

Date: May 30, 2003

Version 2

Test Drug: disodium ethylenediaminetetraacetic acid (EDTA)

Title: Trial to Assess Chelation Therapy (TACT)

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## BACKGROUND

### Introduction

Coronary heart disease (CHD) is by far the leading cause of premature morbidity and mortality in the United States. At present, proven therapies include lifestyle modifications, drugs, and procedures. Due to the availability and underutilization of these proven therapies, many patients seek out and use alternative therapies, including the commonly used complementary and alternative medicine (CAM) practice called chelation therapy. Chelation therapy, as practiced in the CAM community, involves the intravenous administration of disodium ethylenediaminetetraacetic acid (EDTA), combined with high dose antioxidant vitamin and mineral supplements. Thus, any clinical benefit may be due to the effect of EDTA chelation, high dose antioxidant vitamins and mineral supplements, or both. It has been estimated that in the last few years, over one million patients received more than 20 million infusions<sup>1</sup> "with no serious adverse effects", but this has not been well-documented. Due to the prevalence of chelation therapy, the many reports of benefit from its proponents, and the contrary advice of traditional medical organizations have led NCCAM and NHLBI to fund this large-5-year Trial to Assess Chelation Therapy (TACT).

This present document describes the background, rationale, study design, safety monitoring, and analysis plans for TACT.

### EDTA Chelation Therapy

The mechanistic hypothesis of TACT is that EDTA chelation of divalent and trivalent ions such as calcium, iron, zinc, cadmium, manganese, and copper reduces atherosclerotic plaque hence leading to a reduction in subsequent major vascular events. Several potential mechanisms of action for the beneficial effects have been proposed<sup>2</sup>, some of which are reviewed below.

#### 1.2.1 Basic Research

The word chelate comes from "chele" which is Greek for the claw of a crab or lobster implying a firm, pincer-like binding of a metal compound by a chelating agent<sup>3</sup>. EDTA binds ionic calcium and other divalent cations and trace elements (such as zinc) and transports them in bound form out of the body in the urine.<sup>4</sup> EDTA was patented in 1938,<sup>5</sup> at a time when there was a military need to find effective antidotes to possible chemical warfare agents such as arsenic. Also during this time EDTA became a common treatment for lead poisoning. During some clinical applications of EDTA for lead poisoning in patients with established atherosclerotic disease, improvements in symptoms of CAD were reported. Consequently, in the 1950's a series of case reports were written describing the effects of EDTA in treating patients with atherosclerosis. For example, Clarke reported that EDTA was effective in removing metastatic calcium deposits.<sup>6</sup> In another series, he described symptomatic improvements for patients with angina pectoris<sup>7</sup>. Supportive data were offered in the form of serial chest radiographs that showed improvement in mitral valve calcification.

The appreciation that coronary and other vascular calcification exists in atherosclerosis led to the hypothesis that EDTA, by virtue of its calcium-chelating actions, could be anti-atherogenic. Bolick and Blankenhorn<sup>8</sup> performed an *in vitro* study on the effectiveness of calcium removal. They were able to remove calcium deposits from normal and diseased coronary arteries, using a version of EDTA



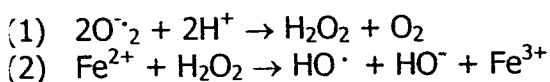
lled NH<sub>4</sub>-EDTA. They demonstrated that coronary atheromatous plaque contained at least as much calcium per unit weight as similar depositions in aortic or iliac lesions. This demonstration of *in vitro* decalcification of heavily calcified coronaries with EDTA gave support to the concept of EDTA as an atherogenic agent. Indeed, it is the central role of the decalcification in the use of EDTA chelation that has led to the consistent use of disodium EDTA, as calcium EDTA will not bind additional divalent cations.

In 1990, Kaman et al<sup>9</sup> reported the effect of EDTA on calcified rabbit aortas. On average, the aortic calcium score of standard diet-fed rabbits was 316; the score of cholesterol-fed rabbits was 696. The score of cholesterol-fed but EDTA-treated animals was much more like that of the animals fed a standard diet (score=292). There was a statistically significant difference in the quantitative analysis of calcium in the groups treated with EDTA, compared to that of the other groups.<sup>9</sup>

From a practical perspective, atherosclerotic plaques are integral components of the arterial wall, and may not be exposed to circulating EDTA. Although elevated amounts of calcium have been obtained in urine samples, the calcium may be more readily mobilized from bones and blood, rather than selectively originating from plaques. Thus, there is little rigorous scientific evidence that EDTA chelation selectively decalcifies atherosclerotic plaque, a mechanism central to the effectiveness proposed for chelation therapy by its proponents.

In addition to the possibility that EDTA chelation therapy assists in the decalcification of atherosclerotic plaque, there is evidence that oxidative stress in the vasculature, a mechanism of endothelial dysfunction in atherosclerosis and related disease states,<sup>10</sup> is reduced by EDTA chelation therapy. Oxidative stress is produced when above-normal levels of superoxide occur which leads to impaired endothelium-dependent vasodilation.<sup>11</sup> Chronic increases in superoxide are associated with lipid peroxidation. Oxidized LDL (ox-LDL) is cytotoxic to endothelial cells<sup>12</sup> and inactivates NO directly.<sup>13</sup> Ox-LDL also reduces eNOS protein in endothelial cells.<sup>14</sup>

Redox active transition metals ions are a well-recognized source of oxidative stress in the vasculature.<sup>15</sup> For example, iron is a catalyst for the formation of the highly reactive hydroxyl radical via the Fenton displayed in reactions 1 and 2.



In the presence of additional superoxide anion ( $\text{O}^{\cdot-}_2$ ),  $\text{Fe}^{3+}$  is reduced back to  $\text{Fe}^{2+}$ , thus establishing a catalytic redox cycle. Similar chemistry exists for copper-mediated formation of hydroxyl radical. Free copper and iron are known to induce oxidation of lipids and proteins, processes that depend, in part, on metal ion-dependent formation of reactive oxygen species.<sup>16</sup> Cell-mediated LDL oxidation also depends on the availability of metal ions.<sup>17</sup>

Some epidemiological evidence shows that increased body stores of iron<sup>18</sup> or copper<sup>19</sup> are associated with increased CAD risk, however, other epidemiological studies have failed to show such a relationship for iron.<sup>20</sup> Further supporting the role of metal ions in the pathogenesis of atherosclerosis is the observation that human atherosclerotic tissue contains redox active iron and copper,<sup>21</sup> while normal tissue does not. In addition to impairing endothelial function by stimulating LDL oxidation, metal ions also may have direct effects that contribute to atherogenesis and vascular dysfunction.



For example, inorganic iron has been shown to accelerate endothelial cell apoptosis.<sup>22</sup> Furthermore, iron contributes to NF $\kappa$ B activation<sup>23</sup> and to expression of VCAM-1 in endothelial cells.<sup>24</sup> Finally, iron directly binds NO, as evidenced by the reaction of NO with heme iron in guanylyl cyclase. On the basis of these observations about metals, investigators posit that transition metals may contribute to atherogenesis by stimulating LDL oxidation. Thus, even if the presence of redox active iron and copper in atherosclerotic lesions is a secondary rather than a causative phenomenon, chelation of these species has the potential to improve vascular function and reduce CAD risk. In fact, iron chelation with intravenous deferoxamine recently was shown to improve endothelium-dependent vasodilation in the coronary arteries of patients with diabetes mellitus.<sup>25</sup>

### 1.2.2 Case reports and case series

The majority of the clinical literature that reports the benefits of chelation therapy is in the form of case reports and case series.<sup>26</sup> Most case series report on an individual practitioner's clinical practice. Cranton<sup>27</sup> reports that by 1993, there were more than 4600 documentary outcome reports supporting chelation therapy. These studies may be interpreted to suggest a striking benefit of chelation therapy; however, most do not have control groups, patient selection criteria are overly broad, measurements of endpoints are inconsistent, and follow up is incomplete. A cautious interpretation of this literature suggests that there are ample suggestions of benefit, but clear evidence is lacking. For the sake of brevity, only 3 representative studies spanning nearly 3 decades will be reviewed here; selected others are listed in Table 1 below.

In 1963, **Kitchell and co-workers**<sup>28</sup> reported on 28 patients with severe angina who underwent chelation therapy. Patients were monitored with exercise testing (fixed speed and inclination treadmill and Master's two-step). The authors concluded that early after chelation, there was little improvement. However, within 3 months of therapy, about 60% of patients reported improvement based both on patients' impression and their documented exercise tolerance. Nonetheless, the benefit was not felt to be long-lasting.

**Olszewer and Carter**<sup>29</sup>, in 1988, reported a retrospective analysis of 2870 patients treated at a private clinic in Sao Paulo, Brazil, who underwent chelation therapy between May 1983 and September 1985. Patients received a total of approximately 81,000 infusions. The protocol used was that recommended by the American Academy of Medical Preventives; and consisted of EDTA 50 mg/kg body weight given over 3 - 3.5 hours. Additives included vitamin C, B complex, and magnesium. There were 120 patients lost to follow up who were censored from the report. Treatments were given 2-3 times weekly. General lifestyle advice and oral multivitamins were also administered. Cardiac disease was present in 29.4%, peripheral vascular disease in 39.4%, cerebrovascular and degenerative disease of the CNS in 17.7%, scleroderma in 0.1%, and other geriatric vascular diseases in 13.4%. Of the 844 patients who had a diagnosis of ischemic heart disease, most (57.6%) had coronary insufficiency without infarction, 27.6% coronary insufficiency and infarction, and 4.8% coronary insufficiency with other complications. The authors report that 76.9% of patients had a marked improvement, defined as a positive stress test that subsequently became negative after a course of chelation therapy.

**Casdoorph**<sup>30</sup>, in 1981, reported a case series of 18 patients in whom left ventricular ejection fraction was measured with radionuclide ventriculography preceding and following 20 weekly



3-hour infusions of 3 grams of disodium EDTA in 250 cc of lactated Ringer's with 200 mg of lidocaine added to the infusate. The average improvement in ejection fraction was 5.8% (range -2% to 16%) and was highly significant ( $p < 0.001$ ).

Table 1: Summary of Case Series

First author (year)	Sample Size	Outcome measures	Result
Clarke (1955) <sup>6</sup>	22	symptoms	some improvements
Clarke (1956) <sup>7</sup>	20	symptoms	19 improved, 1 died
Boyle (1957) <sup>31</sup>	20	symptoms, ECG	significant improvements
Meltzer (1960) <sup>32</sup>	10	symptoms, ECG	9 improved
Clarke (1960) <sup>33</sup>	76	symptoms	58 improved
Kitchell (1961) <sup>34</sup>	10	symptoms	9 improved
Boyle (1961) <sup>35</sup>	10	symptoms, ECG	9 improved
Meltzer (1961) <sup>36</sup>	81	not stated	"effective"
Kitchell (1963) <sup>28*</sup>	28	symptoms, ECG	18 improved,
Lamar (1964) <sup>37</sup>	15	symptoms	15 improved
Lamar (1966) <sup>3</sup>	3	symptoms	1 improved, 1 died
Evers (1979) <sup>38</sup>	3000	symptoms	>90% improved
Casdorff (1981) <sup>30*</sup>	18	ejection fraction	17 improved
Robinson (1982) <sup>39</sup>	248	symptoms, ECG	significant improvements
Olszewer (1988) <sup>4*</sup>	844	symptoms	821 improved
McGillen (1988) <sup>40</sup>	1	angiography	No evidence of benefit
Wirebaugh (1990) <sup>41</sup>	1	angiography	No evidence of benefit
Deycher (1992) <sup>42</sup>	215	symptoms	70% improvement
Hancke (1992) <sup>43</sup>	42	Need for surgery	39 cancelled surgery
Hancke (1993) <sup>44</sup>	470	symptoms	Significant improvements

\*Described in text

most of these case reports and series, severe adverse events were not reported.





### 1.2.3 Randomized Trials

3 randomized trials of EDTA chelation for patients with atherosclerotic vascular disease have been conducted. A fourth trial, our Pilot to Assess Chelation Therapy (PACT), currently is ongoing, and we have analyzed safety data of patients in the chelation arm.

The first trial by Guldager et al<sup>45</sup> enrolled 159 patients with stable intermittent claudication for at least 12 months, and excluded patients with underlying conditions such as renal insufficiency, cardiac disease, or diabetes. The treatment regimen consisted of 20 infusions administered over 5 to 9 weeks. Patients also received oral supplements of multivitamins and magnesium. Findings indicate no differences in any parameters studied in the EDTA-treated group compared to placebo/control group.

