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Test Drug:	disodium ethylenediaminetetraacetic acid (EDTA)
Title:	Trial to Assess Chelation Therapy (TACT)
Principal Investigator:	Gervasio A. Lamas, MD

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1.0 BACKGROUND

1.1 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. Despite the availability and underutilization of these proven therapies, many patients seek out and receive 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[1] "with no serious adverse effects", but this has not been well-documented. The prevalence of chelation therapy, the many reports of benefit from its proponents, and the cautionary advise of traditional medical organizations have led NCCAM and NHLBI to fund this large-scale 5-year Trial to Assess Chelation Therapy (TACT).

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

1.2 EDTA Chelation Therapy

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

1.2.1 Basic Research

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[3]. 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 urine.[4] EDTA was patented in 1938,[5] 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 the 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.[6] In another series, he described symptomatic improvements for patients with angina pectoris[7]. Supportive data were offered in the form of serial chest radiographs that showed improvement in mitral valve calcification.

An 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[8] 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

called NH4-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 antiatherogenic 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[9] 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.[9]

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

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

(1) $2O^{-\cdot}_2 + 2H^+ \rightarrow H_2O_2 + O_2$
(2) $Fe^{2+} + H_2O_2 \rightarrow HO^{\cdot} + HO^- + Fe^{3+}$

In the presence of additional superoxide anion ($O^{-\cdot}_2$), Fe^{3+} is reduced back to 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.[16] Cell-mediated LDL oxidation also depends on the availability of metal ions.[17]

Some epidemiological evidence shows that increased body stores of iron[18] or copper[19] are associated with increased CAD risk, however, other epidemiological studies have failed to show such a relationship for iron.[20] 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,[21] 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.[22] Furthermore, iron contributes to NFκB activation[23] and to expression of VCAM-1 in endothelial cells.[24] 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.[25]

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.[26] Most case series report on an individual practitioner's clinical practice. Cranton[27] 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**[28] 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[29], 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 Preventics; 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.

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

*Described in text

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

1.2.3 Randomized Trials

Only 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, but we have analyzed safety data of patients in the chelation arm.

The first trial by Guldager et al[45] 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.

Van Rij[46] 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 of 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.

Knudtson and colleagues[47] carried out the Program to Assess Alternative Treatment Strategies to Achieve 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 $\geq$ 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

supplementation 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 PACT," PACT provides reassuring data on blood pressure, pulse, renal, electrolyte, calcium and hematological parameters.

1.3 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 insufficient 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.[1] 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).

All 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.

2.0 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:

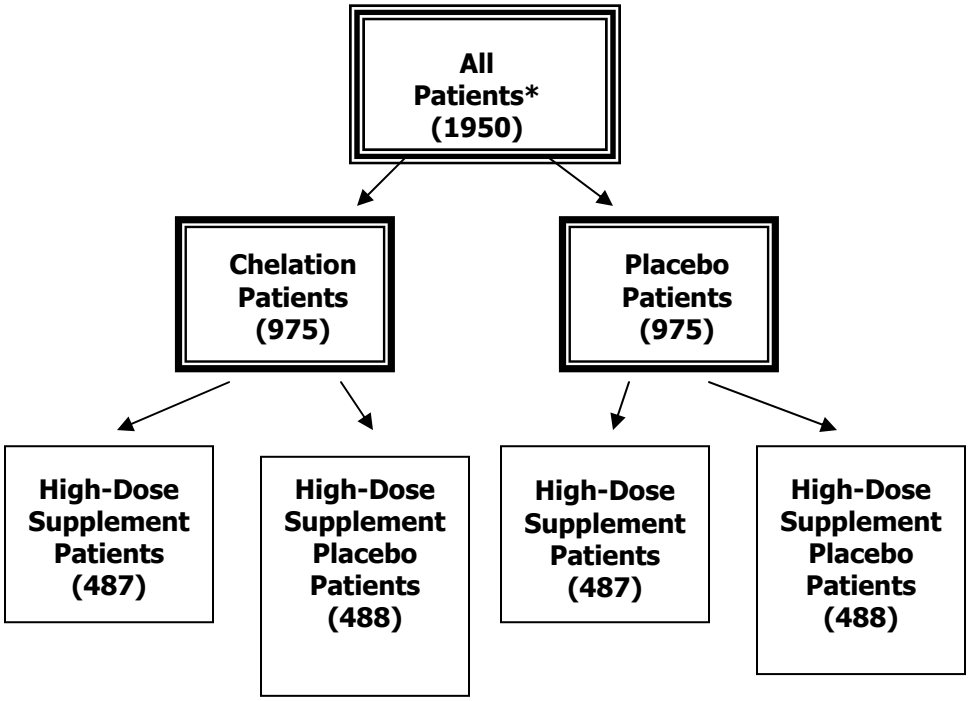
- To determine whether chelation or high-dose supplements improve quality of life;
- To conduct an economic analysis of chelation therapy and high dose supplements.

