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Cell therapy and satellite centers: The cardiovascular cell therapy research network experience

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ABSTRACT

Due to the changing population in patients with myocardial infarction, recruiting patients in clinical trials continues to challenge clinical investigators. The Cardiovascular Cell Therapy Research Network (CCTRN) chose to expand the reach and power of its recruitment effort by incorporating both referral and treatment satellite centers. Eight treatment satellites were successfully identified and they screened patients over a two year period. The result of this effort was an increase in recruitment, with these treatment satellites contributing 30% of the patients to two of the three Network studies. The hurdles that these satellite treatment centers faced and how they surmounted them provide instruction to clinical research groups eager to expand to satellite systems and to health care practitioners who are interested in taking part in multicenter clinical trials.

1. Introduction

A critical challenge to clinical trials is recruitment.[1,2] In some instances the circumstances are foreseeable, e.g., main centers overestimate their ability to recruit subjects [3] or there is a change in the characteristics or size of the target population that affects enrollment.[4] On some occasions, a multi-center clinical trial will attempt to increase the number of recruiting centers, a maneuver which can spur recruitment and in

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addition, generate new heterogeneity in the target population. Recruitment strategies to either avoid or respond to lapses in recruitment are a common literature theme [5–7]; however, there is little literature on the process by which satellites are accepted and operationalized into a multicenter study.

Most recently, the Cardiovascular Cell Therapy Research Network (CCTRN) has been challenged to improve recruitment for two of its three clinical trials. This manuscript describes the process of satellite center accrual, and is designed to illuminate the network's processes for identifying 1) new referring centers that will identify patients who will be treated at CCTRN main centers and 2) treatment facilities capable of carrying out cell delivery themselves. The satellite accrual process is described from each of the perspectives of the main centers and the satellites with the hope of providing a useful starting model for satellite center accrual in cardiovascular clinical trials.

2. Organizational structure and oversight of the CCTRN

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 stem cell therapy on cardiovascular disease. The Network built on contemporary findings of the cell therapy basic science community and translated newly acquired information to the cardiac clinical setting in the Phase I/II study paradigm.[8] It consisted of five main clinical research centers who received initial grants from the NHLBI (Cleveland Clinic Foundation, University of Florida, Minneapolis Heart Institute Foundation, Texas Heart Institute and Vanderbilt University). In addition, the Network included a data coordinating center (DCC) (University of Texas School of Public Health) that provided trial management and data analysis, a cell processing quality control center [9] and five core laboratories. Together, these Network components provided standardization of cell therapy preparation and endpoint measurements. All main centers participated in the selection and design of Network protocols that were also reviewed by an independent Protocol Review Committee (PRC) and a Gene and Cell Therapies Data Safety and Monitoring Board (DSMB) under the aegis of the NHLBI. Each main center and the DCC have independent Institutional Review Board (IRB) approvals and oversight. The Network simultaneously conducted two trials in the acute myocardial infarction (AMI) environment, TIME [10] and LateTIME [11] and one trial in patients with chronic heart failure and ongoing ischemia, FOCUS [12]. This manuscript focuses on recruitment in the two AMI studies.

3. Satellite center application process

The CCTRN main centers were required to supply estimates of their recruiting ability upon entrance into the Network. However, these enrollment estimates were requested before any Network protocol with targeted inclusion/exclusion criteria was selected. Later, when recruitment to the AMI protocols proved to be a challenge, the Network turned to the concept of satellites (first suggested by several of the main centers during their application process) to help bolster recruitment, diversify the trial patient population, and more deeply embed the Network into the local research community. The Network understood that this decision required increased workloads on all Network participants to ensure that all regulatory, safety, and logistical requirements were met.

4. Referral versus treatment satellite centers

The network defined a satellite as a clinical research site within the network that was not a primary awardee of the CCTRN grant. The Network included two separate satellite models — a referral model and a treatment model. The five main sites had the opportunity to promote and create both referral and treatment satellites in their locale.

