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VIEWS

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CIRM was established in November 2004 with the passage of Proposition 71, the California Stem Cell Research and Cures Act. The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was overwhelmingly approved by voters, and called for the establishment of an entity to make grants and provide loans for stem cell research.

The Proceedings of the California Stem Cell Agency is a monthly series of commentaries, articles, interviews, webinars, forums, and concise reviews on a wide range of topics in regenerative medicine.

Proceedings: Accelerating Stem Cell Treatments for Patients: The Value of Networks and Collaboration

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INTRODUCTION

Since the early pioneering cell-based therapeutic experiences with bone marrow, cord blood and peripheral blood stem cells, embryonic stem cell-derived cells, and gene-modified cell therapeutics, the pipeline for stem cell-based therapeutics entering clinical trials has grown considerably [1]. The California Institute for Regenerative Medicine (CIRM) has funded more than 90 developmental-stage programs with 12 accepted investigational new drug applications [2]. This growing pipeline has important operational implications for the development of stem cell research-derived therapeutics. Specifically, the prospect of pipeline growth creates an opportunity to develop sustainable clinical capacity dedicated to treating patients with stem cell-related medicines.

In early 2015, CIRM launched the Alpha Clinics Network, which is designed to catalyze the development of specialized clinical capacity in California [3]. The clinics are centers of excellence that will maintain the clinical and regulatory expertise needed to deliver what, in many cases, will be first-in-human clinical trials and that will also have trained personnel, state-of-the-art facilities, stem cell trial counseling, patient care coordination, and long-term follow-up capacity [4].

The Alpha Clinics Network is anchored by three lead programs at (a) City of Hope National Medical Center, (b) the University of California San Diego, and (c) the University of California Los Angeles and Irvine collaborative program. The network is designed to be a platform for rigorous clinical testing of stem cell therapies. Each Alpha Clinic is located within the host institution as a fully integrated unit that is enabled to leverage the infrastructure and assets of the institution's medical center to support stem cell clinical trials. The Alpha Clinics were selected, in part, because they bring a variety of unique assets to the network. Extensive CIRM funding for this initiative is designed to allow the clinics to leverage their institutional assets so they may be developed and adapted to address the unique needs of stem cell clinical trials.

GENERAL CONSIDERATIONS

As new trials enter the network, there is an opportunity to develop core infrastructure to support a variety of stem cell research-informed therapeutic approaches targeting a diverse array of indications. The experience gained from these projects, and others, will provide further insights into a variety of issues related to the clinical testing and delivery of stem cell therapies. Having a platform dedicated to these therapeutic activities creates the opportunity for continuous-loop learning and development of quality systems. CIRM believes such a platform can facilitate the entry of patient treatments into clinical practice and, ultimately, into commercial success.

Each of the network sites will maintain core infrastructure necessary to support clinical trials emerging from its institutional pipeline or outside sponsors. The network will also share best practices and accelerating and added-value resources (AAVRs) while aggregating experiences and data that would inform how best to support future trials and activities with stem cell therapeutics. As available, the Alpha Clinics Network would adapt and refine other operational efficiency resources of existing research networks. Pipeline development is a key component of the Alpha Clinics program. Consequently, an early focus of planning is to identify ways in which the network can provide value to outside sponsors.

ACCELERATING AND ADDED-VALUE RESOURCES

The value of a network may be measured in its ability to achieve greater or more efficient results than the member organizations would if they were acting independently [5].

There are numerous examples of clinical networks forming to address a particular disease indication (e.g., cancer) or therapeutic approach (e.g., gene therapy). Networks enhance the development of patient therapies by leveraging

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participant assets. The National Cancer Institute's Clinical Trials Network, for example, focuses on a variety of operational efficiencies across clinical activities. Stem cell therapies and regenerative medicine are ripe for a network approach; the therapeutic pipeline is robust but unique clinical challenges remain.

This concept of network synergy is a fundamental organizing principle for the Alpha Clinics. Each program has identified specific resources and expertise that it brings to the network. These are termed "accelerating and added-value resources."

Key Focus Areas

The network currently has three primary focus areas for accelerating and added-value resources.

Operational Efficiencies

This category of AAVRs encompasses operational considerations spanning practical aspects of clinical care and business aspects of fiscal sustainability. An area of clinical focus, for example, is on nursing acuity. A key question to be addressed is, "What is the optimal staffing of clinical trails based on well-defined competencies?" Nursing acuity is critical for serving patients as effectively as possible.

The network focus on business sustainability is designed to consider the areas in which cell-based therapies provide value in health care. The Affordable Care Act is the major U.S. health policy addressing and rewarding value delivery in care. For cell-based therapies to be successful, their comparative effectiveness against the standard of care must be measured. Currently, value-based metrics for stem cell therapies are limited. This AAVR will focus on developing quality and value metrics for cell-based therapies to support effectiveness evaluation. Aggregating this experience and collecting data are critical in discussions with third-party payers and enabling a data-driven approach to modeling the best health care delivery model for stem cell therapies.

Shared Resources

This category of AAVRs is designed to leverage assets already existing at the network sites. Multisite clinical data repositories enable patient information to be aggregated and queried for cohort discovery. The network, for example, can facilitate access to the University of California Research Exchange (UC ReX), representing approximately 13.6 million patient records [6]. Although the patient population is substantial, there is a need to develop queries to identify key patient attributes depending on a proposed clinical trial.

