Published in final edited form as:

Contemp Clin Trials. 2011 September ; 32(5): 614–619. doi:10.1016/j.cct.2011.05.003.

Oversight and Management of a Cell Therapy Clinical Trial Network: Experience and Lessons Learned

Lemuel A. Moyé, MD, Ph.D.¹, Shelly L. Sayre, MPH¹, Lynette Westbrook, RN, M.S.², Beth C. Jorgenson, RN³, Eileen Handberg, Ph.D.⁴, Saif Anwaruddin, M.D.⁵, Kristi A. Wagner⁴, and Sonia I. Skarlatos, Ph.D.⁶

the Cardiovascular Cell Therapy Research Network Investigators (CCTRN)

Coordinating Center for Clinical Trials, The University of Texas, Health Science Center Houston, Texas

¹University of Texas School of Public Health, Houston, Texas ²Texas Heart Institute, Houston, TX ³Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, Minnesota ⁴University of Florida College of Medicine, Gainesville, Florida ⁵The Cleveland Clinic Foundation, Cleveland, Ohio ⁶The National Heart Lung and Blood Institute, Bethesda, Maryland

Abstract

The Cardiovascular Cell Therapy Research Network (CCTRN), sponsored by the National Heart, Lung, and Blood Institute (NHLBI), was established to develop, coordinate, and conduct multiple collaborative protocols testing the effects of cell therapy on cardiovascular diseases. The Network was born into a difficult political and ethical climate created by the recent removal of a dozen drugs from the US formulary and the temporary halting of 27 gene therapy trials due to safety concerns. This article describes the Network's challenges as it initiated three protocols in a polarized cultural atmosphere at a time when oversight bodies were positioning themselves for the tightest vigilance of promising new therapies. Effective strategies involving ongoing education, open communication, and relationship building with the oversight community are discussed.

Keywords

cell therapy; clinical trial network; institutional review boards; data safety and monitoring boards

Introduction

Clinical trial networks are uniquely positioned to conduct simultaneous research studies at multiple locations on a variety of related health topics. The central development of these trials allows them to be executed in ways that maximize the scientific knowledge gained while utilizing standardized methods of protocol development, scientific and safety review,

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Corresponding Author, Dr. Lemuel A. Moyé University of Texas, School of Public Health 1200 Herman Pressler, E801 Houston, Texas 77030 713-500-9518 (voice) 832-355-6810 (fax) Lemmoye@msn.com.

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and safety reporting [1]. Networks also provide the opportunity for sequential development of new therapies which represent logical extensions of previous work conducted by those with demonstrated leadership in the field. The structure and support provided by a network can be used to facilitate clear communication of results and provide consistency in new emerging fields for which there is both great promise and apprehension.

This article describes the ethical and political research environment into which the Cardiovascular Cell Therapy Research Network (CCTRn) was founded, the resultant challenges of critical review by numerous oversight committees, and the management and educational strategies utilized to successfully establish and maintain working relationships with these oversight groups.

Research Environment

The 1990's opened to the great promises of gene therapy; however the Jesse Gelsinger case at the University of Pennsylvania highlighted the potential for serious lapses in reporting prior research experience, safety monitoring, and conflicts of interest [1]. Simultaneously, a sharp rise in the number of adverse event reports to the FDA occurred, and the number of drugs withdrawn from the market increased. The removal of twelve drugs from US formularies in the four year period from 1997–2000 including pondimin (a component of the popular fenphen weight reduction compound) [2] sharpened the focus on safety oversight. In addition, in 2003, the FDA temporarily halted 27 gene therapy trials using retroviral vectors in blood stem cells in the face of new leukemia related syndromes in two children [3].

The unfortunate early failures of gene therapy did not bode auger well for cell therapy, a separate treatment modality that was new and untested at the millennium's start. Early progress was slow, and in 2006, some argued that cell therapy was not yet ready for clinical investigation at the clinical trial level [10]. Nevertheless, the large burden of cardiovascular disease and the initial promising safety record of autologous bone marrow mononuclear cells [4], created the supportive environment for clinical trials in cell therapy in the United States [14]. However, oversight and management sensitivities raised by the earlier safety concerns and ethical lapses, set the stage for increased vigilance by the review committees of this promising therapeutic cell therapy modality with its unknown risks.