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 1950 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 infusions administered 2 –6 weeks apart. Following the infusions, patients will continue high-dose vitamin supplements and be contacted quarterly until 60 months of participation or the end of the study. All patients will receive low-dose supplementation to replete chelation losses during the infusion period only. In this 2x2 factorial design, each of these groups also will be randomized to either high-dose supplements or high-dose supplement placebos as shown in diagram below. This factorial design will permit the estimation of the contribution of high-dose supplementation 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.



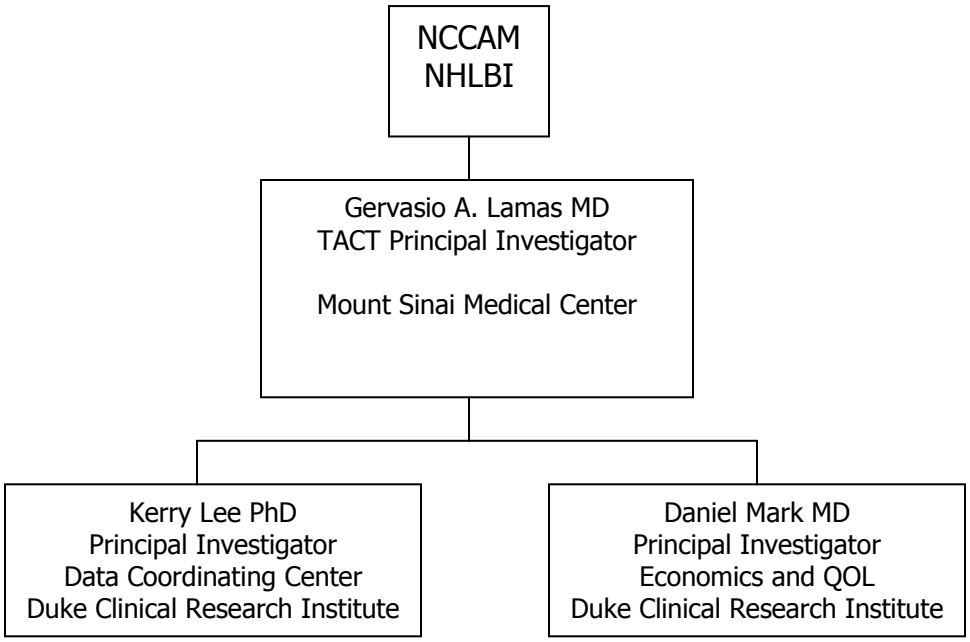
*All patients will receive low-dose supplementation during the infusion period only.