The network aims to develop the capacity to accrue patients at multiple clinical sites. To ensure timely and comprehensive enrollment, institutional review board reliance agreements are being developed to allow one review of record for a specific trial. Adopting best practices for precontract activities, shared model contracts, and standardized approaches to accessing critical hospital services and ancillary support should improve efficiencies and accelerate timelines.

Knowledge Efficiencies and Outreach

This category of AAVRs is designed to capture an experience gained across a variety of preclinical and clinical research activities. By addressing knowledge gaps, the network aims to accelerate therapeutic pipeline development. The regulatory landscape for clinical trials with novel stem cell-based therapeutics, for example, is in a state of dynamic flux and is being constantly shaped by interactions between the developers and the regulatory bodies. Pooling knowledge, data, and experience from stem cell clinical networks would be critical for informing regulatory processes and policy. Experience gained from the expanding pipeline of stem cell therapies delivered across clinical sites will strengthen the evidence base and, in turn, should improve regulatory efficiency.

With all these resources and assets in place, the Alpha Clinics Network would provide access to credible high-quality clinical trials and associated information to patients and the public. In addition, the network would provide experienced and efficient clinical trial sites for corporate or academic sponsors developing stem cell therapies.

CIRM 2.0 Ready

The Alpha Clinics Network is one component of a larger effort by CIRM to accelerate development of stem cell treatments. In 2015, CIRM transformed business operations to more efficiently meet patient care needs, as reflected in a new operational plan called CIRM 2.0. This plan was designed to place added emphasis on speed, partnerships, and patients [7]. The process makes it easier for companies and academic researchers with promising clinical trials to partner with CIRM to obtain the requisite support to launch effective trials. One key aspect of the CIRM 2.0 Clinical Stage program is that it provides frequent and predictable funding opportunities. CIRM, for example, accepts proposals for completion of phase I, II, or III clinical trials on a monthly basis [8]. Thus the Alpha Clinic Network platform and CIRM 2.0 funding opportunities create a powerful synergy designed to accelerate stem cell treatments.

A major objective of the Alpha Clinic Network is to support the efficient conduct of a robust pipeline of stem cell clinical trials. The combination of the clinical capacity provided by the network and funding support from CIRM is designed to serve the primary CIRM 2.0 objective: accelerating stem cell treatments for patients with unmet medical needs. The network is open for national and international collaborations, and CIRM 2.0 can support sponsors seeking to bring trials to California regardless of the location of their corporate headquarters to ensure that stem cell therapies for a plethora of degenerative disorders come to clinical fruition.

Further Considerations

The success of individual AAVRs is predicated on building the evidence base with clinical and economic metrics and rigorously analyzing the cumulative clinical trial data to advance patient care. Patient care coverage analysis, for example, would be informed by shared experience with stem cell clinical trials and would create efficiencies in obtaining patient coverage, would promote patient access to these trials, and would provide a collective data set to support discussions with third-party payers and organizations for future coverage models. Uniform quality systems and data sets by which to evaluate performance metrics and cost analysis would be possible within the network. Drawing on these types of experience and data sets in early stage trials is critical to inform and promote downstream commercial development.

Network partners see the need for systematic and comprehensive data analysis designed to address safety, efficacy, and regulatory and economic considerations. Currently, the capacity to aggregate data across sites does not rest within any of the individual Alpha Clinics. CIRM will consider the role of a data coordinating, processing, and reporting center to address this gap. Pooling knowledge, data, and experience from stem cell clinical networks would be critical for informing regulatory processes and policy, but most important, it will inform patients about stem cell clinical trial-related progress. Experience gained from the expanding pipeline of stem cell therapies delivered across clinical sites will strengthen the evidence base and, in turn, should improve regulatory efficiency. In addition, a network would allow sharing of expertise for local, national, and international collaborators; study sponsors; other academic and charitable funding organizations; institutional review boards; and data safety monitoring boards for stem cell clinical trials.

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The CIRM Alpha Clinics Network steering committee is composed of John S. Adams, M.D., Distinguished Professor, Orthopedic Surgery, Medicine and Molecular, Cell, and Developmental Biology, Associate Director, University of California Los Angeles (UCLA) Clinical and Translational Science Institute, Assistant Dean for Translational Research, Program Director, CIRM Alpha Clinic at UCLA-University of California Irvine Consortium—UCLA; Catriona Jamieson, M.D., Ph.D., Associate Professor of Medicine, Chief, Division of Regenerative Medicine, Deputy Director, Sanford Stem Cell Clinical Center, Program Director, CIRM Alpha Clinic at University of California (UC) San Diego, Co-Leader, Hematologic Malignancies Program, Moores Cancer Center—UC San Diego; John A. Zaia, M.D., Director, Center for Gene Therapy, Aaron D. and Edith Miller Chair for Gene Therapy, Program Director, CIRM Alpha Clinic at City of Hope, Hematologic Diseases and Stem Cell Transplantation Institute—City of Hope; and Maria T. Millan, M.D., Director, Medical Affairs and Stem Cell Projects and Centers—CIRM.

Disclosure of Potential Conflicts of Interest

G.P.L. has uncompensated employment with CIRM. J.A. and J.Z. have compensated research funding from CIRM. C.J. has compensated research funding through the Alpha Clinics Award. The other author indicated no potential conflicts of interest.

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