direction, and has scientific and financial accountability. The PI should be a practicing professional with a record of effective scientific leadership. The Co-PI works jointly with the PI to direct the scientific development and execution of the funded project. The Project Manager coordinates project activities, manages the timeline and ensures communication, coordination and collaboration among members of the team, consultants and collaborators and with CIRM.

Achieving the objectives of the project is important to CIRM's mission, and progress will be closely monitored by CIRM. CIRM (or its designee), the PI, Co-PI, if applicable, and the Project Manager will be involved in the active management of these projects. In addition to annual Progress Reports, as required by the Grants Administration Policy (GAP, section XIV. A), communication and reporting responsibilities of the grant or loan recipient to CIRM will include: 1) quarterly updates; 2) routine communication by the PI or Project Manager; 3) notification of any serious adverse event as required by the GAP (section XIV.A) and 3) participation in Evaluation Meetings. CIRM responsibilities will include: progress monitoring via written reports and teleconferences, establishing oversight advisory committees, and the conduct of the Evaluation Meetings. Continued funding is contingent upon timely scientific progress as outlined in the project milestones and timeline established under the NGA or NLA or as jointly agreed to upon renegotiation.

Evaluation Meetings will occur at key decision points in the development projects, at which time Go / No Go decisions are made, or when there are significant delays in performance on progress milestones. Evaluation Meetings may also be held minimally at annual intervals. Key decision points occur upon:

- Completion of a clinical study and prior to initiation of the next clinical study
- Occurrence of any unexpected event(s) that significantly alters the risk-benefit profile of the candidate therapeutic
- Occurrence of an event that significantly impacts the ability of the project to proceed in accordance with the timeline
- Being placed on clinical hold by FDA after project start.

Evaluation Meetings will be chaired by CIRM's Vice President of Research and Development (or other individual as designated by CIRM's President), and will include members of an oversight advisory committee, CIRM staff, and project representatives. The Project PI, Co-PI, Manager and relevant project personnel will present their project data including progress against the project milestones, any issues and corrective actions, an updated Target Product Profile (section IX.B.6), an updated Project Plan including milestones and timeline (section IX.B.10-12), an updated Budget (section IX. B.5), other materials as requested, and a recommendation for action. Possible outcomes of an Evaluation Meeting include: continuation of successful projects, redirection if appropriate, or project discontinuation. Go /No Go determinations will be made by the CIRM President based on recommendations by the oversight advisory committee in consultation with staff.

Review criteria for the application (section VIII) will form the basis of the evaluation. In addition, the oversight advisory committee will consider:

1. Performance: The project team has achieved or is on track to achieve the project milestones on time and within budget.

2. Therapeutic Candidate Competitiveness and Impact: The therapeutic candidate offers an advantage(s) over other therapies in practice or in development, based on current data, Target Product Profile and competitive assessment. Results achieved to date demonstrate a trend toward clinically significant efficacy with no limiting toxicities.

3. Feasibility and Next Steps: Feasible plans and key issues in all areas (manufacturing, clinical, and regulatory) critical to the successful achievement of the next phase of the project are defined and addressed in the updated Project Plan. Where issues have been identified that impact milestone achievement, timeline or budget, the plan for corrective action is feasible and achievable. The project can meet its objective and the goal of the RFA within the award period.

VII. Application and Evaluation Process

Submission of an application for the CIRM Targeted Clinical Development Awards RFA involves a two-step process. Any eligible applicant may submit a Letter of Intent (LOI, see section V for eligibility criteria). Applications will only be accepted from Principal Investigators (PIs) who submitted an LOI that was accepted by CIRM. The PI, Co-PI (if applicable), and the clinical development project proposed in the application must be the same as those described in the LOI; otherwise, the application is deemed ineligible.

Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The membership of the GWG can be found at http://www.cirm.ca.gov/GrantsWkgGrpMembers. The composition of the Governing Board can be viewed at http://www.cirm.ca.gov/GoverningBoard. The fifteen scientists on the GWG will review the applications and score them for scientific and clinical merit, applying the review criteria described in section VIII below. The scientific members of the GWG will consider the entire project including those portions of the project proposed to be funded by matching and potentially additional funds provided by the applicant. Following the scientific scoring, the full membership of the GWG will then review the entire portfolio of applications, taking into consideration the following criteria:

- Impact of the proposed project on the development of pluripotent stem cell-based therapies and on regenerative medicine.

- Appropriate balance between feasibility, risk and benefit.

- Appropriate balance in the context of CIRM's development portfolio (comprised of funded Disease Team Research Awards, RFA 09-01, and Early Translation Research Awards, RFA 08-05 targeting a development candidate, see http://www.cirm.ca.gov/for-researchers/researchfunding) in order to enhance portfolio diversity and reduce risk.

