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Implementation of Cardiovascular Cell Therapy Network Trials *Challenges, Innovation, and Lessons Learned: Experiences of the CCTRN*

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Abstract

The Cardiovascular Cell Therapy Network (CCTRN) was developed by the National Heart, Lung, and Blood Institute to design and conduct clinical trials to advance the field of cardiovascular

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(CV) cell-based therapy. The CCTRN successfully completed three clinical trials involving approximately 300 subjects across five centers and six satellites. Although the concept of a network within clinical trials research is not new, the knowledge gained in the implementation of such large-scale trials, particularly in novel therapeutic areas such as cell therapy is not often detailed in the literature. The purpose of this communication is to summarize key factors in achieving Network goals and share the knowledge gained to promote success in future CV disease cell therapy trials and networks.

Keywords

stem cell therapy; network; cardiovascular disease; acute myocardial infarction; heart failure; TIME; LateTIME; FOCUS; Cardiovascular Cell Therapy Network

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Introduction

While the challenges of clinical trial design are appreciated by the most sensitive investigators at the inception of the study, these same challenges are well understood at the study's conclusion by everyone. This is amplified in new fields e.g., cell therapy where the absence of experience in the field can make even the most intrepid scientists feel ill-equipped to overcome the design and execution obstacles. This manuscript describes the experience of the CCTRN as it conducted its early cell therapy trials in the setting of acute myocardial infarction and heart failure.

Background

Small-scale animal investigations in the early part of the last decade led to interest in the possibility of cell therapy for treatment of cardiovascular (CV) disease [1-3]. Early trials in the following years confirmed the potential for use in humans [4-7]. Although these trials varied widely in scope and design, they generated evidence of safety and suggested a signal of efficacy with regard to improvement in left ventricular (LV) function. This led to heightened interest in the development of this field within the United States where, until that time, experience had been very limited. It became clear that to further develop this area, it would require collaboration amongst diverse centers targeted to carry out a multi-center trial of cell therapy for a relatively new application. Thus, the NHLBI set forth an initiative for development of the CCTRN that was charged to design, implement, and execute clinical trials of cell-based therapies for CV disease.

The concept of a network framework for multi-center trials is not novel and experiences from other clinical specialties such as oncology and urology have been published, although the overall literature is still sparse [8,9]. Other network studies have primarily targeted the evaluation of previously established medications and procedures to standard of care. However, until the advent of the CCTRN, a network had not been previously developed trials in the CV disease cell therapy arena. The CCTRN was not only tasked to establish multiple studies across five centers but to do so in a still emerging field [10]. The five centers involved in these phase II studies included: Cleveland Clinic Foundation, University of Florida Department of Medicine, Minneapolis Heart Institute Foundation, Texas Heart

Institute, and Vanderbilt University School of Medicine. Additionally, the trials were supported by the Data Coordinating Center (DCC) located at the University of Texas – Houston School of Public Health. Each of these groups brought their own unique set of experiences and expertise to the group across diverse areas including cardiac imaging, cell processing, and cell delivery. Although each of these centers had experience with large clinical trials, cardiovascular cell therapy within itself poses several challenges that included advancement of an emerging cell therapy field within the confines of a unique regulatory environment, development of active relationships with industry and identifying the appropriate target CV populations who will benefit from cell therapy. In addition, the multiple layers of regulatory oversight involved with such trials conducted at multiple centers added complexity that was not experienced in single investigator/center initiated trials. Thus, while the multi-center concept clearly aided recruitment and expertise, it was not without its own unique challenges.