4.1. Referral satellite

A referral satellite was a facility that served as a screening hub to refer patients to the main center. It identified patients who met the inclusion and exclusion criteria of the study and then referred the patient to the main center where consent was obtained, additional per protocol research testing carried out, bone marrow aspiration performed, cells processed, and infusion completed. Thus, the only role the satellite served in the referral model was to identify and refer patients.

The main centers were not required to gain prior CCTRN approval for any referral satellite, which made this an attractive option. Minimal administrative activity was needed for referral satellites, and a relatively low level of regulatory oversight required (although IRB approval was required by at least one referral facility to permit the main center to screen their records for potential study participants). The referral satellite personnel required training on basic knowledge of the protocols, as well as, on the inclusion and exclusion criteria. The referral satellites did not have access to the CCTRN database and did not complete CCTRN case report forms. Referral satellite principal investigators (PIs) neither participated in CCTRN conference calls nor attended CCTRN meetings.

4.2. Treatment satellite

In the treatment model, the satellite screened the patient, obtained the informed consent, carried out the bone marrow aspiration procedure, and infused cell product. However, the bone marrow aspirate was required to be processed by the same cell processing center that serviced the main center.

Because of the complexity of their operation, treatment satellites required the same level of regulatory and administrative review as the main center. The main center was responsible to ensure the technical capability of the treatment satellite's personnel, and quality assurance of the study product delivery. The CCTRN DCC provided administrative and regulatory oversight.

The CCTRN recognized that there was a wide range of local resource requirements, community needs, and geographic distances that characterized each satellite center. Therefore, a standard application was created to be completed and submitted to the CCTRN Steering Committee (SC) by the petitioning main center interested in sponsoring a satellite.

Satellite approval was a two step process of 1) application, and, if approved, 2) certification.

The purpose of the application was to unify the review process for satellites. Both the main center, the SC Chair, NHLBI and the DCC assessed each satellite PI, clinical research staff, facilities, and enrollment capabilities. The satellite's access and ability to utilize the main clinical site cell processing resources was also required. (Table 1)

Once a treatment satellite application was approved, the DCC began the certification process. This complex set of administration procedures required the collection of conflict of interest information, IRB approvals, delegation of authority statements in addition to core lab qualifications. (Table 2).

This was a critical, but time consuming process, taking months, and in some cases, years. For example, each of the centers and satellites were charged with completing a delegation of roles and responsibilities form. Experience with generating this document varied. For some institutions, this was a relatively easy exercise. Other sites were unable to generate this document until the very end of the satellite approval process.

In addition, CCTRN had three core labs for its AMI protocols. The treatment satellites had to have their echocardiographic and cardiac magnetic resonance imaging (cMRI) lab technicians certified by the CCTRN core labs. A major issue in the core lab certification process proved to be interdepartmental coordination and research billing processes with the satellite sites, themselves. While this was ultimately managed, it took substantial meeting time with the research and administrative staff at each satellite site. In at least one case, some investment in equipment was required to meet the core laboratory standards for cMRI.

To complete satellite certification, each of the treatment centers had to participate in at least two observed therapy delivery procedures. The purpose was to ensure that the satellite PI and research coordinator (RC) be able to get hands on experience with a complex protocol while providing a supportive environment. In most cases, the treatment satellite PI and RC would observe a case at the main center, and then the main site PI and RC would observe a case at the satellite center.

Table 1
Treatment satellite application.

1. Satellite institution name and address
2. Primary sub-PI contact information
3. Primary research coordinator contact information
4. Description of research capabilities of the satellite
5. Letter of commitment from satellite institution
6. Demonstrated recruitment ability
7. Letter of commitment from satellite
8. How many miles is satellite from CCTRN clinical center
9. If approved how long do you anticipate it would take to recruit first patient?
10. Has this center conducted multicenter cardiovascular research before?
11. Satellite investigator has reviewed protocols with respect to cell processing?
12. Distance between satellite and cell processing appropriate
13. How long will it take to transport cells from bone marrow aspiration to the cell processing lab?
14. Cell transport procedure developed and validated
15. Cell processing lab agrees site meets protocol requirement
16. Validation document
17. Satellite investigator has reviewed relevant documents, IB and MOPs
18. Home center PI will observe 2 Rx deliveries at satellite
19. No FDA audit concerns
20. PI-Sponsoring clinical center sign off
21. PI-Candidate satellite center sign off

Table 2
Requirements for certification.