- Other considerations from the perspective of the patient advocates.

The GWG will make funding recommendations to the Governing Board, which will make final funding decisions.

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.

VIII. Review Criteria

Applications will be evaluated in four key areas: 1) Significance and Impact; 2) Project Design and Feasibility; 3) Principal Investigator, Development Team and Clinical Investigators and (4) Collaborations, Assets, Resources and Environment. The specific criteria for review of applications are based on the standard review criteria described in the CIRM Grants Administration Policy (GAP, see section XIV of this RFA).

1) Significance and Impact

a. Appropriate Target Product Profile: The target product profile (TPP) is appropriate and achievable. The proposed therapeutic candidate addresses an unmet medical need and/or has the potential to significantly improve patient care compared to other therapies that are available or in late-stage development. The intended patient population indicated in the TPP is reflective of the overall unmet medical need.

b. Responsiveness: The proposed clinical and supporting studies could meet the objectives of this RFA which are to provide, within three years, 1) evaluation of preliminary safety in humans, and 2) evidence of mechanism in humans as well as preliminary evidence of clinical efficacy.

c. Impact: The overall development strategy is well considered and reflects thought and commitment to moving the candidate cell therapy through development for the benefit of patients or persons with serious disease or injury. The proposed project is integral to the overall development strategy and supports achievement of the Target Product Profile.
The proposed cell therapy, if successfully developed and made available to patients, would have a significant impact on standard of care medical management of the disease or injury. The project could significantly advance the field of stem cell therapy and regenerative medicine by pioneering innovative approaches and by generating and applying new knowledge, methods and strategies.

2) Project Design and Feasibility

a. Strong Rationale: There is strong scientific and clinical rationale for the proposed therapeutic intervention in the target disease or injury. The therapeutic rationale is justified by preclinical/other evidence.

b. Potential Benefits and Risks: The overall Risk/Benefit analysis is favorable, based on the target patient population, other therapeutic options for that population, the scientific rationale, preclinical pharmacology and toxicology studies, and the therapeutic approach. There is a reasonable expectation that the proposed therapeutic approach will have clinical benefit for patients. The potential risks to subjects are deemed manageable and

acceptable in the context of the target patient population and the potential benefit. The potential benefits to subjects outweigh the risks and justify use of the proposed cell therapy in the target disease.

c. IND Clinical Hold: The plan to address clinical hold issues that may be present is feasible and likely to result in clinical hold being lifted within a reasonable time frame.

d. Meaningful Milestones and Feasible Timeline: The project milestones describe key activities and deliverables that will be funded under this RFA. The project milestones are reliable indicators of the project's progress. The criteria for Go/No Go decisions are adequately defined and provide quantifiable measures of the project's performance. The project timeline is complete, highlights key progress and Go/No Go decision milestones and is realistic.

e. Clinical Studies:

(1) ***Clinical Protocol Synopsis***: Evaluate the CLINICAL PROTOCOL SYNOPSIS for each proposed study against the following criteria:

- The overall study design and objectives together with proposed supporting studies (such as imaging, biomarker analyses, immune monitoring) are feasible and adequate to meet the objectives of this RFA.
- The choice of patient population is appropriate and the enrollment projections are realistic and achievable within 3 years.
- Criteria for a positive/negative study outcome have been adequately defined, based upon the primary objective and designated secondary objectives. There is a reasonable likelihood of success so defined.
- The plan for immunosuppression and immune monitoring is justified and appropriate.
- The proposed supporting studies are well designed to provide meaningful data that advances knowledge on the safety and/or effectiveness of the candidate cell therapy in humans and will provide useful information to inform decisions on continued clinical testing. The proposed methodologies are sufficiently qualified/validated to be suitable for their intended use and to meet the objectives of the supporting study.
- The process and criteria for selection and oversight of clinical sites will ensure selection of high quality sites and adherence to Good Clinical Practice (GCP) and to the clinical protocol.

(2) ***Protections for Human Subjects***:

- The proposed Data and Safety Monitoring Plan (DSMP) is

adequate to protect human subjects from risks of the proposed clinical research and will ensure appropriate oversight and monitoring of the conduct of the clinical investigation. The proposed Data and Safety Monitoring Plan makes adequate provision for monitoring the data collected to ensure the safety of participants and the validity and integrity of the data. Non-standard of care tests or procedures that will be performed for research purposes are justified by the knowledge to be attained and do not significantly increase risks to subjects.

f. CMC/Manufacturing Activities: The manufacturing strategy is feasible. Sufficient product can be prepared and released within the necessary time frame to meet the enrollment requirements. The CMC activities proposed for funding (including manufacture of the clinical supplies) are necessary to support the clinical work proposed in this application. The plan for managing technology transfer and product handling at the clinical sites is adequate to ensure safety and quality of the test article.