Rij<sup>46</sup> reported the second trial in 1994. This trial included 32 patients with peripheral vascular disease confirmed by angiography. Diabetics were excluded, and patients were required to stop smoking. The active infusion consisted of 3.0 g of EDTA 0.76g magnesium chloride, and 0.84 g sodium bicarbonate in normal saline, to a total volume of 500 ml. The placebo infusion was 500 ml normal saline. Both groups received parenteral vitamin supplements. There were no significant differences reported in pain-free walking distance, or total walking distance when the EDTA-treated group was compared to the placebo group. At 3 months after treatment, however, resting ankle-brachial index showed some improvement in the chelation group in both legs, with a significant between-groups effect favoring chelation. An extensive analysis of quality of life also was performed, with mixed results. Although there were no differences in scales measuring general health and effect of poor circulation on life activities, chelation patients scored better on 2 scales that rated the level of physical activity ( $p < 0.05$  for between-groups differences) 3 months after therapy.

Judtsen and colleagues<sup>47</sup> carried out the Program to Assess Alternative Treatment Strategies to Improve Cardiac Health (PATCH), a 6-month randomized trial that measured exercise capacity in 84 stable angina patients randomized to receive either EDTA treatment or placebo. Patients were eligible to participate in the trial if they were over the age of 21, had proven CAD, stable angina pectoris, and 1 mm ST-segment depression within 2-14 minutes on a gradually ramping treadmill test. There were 39 patients ultimately randomized to each treatment group, receiving 40 mg/kg of EDTA up to a maximum of 3 g, or placebo. Both were administered in an IV saline solution over a 3-hour period, 2 times per week over 15 weeks, then once per month for 3 months, for a total of 33 treatments. All patients were given oral multivitamins. There were no significant differences in clinical outcomes between the treatment groups. There were no deaths, 2 MIs (1 in the chelation group and 1 in the placebo group), and 15 hospitalizations for worsening angina (9 in the chelation group and 6 in the placebo group). Both groups were able to increase their exercise times approximately 1 minute, an improvement that the investigators attributed to placebo or "training" effect. The investigators concluded that a trial of far larger sample size was necessary to reach any definitive conclusions.

The Pilot to Assess Chelation Therapy (PACT) is an ongoing 40 patient randomized trial of chelation therapy versus placebo, with change in endothelium-dependent, flow-mediated brachial artery dilation as its primary endpoint, in patients who fulfill the TACT entry criteria. The chelation protocol consists of 15 weekly infusions of chelation therapy according to the protocol of ACAM. The placebo group receives 15 infusions of normal saline. The methodology and algorithms for calculating and adjusting EDTA dose are identical to those of TACT. All patients receive a low-dose vitamin



plementation regimen. The total cohort of 40 patients has been enrolled (chelation=30 patients; placebo =10 patients). Although the study has not yet finished, we have analyzed safety data in the 30 chelation patients. As presented in detail in Section 6.2.1.3, "Reports of Human Toxicities in TACT," PACT provides reassuring data on blood pressure, pulse, renal, electrolyte, calcium and hematological parameters.

### 3 TACT: Closing the Gap in Knowledge

At present, the totality of evidence on chelation therapy includes basic research, clinical investigation, descriptive and observational epidemiologic studies and 3 small, randomized trials. Despite the sufficient totality of evidence on which to safely base rational individual patient as well as policy decisions, there have been over 20 million infusions given over the last few years.<sup>1</sup> There are standardized infusion protocols and training programs. Furthermore, chelation therapy is taught to physicians by organizations such as the American College for Advancement in Medicine (ACAM), and the International College of Integrative Medicine (ICIM). Following adequate training, practitioners who pass an examination become certified by the American Board of Chelation Therapy (ABCT).

For these theoretical and practical reasons provide support for the conduct of TACT, a large scale, randomized, double-blind, placebo controlled trial with clinical CVD endpoints. In general, the timing of a trial is a delicate matter. On the one hand, there must be sufficient belief in a favorable benefit to risk ratio of the intervention to justify exposing half the subjects. On the other hand, there must be sufficient doubt to justify withholding the intervention from the other half. Thus a state of equipoise exists. From a clinical and public health perspective, chelation is in equipoise and TACT will close the gap in knowledge regarding the potential benefits and risks of chelation therapy.

### 4.0 TACT STUDY DESIGN

The Trial to Assess Chelation Therapy (TACT) is a 5-year randomized, double-blind, placebo-controlled 2X2 factorial trial designed to test the effects of the standard chelation solution recommended by the American College for Advancement in Medicine (ACAM), as well as the effects of a high-dose antioxidant vitamin and mineral supplementation, versus a low dose regimen to simply replace chelation-related losses.

Specific aims for this trial include:

- To determine whether chelation or high-dose supplements in patients with CHD will reduce the incidence of clinical cardiovascular events;
- To determine whether chelation and high-dose supplements have acceptable safety profiles.

In addition, two substudies will be conducted whose specific aims are as follows:

- To determine whether chelation or high-dose supplements improve quality of life;
- To conduct an economic analysis of chelation therapy and high dose supplements.

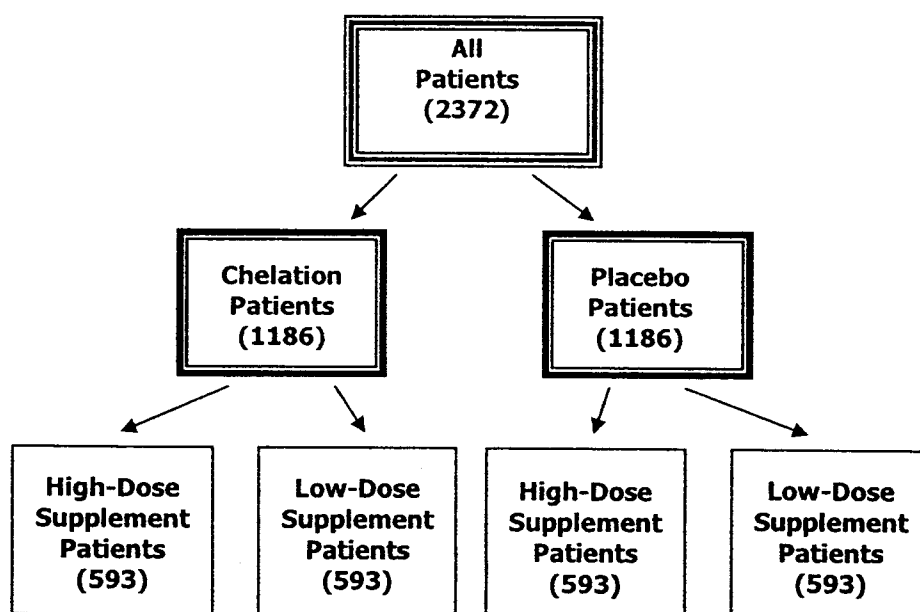
The primary endpoint of this trial will be a composite of: all cause mortality, nonfatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for angina. TACT will have excellent statistical power to detect a small to moderate reduction in this primary endpoint. See Appendix 1 for statistical considerations, including rationale for study design and statistical analyses plans). Major secondary endpoints will include: (1) cardiovascular death, or non-fatal MI or



non-fatal stroke; (2) individual components of the primary endpoint (3) safety profiles of the interventions including indices of renal, hepatic, and hematological function; and (4) health-related quality-of-life and the cost of chelation therapy will be examined in a randomly selected subset of the patients in the trial.

## **2.1 Sample and Methodology**

We will enroll 2372 patients 50 years of age or older with a prior myocardial infarction. Following baseline assessments, patients will be randomly assigned to receive 40 infusions of either the chelation or placebo solution, administered as 30 weekly infusions followed by 10 bi-monthly infusions. Patients will be followed an average of 2.5 years. In this 2x2 factorial design, each of these groups also will be randomized to either high-dose supplements or low-dose supplements as shown in diagram below. If both therapies are effective, this factorial design will permit the estimation of the contribution of each to the overall effect. All patients will be followed for clinical events until the end of the trial. The results of TACT will provide either a significant positive result or an informative null or negative result upon which rational clinical decision-making and health policy can be based.



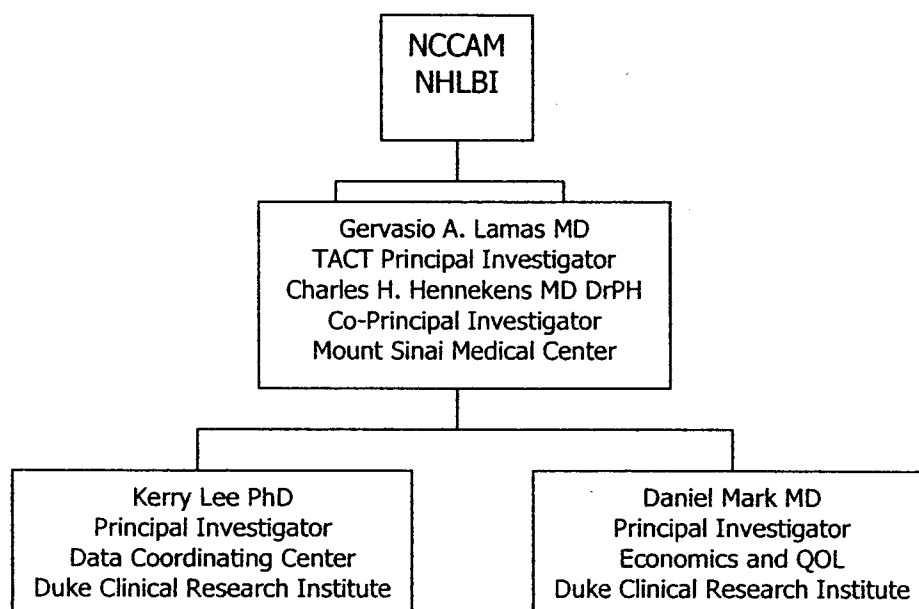


## OVERVIEW OF THE TRIAL ORGANIZATION

### TACT Organizational Units

The organizational units of the trial are depicted in the following figure.

Figure 1

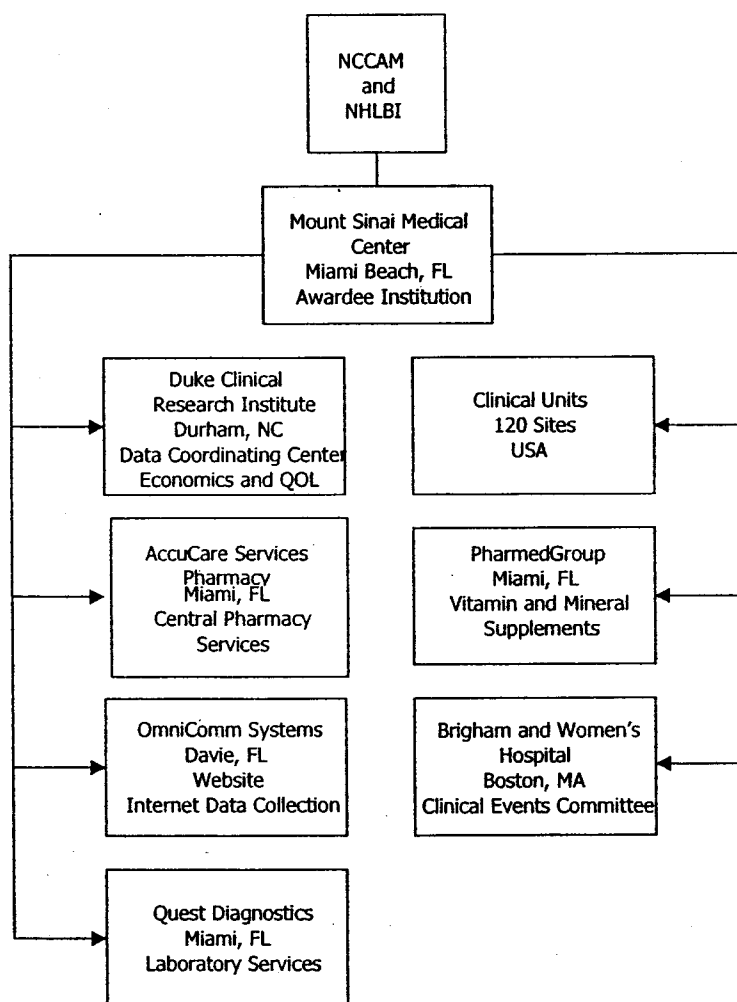




## .2 Contractual Relationships

rganizations that will conduct various TACT activities, under contract with the Clinical Coordinating Center:

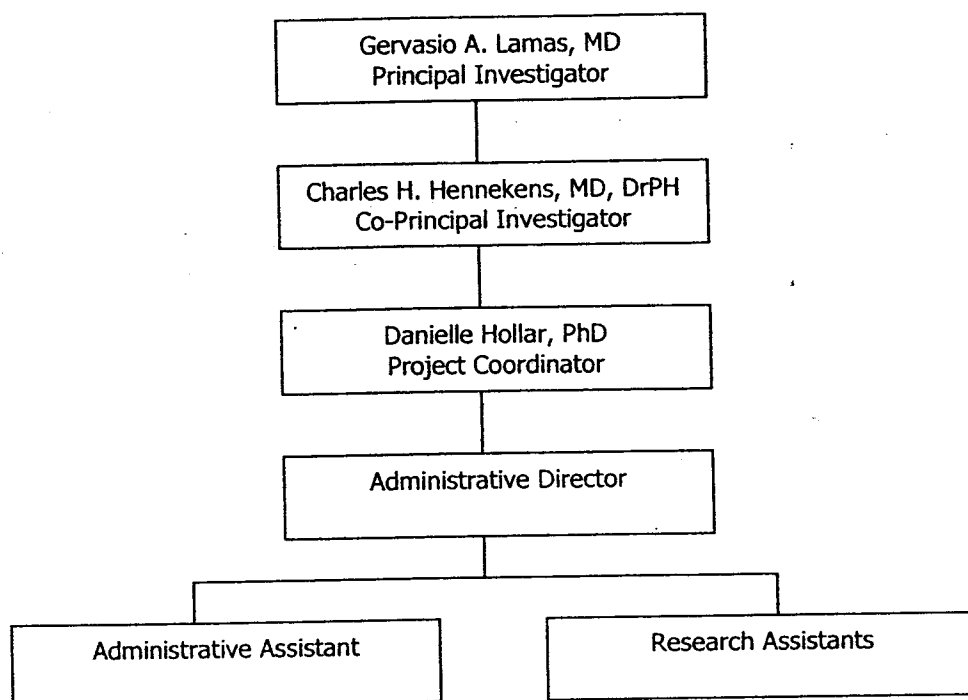
Figure 2





### 3.3 Clinical Coordinating Center

Figure 3



The Clinical Coordinating Center (CCC), as illustrated in the above figure, is located at Mount Sinai Medical Center-Miami Heart Institute, Miami Beach, FL. Dr. Gervasio Lamas, the TACT Principal Investigator, will be responsible for the scientific and administrative oversight of the trial. The CCC is responsible for all aspects of conducting this trial, including protocol development and amendments, site recruitment and retention, regulatory documentation, protocol adherence, site reimbursement and leadership in data analysis, study presentations and publications. Dr. Lamas will be responsible for all sub-contracts with the other organizational units. A Co-Principal Investigator (Dr. Hennekens), two Chelation Consultants, two Project Co-Directors, a Project Coordinator (Dr. Danielle Hollar), and Study Staff will assist Dr. Lamas in coordinating TACT. Dr. Lamas will submit quarterly progress reports to the NCCAM Project Officer and the NHLBI Project Officer. These reports will include recruitment data, indices of quality control, as well as the disposition and management of any reports of significant side effects or morbidity previously reported to him by the DSMB. Dr. Lamas will remain blinded to treatment assignment and treatment-specific clinical outcomes for the entire duration of the trial.

Dr. Lamas will also submit annual Awardee Non-Competing Progress Reports to NCCAM. He will also, on an ongoing basis, provide any additional non-confidential information required by the DSMB. Finally, Dr. Lamas will also present a mid-term and final report to the NCCAM Advisory Council.

If scientific misconduct or other events that have significantly affected the quality or integrity of trial data have occurred, Dr. Lamas will immediately notify the DSMB, NIH, the collaborating investigators, the appropriate IRBs, the FDA, and other sponsors of the affected work in accordance with established NIH standards.



#### **4 Data Coordinating Center**

The Data Coordinating Center (DCC, Dr. Kerry Lee) is responsible for the treatment allocations of eligible patients, receipt and processing of all data collected by the Clinical Sites and Central Units except economic data, quality control programs, and analysis of all study data except economic and quality of life data. DCC staff will prepare data reports at specified intervals for review by an independent DSMB and will collaborate with other study investigators in the preparation of study presentations and publications. The DCC is also responsible for quality assurance of the electronic data capture system and the internet-based communications network between management and performance sites. The DCC also will visit selected sites prior to site activation to ensure that resources to carry out the trial are present. Additionally, the DCC will visit all sites during the course of the trial.

#### **5 Economic and Quality of Life Coordinating Center**

In collaboration with the Clinical Coordinating Center and the Data Coordinating Center, the Economics and Quality of Life Coordinating Center will perform the following major functions: 1) obtain baseline economic status, quality of life, and angina and symptom status data from all patients enrolled at each participating study site at the time of randomization; 2) assess interval resource utilization, including major medical encounters, during each study follow-up; 3) assess detailed QOL data at 6 months, 1 year and 2 years after enrollment in a random subset of 1,000 patients; 4) compare cost and quality of life outcomes for each treatment factor (i.e., each factor in the factorial design) according to intention-to-treat; 5) estimate the incremental cost effectiveness ratio for the experimental arm(s) and perform extensive sensitivity analyses.

#### **6 Accu-Care Services Pharmacy**

The Accu-Care Services Pharmacy will:

- mix over 80,000 bags of blinded trial solution;
- preserve the blind;
- deliver refrigerated study solution to clinical sites within 48 hours after ordering;
- communicate on a real-time basis (internet-based) with sites, CCC, and DCC;
- change dosing immediately based on safety labs and standing orders;
- suspend shipment and notify DCC and CCC when safety labs are not received, or have reached predefined alert values;
- deliver blinded vitamins and supplements or their identical placebos;
- perform all of the above at a reasonable cost.



### 3.7 TACT Laboratory Services

Laboratory services consist of:

- analysis of all screening and safety laboratory tests, as specified in the protocol, excluding the specialized markers of oxidative stress and inflammatory processes
- providing the clinical sites with pre-printed ordering requisition forms
- collecting the lab specimens from the clinical sites
- processing all labs within 48 hours of drawing
- providing results to the respective clinical sites

### 3.8 Clinical Sites

The clinical sites will play a major collaborative role with the CCC in the recruitment, retention, and drug administration efforts in TACT. We estimate that 120 clinical sites will be sufficient to enroll 2372 eligible patients over 36 months.

Patients	Enrollment (months)	Active sites	pt/site/mo	pt/site
2372	36	130	0.51	18
<del>2372</del>	<del>36</del>	<del>120</del>	<del>0.55</del>	<del>20</del>
2372	36	110	0.60	22
2372	36	100	0.66	24

The Senior Investigator for each trial site in the consortium will be responsible for on-site clinical and scientific implementation, direction and management of the trial protocol, as well as the coordination of requirements for any adjunct studies of underlying mechanisms and surrogate markers. Senior Investigators will

commit at least 10% effort to this trial. All Senior Investigators have will have experience in the treatment and management of CAD and, at least, experience in participation in clinical trials, or equivalent training provided by TACT.

The organization of each clinical site requires:

- a Senior Investigator at the enrolling site with the above qualifications and commitment, in addition to sufficient clinical volume for recruitment of eligible patients, training in chelation therapy, in the evidence-based management of post-MI patients, and in the conceptual and practical basis of clinical trials;
- the above training must take place at a TACT initiation meeting or in other formats approved by the TACT Executive Committee;
- certificate of completion of NIH Human Subjects Protection Education, available through the Office of Human Research Protections (<http://cme.cancer.gov/c01/>), if there is no specific institutional-based course;
- a research coordinator;
- ability to draw blood;
- ability to detect and manage potential chelation-associated emergencies as they arise, including hypoglycemia, hypotension, cardiac arrhythmias, and hypocalcemia;
- Internet access on-site, so sites can comply with the electronic data capture system;
- The CCC recognizes that the characteristics of the infusion sites will be an important determinant of patient compliance. For example, such characteristics may include clinical areas where infusions are part of daily care, and the infrastructure for administering infusions already exists, such as an ongoing chelation practice. However, prior to final approval of any clinical site, the CCC will review and approve the characteristics of all infusion sites.





The interest in TACT expressed by both the cardiology and chelation community has led to 2 general types of clinical sites in TACT: those led by a cardiologist, and those led by a chelation practitioner. TACT recognizes that these clinicians will likely have different knowledge bases and practice patterns. Thus, in order to enhance uniformity of training and evidence-based management of study participants, one physician-leader in each enrolling site must complete TACT-sanctioned training at an initiation meeting.

Each trial site will follow the procedures required by this protocol regarding study conduct and monitoring, patient management, data collection, data management, data analysis and quality control. All proposed trial sites must agree to accept and implement the common protocol and procedures approved by the Steering Committee. Furthermore, all potential sites agree to preferentially enroll patients into TACT when competing studies are ongoing. The investigator letters of agreement, administrative letters, site surveys, and other clinical site characteristics will be completed prior to site training and activation. Finally, the clinical sites to start the trial will be selected based on a thorough review of their qualifications by the CCC, DCC, and NIH Program Staff.

## **4.0 INTERNET-BASED COMMUNICATIONS BETWEEN MANAGEMENT ORGANIZATIONS AND CLINICAL SITES**

Accurate and rapid communication of clinical and infusion data, carried out in a cost-effective fashion, is essential. In order to maximize accuracy and speed of communications between the CCC, DCC, the Accu-Care Services Pharmacy, and the clinical sites, an enhanced Internet-based data collection will be used in TACT. Therefore, Internet access is a requirement at patient-care and infusion sites. The minimal system requirements are Internet Explorer version 5.0 or 5.5. Sites will be trained and provided as needed with Internet Explorer. TACT has unique needs for rapid Internet-based communication in order to properly schedule preparation of infusions, delivery, and administration. Additionally, adjustments in the content of EDTA and heparin in the infusion are based on laboratory studies and must be made prior to preparation of the next scheduled infusion. In the unlikely event that internet access is transiently unavailable at the clinical site (due to power failure, for example), the clinical site will be instructed to call the CCC, and data will be entered from the CCC into the internet-based system.

## **5.0 MAJOR STUDY COMMITTEES**

### **5.1 The Steering Committee**

A Steering Committee will be established to serve as the main governing body of the trial. The Steering Committee will be composed of the Study Principal Investigator, the Study Co-Principal Investigator, the Data Coordinating Center Principal Investigator, the EQOL Principal Investigator, up to five trial site Senior Investigators, the NCCAM Project Officer, and the NHLBI Project Officer. The Trial Coordinator and Co-Managers will be ex-officio, non-voting members. The initial Steering Committee Senior Investigators members will be nominated by the Study Principal Investigator and elected by the Steering Committee to serve terms of 1 year. Senior Investigator members of the Steering Committee will be nominated by the Trial Principal Investigator, approved by the members of the Steering Committee, and appointed after NCCAM and NHLBI review. The Trial Principal Investigator and the Co-Principal Investigator will serve as Co-Chairs of the Steering Committee. All major scientific decisions will be determined by the Steering Committee, with the Co-Chairs, the Data



inating Center Principal Investigator, the EQOL Principal Investigator, Senior Investigators, the M Project Officer, and the NHLBI Project Officer, having one vote each. This Committee will primary responsibility for finalizing the trial protocol, and approving the design and mentation of all adjunct studies, facilitating the conduct and monitoring of the clinical trial and t studies, analyzing and interpreting study data, reporting study results, and setting guidelines thorships. Each Steering Committee member will be expected to participate in all other Steering ittee activities, e.g., conference calls, special subcommittees, as may be necessary.

### **Executive Committee**

Executive Committee will be chaired by the TACT Principal Investigator, and additionally osed of the TACT Co-Principal Investigator, the PI of the DCC, the NCCAM Project Officer, and HLBI Project Officer. The Executive Committee will make recommendations to the Steering ittee regarding study conduct. The Executive Committee will meet to monitor study progress o review non-endpoint data. Executive Committee meetings will be scheduled for the day prior ering Committee meetings. The Trial Principal Investigator and the Principal Investigator of the vill update the recruitment progress of each center and of the whole trial bimonthly for the tive Committee. Other reports for the Executive Committee may be requested of the Steering ittee as needed. In any votes of the Executive Committee, each member will have a single

### **The Clinical Events Committee (CEC)**

ded and independent committee will review abstracted clinical data to determine whether l endpoints and major events have occurred. All criteria and definitions are pre- specified in the al of operations of the CEC.