Expected monthly patients
Resource availability
Appropriate lines of communication
Ability to conduct protocols
Facility proximity to home center
Enrollment initiation time lines
Experience with multi center trials
Complete site info and contact sheet
Cell processing validation document
Echo capability
MRI capability
Coordinating center principal investigator sign off
Chairman of the steering committee sign off
NHLBI sign off

Reimbursement for patient care costs at treatment satellites was made through the main centers at their same negotiated rate. Since the DCC has prior contracts with the main centers, this seemed to be the most direct way to pay the satellite sites. It therefore became the responsibility of the main center to develop any needed business relationship with its treatment satellite(s) in order to ensure that each satellite received funds for its treated patients. In several cases, this business contract was the rate-limiting step that significantly delayed the satellite certification process.

Once certified, the treatment satellite was expected to screen, treat and follow its own patients with DCC oversight, including quality control review of regulatory documents and data submissions, patient monitoring, fielding site's questions, document control, and training and certification oversight with the support and coordination of the main center.

The satellite PIs and staff were welcome to participate in CCTRN SC activities, including bi-monthly conference calls and face-to-face meetings held every four months. However, they were not extended voting privileges; this privilege remained only with the main center PIs.

The CCTRN Executive Committee received regular verbal reports from the DCC concerning regulatory compliance at the treatment satellite sites. No “audit for cause,” was ever recommended for a satellite, nor has a satellite been terminated due to safety violations.

5. Referral satellite network experience

The main centers were all encouraged to use the referral model from the outset of randomization, and each of the centers attempted to either utilize or develop a referral system. In fact, several main centers had well-established referral relationships already in place and had been able to draw patients successfully from these during prior studies. Relationship building was eased in the presence of prior positive collaboration history.

However, from the referring centers perspective, no relationship with the main center could move forward unless

there was foundation of trust. It was critical that referral sites, often comprised of private practitioners, keep control of their patients even as they referred them to the main centers for study participation. The threat of reimbursement loss for medical procedures at referral sites was an obstacle. An additional consideration was the new difficulty a subject faced when they visited a referring facility that could be hours away from their usual health care facility. Managing these problems required continued communication between the referring satellite and the main center, usually maintained through phone calls, meetings, and timely reports from the main center to the satellite of the patient's progress through the study. Alternatively, referral satellite investigators appreciated the availability of state of the art cell therapy for their patients as a tangible advantage. In addition, the availability of research initiatives, the possibility of academic affiliation, and the opportunity to publish with the network were considerable inducements.

The main site that led the way in building a strong network of referral satellites often began by sending a letter to the potential referral site, stating the center's intent to generate research patients while also clarifying that the main site would not take over the patient's primary care. The center emphasized that patients would be expected to return to the referring site for cardiac care unrelated to the study. In addition, the center would send a nurse-doctor team to the potential site in order to forge a relationship and provide study in-services for key personnel in many different areas, including basic research principles to more detailed presentations about stem cell research and the CCTRN protocols.

Challenges to establishing referral satellites were sometimes hard to overcome. It was commonly difficult for main centers to forge a first time relationship with potential referral networks in their proximity despite multiple outreach attempts. In some cases, political and economic relationships within a hospital system had already established a well recognized referral pattern for patients. These established patterns of patient referral were sensitive to changes and easily threatened by a potential new referral conduit, even if only for research purposes.

6. Treatment satellite experience

Four of the five CCTRN main centers were able to identify at least one treatment satellite. (Table 3).