Additionally, the three completed trials, although related (same centers, bone marrow mononuclear cell preparation with automated processing, and disease) each had their own inherent challenges. The TIME and LateTIME trials [11-14] were primarily designed to address the question of optimal timing of cell harvest and delivery in clinically stable patients with LV dysfunction persisting after successful reperfusion by percutaneous intervention (PCI) with stenting following acute myocardial infarction (AMI). These questions were based principally on data from the REPAIR-AMI study that suggested an enhanced effect on LV ejection fraction of cell administration beyond the initial few days after reperfusion. The FOCUS trial targeted an ischemic population (without recent infarct) who had chronic LV dysfunction without other options for revascularization [15, 16]. CCTRN was charged to implement these trials within a five-year time period. With the many stages of protocol development, oversight review, and logistical administration, a staged approach which included milestone deadlines was adopted, Figure 1. CCTRN was able to maneuver a complicated landscape and successfully completed these three trials in a timely fashion. As part of the CCTRN initiative, several manuscripts have been published, or are in press, detailing the experience of the Network in regards to details of cell processing, use of satellite centers for recruitment and oversight/management challenges [17-19]. However, in addition to these logistical and scientific hurdles, several unique challenges not all of which were anticipated, were encountered by the Network, which was able to successfully navigate them in an efficient manner. These challenges included communication within the Network, targeted use of subcommittees, recruitment challenges, and development of partnerships with industry. Although the limited experience of other trial networks as well as CCTRN have been published, here we aim to provide unique insight into different and useful observations of multi-center trial implementation which have not been previously described in depth in the literature.

Lesson 1: Communication is Key

One of the remarkable aspects of CCTRN is its highly developed integral nature. At its inception, leadership had no joint experience. Of the three members of the Executive Committee, one had experience in multi-center clinical trials, but no experience in cell based

interventions. One had cell therapy experience; the other had basic science and an administrative background.

The Data Coordinating Center had no history of working with any of the clinical centers, and many of the clinical centers knew of each other by reputation only. From this disparate group, CCTRN was required to meld a cohesive network that would react nimbly to new administrative and scientific issues.

General Communication

The intellectual infrastructure of the Network is communication. The Executive Committee, Principal Investigators, and NHLBI established and continue to sustain the importance of regular and frequent communication in an environment in which the science moves at sometimes breathtaking pace and trials are conducted simultaneously. The Network consists of close to three hundred members currently and all must be apprised of new germane scientific articles, progress and issues in trials, safety concerns, in addition to the ongoing “housekeeping traffic”. In response, the Network has constructed a rich lattice that includes frequent conference calls and “one on one” discussions, in addition to email that is built on a CCTRN website infrastructure. With more experience, emphasis was placed on adding additional materials to a secure website that now contains password protected access to agendas and minutes of conference calls protocols, manuals of operation, published Network manuscripts, slide templates to plan future Network presentations and, most recently, datasets from all of our completed trials.

However, there is no substitute for verbal communication to convey real-time updates and to manage the occasional crisis. DCC staff are accessible and DCC leadership is available 24 hours a day to facilitate essential communication. The clinical center Principal Investigators and Steering Committee chair make themselves available for consultation of patient related issues, and clinical questions from the centers are addressed within twenty-four hours. Communication between NHLBI, Subcommittee Chairs, and the DCC occurs daily in an atmosphere that promotes the quick accessibility and rapid response of key personnel to manage important issues in real-time.

Targeted Use of Subcommittees

Discussion of interactions on conference calls, with satellites and with the DSMB have been reviewed in detail in other manuscripts published from the CCTRN [17]. However, an underdeveloped resource that is now being more fully utilized is the targeted use of subcommittees; specifically the protocol development committee (PDC). CCTRN created PDCs, but learned early on that the expertise gathered in these committees rapidly dissipated once the successful administrative review of the protocol was complete and recruitment was initiated. Initial questions from the recruiting centers, many of which required urgent and comprehensive answers about the applicability of selected inclusion and exclusion criteria, required knowledgeable investigators who could quickly respond to colleagues.

Review of this entire process identified the absence of an operational PDC during the execution of the study as a critical weakness. The Network has therefore moved to a new

model which supports the continued support of and reliance on the PDC. The PDC now functions as a *de facto* protocol operations group that is responsible for not just the final vetting of the protocol but in monitoring ongoing recruitment for that protocol including the consideration of individual challenging cases. The PDC discusses and develops solutions to ongoing protocol issues including further refinements to the protocol as needed. This group is also the source of manuscript idea generation, including the design paper, the main outcomes paper, and desired secondary outcomes papers.