3.0 OVERVIEW OF THE TRIAL ORGANIZATION

3.1 TACT Organizational Units

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

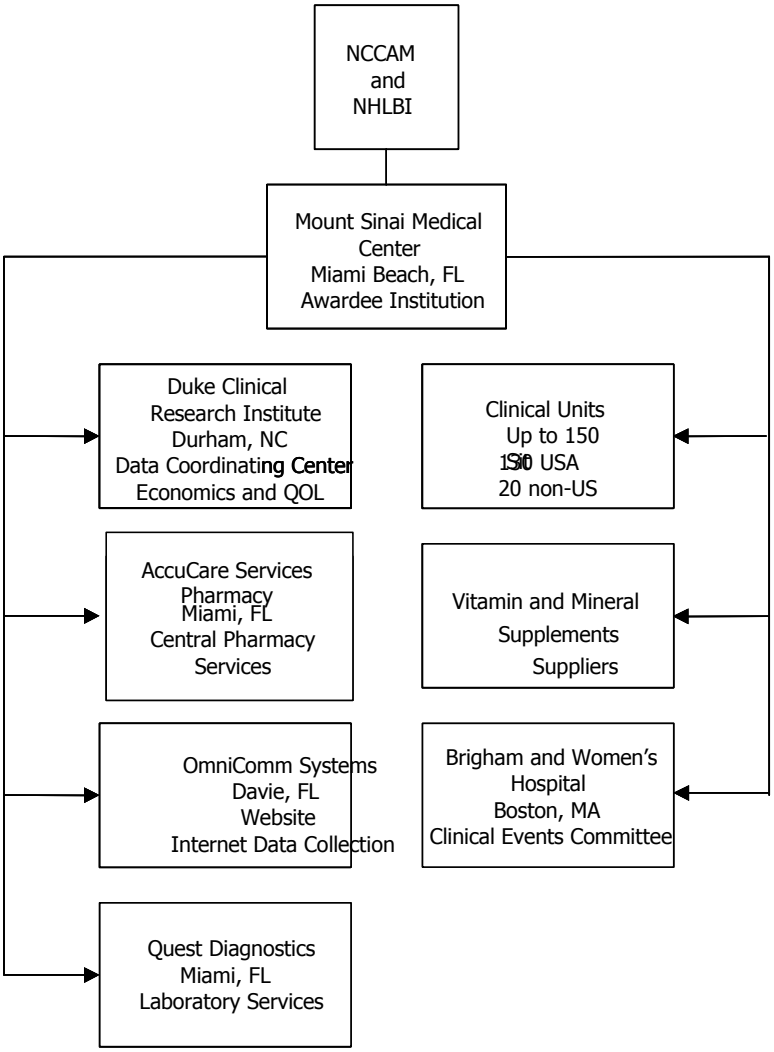
Figure 1



3.2 Contractual Relationships

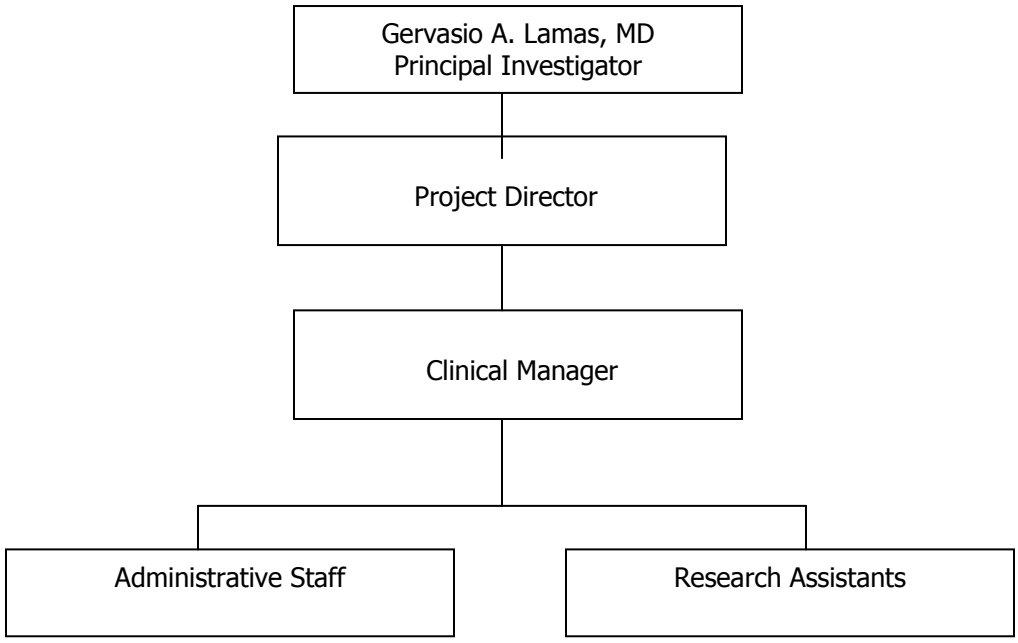
Organizations that will conduct various TACT activities, under contract with the Clinical Coordinating Center:

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. Two Chelation Consultants, a Project Director, and Study Staff, including consultants, will assist Dr. Lamas in coordinating TACT. Dr. Lamas will submit quarterly detailed recruitment reports to the NCCAM Project Officer and the NHLBI Project Officer. Trial progress reports will be given during TACT Operations meetings. 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. In order to preserve the blinded nature of the trial, two physician Research Associates have been identified who are not directly involved with the day-to-day coordination and administration of the CCC. These Research Associates will approve all prescriptions and deal with any items brought up by pharmacy that may require unblinding information. The Research Associates will not have any role in clinical patient management and recruitment at Mt. Sinai Medical Center or other clinical units. Prior to beginning this position in TACT, the Research Associates will undergo protocol training.