3) Qualifications and Experience of the Principal Investigator (PI), Core Development Team and Clinical Investigators

a. Experienced Team Leader(s): Evidence of prior success and track record supports the qualifications of the PI and the Co-Principal Investigator (Co-PI, if applicable) to successfully lead and execute the proposed project.

b. Development Team (including consultants): An appropriate multidisciplinary team has been assembled that includes a Clinical Lead, CMC Lead, Regulatory Lead, Translational Research/Non-Clinical Lead and a Project Manager. Evidence of prior relevant experience supports the qualifications of the Team Members to successfully implement the proposed plan.

c. Clinical Investigators: The lead clinical investigators that will participate in the study at study sites are recognized opinion leaders or experts in the target disease/injury area and have relevant experience in conducting clinical studies in that disease/injury area.

d. Leadership Plan: The PI has developed a leadership plan that will ensure successful execution of the project. The structure and governance of the team will support status assessment, progress monitoring, and project decision-making. The PI together with the Project Manager will foster communication, coordination and collaboration among members of the team, consultants and CROs/CMOs. A comprehensive leadership plan for functional area operations and decision making has been established and includes: Clinical, Clinical Operations, Regulatory, Product Manufacturing and Translational Research.

Designated team members will be responsible for regulatory and safety filings, data collection and monitoring, maintenance of databases, product manufacturing, quality control; training and oversight of clinical sites and adherence to the clinical protocol. Plans and strategies have been developed for communication with and oversight of CROs/CMOs. There is a plan for resolving potential issues or conflicts.

e. Budget: The team leaders have developed a budget that is focused and appropriate.

4) Collaborations, Assets, Resources and Environment

a. Collaborations/CROs/CMOs: The planned Collaborations/CROs/CMOs/consultants are necessary and appropriate. The plan for CRO (contract research organization) identification and contracting is adequate to ensure that proposed CROs/consultants that will participate in the proposed clinical research have the necessary experience and expertise to successfully meet expectations, deliverables and timelines. CMO's (contract manufacturing organizations) contracted for manufacture or release testing of the therapeutic candidate have the necessary experience and track record to successfully produce the clinical supplies needed to support the proposed clinical studies.

b. Relevant Assets: Relevant assets (i.e. intellectual property, licenses) are available to the project.

c. Resources and Environment: The Team has access to infrastructure to ensure successful execution of the proposed project. Resources critical to the success of the project, including manufacturing and testing facilities, data management, major equipment, and services (through advisors, subcontractors) are available.

d. Clinical Sites: The clinical sites that will participate in the study/studies have the ability to meet the enrollment requirements and execute the protocol.

IX. Application Procedure

Applicant institutions and PIs must follow these instructions for submission of a Letter of Intent and Application for the CIRM Targeted Clinical Development Award. Applications will only be accepted from PIs who submitted a Letter of Intent that was accepted by CIRM. The PI and Co-PI (if applicable), and the clinical development project proposed in the application must be the same as those described in the Letter of Intent; otherwise, the application is deemed ineligible.

A. Letter of Intent (LOI)

A PI may submit only a single LOI for this RFA using the LOI template that will be provided by 9/1/10 at http://www.cirm.ca.gov/RFA_10-03. The LOI should concisely describe the proposed clinical development project and explain how it will within three years: 1) evaluate preliminary safety in humans, and 2) provide evidence of mechanism in humans as well as preliminary evidence of clinical efficacy that could lead to more definitive efficacy studies. Applicants must answer the questions included in the LOI template provided. **The completed LOI must be submitted online as instructed on the CIRM web portal (**http://www.cirm.ca.gov/RFA_10-03**) and must be received by CIRM no later than 5:00PM (PDT) on September 29th, 2010**. **No exceptions will be made.**

B. Application Forms

Application forms and instructions will be available on the CIRM website (http://www.cirm.ca.gov/RFA_10-03_Application_Instructions) in early October 2010. Only those applicants that submitted an LOI that was accepted by CIRM may submit an application.