Another essential element of communication that should be further developed is the idea of a “rapid response” team. As cell therapy is a new field, complex protocols in multiple areas (interventions, cell processing and delivery, instrumentation) suggest the Network is best served by implementing a stand-by “rapid response team” to be composed of experts within the Network centers and cores (as well as industry support for equipment like NOGA and Sepax) on call 24/7 to answer questions within minutes to avoid delays in areas that are time sensitive such as troubleshooting problems with cell processing or cell delivery which could impair protocol driven implementation of crucial steps in the trial process.

Lesson 2: The cost of clinical holds are multidimensional

Impaired LV function secondary to ischemia incurred in a large region of myocardium during an AMI leads to progressive adverse ventricular remodeling and subsequent heart failure. Prevention of persistent abnormal LV function is a primary goal for any proposed therapy in the treatment of AMI as it is known that the relationship between lower ejection fraction (EF) and increasing mortality disappears with EF >45% [20]. Initial trials of cell therapy for acute MI have primarily targeted patients with large infarcts such as the BOOST trial [21] and/or EF <45% immediately after infarct such as the REPAIR-AMI trial [22]. These, amongst many others conducted around 2004-2006 [23], suggested that cell therapy could lead to significant improvements in LV function and reduction in adverse CV outcomes in patients with ST segment elevation myocardial infarctions (STEMI).

Based on these and other initial trials, TIME and LateTIME focused on recruitment of STEMI patients with EF<45% by screening echo performed after successful reperfusion with PCI and stenting. However, a number of hurdles were encountered primarily with recruitment and assessment of baseline EF. First, enrollment of patients into TIME and LateTIME was more difficult than anticipated, due to the fact that many cases had higher than anticipated EFs after successful reperfusion with PCI and stenting. For example in TIME, during the three year recruitment period, a total of 3347 patients were screened and half (1515 patients) were excluded by LVEF >45% [12]. For LateTIME, out of 2201 patients, more than a third (854) were excluded due to EF >45% [11]. Furthermore, amongst those patients who were enrolled, there appeared to be continuing improvement between the screening EF after reperfusion and EF at the time of bone marrow harvest and cell administration. For TIME, the qualifying EF assessed by echocardiography within 48 hours of PCI was 36.1-37.8%. By MRI, EF at three days post PCI ranged from 41-46%, and at seven days post PCI averaged 44-48%. Although EF at screening was performed by echo and that at treatment was assessed by MRI, the difference between the two values is well above the 3-4% that would be expected based on different imaging methods alone.

Additionally, overall EF continued to improve in TIME by 3.2% to 3.3% in both treated and placebo groups at 6 months, documenting continuing post perfusion recovery of LV function. Such improvement makes it more difficult to detect an effect of cell therapy. These results were similar to findings from the BOOST trial which demonstrated an initial significant improvement in EF compared to placebo at 6 months which was not present at 18 months as EF improved by 5.9% in cell treated but also increased by 3.1% in the placebo group. These findings were also true for LateTIME which was a relatively higher risk cohort due to persistent low EF over 2-3 weeks after MI despite revascularization. Despite qualifying echo EF less than 45% at time of screening, average MRI EF at time of treatment was 45-48%. Even when accounting for patients with the lowest EF in the LateTIME cohort, cell therapy did not lead to improvement in EF.

The low screening to enrollment ratio in TIME and LateTIME along with continued improvement in EF after initial event likely reflected the significant advancements made in recent years in the acute reperfusion and medical management of AMI. Per the most recent AHA 2013 statistics, there has been a significant decline in STEMI from 133 to 50 cases per 100,000 person-years [24] just within the past decade. Additionally, in-hospital and 1-year STEMI mortality rates have also concurrently declined, reflecting improved timeliness of reperfusion [25-27]. It is known that mortality rates in STEMI patients are directly proportional to time to presentation and treatment [28]. For TIME, the average ischemic duration was 3-4 hours with a door-to-balloon time of 1.2-1.3 hours; consistent with current guideline recommendations for STEMI care [29].

Additionally, greater than 75% of patients in both TIME and LateTIME were treated with ace-inhibitors and greater than 90% of patients were on aspirin, beta blockers, and statins. Thus, these statistics indicate that with contemporary door-to-balloon strategies leading to timely reperfusion and improved standard medical therapy, residual LV dysfunction may not be as prevalent as once believed. Improvements in door-to-balloon times and overall improved medical therapy have therefore contributed to a more limited population who may benefit from post STEMI cell therapy. Thus, considerations for future AMI trials should consider inclusion of patients with prior infarct with residual LV dysfunction, multi-vessel disease, and patients who did not receive adequate reperfusion with PCI.