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.

3.4 Data Coordinating Center

The Data Coordinating Center (DCC, Dr. Kerry Lee) is responsible for the treatment allocations of eligible patients, review and monitoring 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 NIH and 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 TrialMaster®, the electronic data capture system and the internet-based communications network between management and performance sites. The DCC will visit all sites annually during the course of the trial.

3.5 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 900 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.

3.6 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 with sites, CCC, and DCC;
- Adjust accordingly the EDTA dose as calculated by electronic data capture system or via verbal order by Clinical Trial Manager.;
- Identify patients who are not scheduled to receive weekly infusions and coordinate with Clinical Trial Manager if the patient's infusion shipment should be suspended due to entry into maintenance phase, study safety lab delay, missed visit, or other event(s) as identified by Clinical Trial Manager;
- deliver blinded vitamins and supplements or their identical placebos; identify and coordinate

with Clinical Trial Manager if patient's vitamin shipments should be changed due to patient intolerance to vitamin or entry into follow-up phase of study
- 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
- providing the clinical sites with blood collection supplies and pre-printed ordering requisition forms
- collecting the lab specimens from the clinical sites
- processing all labs within 48 hours of drawing (except high sensitivity C-reactive protein)
- 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 up to 150 clinical sites will be sufficient to enroll 1950 eligible patients over 54 months.

Patients	Enrollment (months)	Active sites	pt/site/mo	pt/site
1950	54	130	0.28	15
1950	**54**	**120**	**0.30**	**16**
1950	54	110	0.33	18
1950	54	100	0.36	20

The Site 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. Site Investigators will commit at least 10% effort to this trial. All Site Investigators 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 Site 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;
- High-speed 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 clinical 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 clinical 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. Services for this system, TrialMaster® will be provided by Omnicomm Systems. 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.

Omnicomm Systems will:

- Provide platform for electronic data capture system;
- Adjust programming to enhance data collection and patient monitoring by clinical sites;
- Maintain study's website www.tactnih.com;
- Work with DCC to ensure quality and integrity of *TrialMaster®,* the electronic data capture system and the internet-based communications network.

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 TACT Principal Investigator, the TACT Project Director, the TACT Clinical Manager, the Data Coordinating Center Principal Investigator, The Data Coordinating Center Project Leader, the EQOL Principal Investigator, up to five clinical unit Site Investigators, the NCCAM Program Officer, and the NHLBI Program Officer. The TACT Project Director, Clinical Manager and the Data Coordinating Center Project Leader will be ex-officio, non-voting members. The initial Steering Committee Site Investigator members will be nominated by the TACT Principal Investigator and elected by the Steering Committee to serve terms of 1 year. Site Investigator members of the Steering Committee will be nominated by the TACT Principal Investigator, approved by the members of the Steering Committee, and appointed after NCCAM and NHLBI review. The TACT Principal Investigator will serve as Chairman of the Steering Committee. All major scientific decisions will be determined by the Steering Committee, with the Chairman, the Data Coordinating Center Principal Investigator, the EQOL Principal Investigator, Site Investigators, the NCCAM Program Officer, and the NHLBI Program Officer, having one vote each. This Committee will have primary responsibility for finalizing the trial protocol, and approving the design and implementation of all adjunct studies, facilitating the conduct and monitoring of the clinical trial and adjunct studies, analyzing and interpreting study data, reporting study results, and setting guidelines for authorships. Each Steering Committee member will be expected to participate in all other Steering Committee activities, e.g., conference calls, special subcommittees, and others, as may be necessary.

5.2 Executive Committee

The Executive Committee will be chaired by the TACT Principal Investigator, and additionally composed of the TACT Project Director, the Principal Investigator of the DCC, the Principal Investigator of EQOL, the NCCAM Program Officer, and the NHLBI Program Officer. The Executive Committee will make recommendations to the Steering Committee regarding study conduct. The Executive Committee will meet to monitor study progress and to review non-endpoint data. Executive Committee meetings will be scheduled for the day prior to Steering Committee meetings. Other reports for the Executive Committee may be requested of the Steering Committee as needed. In any votes of the Executive Committee, each member will have a single vote.