The Application for the CIRM Targeted Clinical Development Awards consists of five parts:

Part A: Application Information Form (Adobe PDF template). Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, and Budget (section numbers 1- 5 below). Part A consists of the following subparts:

Part A – PI Application Information Form
Part A subpart I – Co-PI Information Form (if applicable)

Part B: Targeted Clinical Development Award Proposal (MS Word template). Part B includes: Objective, Target Product Profile, Aims; Overall Development Strategy; Impact; Rationale & Risk/Benefit; Proposal Overview; Clinical Protocol Synopsis/Synopses; Manufacturing Plan Synopsis; Leadership Plan; Collaborations, Consultants, CROs/CMOs; Assets, Resources and Environment, References (section numbers 6-16 below). Part B consists of the following subparts:

Part B – Targeted Clinical Development Award Proposal
Part B subpart I – Clinical Protocol Synopsis/Synopses
Part B subpart II – Manufacturing Plan Synopsis
Part B subpart III – Activity-Based Budget (MS Excel)

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

Part D: Reference Materials (Adobe PDF files). Part D includes: Investigator Brochure for the candidate cell therapy; Specialized assay methods and summary of assay qualification/validation (section numbers 17-18 below)

Part E: Related Business Entities Disclosure Form (Adobe PDF template). In order to comply with the Conflict of Interest policies under which CIRM operates, Part E must be submitted to indicate whether the application would, if awarded, provide funding from CIRM to a for-profit organization that is either: 1) the applicant organization; 2) a subcontractor; or 3) the employer of a Co-Principal Investigator, co-investigator, consultant or subcontractor (section number 19 below).

The application for a CIRM Targeted Clinical Development Award includes the following sections:

1) ***Abstract*** *(divided in four parts of up to 3000 characters each in Part A)*
   a. Project Description: Provide a brief description of the proposed project. Describe the scientific and clinical rationale for the proposed cell therapy. Address why a pluripotent human stem derived cell therapy is a preferred approach to achieve the desired therapeutic outcome.
   b. Unmet Medical Need/Impact: Describe the unmet medical need that the proposed therapy will address. Summarize the impact that this therapy would have on the target disease or injury, if it were successfully developed.
   c. Project Plan: Summarize the proposed plan and describe how it will achieve the objectives of this RFA which are to 1) evaluate preliminary safety in humans, and 2) provide evidence of mechanism in humans as well as preliminary evidence of clinical efficacy.
   d. Milestones: Summarize the milestones to be achieved within each year of the three year award period.

2) ***Public Abstract*** *(up to 3000 characters in Part A)*
   In lay language, briefly describe the proposed research and how the proposed pluripotent stem cell-derived cell therapy will advance the treatment of disease or serious injury by demonstrating preliminary safety in humans and providing evidence of mechanism in humans as well as preliminary evidence of clinical efficacy that could lead to more definitive efficacy studies. This Public Abstract will become public information and will be available online; do not include proprietary or confidential information or information that could identify the applicant and applicant institution and, if applicable, the Co-PI, and his/her respective applicant institution.

3) ***Statement of Benefit to California*** *(up to 3000 characters in Part A)*
   Describe in a few sentences how the proposed research 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 and the applicant institution and, if applicable, the Co-PI, and his/her respective applicant institutions.

4) ***Key Personnel*** *(included in Parts A and C)*

List all key personnel and their roles on the project. Key personnel are defined as individuals who contribute to the scientific 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, trainees, co-investigators (collaborators), or consultants who meet the above definition. List the lead clinical investigator for each clinical site in key personnel even though he/she will be compensated as part of a subcontract. It is not necessary to name other clinical site personnel who will be participating in the conduct of the study. For applications that designate a CIRM-funded Co-PI, key personnel sponsored by the Co-PI must be listed in Part A subpart I. Where the Co-PI is employed by an institution other than the applicant institution, key personnel for the PI can include a project financial administrator.

For CIRM funded key personnel, a minimum of one percent effort is required for each key person on this project except the PI and the Co-PI (if applicable) who are required to commit a minimum of 30% and 20% effort respectively.

For each key personnel listed (except for technical staff and students) provide a two-page biographical sketch using the template provided. The biographical sketch should highlight relevant research and product development experience, including, for example, team leadership, conduct of clinical studies and/or contribution to regulatory filings for product development. Include relevant publications, patents or patent applications. Following the biosketches for the PI and, if applicable, the Co-PI, provide biosketches for functional area heads and/or members of the development core team (including the individuals responsible for overseeing clinical, clinical operations, regulatory, CMC, data management and translational research activities) and for the lead clinical investigator at each proposed site. Thereafter, include all remaining biosketches in alphabetical order.

5) ***Budget*** *(included in Part A)*

Provide all budget information requested in the budget section of the Application Information Form. The budget includes funding for all necessary project activities required to achieve the objective of the RFA. In addition to the budget overview, applicants must provide an Activity-Based budget for the entire project, and must designate CIRM or applicant as the funding source. The applicant's funding contribution to the proposed project must be at least equal to that of CIRM. Funding from both the applicant and CIRM are expected to be reasonably distributed over the project period. Successful applicants will be expected to address status and sources for their funding contributions during Pre-Funding Administrative Review (PFAR).