Although these restrictions on patient enrollment are needed to ensure adequate interpretation of therapeutic effect, they also limit the application of results as many patients who present with AMI do not necessarily fall into such criteria. This is exemplified in the two CCTRN AMI trials as 222 patients in TIME and 156 patients in LateTIME were excluded due to prior MI. Additionally, the majority of patients who present with acute coronary syndrome present with either unstable angina or non-STEMI which do not necessarily portend lower long-term risk. Specifically, patients presenting with non-STEMI have a higher likelihood of residual ischemia which is associated with a significant increase in mortality [30, 31]. While the incidence of STEMI is decreasing, the occurrence of non-STEMI has not changed significantly with estimation of 1 year post admission fatality rate of 18% [32]. Thus, future trials may consider focusing on non-STEMI populations and those with prior infarct and/or LV dysfunction who remain at high risk. Additionally, cell therapy may be most beneficial for those who did not recover EF greater than 45% at 6 months such

as those younger patients in the FOCUS trial which demonstrated a statistically significant improvement in EF. Thus, in depth examination of individual patient characteristics to identify those patients who may have persistent LV dysfunction after MI may be useful to better target cell therapy in patients who are most likely to benefit.

In addition to the inherent recruitment challenges within the targeted pool of AMI patients, the Network faced an additional, external hurdle to recruitment which was unanticipated. In August 2009, the Network experienced a Food and Drug Administration (FDA) hold on both the TIME and LateTIME studies. The FDA clinical hold occurred approximately one year after enrollment initiation. The clinical hold was placed to ensure proper screening and monitoring of subjects with left ventricular thrombus and those requiring anti-coagulants and to evaluate the risk to subjects. Approximately four weeks after the hold was issued, the FDA agreed to lift the clinical hold with protocol modifications. Recruitment was directly affected for several months after the hold was lifted. The DCC's Institutional Review Board (IRB) as well as each site's IRB (seven separate boards at that time) needed to review the amended protocol prior to continuing patient enrollment. It took the DCC's IRB approximately four weeks to obtain approval for the revised protocols. Following that, the IRB review by the sites lasted an average of an additional four weeks. Sites had to reestablish momentum for referrals and notify all service areas that the trial was again active and accepting patients. It was time intensive for the sites to educate their staff on the study protocols following the approximately eight week hiatus.

While the Network has acknowledged that holds are measured pauses and opportunities to reassess for safety and efficacy, it is also true that there are downstream impacts of such pauses on the timely completion of the trial. For example, during the hold period average recruitment for TIME dropped by an average of 2.5 patients per month for a 5 month period. The recruitment rate did not recover from the hold until January 2010 (see Figure 2). This total projected loss of patients over this time period equated to approximately three months of enrollment and had the trial proceeded without the hold TIME may have ended four-five months sooner.

Such hurdles, which were not anticipated during the timeline development of these trials, raise several considerations for the development of similar trials in the future. A scenario such as this suggests that additional time should be built into the original timeline. Although this may appear to be a straightforward solution, it must be considered that timelines are developed for an express purpose to guide enrollment towards an ideal goal for completion of the trial in a timely manner. Trial completion serves to expedite publications and move forward in future trials and, in the highest hopes, advance the therapy being tested towards implementation into actual clinical practice. Thus, protocol/timeline development must strike a balance between anticipating delays and also setting forth a goal for completion in an expeditious manner.

An additional consideration is the extensive time, several months, which was necessary to have protocol amendment approved by a multitude of IRBs. This raises the question of whether consolidation of review to a single process by a centralized IRB could have

significantly decreased the overall review time; however the concept of centralized review of federally-funded studies is still under consideration as a change to the Common Rule.