5.3 The Clinical Events Committee (CEC)

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

5.4 Operations Committee

The Operations Committee will include the Chairman of the Steering Committee, the Principal Investigator of the DCC (Dr. Lee), the Project Leader of the DCC, the EQOL Principal Investigator, the Clinical Manager, the CCC Project Director, the NCCAM Program Officer, the NHLBI Program Officer, and other study team members as needed. This committee is charged with day-to-day trial

management, including final protocol development and implementation, conduct of the protocol, feasibility (patient burden, site burden, cost), evaluation of resolution of issues raised by the site and core laboratories. One of the two Chelation Consultants will join the conference once monthly. Such calls will ensure smooth day-to-day operations of the trial and help to identify issues that need to be brought before the Steering Committee.

5.5 Data and Safety Monitoring Board

The Directors of NCCAM and NHLBI will appoint an independent Data and Safety Monitoring Board, with input from the TACT Principal Investigator, 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.

5.6 Databank and Ancillary Studies, Presentations, and Publications Committee

This Committee is charged with the timely review of all proposals for data analysis, as well as research abstracts, presentations and manuscripts before submission. The committee will also review proposals for ancillary studies. This Committee will be Chaired by the TACT Principal Investigator, and will include the Project Director, the TACT Clinical Manager, the DCC Principal Investigator, the EQOL Principal Investigator, at least one Chelation Consultant, the NCCAM and NHLBI Program Officers, and 2 Site Investigators, one a cardiologist, and the other a chelation practitioner, to be appointed by the Steering Committee. The Committee will develop operational policies to be reviewed and approved by the Steering Committee.

6.0 RESEARCH DESIGN AND METHODS

6.1 Study Population

6.1.1 Patient Recruitment

TACT will randomize 1950 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(See Appendix 2 for a prototype HIPAA compliant informed consent form).

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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 study 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-scale 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 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 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
- 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 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.
- Extend the study to selected non-US sites.
- Strategies to increase enrollment of US sites have been in effect and will continue vigorously with new enhancements.

Tier 2 – Patient recruitment within established clinical 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.

- 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 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.
- Target increased reimbursement to productive sites by developing an incentive system.
- Host additional study meetings for all approved sites.
- Enhance communication between study leadership and sites.
- Appoint a recruitment and retention subcommittee that includes high performing site investigators and coordinators.
- Establish a study coordinator mentoring program to link experienced coordinators with new or struggling coordinators to accelerate the learning curve of the inexperienced study coordinators.
- Increase participation of site investigators by identifying investigator leaders for each region (to be defined) to include monthly in weekly Operations Committee calls, writing newsletter articles, and presenting proposals for abstracts and publications.

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.

1. Men and postmenopausal women age 50 years and older at time of randomization.

2. Documented myocardial infarction (MI) over 6 weeks prior to randomization. The criteria for MI will be based on the ESC/ACC[48] definition as follows:
Patients meeting either of the following criteria (A, B or C) will qualify:

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.

An additional criterion for the diagnosis of MI, (C), always requires that the Clinical Coordinating Center review the patient history, ECG, and other clinical data, and concur with the enrolling site:

C. Past ischemic symptoms, electrocardiographic abnormalities consistent with myocardial infarction, and corresponding segmental wall motion abnormality or scar on an imaging study.

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. *Patients with known heparin allergy may be enrolled, as heparin will be omitted from the chelation solution.*
- Coronary or carotid revascularization procedure within 6 months prior to randomization.
- 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 3).
- Hospitalization for heart failure within 6 months prior to randomization.
- Stage II hypertension, defined in the JNC6 guidelines as a blood pressure $\geq$160/100.[49] 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/mm.[50]
- History of cigarette smoking within 3 months prior to randomization.
- 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 fluids).
- 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 after randomization (e.g. significant pulmonary disease or malignant cancer or valvular disease). If uncertain contact Clinical Coordinating Center prior to randomizing patient.
- 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 trial 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

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. You must schedule the patient within 30-days of screening labs, since they expire after 30 days. If the patient is unable to receive their first infusion within 30 days, new screening labs must be drawn and the lab results must be reassessed for eligibility. Next, the Site Coordinator will log on to www.tactnih.com and complete the randomization screen in the Trial Master System. 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.