The Network

Earlier this decade, intriguing small animal studies demonstrated that delivery of bone marrow-derived mononuclear cells enabled improved ventricular function following induced myocardial infarction [5,6, 7]. In response to the pervasive morbidity and mortality resulting from coronary artery disease in the US, the CCTRn was established by the National Heart, Lung, and Blood Institute (NHLBI) to develop, coordinate, and conduct multiple collaborative protocols testing the effects of cell therapy on cardiovascular diseases [8]. The Network was given five years to design and execute simultaneous multiple cell therapy protocols [9]. The Network accepted as its charge the initiation of at least three trials in this timeframe to ensure a viable collaboration that would endure. Two trials (TIME and Late TIME) assessed the effects of cell delivery in patients experiencing an acute myocardial infarction (AMI) [10,11]. The third trial (FOCUS) addressed patients with ischemic heart disease and low ejection fraction who have no other therapeutic alternatives [12].

To successfully implement these trials, the protocols would need to be reviewed by several oversight groups responsible for the scientific rigor as well as the global and local safety of trial participants. There was a specific sequence of reviews that the NHLBI required for each of the three protocols before protocol execution could begin (Figure 1). The initial review of the science was conducted by a Protocol Review Committee. This was followed by an

independent and comprehensive review of safety by a separate Data Safety and Monitoring Board (DSMB) and the Federal Food and Drug Administration (FDA) as well as a local safety review by Internal Review Boards (IRB) of each of the centers. Before initiating this review cycle however, the Network would need to fortify the protocols with sound science, strategic endpoints, a strong safety review, and efficient event reporting strategy.

The CCTRN leadership (comprised of the principal investigators of the five clinical centers, the Network chair, the NHLBI project officer, and the Data Coordinating Center (DCC) principal investigator), and research coordinators met in January 2007 for initial discussions. To expedite successful protocol approval by the FDA, the Network believed that its best strategy would be to develop protocols for which sufficient experience existed that maximized the ability to obtain an IND but also minimized the need for new preliminary data. The Network emerged with three research concepts that met these criteria.

During development of the protocols, the selection of endpoints dictated that five core labs in the areas of imaging, exercise, and biospecimen collection/storage be established. The selection process yielded five internally selected cores. Included are three imaging core laboratories: Echo-Cleveland Clinic Foundation, MRI-University of Florida, and SPECT-Vanderbilt University, an exercise core laboratory (MVO2-University of Florida), and a biorepository (a joint effort of University of Minnesota and the University of Florida)[8]. A Noga core was initially considered, but since expertise was available at the investigator level, was set aside.

Scientific Review

The Principal Investigators devoted themselves to writing protocols that would test the ability of cell therapy to improve LV function in the AMI and heart failure setting. To facilitate this work and distribute the labor, internal subcommittees were established. Each committee was charged with creating a protocol sufficiently organized and detailed to be reviewed by the NHLBI established protocol review committee.

Protocol Review Committee (PRC)—The PRC, comprised of several cell therapy specialists, a biostatistician, and an ethicist, was charged by NHLBI with assessing the scientific integrity of the protocols and the likely benefits and risks these investigations might hold for the target communities. This group was assembled by the NHLBI and would be the first committee that would review the Network generated protocols. The Network's charge was to interact with them on a cyclical basis, sharing each new protocol with this group for their advice and approval. By design, this PRC represented the prevailing wide spectrum of opinions regarding the utility of cell therapy. Reflecting the cultural sensitivity of the scientific and lay community to human cell therapy trials, discussions between the Network leadership and the PRC were to be among the most dynamic in the Network's experience, expressing a wide range of opinions concerning the utility of this modality in humans.

The Network submitted its three protocols to the PRC in May of 2007. Each protocol was novel and complex in its own right, proposing to deliver new and relatively large cell doses to different populations using a novel cell processing system and utilizing state of the art imaging endpoints. After review, the PRC expressed substantial concerns relating to 1) the inclusion and exclusion criteria, 2) the proposed cell processing methods and, 3) whether the risk benefit ratio was favorable for the given population. However, comments from the Committee were received, not in a single coordinated document, but rather as a number of correspondences which were received independently and therefore (in some cases) were contradictory. The Network was challenged with how to provide a coherent response to address all of their concerns.