Lesson 3: Understand the vested interest of Network partners

Prior to the development of the Network, many of the investigators' experiences with multi-center trials were limited to that of industry sponsored trials; trials in which a company would serve as the study Sponsor and would provide the cellular product and study materials to conduct the trial. Under such a model, the company would own the rights to the Investigational New Drug Application (IND) and the resultant patient data. Initiating an alternate model in a federally-funded trial where Investigators could conduct their *own* science, with the assistance of industry, represented a new challenge. This new model would need to be attractive to industry partners as well as consistent with the mission of the Network in producing high quality, informative Investigator-initiated trials within the cell therapy community.

As the Investigators considered the overall needs of each type of study, it became clear that there would potentially be two scenarios in which the Network would need to partner with industry; a *study product support model* in which the industry partner had a fixed role or a *trial support model*, in which the industry partner had an integrated role. While the former was utilized in the first three trials of the Network, the experience has prepared CCTRN as it moves forward with extensions into the latter. The two models are further outlined below.

Study Product Support Model

The first three trials (TIME, LateTIME, and FOCUS) used autologous bone marrow cells (BMCs). Given that the patients were the source of their own product and that processing occurred at each of the Network's five local cell processing laboratories, a study product produced by a company was not needed. However, standardized techniques and delivery methods would be essential to ensuring uniform product processing and administration. Industry partners in this model had a fixed role of providing equipment and technical support for the life of the trial and were cited in the resultant study design and outcome publications. Examples of partnerships in this model include CCTRN partnership with Biosafe (Geneva, Switzerland) for use of the Sepax device for cell processing; partnership with Biologics Delivery Systems (Cordis Corporation) for the use of the NOGA mapping and injection system; and partnership with Boston Scientific (Natick, Massachusetts) for use of the Maverick over-the-wire angioplasty balloon catheter.

Trial Support Model

As the Network is now moving into the next series of investigations, the variety of cell types and the select processing methods that are employed by industry partners are once again being explored. Industry partners with cell products and select processing techniques represent an opportunity for the Network to avail itself of the some of the newest advances in biotechnology and to couple that with unmet needs in the field of cell therapy. This creates an opportunity for a model wherein the Network Investigators develop their own protocol which includes a cell type or processing method that is already under investigation

by an industry partner through a similar application with the FDA. Through negotiations with the industry partner, the Network is able to initiate a new IND application (with CCTRN as the Sponsor) which cross-references this early work and relies on the company's expertise and technical support with the product. An industry partner representative provides technical product and delivery guidance in the development of the protocol which allows for a more integrated role than in the study support model. While this type of model affords reduced variability in the study product or processing, its application to the general practice may be less practical. Several of our new trials are currently exploring this model further.

Contractual Agreements

In both models, an agreement must be reached between the NIH and the industry partner. The clinical trial agreement (CTA) is a standard agreement which includes the following: 1) the specifics of the cell, device, or technology that is being provided in the partnership and under what conditions it is being provided (*gratis*, reduced cost, rental agreement, etc. 2) assurances for the adequate supply and distribution of any devices or equipment for the life of the trial and the terms of servicing or replacement if warranted 3) responsibilities of each party with regard to the protocol, its execution, event reporting, and data collection, analysis, and publication and 4) outlines the CCTRN as the Sponsor of the IND with the responsibilities for FDA reporting. All agreements include a clause regarding premature termination of the trial to protect both parties.

Future Directions

The Network was tasked with the implementation of three trials for CV cell therapy across multiple centers which it successfully completed in the expected time period of five years. Taking into consideration what has been learned from the successful completion of the initial phase of CCTRN trials, several crucial elements were necessary for success and should be utilized and expanded upon for implementation of future CV cell therapy trials. Overall, the innovation and adaptability of the CCTRN leadership along with a solid regulatory and scientific foundation for the trials led to successful negotiation of challenges. Active lines of communication amongst varied Network components were absolutely crucial. Targeted use of subcommittees allowed for efficient division of duties amongst committee members who could, in parallel, review relevant issues that were time critical and provide feedback to the central CCTRN leadership. Significant advances in the management of AMI patients, leading to a reduced number of patients with reduced LV function along with the FDA hold, were both significant barriers to recruitment. However, although these challenges led to pause within the trial implementation timeline it was felt they ultimately led to improvement in the quality of trial processes. Additionally, the strategies developed to build working industry relationships within the context of a federally funded trial will serve as invaluable tools going forward into future CV cell therapy trials in which the interface between advancing cell therapies and industry support will only continue to grow. During the second phase of CCTRN trials, the Network has put into place a system to keep track of both the performance of each protocol (measuring over time, enrollment, serious adverse event reporting, data collection) as well as the global issues of budget and publications, permitting the self-monitoring of important aspects of clinical trial management.