Budgets must be described and justified in sufficient detail for reviewers to assess and must include subcontracts and consulting fees. For applications that designate a Co-PI, where that Co-PI will be responsible for activities funded by CIRM, the PI and the Co-PI will each be responsible for an individual budget (comprised of CIRM Direct Project Costs, CIRM Direct Facilities Costs and CIRM Indirect Costs) for that portion of the proposed project funded by CIRM.

All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see section XIV.A of this RFA). Under this RFA, CIRM-funded allowable costs include the following:

A. *Salaries for Key Personnel*
   Salaries for Key Personnel may include the salaries for the Principal Investigator, Co-Principal Investigator, Co-Investigators, Research Associates, and technical support staff (all of whom 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 total salary requested by the PI and the Co-PI must be based on a full-time, 12 month staff appointment or the full time annual salary for employees of a for-profit institution. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. With the exception of the project financial administrator for projects where a Co-PI is at an institution other than that of the PI, administrative support salaries are expected to be covered exclusively by allowed Indirect Costs.

B. *Supplies*
   Supply expenses may include specialized reagents, core services and animal costs. Minor equipment purchases (less than $5,000 per item) are considered Supplies and may be included as direct costs in the budget.

C. *Travel*
   Recipients (PIs) of CIRM Targeted Clinical Development Awards are strongly encouraged to attend the CIRM-organized grantee meeting held in California and should include travel costs for this meeting in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the CIRM GAP (see section XIV.A of this RFA).

D. *Equipment*
   Major equipment ($5,000 or more per item) necessary for conducting the proposed research at the applicant institution 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. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

E. Consultants/Subcontracts

Grantees that subcontract CIRM-funded work should note that CIRM-funded **research** must generally be conducted in California. Examples of such research include study design; clinical protocol development; design of a toxicology study; analysis and interpretation of data; development of new methods.

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 execution of a clinical trial according to a protocol, execution of a toxicology study performed according to an existing protocol, GMP production. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and IRB activities.)

For any clinical trial that is part of the proposed project, at least one of the clinical sites implementing the protocol must be in California, unless the President determines, in his sole discretion and based on information provided by the Grantee, that it is not reasonably possible to have such a site in California. To the maximum extent reasonably possible, matching funds should be used to pay for clinical trial execution that is conducted out-of-state.

F. Indirect Costs

Indirect costs will be limited to 20 percent of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, and subcontract amounts in excess of $25,000.

6) ***Objective/Target Product Profile/Aims*** *(up to 2 pages in Part B)*

State the objectives of the proposed project. Provide a Target Product Profile for the proposed cell therapy in the format provided in the CIRM Target Product Profile table in Part B of the application. For each Profile Component (Indication, Patient Profile, Efficacy, Safety/Contraindications, Dose/Regimen, Dosage form/Route of Delivery), list the target attributes/claims. List the project aims that will support the Target Product Profile and achieve the objectives of the proposal and of this RFA within the three-year award period.

7) ***Overall Development Strategy*** *(up to 2 pages in Part B)*
Summarize the strategy to develop the candidate cell therapy and bring the therapy to patients. Provide a high-level timeline of the Overall Development Plan to obtain market approval or become accepted medical practice for treatment of the target disease/injury. Include key clinical, CMC, regulatory and other milestones.

8) ***Impact*** *(up to 1 page in Part B)*
Summarize the current standard of care and competitive landscape for the target disease or serious injury indication. Describe how the proposed novel cell therapy could lead to a significant improvement in patient care compared to existing therapies or to other therapies currently in late-stage development.

9) ***Rationale and Risk/Benefit*** *(up to 6 pages in Part B)*
Summarize the scientific and clinical rationale for testing the proposed cell therapy in the target disease/injury (you may reference appropriate sections of the Investigator Brochure).

Summarize the results of preclinical efficacy studies and other supporting data that justify the therapeutic approach. Provide a summary (in tabular form) of the preclinical safety studies and major findings.

Describe the potential benefits to patients of the proposed cell therapy, and the potential risks. Explain why the potential benefits to subjects outweigh the risks and justify use of the proposed therapeutic intervention in the target disease/injury. The Risk/Benefit analysis is based on the target patient population, other therapeutic options for that population, the scientific rationale, preclinical pharmacology and toxicology studies, and the therapeutic approach.

Summarize the IND status for the proposed cell therapy. Briefly summarize any past clinical hold issues and explain how they were resolved. If currently on clinical hold by FDA, summarize the issues, plans to mitigate and risk/benefit impact.