### **Operations Committee**

Operations Committee will include the Steering Committee Co-Chairs, the PI of the DCC (Dr. the EQOL Principal Investigator, the Trial Co-Managers, the CCC Project Coordinator, and the istrative Coordinator, the NCCAM Project Officer, and the NHLBI Project Officer. This committee arged with day-to-day trial management, including final protocol development and mentation, conduct of the protocol, feasibility (patient burden, site burden, cost), evaluation of tion of issues raised by the site and core laboratories. One of the two Chelation Consultants will ie conference once monthly. Such calls will ensure smooth day-to-day operations of the trial elp to identify issues that need to be brought before the Steering Committee.

### **Public Information Committee**

tanding Committee has as its charge to keep the medical and lay community informed as to the ss of TACT, and to bring to the TACT investigators any new advances that may be applicable o conduct of the trial. Additionally, the Committee assists the Study Chairman in integrating ementary, alternative, and traditional medicine for the benefit of TACT. The Committee already een instrumental in identifying qualified practitioners who are interested in performing infusions ouble-blind placebo-controlled manner, and in developing the TACT chelation, vitamin, and al treatment protocol. This Committee is chaired by the Study Principal Investigator, includes six



in chelation therapy, and 6 lay representatives with special interests in cardiac care and preventive medicine. This committee will meet in person yearly and hold conference calls on a regular schedule between meetings.

### **Data and Safety Monitoring Board**

Directors of NCCAM and NHLBI will appoint an independent Data and Safety Monitoring Board, separate from the Study Chairman, as suggested in the RFA. The DSMB will meet at least twice a year. DSMB meetings will be open only to designated NCCAM and NHLBI staff and other individuals who have been approved to have access to unblinded data. The DSMB will serve in an advisory role to the Directors of NCCAM and NHLBI. Any recommendations for alteration or termination for part or all of the trial shall be based on consideration of the accumulating data in the context of totality of evidence. Specific statistical monitoring guidelines for safety and efficacy concerning the primary and secondary endpoints will be developed in cooperation with the DSMB.

### **Data Bank and Ancillary Studies, Presentations, and Publications Committee**

This committee is charged with the timely review of all proposals for data analysis, as well as abstracts, presentations and manuscripts before submission. The committee will also review proposals for ancillary studies. This Committee will be Chaired by the Trial Co-Principal Investigator, and will include the Trial Principal Investigator, the DCC Principal Investigator, two CCC Consultants, The NCCAM and NHLBI Project Officers, and 2 Senior Investigators, one a cardiologist, and the other a chelation practitioner, to be appointed by the Steering Committee. At its first meeting, the Committee will develop operational policies to be reviewed and approved by the Steering Committee.

## **RESEARCH DESIGN AND METHODS**

### **Study Population**

#### **6.1.1 Patient Recruitment**

The study will randomize 2372 patients with a prior MI who are 50 years or older in a, double blind, placebo-controlled, 2X2 factorial trial of EDTA chelation therapy and/or high-dose vitamin therapy. All patients must complete the informed consent process prior to being randomized into TACT.

##### **6.1.1.1 Recruitment Strategies**

Recruitment strategies for TACT are thoughtfully targeted to specific groups in order to meet study goals with respect to patient enrollment and demographics. Meeting these goals, which results in a representative population that reflects the typical patient population with the disease/health characteristics of interest, is necessary for making informed conclusions based on data collected during the study.

Traditionally, cardiology or internal medicine practices are the most productive sites for patient recruitment. Focusing recruitment efforts in these locations proved fruitful for the PACT, as patients were recruited from cardiology practices and general internal medicine clinics. However, for the full-



TACT that includes a far larger sample size and increased diversity of patients, new recruitment strategies must be developed.

Building on patient recruitment successes of previous studies/trials, the CCC and DCC have developed a two-tiered recruitment strategy for TACT. Tier one comprises the majority of recruitment work and emphasizes recruitment strategies for locating clinical research sites. Tier two focuses on patient recruitment within clinical research sites, with an emphasis on strategies for enrolling a sufficient number of patients, including women and ethnically and racially diverse patients. Specific strategies for each tier are listed below.

#### Tier 1 – Clinical research site recruitment

In cooperation with and with guidance from DCC and ACAM, the CCC developed the following list of recruitment activities as part of the Tier 1 strategy to ensure a study group that is representative of the US population:

- Announce TACT during professional association meetings, and create recruitment materials for booth displays located at these meetings.
- Contact minority professional associations for recommendations and membership lists
- Follow-up on leads from minority recruitment professionals via faxed letters, emails, and telephone calls to enlist minority site participation.
- Create site recruitment materials (possibly a video), including a standardized TACT presentation/slides, for local investigators' use in regional settings (during regional professional association meetings, grand rounds, etc.), to recruit new sites and patients.
- Contact VA Medical Centers with experience in clinical trials in Puerto Rico, Hawaii, and other locations.
- Conduct search of Computer Retrieval of Information on Scientific Projects (CRISP) (<http://crisp.cit.nih.gov/>) to locate NIH-funded research taking place in key minority locations (Hawaii, etc.).
- Focus part of recruitment efforts on large clinics that are more likely to care for women patients.
- Focus recruitment activities in clinical areas with a high density of post-menopausal women, such as women's health clinics.
- Contact women's professional associations.
- Conduct Internet searches of women's cardiovascular research activities (WHI, and other current studies, workshops on women's cardiology issues, etc.).
- Advertise TACT in medical journals such as JAMA and the JNMA, the journal of the National Medical Association that focuses on topics relating to health issues of urban and minority patients, and practice and clinical issues relating to African-American physicians.
- Place radio and print advertisements in minority-friendly media.



## Tier 2 – Patient recruitment within established clinical research sites

The CCC plans to carry out the following list of recruitment activities as part of the Tier 2 strategy:

- Create media templates for patient recruitment, catered to the local contexts of TACT sites, for print, radio, and television.
- Place radio and print advertisements in minority-friendly media.
- Develop a public interest section on the TACT web page including a Spanish-language information section.
- Respond to individual site requests for assistance with media relations, providing experts for media activities.
- Develop a web-based training system for patient recruitment and retention
- Train clinical research site coordinators about recruiting and retaining patients during study meetings and telephone sessions.
- Set goals for women and minority enrollment for each enrolling site.
- Track minority enrollment and report data monthly.
- Recognize sites meeting minority and women recruitment goals during study meetings.

Both Tiers 1 and 2 may be modified throughout the course of TACT as needed. All these activities, in particular the recruitment of enrolling sites with a high minority patient base, will be carried out in close collaboration with Program staff. To facilitate these strategies, the CCC will create a set of media templates to be disseminated with local IRB materials, as requested by current and new TACT sites. All recruitment materials will be reviewed by the CCC and approved by the local IRBs.

### **6.1.1.2 Enrollment of Women and Ethnic as well as Racial Minorities**

The TACT study design includes specific goals with respect to the enrollment of women and ethnic and racial minorities. With respect to gender, the goal is to enroll a sample of women and men that is representative of a typical patient population with the disease/health characteristic of interest – in this case CHD. Based on this criterion, we expect to enroll a study population comprised of 30 percent women. With regards to ethnic and racial minorities, the goal in TACT is to enroll a representative sample of the United States minority population that includes at least twelve percent African Americans, eight percent Hispanics, two percent Asian Americans, two percent Pacific Islanders and Asian Americans, and one percent Native Americans.

Achieving the gender and ethnic and racial enrollment goals above requires strong efforts on the part of study leadership, including the implementation of the recruitment plan described above.



### 6.1.2 Inclusion Criteria

All of the following inclusion criteria must be present for the patient to be enrolled in the trial.

Men or women age 50 years and older (women must be post-menopausal).

2. Documented myocardial infarction (MI) over 6 weeks prior to evaluation. The criteria for MI will be based on the ESC/ACC<sup>48</sup> definition as follows:

Either of the following criteria (A or B):

A. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

- 1) Ischemic symptoms;
- 2) Development of pathologic Q waves on the electrocardiogram (ECG); or
- 3) ECG changes indicative of ischemia (ST-segment elevation or depression);

or

B. Imaging evidence of myocardial scar, and coronary angiographic evidence of epicardial coronary disease in the same distribution. A prior MI may be diagnosed in patients with angiographically defined coronary artery disease (a luminal narrowing >50% of a major epicardial coronary artery) and imaging evidence of myocardial scar in the anatomically corresponding distribution. Imaging evidence of myocardial scar includes a non-reversible perfusion defect on myocardial radionuclide perfusion imaging or severe wall motion abnormality on contrast angiography, radionuclide angiography, or echocardiography.

### 6.1.3 Exclusion Criteria

In order for patients to be enrolled in the trial, none of the following exclusion criteria may be present.

- Prior chelation therapy within 5 years of proposed randomization date.
- History of allergic reactions to any of the components of the chelation solution (see description of chelation solution) or the vitamins and minerals.
- Coronary or carotid revascularization procedure within the last 6 months.
- Planned revascularization.
- Symptomatic heart failure at proposed time of enrollment.
- Clinically evident heart failure, visible symptomatic volume overload, in the opinion of the treating physician (Heart failure is defined in Appendix 2).
- Hospitalization for heart failure within 6 months.
- Stage II hypertension, defined in the JNC6 guidelines as a blood pressure  $\geq 160/100$ .<sup>49</sup> If blood pressure  $\geq 160/100$ , then the patient may be treated and reevaluated for enrollment at a future date.
- No venous access in the upper extremities.
- Baseline serum creatinine  $>2.0$  mg/dl.
- Baseline platelet count  $<100,000/\text{mm}^3$ .<sup>50</sup>
- History of cigarette smoking within the last 3 months.
- History of liver disease.
- ALT or AST  $> 2.0$  times the upper limit of normal.



- Diseases of copper (Wilson's Disease), iron (hemochromatosis, iron deficiency), or calcium (calcium < 8.0mg/dl) metabolism.
- Inability to tolerate the weekly fluid load (500cc of normal saline).
- Any condition or circumstance such as chronic non-compliance or an itinerant lifestyle that will affect compliance with the study interventions.
- Any severe, non-coronary medical condition likely to affect patient survival within 4 years.
- Women of child-bearing potential including those with plans for post-menopausal in vitro fertilization.

#### 6.1.4 Screening/Baseline Evaluation

potentially eligible patients will undergo an initial visit in which eligibility will be confirmed and the protocol explained in detail. All willing and eligible patients providing informed consent will have baseline data obtained including relevant history and use of all conventional and alternative therapies. Baseline laboratory tests will be performed and information on quality of life will be obtained.

#### 6.1.5 Randomization

On the next working day after the patient visit, the Site Coordinator will check lab results for any previously undetected exclusion criteria. The Site Coordinator will call the patient to notify him or her of final eligibility for TACT, and if applicable, schedule the first infusion. Next, the Site Coordinator will log on to [www.tactnih.com](http://www.tactnih.com) and complete the randomization screen. After completing this form, and hence verifying eligibility, the patient will be randomly assigned to one of the four treatment arms and given a unique trial identification number. The Accu-Care Services Pharmacy and DCC will be instantaneously notified electronically of the random assignment number and the date of the first infusion. The DCC will track the number of screen failures for each site.

### 6.2 Treatment Regimens

The chelation solution<sup>50</sup> will be administered over 3 hours at an administration rate of 166 cc/hour and consist of 500ml of sterile water and the additives listed in the chart below. Every effort will be made to conduct infusions with the smallest gauge catheter or a 25 gauge butterfly needle as this will limit the maximum infusion rate.



Additive	Role of Additive
Up to 3 grams of disodium EDTA 2 grams of magnesium chloride 100 mg of procaine HCL 2500 units of heparin 7 grams of ascorbate 2 mEq KCl 840 mg sodium bicarbonate 250mg pantothenic acid 100mg of thiamine 100mg of pyridoxine	To reduce local discomfort and replace losses To reduce local discomfort To reduce local phlebitis Anti-oxidant and to achieve isoosmolarity To replace losses To act as a buffer and reduce discomfort For anti-oxidant properties For anti-oxidant properties To replace chelation losses

The maximum dose of EDTA is 3 grams for patients who have at least 60 kg of lean body weight and normal kidney function. Reduction in kidney function and/or lower lean body weight will each lead to reduction in the total EDTA dose infused. The EDTA dosing for each infusion is computed<sup>50</sup> as follows:

$$50\text{mg(EDTA)} \times (\text{lean body weight} \times 1.33) \times \frac{(\text{creatinine clearance})}{100}$$

Lean body weight is calculated as follows:

For men the weight is computed as 50 kg plus 2.3 kg for each inch of height over 5 feet (or 60 inches).

For women the weight is computed as 45.5 kg plus 2.3 kg for each inch of height over 5 feet (or 60 inches).