Expert Commentary and Five-year View

This article describes the experience of the CCTRN in the successful development and implementation of three stem cell cardiovascular therapy trials. Several key elements were examined which were necessary for completion of these trials in the designated time period including building an efficient communication infrastructure, unexpected recruitment challenges and development of industry relationships. Most importantly, are highlighted the innovations and advances made in implementation of such a complex Network across multiple centers. These lessons should provide important directions for not only future cardiovascular cell therapy trials but are equally applicable to any multi-center clinical trial requiring coordination amongst diverse areas of expertise.

Over the next several years, the field of cardiovascular cell therapy will continue to evolve with advancement of new cell types, delivery techniques, and imaging modalities. Such a rapidly advancing field will continue to require collaboration amongst a variety of cardiology based sub-specialties as well as cell therapy experts. This is an exciting time with tremendous opportunities to advance not only cell therapeutic options but also to expand target populations. The initial phase of CCTRN targeted AMI and chronic heart failure patients. However, there is still a relatively untapped pool of patients presenting with non-STEMI in addition to expansion of therapy to vascular beds outside of the coronary/myocardial arena, such as peripheral arterial disease. As therapeutic options and cell types continue to be investigated, it is anticipated that the tremendous advancements in cardiovascular cell therapy will only continue to grow over the next five years.

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Key issues

- The concept of a Network, although not new, had not been previously utilized in the field of cardiovascular cell therapy.
- Early stem cell trials for CV disease therapy indicating benefit in LV function prompted the development of the CCTRN trials.
- The NHLBI initiated Network was tasked to design and implement multiple trials of CV disease cell therapy for AMI and chronic LV dysfunction.
- The Network was able to successfully complete three studies, TIME, LateTIME, and FOCUS, across five centers in a timely fashion.
- Development of a solid communication structure was an important factor in successful implementation of these trials as it allowed efficient flow of information and timely feedback on time-sensitive issues.
- Although recruitment was challenged by better than expected recovery of LV function and an FDA hold, all three trials reached their targeted recruitment goals.
- The Network was able to forge new ground in actively working with industry to develop strong relationships within a network setting which had been previously not been done within the CV cell therapy field.
- As the field of CV cell therapy rapidly expands into new target populations and alternative cell types, the Network experience lends new insight going forward into implementation of trials in this burgeoning field.

	Task Name	Time	Q1-Y1			Q2-Y1			Q3-Y1			Q4-Y1			Q1-Y2		
			Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
1	Final protocol draft	7 months															
2	Steering Committee approved protocol	2 weeks															
3	PRC approved protocol	6 weeks															
4	IND preparation	2 months															
6	FDA approved protocol	1 month															
7	DCC IRB approved protocol	1 month															
5	DSMB approved protocol	1 month															
8	IRB approvals	4 months															
9	Center budgets	5 months															
10	Center subcontracts	4 months															
11	Core Lab applications & review	3 months															
12	Core Lab SOWs & subcontracts	3 months															
13	Core Lab training & site visits	3 months															
14	Cell Processing SOP/batch record development	5 months															
15	Cell Processing training	2 months															
16	CRFs development	6 months															
17	eCRFs - database programming & testing	8 months															
18	MOP development	3 months															
19	eCRFs/CRFs training	6 weeks															
20	Site initiation visits	3 months															
21	Enrollment begins																0

Q=quarter, Y=year, PRC=Protocol Review Committee, IND=Investigational New Drug (application), FDA=Food and Drug Administration, DCC=Data Coordinating Center, IRB=Institutional Review Board, DSMB=Data Safety and Monitoring Board, SOW=Scope of Work, SOP=Standard Operating Procedure, CRF=Case Report Form, MOP=Manual of Operations

Figure 1.
Protocol Initiation Timeline

Figure 2.
Recruitment in TIME