6.2 Treatment Regimens

The chelation solution[50] will be administered for a minimum of 3 hours at an administration rate of 166 cc/hour and total of 500ml of sterile water and the additives listed in the chart below. The high-dose vitamin pills are administered daily from the first infusion visit until end of patient follow-up. 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	To reduce local discomfort and replace losses
100 mg of procaine HCL	To reduce local discomfort
2500 units of heparin	To reduce local phlebitis
7 grams of ascorbate	Anti-oxidant and to achieve isoosmolarity
2 mEq KCl	To replace losses
840 mg sodium bicarbonate	To act as a buffer and reduce discomfort
250mg pantothenic acid	For anti-oxidant properties
100mg of thiamine	For anti-oxidant properties
100mg of pyridoxine	To replace chelation losses
QS with sterile water to 500ml	

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 a reduction in the total EDTA dose infused. The EDTA dosing for each infusion is computed[50] as follows:

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

The 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.

EDTA dose is automatically adjusted by the electronic data capture system based on the most recently calculated creatinine clearance value. If a prescription change for EDTA is required, the pharmacy is automatically notified by the electronic data capture system. The pharmacy will adjust the EDTA for the patient's next scheduled infusion. Each clinical site is responsible for entering into the electronic data capture system their patient's safety lab results. Not entering patient lab data may result in delays for receiving next study infusion.

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:[50]

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

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).

If there is any upward change in creatinine, but not enough to reach the threshold for withholding an infusion, the EDTA content will be adjusted downward according to estimated creatinine clearance.
Serum calcium is corrected by albumin level to generate a corrected calcium value that is an estimation of ionized calcium as follows:

corrected calcium = serum calcium + (0.8 x [normal serum albumin - patient's albumin])

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.[51] 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.[51] Calcium and other chelates 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.[52] Transient but mild reduction of serum calcium can be observed following the slow intravenous infusion of EDTA. 1gm of EDTA can effectively bind approximately 120mg 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.[53,54] Magnesium, however, is the metallic ion least likely to be removed by EDTA.[1] 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[55] 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%.[56]

EDTA (calcium disodium) is approved by the FDA for the treatment of lead poisoning and EDTA (disodium) 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 4, 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_{50} varied from 500 to 7000 mg/kg/day, depending on the species, route, and mode of administration.[57] 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.[52] 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.[57] 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[58] 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[59] and Foreman[60] 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,[61] 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[62] et al reported 2000 infusions given on alternate days over 2-years in 81 patients without a single case of nephrotoxicity. McDonagh[63] 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).

Table 2
Creatinine Levels for PATCH[64]
84 Participants Randomized to Chelation

Infusion #	Creatinine (Mean±SD)
Baseline	0.91 ± 0.19
5	0.90 ± 0.21
10	0.89 ± 0.22
15	0.89 ± 0.21
20	0.91 ± 0.20
25	0.89 ± 0.22
30	0.91 ± 0.21
33	0.91 ± 0.17

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[1]. 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.[65]

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.[66] 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.[67] 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[68] 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.

Table 3
Pulse For PACT
30 Participants Randomized to Chelation

Infusion Number	Pulse (Mean±SD) Pre-Infusion	During Infusion	Post-Infusion
1	64.9 ± 9.3	63.2 ± 8.8	64.2 ± 8.5
2	65.8 ± 10.1	63.3 ± 9.2	63.8 ± 9.0
3	66.8 ± 10.6	64.2 ± 8.7	64.4 ± 8.8
4	68.8 ± 13.5	67.5 ± 13.0	66.5 ± 12.6
5	68.3 ± 10.4	66.6 ± 8.7	66.4 ± 9.0
6	69.0 ± 13.8	65.9 ± 12.6	67.4 ± 12.5
7	67.4 ± 10.6	63.9 ± 9.6	64.0 ± 8.4
8	67.7 ± 8.7	64.3 ± 7.5	65.5 ± 8.0
9	66.7 ± 8.2	63.7 ± 7.0	65.2 ± 8.2
10	67.1 ± 8.1	65.8 ± 6.7	66.0 ± 7.3
11	66.3 ± 8.3	64.0 ± 8.5	65.6 ± 8.4
12	67.5 ± 9.8	64.0 ± 7.3	64.5 ± 8.7
13	65.9 ± 7.8	63.6 ± 8.6	65.0 ± 12.8
14	64.7 ± 8.1	64.7 ± 8.1	63.9 ± 6.2
15	66.3 ± 8.7	65.4 ± 7.8	65.9 ± 9.7

6.2.1.2.11 Pregnancy

One reproduction study was performed in rats at doses up to 13 times the human dose and revealed no 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.