Actual body weight is used whenever it is less than computed lean body weight.

Correction for creatinine clearance should only be done if clearance is less than 100. Creatinine clearance will be computed by using a modified version of the Cockcroft-Gault equation:<sup>50</sup>

$$\text{Creatinine Clearance(ml/min)} = \frac{(140 - \text{age}) \times (\text{LBW} \times 1.33)}{(72 \times \text{Cr})}$$

Creatinine Clearance = computed renal glomerular filtration rate in ml/min

Age = patient's age

LBW = computed lean body weight in Kg

Cr = serum creatinine in mg/dL

For women, multiply the above result by 0.85

Thus, when renal clearance is less than 100 ml/min, the amount of EDTA administered is reduced proportionately (i.e., if creatinine clearance is 70 ml/min, then EDTA should be 70% of the full calculated dose).





there is any upward change in creatinine, but not enough to reach the threshold for withholding an infusion, the Accu-Care Services Pharmacy will adjust downward the EDTA content of the infusion according to estimated creatinine clearance.

### 6.2.1 EDTA Pharmacology

EDTA is poorly absorbed from the gastrointestinal tract. Only 5-10% of an oral dose is absorbed in the body, 91% of an oral dose is recoverable from the feces, and 4 % is recoverable from the urine.<sup>51</sup> In blood, all of the drug is found in the plasma. EDTA does not appear to penetrate cells; it is distributed primarily in the extracellular fluid with only about 5% of the plasma concentration found in the spinal fluid. The half-life of EDTA is 20 to 60 minutes. EDTA is excreted primarily by the kidneys, with about 50% excreted in one hour and over 95% within 24 hours.<sup>51</sup> Calcium and other metals are excreted in the urine bound to the EDTA. Almost none of the compound is metabolized.

The pharmacologic effects of EDTA are due to the formation of chelates with divalent and trivalent metals. The stability of the metal-EDTA complex is directly related to its pH – the higher the pH, the more stable the chelate. Intravenous infusions of disodium EDTA result most prominently in the chelation of ionized calcium.<sup>52</sup> Transient but mild reduction of serum calcium can be observed following the slow intravenous infusion of EDTA. 1gm of EDTA can effectively bind approximately 20mg of calcium. Among metals normally found as trace metals and metals present pathologically, EDTA has been demonstrated to bind and promote the excretion of calcium, zinc, copper, iron, cadmium, manganese, vanadium, and lead.<sup>53,54</sup> Magnesium, however, is the metallic ion least likely to be removed by EDTA.<sup>1</sup> Virtually all of the metals chelated by EDTA are excreted in the urine within 24 hours. In the case of calcium, 28% is excreted during the infusion, 60% in the 6 hours following the infusion, and the remainder between 6 and 12 hours<sup>55</sup> after. Among the metals chelated by disodium EDTA are copper and iron. Both of these metals have an important role in oxidative state and generally exist in an intracellular compartment or protein-bound. However, there is an important, non-protein bound component that may be chelated by EDTA salts. EDTA salts may promote the excretion of up to 10 mg/day of iron and increase urinary copper by almost 140%.<sup>56</sup>

EDTA is approved by the FDA for the treatment of lead poisoning and is also used to treat hypercalcemia. In both these patient groups, there is a higher probability of renal toxicity independent of the therapy. While the doses are similar, the treatment regimens for lead toxicity and hypercalcemia are for five days whereas for TACT, chelation therapy is administered once weekly. In Appendix 3, we present the EDTA dosing regimen and renal adjustments for lead toxicity, hypercalcemia in TACT.

#### 6.2.1.1 Animal toxicity

Animal data on disodium EDTA were reported prior to US marketing. The LD<sub>50</sub> varied from 500 to 7000 mg/kg/day, depending on the species, route, and mode of administration.<sup>57</sup> Early toxicology detected that rapid administration could dangerously lower calcium levels. In animals, the rapid induction of severe hypocalcemia could result in tetany, seizures, and death.<sup>52</sup> However, within a decade of the introduction of EDTA for human use, it became accepted that infusion rates below 20mg/min would not produce symptomatic hypocalcemia.<sup>57</sup> A maximum infusion rate of 17mg/min will be used in TACT.



## **6.2.1.2 Specific Human Toxicities**

### **6.2.1.2.1 Renal toxicity**

The most important potential adverse event from administration of salts of EDTA is renal toxicity. Holland<sup>58</sup> in 1953 described 5 patients treated with very large, rapidly administered doses of EDTA for hypercalcemia of malignancy. For example, one patient received 20g EDTA over 15 minutes. One patient died directly as a result of the infusion, and 2 others had some degeneration of renal cells. Overall, the reports of nephrotoxicity mostly focus on EDTA treatment for hypercalcemia or lead intoxication, conditions with independent reasons for renal failure. Indeed, Doolan<sup>59</sup> and Foreman<sup>60</sup> found that nephrotoxicity required the administration of 300-500 mg/kg/day for 10 days and 203mg/kg/day for 16 days, respectively – doses far higher than will be used in TACT. Recommended doses of EDTA have been associated with nephrotoxicity in certain cases. However, like in the case reported by Oliver,<sup>61</sup> the development of renal failure was made more likely by the presence of underlying renal disease (baseline creatinine of 2.1 – too high for TACT), and daily administration of EDTA over 4 weeks with breaks only on weekends, in contrast to the TACT infusion regimen, which occurs once weekly. Meltzer<sup>62</sup> et al reported 2000 infusions given on alternate days over 2-years in 81 patients without a single case of nephrotoxicity. McDonagh<sup>63</sup> et al (as cited in Rozema) reported that among 383 patients treated with 10 infusions, 50% demonstrated an improvement in creatinine, while 34% a mild rise.

In summary, EDTA can be a nephrotoxic agent, especially in cases of lead poisoning, or in conjunction with other chelating agents, and in the setting of high doses and frequent administration. When administered on a weekly schedule, with intermittent monitoring of creatinine leading to dose adjustment, the rate of renal adverse events is expected to be very low. This is supported by the benign course of creatinine levels of patients receiving chelation therapy in the PATCH randomized trial (Table 2).



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In TACT, renal function is measured 10 times during the infusion phase, and dipstick urinalysis is recorded 4 times. The dose of EDTA is adjusted based on creatinine clearance, and stopping for a doubling of creatinine or exceeding a creatinine of 2.5 mg/dl is built in to the clinical and pharmacy protocols.

#### **6.2.1.2.2 Hypocalcemia**

**Immediate:** Rapid infusions of EDTA can cause tetany, seizures, and death. Thus, careful attention to the TACT infusion regimen so as not to exceed 166 cc/ hour is mandatory. Clinical sites will be required to have infusions of intravenous calcium gluconate available and will be trained in recognizing and treating hypocalcemia.

**Long-term:** The mobilization from bones is thought to be due to pulsatile lowering of calcium stimulating the parathyroid to release parathormone thus pulling calcium out of the bones. The kidneys respond by releasing phosphorus and thus stabilize the calcium/phosphorus ratio. Because the release of parathormone is pulsatile, an increase, rather than decrease, of new bone formation occurs<sup>1</sup>. Osteoporosis has been monitored in patients undergoing chelation therapy. In one study of 61 patients (38 women), bone densitometry was performed before and after EDTA chelation therapy. They noted no decrease in actual bone density levels and a slight, though non-significant increase. They noted no gender differences.<sup>65</sup>

#### **6.2.1.2.3 Hypoglycemia**

All preparations of EDTA may cause hypoglycemia in insulin-requiring diabetics. It is unclear if this is due to an effect on the absorption of the exogenously-administered insulin, or to an effect on glucose



tolerance.<sup>66</sup> Nonetheless, the study protocol calls for diabetics on insulin to snack before the infusion, and for study sites to be able to recognize symptoms of hypoglycemia and have oral and intravenous glucose supplements available for use if necessary. Hypoglycemia has not been observed in the PACT. If hypoglycemia occurs during or after infusions despite compliance with the advice to snack before infusions, diabetics will be requested to reduce the dose of their morning insulin by 50% on infusion days, and their primary physician will be notified.

#### **6.2.1.2.4 Hypotension**

A fall in systolic blood pressure >20mmHg may rarely be observed. Meltzer reported it during 33 of 2000 infusions (1.75%). In PACT, during 1 out of 395 infusions, a patient experienced transient hypotension, which resolved within 15 minutes. This did not recur in the same patient during subsequent infusions and was not experienced by any of the other patients (Table 6).

#### **6.2.1.2.5 Trace metal and vitamin deficiency syndromes**

The principal B-vitamin deficiency syndrome reported has been related to skin rashes and glossitis, and has been responsive to repletion of pyridoxine. The TACT infusion regimen and the supplements taken by all participants include pyridoxine supplements. Zinc excretion has been found to increase more than 20-fold following EDTA chelation. Despite the absence of clear evidence that a zinc-deficiency syndrome exists in association with chelation therapy, the current recommendations are for zinc supplementation, as is being done in TACT.

#### **6.2.1.2.6 Local venous symptoms**

Local symptoms are common in patients receiving multiple infusions. In TACT, patients are ineligible if they do not have venous access. In addition, a small dose of heparin is added to the infusion to prevent phlebitis. Finally, magnesium is added to the infusion to decrease the discomfort. These techniques have proven successful in maintaining the blind in the PACT.

#### **6.2.1.2.7 Clotting parameters**

There are reports that EDTA prolongs platelet aggregation in the presence of thrombin.<sup>67</sup> The present recommended chelation regimen calls for 2500 units of unfractionated heparin with each infusion. As heparin can cause thrombocytopenia, the principal safety parameter to be followed will be platelet count. Heparin will be omitted from the infusion if the platelet count falls below 100,000, or decreases by 50% from baseline.

#### **6.2.1.2.8 Febrile episodes**

A flu-like syndrome was reported as occurring with EDTA chelation in the 1950s. However, this has become a rare phenomenon at present. The TACT investigators and coordinators will monitor for and report this syndrome.



#### **6.2.1.2.9 ECG changes**

Soffer<sup>68</sup> et al report that disodium EDTA infusions suppressed ectopic ventricular beats and ventricular tachycardia, slowed sinoatrial node discharge, enhanced AV nodal automaticity, and increased the automaticity of ventricular foci during complete heart block. Some investigators have reported T-wave changes, and still others increased heart rate without T wave changes. PACT did not detect significant changes in heart rate/pulse as is reported below (Table 3).

#### **6.2.1.2.10 Heart Failure (HF) / Fluid Overload**

Fluid overload leading to HF is occasionally reported in chelation patients, particularly those with a prior history of HF. In PACT, one patient developed atrial fibrillation with a slow ventricular rate, and, secondarily, heart failure.

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#### 6.2.1.2.10 Pregnancy

A reproduction study was performed in rats at doses up to 13 times the human dose and revealed evidence of impaired fertility or harm to the fetus due to EDTA. Another reproduction study performed in rats at doses up to about 25 to 40 times the human dose revealed evidence of fetal malformations, which were prevented by simultaneous supplementation of dietary zinc. There are, however, no adequate and well-controlled studies in pregnant women. Because female study participants will be post-menopausal, pregnancy will not be a problem.

#### 6.2.1.2.11 Miscellaneous

There are a series of miscellaneous symptoms and laboratory abnormalities that have been reported. These include: tremors, headache, numbness, tingling, cheilosis, nausea, vomiting, anorexia, excessive thirst, mild increases in ALT and AST, histamine-like reactions (sneezing, nasal congestion, urticaria), rash, transient bone marrow depression, anemia. These reactions are generally both unusual and mild, and will be monitored by laboratory exams and by clinical history.

#### 6.2.1.3 Reports of Human Toxicities in PACT

PACT has enabled us to examine the occurrence of potential toxicities via collection of numerous safety data that demonstrate stability of renal, electrolyte, calcium, and hematologic parameters. Data collected show little change in laboratory values over 14 infusions (see Tables 4, 5, and 6). Of note, similar to our findings in PACT, PATCH, the Canadian pilot study of chelation in patients with angina, safety data showed that creatinine remained stable over the course of 33 infusions (refer to Table 2). In PACT, only 1 patient was found to have a significant increase in AST and ALT (See Table for a list of adverse events in PACT).

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proprietary information

#### **6.2.1.4 Reports of Human Toxicity in Randomized Trials**

In the randomized trials, the laboratory data are collected in an unbiased and blinded fashion and are available for three of the four published trials. In the Guldager study,<sup>45</sup> adverse event data were reported on the 153 randomized patients. In PATCH, with the cooperation of the investigators, we have secured further unpublished laboratory data on creatinine for their 84 randomized patients. Finally, in PACT, we have unblinded the data for the 30 patients who have undergone chelation therapy. In the van Rij study,<sup>46</sup> adverse events were not reported.