CCTRN's response was to coordinate the activity itself; much like a response to the complex comments of multiple peer reviewers for a submitted manuscript. The Investigators felt compelled to respond to each of the reviewer's comments, keeping track of which protocol change requests would produce protocol inconsistencies. When the first round of responses was complete, these were submitted in writing followed by a request for a conference call with the PRC. This produced a cycle of conversations and written responses over a three month period that gradually reduced inconsistencies until agreement was reached and the protocols were approved. It was helpful for the Network to recognize that it was not submitting "finalized" protocols for their review but was instead providing an advanced draft that the PRC would help to further refine and develop. Ultimately, the joint effort between the PRC and the Network Investigators forged a relationship that will smooth the way for future protocol review and development.

Global Safety Review

Data and Safety Monitoring Board (DSMB)—The Network's DSMB members were appointed in accordance with established NHLBI policies governing the use of advisors who were experts not directly involved in the study. In the case of CCTRN, the NHLBI did not appoint a new board, but extended the purview of an existing DSMB whose standing responsibilities included review of gene therapy research.

Initial review of the protocols by the DSMB yielded concerns about 1) study recruitment plans, 2) standardization of the bone marrow aspiration procedures across centers (to the degree possible), and 3) clarification of some of the eligibility criteria and the imaging modalities. The CCTRN Investigators were able to successfully respond to each of these initial concerns, however during the course of the trials; new concerns arose regarding event reporting. The need for a revised conduit of event reporting and the need for more structured reporting mechanisms were evident.

Similar to the Network's experience with the PRC, the Network leadership began to receive individual DSMB members' opinions and queries directly from the board members themselves as opposed to via a consensus document. Critical to the development of a solution was an open dialogue among the DSMB members, NHLBI, and the Network. In order to control communication, create an effective liaison between the Board and the Network, and avoid the potential for any real or perceived conflicts of interest, the NHLBI identified a clinical research organization to serve as the conduit of information between the two groups.

The types of information the DSMB required included real time reports on the occurrence of each serious adverse event (SAE), in addition to formal tabulations prepared for semiannual meetings. While reporting was prompt, the guidance timeline posed some challenges in instances where the event occurred at outlying treatment facilities and instances in which the research team learned of an event at the patient's next scheduled visit (sometimes months after its occurrence). Additionally, retrieving documentation regarding events occurring at outside hospitals was time intensive on the part of the research team and was contingent upon the efforts of the staff at the cooperating facility. These factors translated into delays in providing the desired detailed preliminary report to the DSMB. However, pressuring the centers to simply decrease their response time would only serve to generate reports with incomplete information (such as an absent discharge summary).

One response of the Network to this challenge was to develop and adopt a structured email notification strategy which permitted electronic notification of NHLBI and the DSMB of the occurrence of a serious event. Upon first notification of an event by the center to the DCC, the safety team generated an email that notified NHLBI with a preliminary assessment of the

severity, expectedness, and relatedness of the event to the study product or procedure. NHLBI would then notify the DSMB of the occurrence of the event. This preliminary assessment was followed in two to three weeks by a detailed report that described the event using the information that became available over time. Thus, NHLBI received a rapid communication informing them of the occurrence of the event, followed by a complete and detailed final report. This report was then transmitted to the Executive Secretary of the DSMB who then reported them to the board Chair where the decision was made about distribution to the entire board (Figure 2). This reporting mechanism had the dual advantage of providing rapid, complete communication to all parties and to serve as a pre-review of any required event submissions to the Food and Drug Administration.

Food and Drug Administration (FDA)—Once the three protocols passed scientific review by the PRC and the safety review of the DSMB, the Network leadership felt that the documents were ready for the FDA review. Like any other new medication or therapy in the US, cell therapy (including number and type of cells delivered and the delivery process itself) requires an investigational new drug application (IND). Before being allowed to proceed, both the product and procedure had to undergo extensive testing for safety and efficacy under the direct guidance of the FDA and its Center for Biologics Evaluation (CBER) and Research Office of Cellular, Tissues, and Gene therapies.