6.2.1.2.12 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, lacrimation), 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 7 for a list of adverse events in PACT).

Table 4
Safety Measurements for PACT
30 Patients Randomized to Chelation

Infusion #	Creatinine	Glucose	Hematocrit	Magnesium	Platelet Count	Potassium
Baseline	1.1 ± 0.2	99.4 ± 34.1	40 ± 8.5	1.9 ± 0.5	203.8 ± 69.3	4.4 ± 0.6
2	1.1 ± 0.2	117.1 ± 34.1	40.7 ± 3.4	1.9 ± 0.5	207.8 ± 57.4	4.4 ± 0.6
5	1.1 ± 0.2	113.7 ± 38.6	40.0 ± 3.8	2.1 ± 0.3	202.8 ± 55.2	4.4 ± 0.6
10	1.0 ± 0.2	109.2 ± 34.8	39.2 ± 3.8	1.8 ± 0.5	201.9 ± 40.0	4.4 ± 0.6
14	1.1 ± 0.2	113.2 ± 36.9	40.0 ± 4.2	2.1 ± 0.3	211.3 ± 47.3	4.6 ± 1.0

Table 5
Initial and Final Safety Measurements For PACT
10 Patients Randomized at MSMC to Chelation

	Calcium		AST		ALT	
Patient #	**Initial**	**Final**	**Initial**	**Final**	**Initial**	**Final**
1	9.5	9.2	-	-	-	-
2	10.4	9.8	27	32	33	35
3	9.4	9.3	-	-	-	-
4	9.3	9.4	17	21	23	24
5	9.7	9.6	27	29	23	25
6	9.0	8.9	20	21	14	19
7	9.2	10	22	66	20	130
8	9.6	9.7	19	22	27	28
9	8.8	8.5	-	-	-	-
10	8.9	8.9	27	22	32	27
Total Mean ±SD	9.38 ± 0.47	9.33 ± 0.47	21.89 ± 4.27	30.42 ± 16.28	24.57 ± 6.70	41.14 ± 39.48

Table 6
Systolic BP For PACT
30 Participants Randomized to Chelation

Infusion Number	Systolic BP (Mean±SD)		
	Pre-Infusion	During Infusion	Post-Infusion
1	126.7 ± 15.8	122.4 ± 15.0	126.4 ± 19.0
2	120.9 ± 15.7	120.9 ± 15.7	121.8 ± 20.0
3	122.8 ± 14.1	114.6 ± 24.4	119.6 ± 17.5
4	125.8 ± 18.0	122.1 ± 15.1	126.2 ± 19.4
5	124.7 ± 19.8	121.8 ± 18.0	121.3 ± 14.5
6	117.2 ± 14.9	119.3 ± 17.3	124.4 ± 18.3
7	117.2 ± 14.2	124.7 ± 20.7	124.9 ± 16.3
8	123.4 ± 18.0	121.5 ± 16.7	124.2 ± 16.2
9	124.5 ± 18.4	121.6 ± 16.8	123.4 ± 19.6
10	123.3 ± 25.6	124.6 ± 25.0	125.5 ± 22.4
11	120.9 ± 19.0	121.3 ± 17.4	121.4 ± 17.9
12	120.4 ± 18.7	115.3 ± 14.1	117.4 ± 12.3
13	123.2 ± 18.4	122.3 ± 18.9	122.7 ± 15.6
14	125.6 ± 17.7	120.4 ± 14.8	119 ± 16.3
15	123.0 ± 16.4	119.4 ± 17.8	121.6 ± 15.6

Table 7
Summary of Adverse Events in PACT

	# of Events
Cessation for doubling of baseline creatinine or rise in creatinine >2.5	0
Fall in platelets below normal range	1
Cessation of heparin	2
Hypocalcemia	0
Hypoglycemia	0
Doubled Liver Enzymes	1
Progressive angina and cardiac catherization	1
AF, Bradycardia, and Heart Failure	1
Bladder Tumor	1
Diverticulitis	1
Hematoma at the site of infusion	1

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,[45] 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,[46] 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 Knudtson 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
PACT (unpublished)	30 Chelation Patients	post myocardial infarction	Endothelial function	1 underwent catheterization		Bradycardia and AF resulting in HF	0		1 thrombo-cytopenia	0		0	1 back pain	1 doubled liver enzymes 1 bladder tumor 1 diverticulitis