10) ***Proposal Overview*** *(up to 4 pages plus 1 page for timeline, the latter in Gantt chart format or equivalent, in Part B)*

Provide an overview of the proposed project and describe the activities proposed for funding under this RFA. Include:

- Clinical studies; and ii. CMC/Manufacturing activities to enable the clinical work that is part of this proposal.
- List major milestones (Progress and Go/No Go) and specify the criteria that will be used for decision making at each Go/No Go decision point. Discuss program implications of Go/No Go decision points.
- Provide a ***timeline*** (in Gantt chart format or equivalent) for the proposed project and include Clinical and CMC activities, other key activities, milestones and Go/No Go decision points.
- Identify potential risks to the project and describe mitigation strategies.
- Explain how the activities of the proposed project contribute to and advance the Overall Development Plan leading to regulatory approval or to become accepted medical practice for treatment of serious disease/injury.

11) ***Clinical Protocol Synopsis*** *(up to 8 pages per synopsis in Part B Subpart I)*

Using the CIRM CLINICAL PROTOCOL SYNOPSIS Template (Appendix A), provide a Clinical Protocol Synopsis for each study proposed for funding under this RFA. Provide all of the information required.

12) ***Manufacturing Plan Synopsis*** *(up to 6 pages in Part B Subpart II)*

Using the CIRM MANUFACTURING PLAN Template (Appendix B), summarize the manufacturing strategy to support the proposed clinical studies. Provide all of the information required.

13) ***Leadership Plan*** *(up to 2 pages in Part B)*

Provide a detailed leadership and management plan. Describe the organizational structure of the development team. List the key members (including consultants) and indicate their roles. Describe the plan for functional area leadership and management (Include: Clinical, Clinical Operations, Regulatory, CMC and if applicable, Translational Research). Indicate who will have responsibility for regulatory and safety filings; data collection and monitoring; maintenance of data bases; product manufacturing; and quality control (If CRO/CMO/contractor function, indicate designated team member responsible for final sign-off). Describe processes for monitoring progress, maintaining team strategy and timelines, and decision-making. Describe the plan for communication with and oversight of CROs. Describe plans and strategies for resolution of potential issues or conflicts.

14) ***Collaborations/Consultants/CROs/CMOs*** *(up to 3 pages in Part B)*

Provide a list of collaborations/consultants/CROs/CMOs (or plans for identification and contracting) that will participate in the proposed project. Summarize their specific roles, expertise and experience and explain how it is integral to the success of the project. If advisors, consultants or

subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

15) ***Assets, Resources and Environment*** *(up to 1 page in Part B)*
Describe relevant assets particularly intellectual property assets (patent applications, patents) and licenses that are available to the project. Intellectual property assets are important to commercialization of therapies. Provide a brief description of the facilities, environment(s), core services, and resources available for conducting the proposed project and discuss how the proposed project will benefit from unique features of these resources. Include a description of resources available for data storage and data management.

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

17) ***Investigator Brochure*** *(in Part D)*
Provide a copy of the Investigator Brochure for the candidate cell therapy.

18) ***Description of specialized assay methods and summary of assay qualification/validation*** (in Part D)

19) ***Related Business Entities Disclosure Form*** *(Part E)*
All applicants must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a Co-Investigator, consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that on Part E and submit the form. If for-profit funding is sought, include the following for each such for-profit organization to be funded:

- A list of any parent organization that owns 50% or more of the for-profit's voting shares;
- A list of all subsidiaries in which the for-profit owns 50% or more of the voting shares; and
- A list of all other related business entities (i.e., entities with which the for-profit shares management and control, or shares a controlling owner).

X. Application Submission Instructions

Applications will only be accepted from PIs who submitted a Letter of Intent that was accepted by CIRM.

The Application consists of five parts: Part A: Application Information Form (including subpart I, if Co-PI), Part B: Targeted Clinical Development Award Proposal (includes subpart I, Clinical Protocol Synopsis; subpart II, Manufacturing Plan Synopsis and

subpart III, Activity-based Budget), Part C: Biographical Sketches for Key Personnel and letters of collaboration and/or institutional support, Part D: Reference Materials, Part E: Related Business Entities Disclosure Form.
All five parts of the Application must be submitted together and received by CIRM no later than 5:00PM PST on December 1, 2010, in both electronic form and in hard copy (a signed original and five copies). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

An electronic copy of all five parts of the Application must be submitted **online** as instructed on the CIRM web portal.