Rather than simply submit the protocols and presume that the PRC and DSMB reviews had identified all related concerns about science and safety, the Network opted to request a pre-IND meeting with the FDA. Pre-IND meetings permit the Investigators and the FDA reviewers to conference on the concerns FDA reviewers may have with the protocol, permitting the investigators to supply answers to reviewer questions on the spot. With complex protocols, pre-IND meetings can help to orient the FDA reviewers, establish open lines of communication, and answer questions. The pre-IND meeting discussion identified safety concerns prior to submitting the final application for each of the two IND applications (one for the AMI trials and one for the heart failure trial). The Network leadership, working with the DSMB, developed targeted responses to ensure that everyone, reviewers and investigators alike, appreciated the state of the science and the sensitivity of the safety.

Despite a productive pre-IND meeting, one of the three protocols was placed on clinical hold because of the absence of a solid knowledge base about the dose response effect of autologous cells. The Network assembled a compendium of preclinical and preliminary clinical information over six months for the FDA, which ultimately strengthened the safety profile of the study. The remaining two protocols were allowed to proceed as submitted.

These initial conversations with the FDA helped to pave the way for future protocol amendment considerations. The challenge the Network faced in processing amendments was the prolonged review timeline. Amendment review by the DSMB, FDA, and the individual IRBs created an assembly line of consecutive review processes that, when combined with three protocols and frequent amendments, threatened to quickly become an administrative log jam. Limiting the number of amendments helped to provide consistent protocol adherence over time and helped to reduce the administrative burden throughout the Network. Annual review of the protocols represents the most effective and streamlined approach to amendment submission to all oversight bodies. It provides a more targeted approach to protocol development, is more readily digestible by various reviewers, and does not tax a frequently overworked system with a continuous review cycle.

It was clear from preclinical conversations with the FDA that substantial questions about the ability to safely deliver cell therapy remained a paramount concern with the agency. While this issue was expressed in conversations with the Agency, their concerns were more

declaratively expressed with the institution of clinical holds. The Network experienced two clinical holds. As previously mentioned the first hold followed the initial pre-IND meeting with the FDA and affected only the FOCUS trial. The second occurred when the acute myocardial infarction (AMI) studies (TIME and LateTIME) were underway. Both were resolved, allowing each research effort to continue. Given the absence of knowledge about cell therapy at the inception of the Network, the clinical holds were perhaps predictable; a natural reaction in an environment where safety is paramount and knowledge is limited.

The Network gained valuable experience in response to clinical holds. While their early institution created trepidation, clinical holds are now viewed by the Network as natural regulatory pauses that are necessary in new, rapidly advancing fields. While clinical holds can be imposed for a variety of reasons, the group learned that these maneuvers must be expected in cutting edge clinical research. Clinical holds are not aspersions; on the contrary, they are measured pauses in research for investigators and oversight managers alike, to take stock of what has occurred and to consider new safety or efficacy measures to keep the trial in ethical balance. However, to an investigative team that is adhering to a tight timeline for planning, executing, and evaluating a study, the effects of the hold are immediate and, like the sudden stop of a wagon train, the linked activities of a protocol come to an unexpected and jarring halt as the research teams and patients must suddenly cease activity and planned interactions. Once the hold is lifted, the re-establishment of activity required clearance by the Network leadership, NHLBI, the DSMB, and the local IRBs before new activity could begin.

Local Safety Review

Institutional Review Boards (IRBs)—IRBs have been charged with a wide spectrum of research oversight responsibilities. In contemporary management these boards are responsible for the simultaneous monitoring of 1) multi-center pharmaceutical & device trials, 2) single investigator initiated trials in hospital and academic settings, 3) basic science studies, 4) social science initiatives, and 5) animal investigations. The composition of such panels often includes physicians, surgeons, pharmacists, nurses, clergy, and laypersons from the community. The varied constitution of these panels may not provide the level of in-depth understanding of the nuances of gene therapy and stem cell research [13] needed for appropriate review. While two IRB's had prior experience with autologous cell delivery, many of the center IRBs faced new challenges as they struggled with the substantial learning curve, while others with active gene therapy and cancer trials were more experienced.