While each treatment satellite was pleased to have been selected, they were all challenged by the administrative burden. Although satellite PIs had good working relationships with their counterparts at the CCTRN main centers, the satellite and main center institutions often had little history of a working together, and in some cases were competitors. Several of the satellites were independent research institutions with a solid research track record (Table 4).

In these cases, the concept of working as a satellite to another institution proved to be a paradigm shift that, while posing serious obstacles, ultimately proved to be manageable. Pre-initiation site visits by the DCC were conducted on site whenever possible. The main center PI and RCs were strongly encouraged to take part in the pre-initiation site visits to foster communication between the satellite(s) and the main center.

Table 3
List of treatment satellites.

Satellite name	Main center affiliation	Date application received	Date of certification
University Hospital Case Medical Center	Cleveland Clinic Lerner College of Medicine	12-23-2008	01-29-2010
Michael E. Debakey VA Medical Center	Texas Heart Institute	12-10-2008	12-2-1010
Pepin Heart Hospital and Patel Research Institute	University of Florida	01-25-2009	08-06-2009
St. Paul Heart Clinic United Hospital	Minneapolis Heart Institute Foundation	12-05-2008	05-11-2009
Metro Cardiology Mercy Hospital	Minneapolis Heart Institute Foundation	01-02-2009	10-21-2009
University of Minnesota	Minneapolis Heart Institute Foundation	03-02-2009	10-21-2009
Mayo Clinic College of Medicine	Minneapolis Heart Institute Foundation	09-01-2009	10-01-2010

Initially, communication with the satellites was conducted principally through the main center. Thus, Sponsor generated information moved from the DCC to the main center and from there to the satellites. Day-to-day communication was primarily between the main center and the satellite. This additional work was an unanticipated load on already burdened main center RCs. Therefore this initial communication model changed to encourage the satellites to communicate directly with the DCC which allowed for a more efficient and cohesive information exchange.

The treatment satellite center configuration was a novel concept to several IRBs. The boards commonly required 1) a detailed description of how subjects were to be managed at each center, and 2) that documentation at the center and its satellite(s) agree, with particular emphasis on the operational plan and the informed consent form (ICF). However, although both a main center and its treatment satellite(s) were committed to producing an ICF that they could be comfortable and confident with in front of subjects, the ICF approval process itself was a challenge, exacerbated by the need for revisions.

The requirement that cell processing (CP) be carried out only at the CP lab used by the main center, and the limitation of these facilities to process only one patient's product per day per center demanded careful coordination and dependable communication between the treatment satellite and the main center. The greater the number of satellites per main center, the more urgent the need was for close coordination between the satellites and the center. The Network responded by increasing the processing capability at each of the critical CP laboratories with additional equipment that allowed them to process two patients a day.

Nevertheless, the requirement that cell processing be conducted at the main center was an operational decision made by the Network in order to maintain consistency of the study product. This was a substantial concern of the satellites whose physical location from the main center was greater than 60 miles. In fact, this requirement required to the

Table 4
Satellite characteristics.

Satellite name	Type of facility	Prior history of research	# of research programs PI has done in last 5 yrs	# of research programs RC has done in last 5 yrs	Past research collaboration with main center
University Hospital Case Medical Center	Tertiary	Active	20	40	Yes
Michael E. Debakey VA Medical Center	Tertiary	Active	10	8	No
Pepin Heart Hospital and Patel Research Institute	Primary	Active	30	25	No
St. Paul Heart Clinic United Hospital	Tertiary	Active	20	15	No
Metro Cardiology Mercy Hospital	Tertiary	Active	17	10	No
University of Minnesota	Tertiary	Active	6	3	Yes
Mayo Clinic College of Medicine	Tertiary	Active	50	16	No

Network to develop a validation report that was required by all satellites that included a test run to validate that cells could be transited, processed, and delivered with all requisite cell viability checks while keeping total out of body time down to less than twelve hours.