In addition, submit an original hard copy of the Application (consisting of Parts A, B, C, and E) plus 5 hard copies (preferably double-sided). The original hard copy must be signed by both the PI and the applicant institution's Authorized Organizational Official (AOO). Applications designating a Co-PI must also be signed by the Co-PI and the Co-PI's institutional AOO. Send the hard copies via express mail or courier service to:

Targeted Clinical Development Awards Application
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

XI. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their clinical development proposal after the application deadline but not later than 5:00pm PST on January 11th, 2011. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission should be in the form of a one-page letter addressed to the Senior Review Officer (submit via email to gsambrano@cirm.ca.gov). The body of the cover letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials:

1) Within the one-page letter, provide specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the letter.

2) Within the one-page cover letter, confirmation of funding secured from other sources or regulatory agency filings or actions (removal of clinical hold) acquired since the application submission deadline.

3) Within the one-page letter, notice of patent application(s) filed, notice of allowance received or patent(s) issued, or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.

The letter may not be used to describe any additional data or experiments.

XII. Schedule of Deadlines and Reviews

Letters of Intent due	5:00 pm (PDT), on September 29, 2010.
Applications due	5:00 pm (PST), on December 1, 2010
Anticipated Review of Applications by Grants Working Group (GWG)	February 2011
Anticipated Review and Approval by ICOC	May 2011
Earliest Funding of Awards	Summer 2011

XIII. Contacts

For information about this RFA:

Ingrid Caras, Ph.D
Science Officer
Email: icaras@cirm.ca.gov
Phone: (415) 396-9114

Patricia Olson, Ph.D.
Executive Director, Scientific Activities
Email: polson@cirm.ca.gov
Phone: (415) 396-9116

For information about 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

XIV.CIRM Regulations

Grant or loan 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/cirm-operations/Regulations

A. CIRM Grants and Loan Administration Policies

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP, the Interim GAP for For-Profit Institutions (For-Profit GAP), and the Interim Loan Administration Policy (LAP) serve as the standard terms and conditions of grant and loan awards issued by CIRM. All research conducted under this award must comply with the stated policies including protections for human subjects. 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 approved timeline.

B. Intellectual Property Regulations

CIRM has adopted intellectual property regulations for non-profit and for-profit organizations. By accepting a CIRM grant or loan, the Grantee agrees to comply with all such applicable regulations.

C. Human Stem Cell Research Regulations

CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110). All research conducted under this award will be expected to comply with these standards.

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 of their studies for the benefit of the field.

XV. APPENDIX A: CIRM CLINICAL PROTOCOL SYNOPSIS TEMPLATE

STUDY TITLE
Provide full title of the study
CLINICAL PHASE
Specify clinical phase (1, 2a)
STUDY OBJECTIVES
Provide a brief description of the study objectives *Primary Objectives:* *Secondary Objectives:* *Exploratory Objectives:*
STUDY RATIONALE
Summarize the rationale for testing the proposed cell therapy
STUDY POPULATION
Briefly describe the study population and explain the rationale for choosing this population
MAIN INCLUSION/EXCLUSION CRITERIA
Specify the main inclusion/exclusion criteria and explain the rationale.
PRIMARY ENDPOINT(S)
Describe the Primary Endpoint(s); Explain how they address the objectives of this RFA
SECONDARY & EXPLORATORY ENDPOINTS
Describe the Secondary & Exploratory Endpoint(s); Explain how they address the objectives of this RFA
STUDY DESIGN
Summarize the study design, including type of study, number of arms, controls or comparators
SUBJECT NUMBER
Provide the total number of study subjects , the number per study arm, and justification

TREATMENT DURATION
Specify the length of the treatment period
DURATION OF FOLLOW UP
Specify the length of the protocol-specified follow up period
DOSE LEVEL(S) AND DOSE JUSTIFICATION
Specify the dose level(s), number of doses, and dosing frequency. Summarize how dosing was determined
ROUTE OF DELIVERY
Specify how the doses will be delivered
DATA and SAFETY MONITORING PLAN (DSMP)
Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)
STOPPING RULES
Specify stopping rules
IMMUNE MONITORING & IMMUNOSUPPRESSION
Describe and justify the plan for immunosuppression and immune monitoring (if applicable)
SUPPORTING STUDIES
Summarize supporting studies that are part of this clinical study (e.g. imaging, biomarker analyses, cell phenotyping, genotyping, gene expression analyses), that will provide critical additional data to address the objectives of this RFA or inform decisions on continued clinical testing. Include: *Objectives and rationale* *Sample collections (specify type, frequency)* *Testing methodology* *Data analysis* *Special considerations*
ASSAYS/METHODOLOGIES
Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies. (Provide a more detailed summary of assay methods and summarize assay qualification/validation in Part D). Indicated where specialized testing will be conducted