In these three randomized trials, as shown in Table 8, the data on adverse event are reassuring for worsening angina, vascular events, cardiac arrhythmia, fatigue/faintness, GI symptoms, hematologic abnormalities, renal insufficiency, phlebitis at the infusion site, hypocalcemia, pain, and other miscellaneous reported events.

Based on these data, and understanding that the randomized trials evidence is most reliable, we expect a low rate of adverse events and an overall safe intervention.

Table 8  
Peer Reviewed Literature: Adverse Events in Randomized Trials of Chelation for CVD

Author (citation)	Sample Size	Entry Criteria	Endpoints	Adverse Events										
				Worsening angina	Vascular event	Cardiac Arrhythmia	Fatigue/ faintness	GI symptoms	Hematologic Abnormalities	Renal Insufficiency	Phlebitis at infusion site	hypocalcemia	Pain	Other
Guldager B, et al Journ of Int Med 1992;231:261- 267.	153	intermittent claudication	pain-free walking, ABI		stroke 1 chelation		23 chelation, 12 placebo	11 chelation, 7 placebo		7 chelation, 9 placebo	35 chelation, 28 placebo	6 chelation, 2 placebo	headache 1 chelation	1 chelation - dermatitis
PATCH Knudsen ML et al JAMA 2002;287(4):481-	84	proven CAD	ischemia by ECG	9 chelation, 6 placebo	MI 1 chelation, MI 1 placebo			1 placebo		1 chelation			lower back 1 placebo	1 placebo - gout
unpublished														

No adverse events reported:  
van Rij AM, et al Circ 1994;90:1194-1199.



### **6.2.1.5 Reports of Human Toxicity in Case Reports and Case Series**

The peer-reviewed literature includes case series and case reports of chelation therapy for CVD as well as for lead poisoning for which EDTA was approved by the FDA. These studies are listed in the Appendix 4. Adverse events were not reported for many of the case series and case reports. Furthermore, the interpretability is limited by the design as well as the lack of standardized protocols and uniformity of patient entry criteria.

### **6.2.2 EDTA: Placebo**

The placebo infusion will consist of a 563cc infusion of 0.9N NaCl, and 1.2% dextrose.

### **6.2.3 Oral Vitamin and Mineral Supplementation and Placebos**

TACT will test the independent benefits of these supplements in a 2X2 factorial design, including two categories of supplements referred to as high-dose and low-dose. If both chelation therapy, as well as vitamin and mineral supplementation therapy, are beneficial, this design alone will permit the estimation of the contribution of each to the overall effect. It is also possible that vitamin and mineral supplementation will be beneficial and that the result for chelation therapy will be null.

To assess whether to use low-dose vitamins and mineral supplementation, high-dose vitamins and mineral supplementation, both active agents, as adjuncts to active chelation therapy or its placebo, we conducted a modified-Delphi process leading to consensus recommendations, over the past three years, with numerous meetings that included face-to-face meetings, teleconferencing, and emails, with the most prominent experts in chelation therapy. All of these experts are past or present officials in ACAM and the RFA had requested that the ACAM protocol be used. This included Drs. Elmer Cranton, Martin Dayton, Ron Hoffman, Alan Magaziner, and Ralph Miranda. While the totality of evidence on vitamin and mineral supplementation supports their safety even in high doses, there is little support for their clinical benefits on CVD.<sup>69</sup> Nonetheless, the experts in chelation therapy were unanimous in their beliefs that vitamins and minerals supplementation in low-doses were a necessity and higher doses may be even more beneficial. Further, they had definite ideas about the doses and constituents of the vitamins and minerals which needed to be used in TACT based on the ACAM protocol. In fact, the proposed regimens for TACT are modifications based on the published recommendation<sup>50</sup> (see Appendix 5). Finally, NCCAM has gone on record stating that there may be times when they support clinical investigation of treatments in widespread public use even before basic mechanisms are understood.

All patients will receive the low-dose regimen that repletes any chelation-related losses. Patients assigned to the high-dose regimen will receive the high-dose vitamin and mineral supplements listed below. Patients assigned to the low-dose regimen will receive matching placebos for the high-dose regimen tablets. The low-dose regimen includes 1 pill containing the following ingredients in an olive oil base, to be taken once daily:

P 38 withheld in entirety  
"proprietary info"



proprietary info

#### 6.2.4 Blinding the Treatment Groups

Fortunately, the chelation solution cannot be supplied mixed to the sites. Neither EDTA nor ascorbic acid are thought to be stable if shipped mixed with the other components of the chelation solution, nor are they thought to be stable if shipped mixed with each other only. The shipped and refrigerated pack will contain an ascorbic acid syringe (or ascorbic acid placebo if the patient is assigned to the placebo arm), one syringe with EDTA (or EDTA placebo if the patient is assigned to the placebo arm), and a bag for intravenous infusion with all the other components mixed (or a bag containing only normal saline if the patient is assigned to the placebo arm). EDTA in solution is clear and of a viscosity indistinguishable by clinical staff from that of water. Thus, the placebo-EDTA syringe will contain normal saline. Blinding the ascorbic acid syringe is more challenging. The ascorbic acid solution is a pale yellow color, which, upon mixing (14ml of ascorbic acid solution in 100ml) becomes indistinguishable from the clear saline placebo solution. In addition, ascorbic acid, at the concentration provided by the manufacturer, is viscous and provides resistance to transfer into the infusion bag through a 21-gauge needle. The blinded solution has to take into account color and viscosity. The pharmacy team has tested different concentrations of glucose and has found that the resistance to transfer through a 21-gauge needle of 5 mL of 50% dextrose mixed with 9 mL of normal saline is indistinguishable by clinical personnel from that of the ascorbic acid concentration that will be used. Blinding the pale yellow color of ascorbic acid is likewise challenging. The syringes containing ascorbic acid or ascorbic acid-placebo will be covered in translucent yellow adhesive tape, thereby obscuring the different colors of the syringe solutions, but permitting visualization of syringe contents. At the time of infusion, the contents of the syringe are injected into the infusion bag by the Site Coordinator. The ascorbic acid is so pale that there is no discernible yellow "puff" as it enters the bag, and the blind therefore is preserved. The Site Coordinator will then administer the infusion, not knowing whether it is chelation solution, or control solution, and the double blind will be preserved. This procedure has been piloted successfully. Regarding blinding procedures for the vitamins and mineral supplements, placebo and active treatment groups will take identical-appearing tablets and capsules.

#### 6.2.5 Treatment Schedule

The treatment schedule recommended by ACAM includes 30 weekly infusions, plus 10 maintenance infusions, for a total of 40 infusions. The schedule of the maintenance infusions is flexible, and may vary as slowly as every 8 weeks for patients randomized early in the trial (total time for scheduled infusions = 110 weeks). TACT projects that the last patient will be randomized 1.5 years (78 weeks) before study close-out. In this case, the 10 maintenance infusions will be administered over 48



weeks, on an every 5-week schedule. The DCC will provide an infusion schedule for each patient upon randomization.

### **6.2.6 Concomitant Surgical and Medical Therapies**

All surgical and medical therapies will be at the discretion of the responsible health care providers. Nonetheless, procedures will be implemented to comply with the TACT protocol and to ensure that TACT participants are afforded the same quality of care that is given in other NIH funded trials.

#### **6.2.6.1 Surgical Therapies**

Health care providers will be informed that patients will be randomized only if there is no planned revascularization procedure. After randomization, all procedures or surgical therapies will be at the discretion of the health care provider.

#### **6.2.6.2 Medical Therapies**

Health care providers will be informed that patients should forego all non-trial chelation, vitamin, and mineral supplementation. Health care providers will be given the most up to date guidelines for medical management of post-MI patients including statins, aspirin, beta-blockers, and ACE inhibitors. To enhance the use of these therapies of proven benefit the following procedures will be instituted:

- 1] Prior to site selection, clinical site Principal Investigators will be asked to commit to closely following prevailing guidelines for post-MI therapy. Sites unable to do so will not be selected as clinical sites for the study.
- 2] The DCC will monitor study-wide and site-specific rates of use of indicated therapies (aspirin, beta adrenergic blocking agents, statins, and angiotensin converting enzyme inhibitors).
- 3] Sites will receive a quarterly "Report Card" of their use of indicated therapies.
- 4] Sites that fall below the latest reported NRMIs [<http://www.nrmi.org/index.html>] incidences will be contacted by the CCC to determine reasons for non-compliance with evidence-based therapies.
- 5] Sites with continued non-compliance with indicated, evidence-based post-MI therapy and no valid reasons for such will be discussed in the Steering Committee. Possible actions range from enhanced educational efforts to suspension from future patient accrual. In all cases they will be obligated to continue infusing and following randomized patients.

Appendix 6 includes the guidelines to be distributed to all health care providers.

### **6.2.7 Overview of Data Collection During Infusion and Follow-up**

The table below illustrates the TACT data collection points. Methods for collecting data include clinical/physical examinations, laboratory tests, chart reviews, and patient interviews.



DATA COLLECTION POINTS	Screen- ing Visit	Infusion Visit (Visit #s 1-30; Weekly Visits)	Infusion Visit (Visit #s 31-39; Bi- monthly Visits)	Final Infusion (Visit # 40; at 28 months)	Follow-up Clinic Visit (1 Visit per Year, 28 months to closeout)	Follow-up Telephone Call (3 per year, 28 months to closeout)	Closeout Clinic Visit
<b>Assessments</b>							
Consent	✓						
Infusion		✓	✓	✓			
Clinical History	✓						
Physical Exam	✓						
Limited Physical Exam Including Cardio- Pulmonary Assessment		✓	✓	✓	✓		✓
Infusion Vitals (one per hour: pre, during, and post infusion)		✓	✓	✓			
Adverse Event & Endpoint Assessment		✓	✓	✓	✓	✓	✓
Inflammatory Markers		At visit #s: 1, 30, & 40					
Phlebotomy/Labs	✓	At visit #s: 1, 2, 5, 10, 15, 20, 25, & 30	At visit # 36	✓			
EQOL Questionnaire	✓	Visit # 21	Visit #s 32 and 38 (at 12 & 24 month marks, respectively)				





### 6.2.8 Infusion Visits

As mentioned previously, patients will receive a total of 40 infusions. The initial infusion will be preceded by the evaluation described in section 6.1.4. Each infusion encounter will be preceded by a brief interview about adverse events and endpoints, with a specific emphasis on cardiac symptoms and clinical events, including hospitalizations. Vital signs and a brief cardiopulmonary exam will be measured before, once during, and after the infusion. Clinical staff will be supervising the infusions, and a physician will respond quickly to clinical events. Any symptoms occurring during the infusions will be elicited and recorded on the CRF. Scheduled labs will be drawn prior to the beginning of the infusion. Safety labs, consisting of CBC, platelet count, creatinine, glucose, magnesium, and calcium will be drawn at baseline, and 9 additional times during the infusion regimen; immediately preceding infusions 2, 5, 10, 15, 20, 25, 30, 36, and 40.

### 6.2.9 Safety of the Interventions

Safety monitoring will be an important part of the thorough evaluation of the treatment interventions. The following parameters will be tracked based on laboratory monitoring:

- **Kidney.** The primary measure of renal function will be serum creatinine. Specifically we will assess both the proportion of patients as well as the time to achieve a doubling of the creatinine from baseline or increase to a level of 2.5 mg/dL, whichever is lower. We will also look for signs of hematuria and/or proteinuria, which will prompt further evaluation, using urine dipstick.
- **Liver.** With respect to liver function, both the proportion of patients as well as the time to achieve a doubling of the ALT, AST, alkaline phosphatase or bilirubin will be assessed.
- **Hematology.** With respect to hematologic parameters, the development of thrombocytopenia to below 100,000 platelets, or a 50% decrease from baseline will be tracked; and the development of either a reduction in total white cell count or neutrophils to below the normal limit will be tracked. Specifically we will assess both the proportion of patients as well as the time to development of a hematologic abnormality.

TACT study leaders request that patients with the special disease characteristics of hypertension and diabetes adhere to the following recommendations:

#### 6.2.9.1 Patients with Hypertension:

Hypertensive patients should hold both alpha and beta blocking medications the morning of the infusion, and take them after the infusion. A list of common alpha and beta blockers is contained in the Manual of Operations.