7. Veterans administration (VA) hospitals as satellites

One of the most daunting management challenges faced by the Network was its pursuit of a local VA hospital as a treatment satellite. Four of our main centers expressed initial hope in recruiting a local VA facility. After much discussion, attention focused on one VA hospital that was affiliated with a CCTRN main center and used the same IRB.

The VA operated within a special administrative environment, and its challenges required a unique combination of perseverance and expertise. Considerable time was spent on learning the research process at the VA and CCTRN devoted substantial local resources to master the institutional policies and procedures. In this case, the main center RCs were required to attend a three-day VA personnel orientation program, as well as, additional web-based training, in order to obtain VA clearance, identification badges and passwords. The RCs who worked with the VA hospital spent the majority of their time maintaining compliance with the institutional policies/procedures and ensuring simultaneous reporting of progress to both the primary and satellite IRBs.

A particular sticking point with the VA was the CCTRN Biorepository, a core laboratory with a storage facility for offsite storage of cell product [9]. In order to begin enrollment, a waiver had to be obtained from the national VA to allow its use on the local level. A waiver was required for each Network protocol in which the VA would participate.

8. Discussion

There has been much written on recruitment in clinical trials. A review of the literature in 1997 identified over 4000 references on recruitment [13]. More recently the reasons for challenging recruitment have been classified as participant-related, research-related, and contextual and environmental [1]. The use of referral centers in clinical trials is a well established procedure to improve recruitment and to expand the heterogeneity of the recruited subjects. And, while there is much literature on recruitment of clinical trials, there is little in the literature about the formal involvement of referral and satellite facilities in clinical trials.

CCTRN developed satellite sites to bolster recruitment, diversify the trial patient population, and to more directly connect the Network in its local research communities, while protecting the resources necessary for patient care costs and ensuring that all regulatory and safety requirements were met. The possibility of simply expanding the number of main centers was considered; however the arbitrary selection of centers would be inconsistent with the competitive selection of the initial five main centers.

Although the choice to seek referral satellites required little contribution from the Network leadership and the DCC, setting up referral satellites was problematic for several centers. The absence of a well established relationship between the main center and the satellite center was a hindrance to relationship development in the competitive referral dynamic. In some circumstances, the creation of a new referral network ran counter to the established referral pattern and hampered the development of a Network-supportive referral grid. One possibility that has been discussed but not yet effectuated is the designation of a referral investigator (RI). The RI would be based at the main center, and their primary role would be to develop and nurture the referral network. They would maintain contact with the referral center. When a referral subject was enrolled in the study, the RI would be notified, and would contact the referring physician, providing reassurance that the patient would remain the referring physician's patient. For each follow-up visit, the RI would contact the referring physician, and discuss the patient's progress in the study. These contacts reinforce the fact that the patient would be returned to the referring physician for ongoing care.

The Network assembled a diligent application process that it hoped would identify treatment satellites of excellence that would add to the recruitment reach and power of the Network. As expected, treatment satellites took longer to set up than referral satellites. However, the Network was surprised at the duration of time from approval of the satellites application to when the satellite first began screening patients. The first treatment satellite took six

months from approval to certification and enrollment. The longest has taken approximately 24 months.

The Network also underestimated the costs of certifying new satellites. The time commitment at the centers (main and satellite) was considerable, as RCs, who already carried a full responsibility load, now had to spend time collecting extensive documentation and participating in training to get the satellite sites certified. The fact that there was no reimbursement of this time made prioritizing work at the satellite site difficult. Costs incurred by the DCC were also considerable as it worked to keep track of the progress of satellite IRBs for protocol approvals, and informed consent form changes. During the process, the CCTRN leadership realized that the new financial burden of identifying and supporting satellites was considerable, and the NHLBI provided supplemental funding for this work.