STATISTICAL ANALYSIS PLAN
Summarize the Statistical Analysis Plan or describe how the data will be analyzed
OUTCOME CRITERIA
Describe criteria that would define a 'positive/negative' study, based upon primary and designated secondary objectives
RISKS
Identify potential risks (e.g. need for and risks associated with long term immunosuppression) and mitigation strategies
CLINICAL SITES
Indicate the number of clinical sites that will participate in the study. Summarize the criteria for site selection. Provide a list of proposed sites with a brief description of the site's experience and capabilities in the conduct of clinical research.
CLINICAL OPERATIONS PLAN
Summarize the plan for managing the conduct of the clinical study. Describe plans for training clinical investigators and personnel at clinical sites and the plan for oversight and monitoring of clinical sites. Indicate who will be responsible for management and sign off of clinical operations activities.
ENROLLMENT
Describe the enrollment strategy and provide a timeline showing enrollment projections *Describe plans for inclusion of women and minorities*
LONG TERM FOLLOW UP
Describe requirements and plans for long term follow up and indicate how these will be supported
TIMELINE
Provide a timeline for completion of the study and indicate relevant milestones

XVI.APPENDIX B: CIRM MANUFACTURING PLAN SYNOPSIS TEMPLATE

TEST ARTICLE
Describe the Test Article
STARTING CELL
Specify starting cell line or cellular source
MANUFACTURING PROCESS
Provide a brief description of the manufacturing process *Provide a flow diagram of the process from starting cell source to final test article* *Describe the plan for shipment of released lot from the manufacturing facility to clinical sites and describe the steps that will be performed at the clinical site*
PROCESS DURATION
Specify the duration of a manufacturing run and time required to test and release a lot
PRODUCT RELEASE
Provide a list of the product release assays and acceptance criteria
IDENTITY ASSAY
Briefly describe the Identity assay(s)
POTENCY ASSAY
Briefly describe the Potency assay(s)
ADDITIONAL CHARACTERIZATION
Briefly describe any additional characterization assays routinely performed (but not required for lot release)
LOT SIZE
Specify the average lot size (number of doses/treatments)
LOT REQUIREMENTS FOR PROPOSED CLINICAL WORK
Indicate the projected number of lots needed to support the proposed clinical work
LOT FAILURE
Specify the % failure of lot release

GMP MANUFACTURING FACILITY
Indicate where GMP manufacturing of the candidate cell therapy will be performed. Describe the experience and track record of the manufacturing facility
RELEASE TESTING FACILITY
Indicate where Release Testing will be performed. Describe the experience and track record of the testing facility
DOSE FORMULATION AT CLINICAL SITES
Briefly describe the plan for managing product quality control at clinical sites
CMC ACTIVITIES PROPOSED FOR FUNDING
Specify all CMC-related activities proposed for funding under this RFA and indicate which activities will be funded by CIRM
RISKS
Identify potential risks(e.g. potential for clinical hold, lot failures) and mitigation strategies
TIMELINE
Provide a timeline for the manufacturing runs planned to support the proposed clinical research and indicate relevant milestones

XVII. APPENDIX C: LOAN INFORMATION

Loan Terms: The Loan Administration Policy ("LAP") is being revised. The new terms are summarized below.

(i) Two types of Loans, Company-Backed Loans and Product-Backed Loans, are available. Company-Backed Loans are subject to repayment regardless of the success of the project, whereas a loan forgiveness mechanism is available for Product Backed Loans. No personal guarantees or collateral are required. Applicants must select the loan type when submitting the full application.

(ii) Term: The term of the loan will be 5 years, subject to extensions as set forth below and in the LAP.

(iii) Payments: All principle and interest will be due and payable at the end of the loan term, unless the repayment obligation has been suspended, forgiven or accelerated or unless the loan term has been extended (see paragraph (vi), below).

(iv) Interest rate: The interest rate of the initial term shall be LIBOR plus 2%, unless the loan term has been extended (see paragraph (vi), below).

(v) Warrants: Loan recipients will be required to provide CIRM with warrants; the amount of such warrant coverage will depend on the type of loan requested and satisfaction of certain criteria as outlined in the revised LAP.

(vi) Extension of Term: Loan Recipient may extend the initial term in one year increments (provided it is in compliance with the Notice of Loan Award and LAP), subject to (a) payment of 25% of unpaid and accrued interest and (b) an interest rate increase in the amount of 1% over the rate in effect the prior year.

(vii) Loan Administration Costs: Approved for-profit applicants who accept a loan will pay for loan administration costs out of indirect costs included in the award. If the term of the loan is extended beyond year 5, the loan recipient must pay any additional loan administration costs. Applicants will be informed of the actual costs once finalized.

Loan applicants will be required to submit financial information. For additional information about the loan program, consult the Interim CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/cirm-operations/Regulations .