#### 6.2.9.2. Patients with Diabetes on Insulin Therapy:

Diabetics on insulin therapy should eat a full breakfast prior to the infusion. In case the patient has forgotten to do so, the clinical site will request the patient have a meal before starting the infusion. Although the risk of hypoglycemia is thought to be small, clinical sites will be trained to recognize symptoms of hypoglycemia, and sites will be required to have dipsticks for rapid measurement of blood glucose in case of symptoms of hypoglycemia. Sites will also be required to have available both oral and intravenous



glucose supplements to treat hypoglycemia. The treatment of hypoglycemia will be reviewed

### **6.2.10 Routine Visits**

Following the infusion phase, patients will have contact with the clinical site 4 times yearly at 3-month intervals. Three of the contacts will be by telephone. During the telephone contacts, patients will be asked whether they have had hospitalizations for cardiovascular or other diagnoses since the last contact. If so, appropriate information will be collected to allow ascertainment of the clinical diagnosis that led to the hospitalization. Additionally, contact information for the patient and next-of-kin will be updated. Once yearly, and at the closeout visit, patients will be seen at the clinical site. The yearly visits and the closeout visit will consist of an interval history designed to capture clinical events.

### **6.2.11 Maintaining High Compliance and High Follow-up**

Maintaining high compliance with the TACT protocol, and high follow-up throughout the duration of the clinical trial, are crucial steps for ensuring validity of results. Hence, TACT requires strong leadership from the Site Coordinators at each clinical site. To assist sites in carrying out compliance and follow-up activities, training on recruitment, retention, and compliance will be offered to Site Coordinators in a variety of formats, including training sessions offered during TACT study meetings, frequent telephone sessions with the CCC and DCC, web-based training applications, and other training modalities.

To assist with the issue of compliance more directly, the DCC will conduct site-visits to the infusion sites as part of their larger, clinical site-visit process. To assist in the identification of sites for review, each clinical site will be required to specify both the clinical and infusion sites prior to receiving final approval to enroll patients. The role of the DCC in monitoring compliance includes:

- 1) Carefully monitoring drop-out rate from the infusion arm throughout the course of the trial.
- 2) Carefully monitoring drop-out rate from the oral supplement arm throughout the course of the trial.
- 3) Carefully monitoring pill counts as reported by sites, both for the low-dose as well as the high-dose regimens.

## **6.3 Reporting of Clinical Events**

Whenever a clinical event occurs that is a component of the primary endpoint or of the secondary clinical endpoints, the clinical site is responsible for notifying the DCC within 24 hours of discovery via the electronic data capture system. Final, complete clinical data will be entered on the appropriate electronic data collection form. Hardcopies of original clinical data will be sent to the DCC, including copies of medical and laboratory records and ECGs for review by the blinded Clinical Events Committee (CEC). In all cases the patient name will be masked and replaced with the TACT ID number prior to transmission to the DCC.



## 6.4 Safety and Other Laboratory Monitoring

In TACT, one responsibility of the DSMB is to monitor the safety of the interventions. Dr. Kerry Lee, PI of the DCC, will continuously monitor the accumulating data for safety and, if necessary, immediately contact the Chair of the DSMB to report any unusual occurrences. Further, since data are presented to the DSMB only a few times a year, we will supplement this aggregated monitoring with procedures at each clinical site to evaluate individual patient tolerance to the treatment interventions. In typical clinical experiences including chelation therapy, laboratory studies are performed prior to beginning chelation therapy, at the fifth treatment, and at each fifth infusion thereafter. In TACT, clinical monitoring for adverse effects with a targeted clinical history will be performed during each visit. Laboratory evaluations for adverse effects for renal, liver, hematologic, and metabolic function will be enhanced by a complete safety profile prior to infusion number 2. Finally, patients that develop abnormalities of renal, liver, hematologic, or metabolic function, will have additional determinations indices of kidney, will be monitored to assure patient safety.

In TACT, the DSMB will have an advisory role to the Steering Committee, NCCAM, and NHLBI. If there emerges any statistically extreme benefit or harm, the DSMB will need to put any such interim data in the context of the totality of evidence. If protocol modifications are to be recommended, the DSMB will consult with the Steering Committee, NCCAM, and NHLBI. A separate DSMB charter that outlines in detail the operating guidelines for the committee and the protocol for evaluation of data will be developed prior to the start of patient randomization and agreed upon in the initial meeting of the DSMB. Minutes of all DSMB meetings will be prepared by the Data Coordinating Center and promptly distributed to the committee members.

In patients whose creatinine doubles from baseline or reaches 2.5 mg/dl,<sup>50</sup> whichever is lower, the following will occur:

- 1) The next infusion will be withheld if the patient is in the weekly infusion phase of the trial.
- 2) Labs will be re-measured prior to scheduling the next infusion 2 weeks later.

With respect to liver function, ALT, AST, alkaline phosphatase or bilirubin > 2 times the upper limit of normal is a relative contraindication to intravenous EDTA. Liver enzymes will be monitored at baseline and twice during the weekly infusion phase. A doubling of liver enzymes will lead to delay of the next scheduled infusion for 2 weeks. Liver enzymes will be re-analyzed, and return of levels to below twice normal confirmed prior to resumption of the treatment schedule. Liver enzymes will then be checked with each infusion for the next 2 infusions.

As regards to hematologic abnormalities, CBC and platelet counts will be monitored. With respect to the CBC, hematocrit, total white cell count and neutrophil count will be monitored. If any of these parameters falls below the lower limit of normal, the site will be notified. A fall of hematocrit, total white cell count or neutrophil count to below the normal range will lead to delay of the next scheduled infusion for 2 weeks. CBC will be analyzed, and return to the normal range confirmed prior to resumption of the treatment schedule. CBC will then be checked with each infusion for the next 2 infusions.



If there is a fall in platelet count below 50% of the baseline platelet count, or to <100,000, infusions will stop for 2 weeks, and the Accu-Care Services Pharmacy will omit heparin from subsequent infusions for that patient. The site will be notified that the platelet count is low. Infusions without heparin will resume after the platelet count has risen to within 20% of the baseline platelet count.

As regards to metabolic functions, serum calcium below 9 mg/dL or glucose below 50 mg/dL shall be deemed a relative contraindication to EDTA. If calcium is low, infusions will be administered over 4-5 hours and calcium will be re-checked. If glucose is low and patients are diabetics that have taken the recommended pre-infusion snack, the dose of morning insulin will be decreased by 50% on the mornings preceding an infusion. Any of the above-mentioned kidney, liver, hematologic, or metabolic abnormalities shall be tracked as adverse events and reported to the DSMB and to the patient.

**Schedule of routine monitoring laboratory examinations to be carried out on all patients; shaded cells represent safety labs.**

	Scre- en	Inf. #1	Inf. #2	Inf. #5	Inf. #10	Inf. #15	Inf. #20	Inf. #25	Inf. #30	Inf. #36	Inf. #40
Creatinine	X		X	X	X	X	X	X	X	X	X
Calcium	X		X	X	X	X	X	X	X	X	X
Hemoglobin	X		X	X	X	X	X	X	X	X	X
Hematocrit	X		X	X	X	X	X	X	X	X	X
ESR/CRP	X		X	X	X	X	X	X	X	X	X
Urea	X		X	X	X	X	X	X	X	X	X
Glucose	X		X	X	X	X	X	X	X	X	X
Iron panel		X							X		
Lipids		X							X		
CRP		X							X		X

## 6.5 Site Monitoring

### 6.5.1 Data Collection and Reporting

The Data Coordinating Center (DCC) will continuously monitor patient recruitment, changes in patient therapy, data submission, and data quality from each clinical site and provide site performance information critical for the management of the trial to the Clinical Coordinating Center on a weekly basis. The DCC will transmit weekly status reports to the CCC. Relevant information from these reports will also be provided to the Economics and Quality of Life Coordinating Center. The weekly reports will contain data regarding overall enrollment, patients randomized during the past week, and any other problems or issues that have come to the attention of the DCC. At the end of each month, the DCC will provide a monthly Delinquency Report. This report will list the number of delinquent forms at each clinical site. DCC personnel will speak with the selected clinical sites with high rates of delinquent electronic and other forms with the assistance of the CCC for follow-up. The DCC will also provide subpopulation-specific information to the CCC. Specifically, every month the DCC will provide reports containing information regarding the randomization and follow-up of women and minorities. In addition, the DCC will produce a listing by center of the proportion of patients enrolled in each of these subpopulations. It is expected that these reports will periodically lead to specific clinical sites being encouraged to recruit more minority patients. Compliance with the patient visit schedule, as



well as compliance with the assigned treatment mode for each relevant subpopulation will be computed and reported to the CCC as well as to the physician investigator at each site.

In addition to the reports outlined above, the DCC will maintain a summary of overall study enrollment and enrollment by individual sites on the TACT web site to ensure that up-to-date enrollment information is always available to study personnel, including project personnel at NCCAM, physician investigators, and Site Coordinators at each clinical site.

### **6.5.2 Site Data Validity Testing**

Numerous checks for consistency of the data, including range and limit checks, will be built into the data entry/data management software and performed automatically. Manual checks of the data also will be performed by DCC staff. After the data have been transferred to the SAS system for statistical summarization and data description, further consistency checking will be performed. Resolution of data problems or discrepant observations will occur through an efficient data query system.

### **6.5.3 Site Visits by DCC**

One of the DCC's monitors will visit each clinical site, including the infusion site, starting relatively early in the patient accrual period to ensure that data collection is proceeding properly, that guidelines for infusions are being observed, and that questions from investigators or coordinators at the clinical sites are appropriately addressed. Priority in sequencing those visits will be given to sites with less clinical trial experience where additional in-service training may be particularly helpful. Each center also will be visited periodically by a trained monitor from the DCC, who will audit data forms of selected patients enrolled since the previous monitoring visit. The monitor will check the accuracy of data recorded on study forms by comparing the information with source documentation in the patient's medical records. In addition they will work with the on-site coordinator and the physician investigator to ensure that any questions regarding the data are clarified and appropriate corrections are made. The monitor will also review each patient's informed consent, verify inclusion/exclusion criteria, and monitor serious adverse events that have been reported. In addition to these multiple levels of data checks, the CEC will conduct an independent and blinded review of the key outcome events.

### **6.5.4 TACT Serious Adverse Event Collection and Reporting Plan**

The following adverse event reporting algorithms are based on and capitalize on the extensive experience of the DCRI Safety Surveillance, and hence have been used in dozens of closely monitored trials.

#### **6.5.4.1 Definitions**

##### **6.5.4.1.1 Adverse Event (AE)**

An adverse event is any undesired, noxious or pathological change in a patient as indicated by signs, symptoms, or laboratory changes that occur in association with the use of trial intervention/medication, whether considered intervention related or not. This definition includes intercurrent illness or injuries, exacerbation of existing conditions, psychological events, psychosocial



events, and adverse events occurring as a result of the study intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporarily associated with the use of an intervention, whether or not considered related to the intervention. Pre-existing conditions, which worsen during a study, are to be considered adverse events. They can become serious adverse events if they fulfil one of the seriousness criteria described below. Note: Diseases, signs, symptoms, and/or laboratory abnormalities already existing at study admission are not considered adverse events when observed during the trial unless they represent an exacerbation in intensity or frequency. (*Definition modified from ICH-E2B*)

#### **6.5.4.1.2 Intensity**

The intensity of an adverse event is an estimate of the relative severity of the experience made by the investigator based on his or her total clinical experience and familiarity with the literature. The maximal intensity reported during the evaluation period should be recorded. The intensity of adverse events will be characterized as mild, moderate or severe as follows:

Mild	Events are usually transient, require no special treatment, and do not interfere with the patient's daily activities.
Moderate	Events usually introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
Severe	Events interrupt a patient's usual daily activity and generally require systemic drug therapy or other treatment.

#### **6.5.4.1.3 Serious Adverse Event (SAE)**

The definition of serious is any adverse event that results in any of the following outcomes:

1. Death
2. Is life-threatening
3. A persistent or significant disability/incapacity,
4. Requires or prolongs hospitalization
5. A congenital anomaly/birth defect
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (*Source CFR: 21 CFR 312.32*)

#### **6.5.4.1.4 Life Threatening**

Life-threatening refers to any adverse event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death. (*Source CFR: 21 CFR 312.32*)



#### **6.5.4.1.5 Requires or Prolongs Hospitalization**

patient must be admitted to the hospital for a period greater than 24 hours, for the hospitalization to be considered a serious adverse event. Elective hospital admissions, scheduled prior to the study, are not considered serious adverse events unless the hospitalization is prolonged. Planned admissions (as part of a study), hospitalizations for less than 24 hours, hospitalization for an elective procedure, and Emergency Room/Department visits are not considered serious adverse events.