The Network provided a two pronged approach to providing additional education and resources to the boards. Center investigators were encouraged to speak at IRB meetings to inform the board on the science and the safety and to answer any questions that might arise prior to the protocol review. Secondly, the Network identified an individual at each clinical center who liaised with the IRB and a single individual at the data coordinating center who interacted with the center personnel on IRB matters. This served to keep the flow of information consistent and streamlined; providing targeted answers in a short turnaround.

With each center simultaneously submitting three protocols to several IRBs, it became increasingly important to condense and emphasize the similarities of the trials (cell harvest, processing, and delivery procedures) while providing more detailed conversation on the distinctions (inclusion/exclusion criteria and endpoints) [7, 8, 9]. Characterizing the three trials as a logical grouping, some centers were able to submit their initial applications to their IRBs under an umbrella mechanism (ensuring that reviews of the three trials would always be reviewed together), still other boards opted for one panel to consistently review CCTRN trials from initial approval through study completion.

Additional challenges are introduced when a clinical center is compelled to work with multiple IRBs (academic and hospital). In these multiple IRB settings, the research team acquainted itself with the environment of each board and correspondingly agreed to a common document flow process. To address such layers of complexity, open sharing of information was advocated [23]. The successful strategy of a consistent audience for the review of protocol amendments, DSMB reports, and continuing reviews associated with these Network trials became part of the ongoing education of the board regarding the safety and efficacy of cell therapy; further strengthening a relationship for future Network trials. Ultimately, all IRB's at the home institutions of the centers approved the studies.

Discussion

The Network and oversight committees faced a daunting challenge—ensuring the safe delivery of autologous cell therapy when the field faced substantial criticism from both lay and scientific groups. CCTRN was conceived into a polarized field and the Network leadership was understandably frustrated at times. The group believed that in order to investigate interventions that would reduce the public health crises of heart disease, it would require a flexible infrastructure that could rapidly integrate new thought and research directions, responding quickly to changes in the direction of the field [14]. Some resonated with a sense in the community that the regulatory burden had become overwhelming [15, 16].

However, the oversight groups themselves had a difficult mission – to ensure that cell therapy trials are conducted ethically and safely and to avoid the setbacks that had befallen early gene therapy studies. They also were required to work in the same culturally charged environment. This was a charge they took to heart, demonstrating their commitment by diligently and repeatedly taking any and all administrative steps to ensure the imprinting of their perspective on the Network. In fact, reflection reveals that the initial challenges between the Network and each of its oversight groups stemmed from 1) the need to address concerns of a PRC and DSMB with representation of a wide range of opinions, 2) the need for open dialogue with the FDA on expectations, and 3) the need for education of IRBs to develop a useful and continuing knowledge base in a rapidly advancing field.

Ultimately, a combination of education, new collective experiences, and calibrated expectation guided the Network leadership in its work with the many different oversight groups. At its inception, each Network member brought their own unique experiences with oversight groups to the table. After many conversations, the group assembled a common metric that guided the Network's decisions. In the five years since the inception of the Network, many other cell therapy studies have appeared. Meta-analyses of AMI stem cell trials [17, 18] have confirmed that administration of bone marrow mononuclear cells (BMMNCs) appears safe over several years of follow-up, and results show a small, but statistically significant improvement in LV ejection fraction (LVEF). More importantly, the growing number of studies and increased number of patient years of follow-up has not revealed a safety signal for the use of BMMNCs for either AMI or heart failure. The establishment of a highly qualified cell processing quality control group helped to convert the complicated production of the cell product into a smooth and predictable operation. The Network's experience has contributed to this surge of new knowledge, and several institutions sought to join the Network as centers or satellites after CCTRN's inception. As the field evolves and the safety record grows [19] the debate shifts from not whether the trials should be done but rather how to standardize them [20]. The Network's renewal goal is to explore new and untested cell types, promising delivery mechanisms, and novel endpoints. CCTRN offers these lessons learned to clinical trial networks who are pursuing leading edge research as well as to fellow cell therapy researchers. This growing experience

with cell therapy has modulated extreme points of view on either side of the cell therapy debate, making the conduct of such clinical trials both more efficient and transparent.

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Figure 1.
Oversight and Management Structure of the Network

Figure 2.
Conduit of Safety Reporting in CCTRN