The expectation of both the NHLBI and the FDA was that CCTRN would have adequate representation of women and minority populations; heterogeneity was part of our original recruitment plan. However, recruiting from main centers alone produced a shortfall in these underrepresented populations that the satellites helped us to overcome. For example, our satellites contributed over one third of our women subjects and just over a quarter of our minority subjects in our AMI trials. This increase in women and minority recruitment will help to relieve any imbalance by therapy group that smaller numbers of these patients might induce. And, while the numbers are still too small to admit a formal subgroup analyses, our ability to generalize to the larger population is eased by improved minority and gender recruitment.

The quality of the data generated by satellites was of the same high quality of that of the centers. There were fewer protocol deviations at the satellites, perhaps due to the opportunity to clean up ambiguities in early protocols versions that the satellites never had to operate under since they came on board later in the studies. Specifically, the satellites were treated the same as the main centers for quality assurance. Each satellite underwent a pre-initiation site visit by the DCC PI and a project manager. Satellite nurse coordinators were invited to take part in biweekly Steering Committee conference calls and monthly nurse coordinator calls. In addition, our clinical monitors visited each of the satellites at least twice a year and conducted comprehensive review of the patient data record including but not limited to an evaluation of inclusion, exclusion criteria and review of accuracy of data entry by comparing the electronic data record to the source documentation. Gender, race, and ethnicity of all consented participants were tracked. Treatment was competently delivered and serious adverse event rates at the satellites were no different from those at the main centers. Since cells were processed by the same laboratories that process cells for the centers [9], there was no difference in the quality of study product between main centers and treatment satellites.

Delays in satellite certification were multifactorial, and primarily local. However, an endemic concern was the lack of funding for treatment satellite infrastructure. While they received full reimbursement on patient care costs (from the main center), neither referral satellites nor treatment satellites received any financial support for time or resource reimbursement at the beginning of the satellite certification process. It soon became clear that this was a major cause of concern for the satellites. The Network responded to this need by providing a modest level of support for the treatment satellite PI and RC in mid-trial.

There was substantial variability on the establishment of solid working relationships between the satellite treatment centers and the main centers. Since the main center advocated the entry of the treatment center, the Network was careful not to intrude on conversations between these two groups as they developed their joint working plan. However, at least one satellite reported that the DCC could have expedited the conversations by providing a framework on which to build this collaboration. One such example would be to provide a template for a contract and an operational plan for future potential treatment satellites.

In addition, interactions between satellite IRBs and CCTRN main centers were commonly a challenge. The correct sequence of informed consent approval was difficult to see prospectively, which led to complications as the IRBs struggled with multiple informed consent versions, two language versions (English and Spanish) at one of the main centers, and mandated protocol changes. While these complications usually did not lengthen the satellite certification process, they did create problems with continuity of patient enrollment during the studies.

Although, the VA welcomed research into their practice and was eager to participate in research, the local VA institutions do not yet offer a structured portal through which outside researchers can offer research opportunities to VA patients. The national VA, recognizing this, is putting new systems in place to facilitate clinical research, however our experience taught us that there is still a long way to go in this process. In addition, given the time required to qualify CCTRN treatment satellites, it may have been wiser to begin the treatment satellite certification process at the onset of the Network, while simultaneously, establishing referral satellites on the periphery of the metropolitan areas serviced by the main centers. Nevertheless, the satellites are contributing to recruitment, providing thirty percent of the total randomized patients in the network's two AMI studies, and overall, the experience has been a positive one with lessons of value learned by the Network. (Table 5).

Table 5
Lessons learned in the satellite experience of CCTRN.

1.	Start the satellite identification and certification process as early as possible in the study period.
2.	In addition to reimbursing patient care costs, provide infrastructure support to satellites.
3.	Consider providing an investigator with the sole charge of soliciting and maintaining consistent contact with referring hospitals.
4.	Foster early development of regular communication between satellite and main center personnel, including face-to-face meetings which keep the teams engaged.
5.	Provide adequate support for personnel at the data coordinating center for the satellite certification process.
6.	Maintain consistent contact with the satellites during the certification process, but allow the satellite's internal process to work without interference.
7.	Choose a satellite that has geographic proximity to the main cell processing lab to streamline operations.

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