#### **6.5.4.1.6 Causality**

Causality can be one of two possibilities:

- .. Associated – There is a reasonable possibility that the adverse event may have been caused by the study intervention
- .. Not Associated – There is not a reasonable possibility that the adverse event may have been caused by the study intervention

Adverse event collection and recording procedures must be designed to meet DSMB review and regulatory submission requirements, and insure drug safety, while not overburdening the study investigators and study budget. Care should be taken to avoid the collection of the voluminous adverse event data with little to no clinical value likely in this patient population.

#### **6.5.4.1.7 Unexpectedness**

“Unexpected” is when the specificity or severity of an AE is not consistent with the applicable product information (e.g., Investigator’s Brochure or risk information described in the investigational plan.) For example: Hepatic necrosis would be unexpected if the investigational brochure or plan only referred to elevated hepatic enzymes or hepatitis.

“Expected” is when the specificity and severity of an AE is consistent with the applicable product information (e.g. Investigator’s Brochure or risk information described in the investigational plan). This term relates only to the drug, not the patient’s underlying condition.

(Adapted from 21 CFR Part 312. 32)

#### **6.5.4.2 Procedures for Investigators for Expedited Reporting of Serious Adverse Events**

All adverse events that occur from initiation of study drug through 30 days post final infusion that result in death or are serious and associated to drug (infusion) therapy are to be reported immediately (within 24 hours) to the DCRI Safety Surveillance Department, which for this trial, will function as an arm of the TACT Data Coordinating Center (DCC). DCRI Safety Surveillance will review the SAE data to verify that all data are complete and follow-up with the site for incomplete data and/or data clarification. This will include ensuring that serious criteria have been met and the SAE data received is reviewed, data based and coded using the MedDRA coding dictionary. The DCRI Medical Monitor will review the data for medical clarity and regulatory reportability.



Safety Surveillance will notify the NIH, Dr. Lamas, and the Data and Safety Monitoring Board (DSMB) chairman of all serious adverse events that result in death and adverse events that are both treatment and drug (infusion) related in a blinded fashion within 1 business day of receipt of the initial notification of the SAE.

DCRI Safety Surveillance will generate a MedWatch form for serious adverse events that are suspected and associated with drug infusion therapy by calendar day 5 for review. Dr. Lee or his designee will notify the FDA by phone or fax of serious, drug related, unexpected adverse events that are life-threatening or result in death within 7 calendar days followed by a written 15 day IND Safety Report. Dr. Lee or his designee will report all other SAEs that are drug related and unexpected to the DCRI written IND Safety Report by calendar day 15.

DCRI will provide Mt. Sinai an Investigator Notification letter by calendar day 13. Mt. Sinai will distribute the letters to the investigators by calendar day 15 of DCRI's initial receipt of the safety Investigator Notification letters will not disclose the treatment group. The Investigator will be responsible for keeping the IRB informed according to local requirements and for notifying study participants of any additional risks. Questions regarding these notifications will be forwarded to DCRI Safety Surveillance.

Adverse event listings, from the clinical database, will be provided to the DSMB chairman on a quarterly basis for review.

Unresolved SAEs will be followed until resolution, stabilization or until the last patient enrolled in the study completes the follow up period. Unresolved SAEs may be closed (final outcome assigned as "resolved") per the discretion of the DCRI Medical Monitor and/or Dr. Lee.

Drug-related serious adverse events must be reported to the site's local IRB/IEC in accordance with the site specific SOP, local IRB/IEC SOP and the local regulations regarding the reporting of adverse events.

#### **6.5.4.2.1 Procedures for enhanced reporting of specific adverse events to DSMB, NCCAM, and NHLBI.**

Specific serious adverse events, not otherwise eligible for expedited SAE reporting as in Section 6.5.4.2, will nonetheless be reported within 2 business days to the DSMB or its designee, and the NCCAM and NHLBI Project Officers. These events would not be eligible for expedited SAE reporting if causality criterion were not met. The adverse events for enhanced scrutiny include:

- 1) Heart failure hospitalization during the weekly infusion phase of the study protocol, not otherwise subject to expedited SAE reporting.
- 2) Following a study infusion, any disposition of the patient to the hospital or emergency room, not otherwise subject to expedited SAE reporting.

Notification of these events will be made electronically.





#### **6.5.4.3 Unmasking Requests from the DSMB and FDA**

Requests from the DSMB and FDA to unmask drug assignments will be forwarded to DCRI Safety Surveillance. DCRI Safety Surveillance will track receipt of the request and forward the request for unmasking information to the trial statistician. The trial statistician (or Dr. Kerry Lee) will provide unmasking information to the DSMB and FDA. These requests will be submitted and handled on a case by case basis.

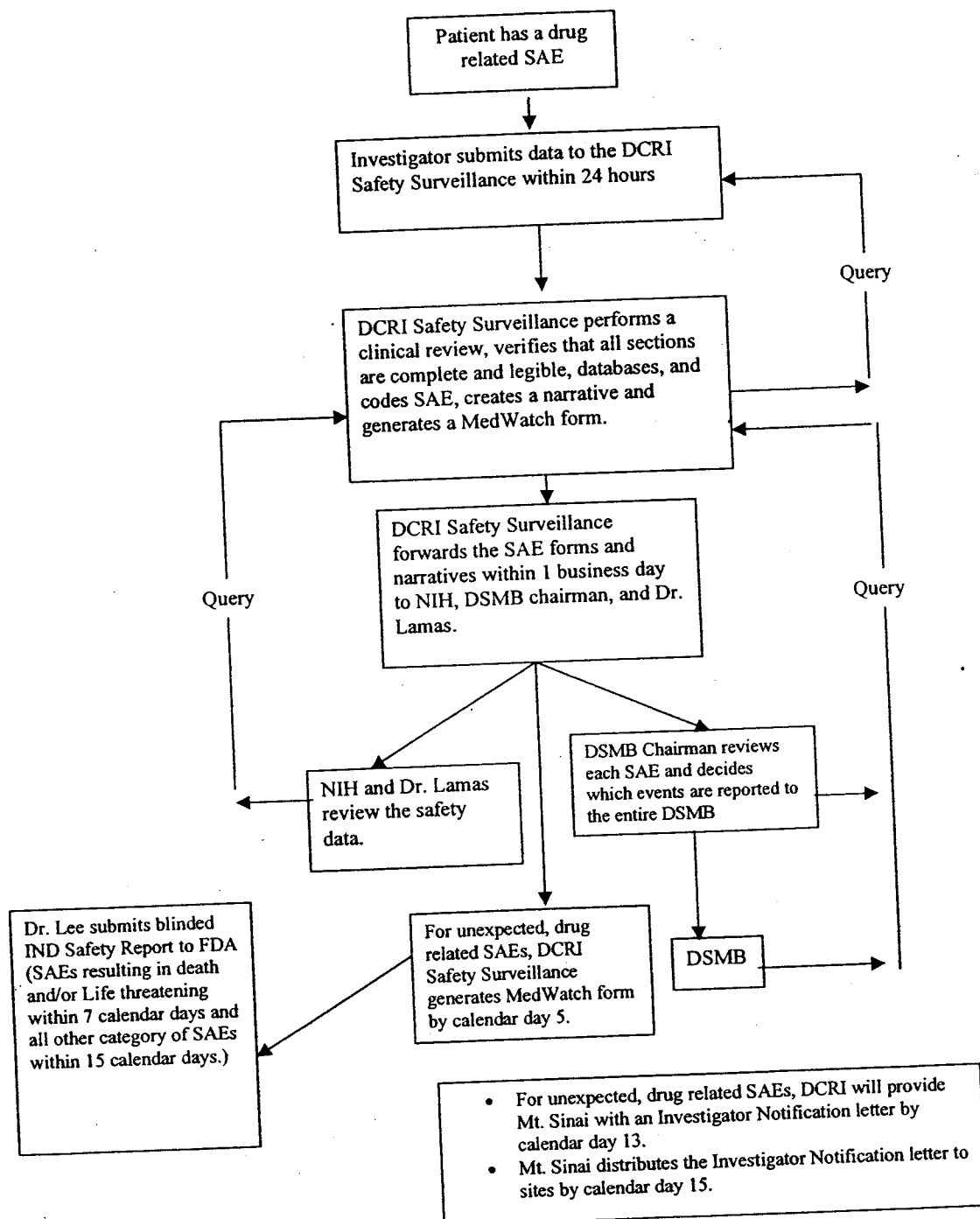
Dr. Lee will provide the FDA with unmasked drug assignments (by patient) once the clinical database is updated and data analysis is completed.

#### **6.5.4.4 Unmasking Requests from the sites to DCRI**

If a clinical site wishes to unmask for an adverse event, the clinical site will contact Dr. Lamas to discuss the clinical details of the case. Following these discussions, Dr. Lamas will contact Dr. Lee to request unmasking of the patient. Possible reasons for unmasking might include, but not be limited to, thrombocytopenia with non-diagnostic HIT antibody titers, or renal toxicity in the presence of or nephrotoxic, but clinically necessary drugs.



### 6.5.4.5 SAE General Process Flow Chart





#### 6.5.4.6 Screening for non-serious adverse events

Non-serious adverse events of interest will be collected on a screening checklist that specifies symptoms by different organ systems, such as gastrointestinal, cardiorespiratory, skin, etc. This data will be collected at multiple points throughout the trial. A by-treatment comparison of these non-serious adverse events will be presented to the DSMB semi-annually for evaluation.

## 7.0 ENDPOINTS

### 7.1 Primary Endpoint

The primary endpoint of this trial is a composite clinical endpoint that includes all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. All randomized patients will be followed until the end of the trial. At each in-person or telephone contact, all patients will be asked about any interval hospitalizations; records for these will be obtained and forwarded to the DCC, then to the CEC. The CEC will adjudicate all deaths as cardiovascular and non-cardiovascular, and all reported non-fatal **vascular events**. All efforts will be made to secure 100% follow-up for hospitalizations as well as the fact and cause of death. Further, at the end of the trial, if there are patients for whom vital status is not obtainable, we will conduct a National Death Index search.

The other components of the primary endpoints include nonfatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for angina. With respect to MIs, silent MIs will not be sought out in this population. However, we will distinguish between Q-wave and non Q-wave MIs. With respect to stroke, persistent neurologic symptoms for more than 24 hours will qualify for stroke diagnosis.

#### 7.1.1 Individual Components of the Primary Endpoint

For each component of the primary endpoint, we will explore the directionality, magnitude, as well as statistical significance of any treatment effects. *A priori*, we hypothesize that any overall treatment benefit (or harm) would be reflected in a similar directionality and magnitude of the individual components of the composite primary endpoint. Any analysis of the components of the primary endpoint must be interpreted with an appreciation that the trial will not have adequate statistical power to test any individual component of the primary endpoint. Further, due to the expertise of the CEC, we will be able to provide information on the cause of cardiovascular death.



## **7.2 Secondary Endpoints**

### **7.2.1 Cardiovascular Death, or Non-Fatal MI or Non-Fatal Stroke.**

This composite secondary endpoint captures serious, irreversible, ischemic events.

### **7.2.2 Subgroup Analyses**

A limited number of pre-specified subgroup analyses of the primary outcome will be performed. These are detailed in Section 1.1 of Appendix 1.

## **8.0 ECONOMIC AND QUALITY (EQOL) OF LIFE DATA**

The philosophy of the TACT proposal includes the integration of economic and quality of life data with the clinical data of each TACT site. Accordingly, relevant baseline economic and quality of life data, including eight scales from the Medical Outcomes Study Short Form (SF-36),<sup>70</sup> the Duke Activity Status Index (DASI),<sup>71</sup> and bed and disability day questions from the National Interview Survey,<sup>72</sup> job class and days lost from work developed for the Bypass Surgery and Revascularization Investigation EQOL Study,<sup>73</sup> and angina symptom status assessment from the Seattle Angina Questionnaire<sup>74</sup> will be collected via a structured interview conducted by the Site Coordinator, prior to randomization. Measurement of utilities by the EuroQol<sup>75</sup> also will be included during this baseline interview. All of these data will be repeated on a random subset of 1,000 patients by telephone interviewer staff from the EQOL Coordinating Center. Medical resource consumption data will be collected on clinical case report forms during infusions and follow-up. These data will be supplemented by the New York Heart Association (NYHA) congestive heart failure class and the Canadian Cardiovascular Society Class for angina. As part of the integration of EQOL into TACT, the enhanced Internet-based data collection will be used by the Site Coordinators and DCRI EQOL staff.

Details for the EQOL subgroup analysis are presented in Appendix 7.