Blank=not reported

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 (calcium disodium) was approved by the FDA. These studies are listed in the Appendix 5. 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 500cc infusion of 0.9% 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.[69] 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[50] (see Appendix 6). 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 vitamin and mineral regimen that repletes any chelation-related losses during the infusion period only. The low-dose regimen includes 1 pill containing the following ingredients in an olive oil base, to be taken once daily:

Low-Dose Regimen (Taken once daily)	Amount	% Daily Value
Vitamin B6 (as pyridoxine hydrochloride)	25mg	1250%
Zinc (as zinc gluconate)	25mg	167%
Copper (as copper gluconate)	2mg	100%
Manganese (as manganese gluconate)	15mg	750%
Chromium (as chromium picolinate)	50mcg	42%

Patients assigned to the high-dose regimen will receive the high-dose vitamin and mineral supplements listed below, or high-dose vitamin and mineral placebos. The high dose regimen consists of 3 pills containing the following ingredients, to be taken twice daily during the infusions and the follow-up periods:

High Dose Regimen (Taken Twice Daily)	Total Amount for 6 Pills	% Daily Value
Vitamin A (as fish liver oil and beta-carotene)	25,000 IU	500%
Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)	1,200 mg	2000%
Vitamin D_3 (as cholecalciferol)	100 IU	25%
Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)	400 IU	1333%
Vitamin K_1 (as phytonadione)	60 mcg	75%
Thiamin (vitamin B_1) (as thiamin mononitrate)	100 mg	6667%
Niacin (as niacinamide and niacin)	200 mg	1000%
Vitamin B_6 (as pyridoxine hydrochloride)	50 mg	2500%
Folate (as folic acid)	800 mcg	200%
Vitamin B_{12} (as cyanocobalamin)	100 mcg	1667%
Biotin	300 mcg	100%
Pantothenic acid (as d-calcium pantothenate)	400 mg	4000%
Calcium (as calcium citrate and calcium ascorbate)	500 mg	50%
Iodine (from kelp)	150 mcg	100%
Magnesium (as magnesium aspartate, magnesium ascorbate and magnesium amino acid chelate)	500 mg	125%
Zinc (as zinc amino acid chelate)	20 mg	133%
Selenium (as selenium amino acid chelate)	200 mcg	286%
Copper (as copper amino acid chelate)	2 mg	100%
Manganese (as manganese amino acid chelate)	20 mg	400%
Chromium (as chromium polynicotinate)	200 mcg	167%
Molybdenum (as molybdenum amino acid chelate)	150 mcg	200%

Potassium (as potassium aspartate and potassium ascorbate)	99 mg	3%
Choline (as choline bitartrate)	150 mg	*
Inositol	50 mg	*
PABA (as para-amino benzoic acid)	50 mg	*
Boron (as boron aspartate and boron citrate)	2 mg	*
Vanadium (as vanadyl sulfate)	39 mcg	*
Citrus Bioflavonoids	100 mg	*

* Daily Value not established. Other ingredients: Croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, silicon dioxide.

Compliance with the vitamin components of the study will be monitored by pill count at the site.

6.2.4 Blinding the Treatment Groups

Unfortunately, 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 500ml) becomes indistinguishable from the clear saline placebo solution. In addition, ascorbic acid, in 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 vitamin and mineral supplements, placebo and active treatment groups will take identical-appearing pills 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 occur as slowly as every 8 weeks for patients randomized early in the trial (total time for scheduled

infusions= 110 weeks). The 30 weekly infusions should be scheduled weekly. Interruptions in the first 30 weekly infusion schedule should not be greater than 6 weeks. TACT projects that the last patient will be randomized 16 months (64 weeks) before study close-out. In this case, the 10 maintenance infusions will be administered over 2 – 6 weeks apart. The DCC will provide a visit scheduler to facilitate scheduling infusion visits.

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, Site 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 10% below the overall study median value 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 7 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)	Final Infusion (Visit # 40)	Follow-up Clinic Visit (1 Visit per Year, from last infusion to closeout)	Follow-up Telephone Call (3 per year 3 months after last infusion)	Closeout Clinic Visit (5 years post randomization or by 7/31/09)
Assessments							
Consent	✓						
Infusion		✓	✓	✓			
Clinical History	✓						
Limited Physical Exam Including Cardio-Pulmonary Assessment	✓	✓	✓	✓	✓		✓
Assess patients for angina, heart failure, and dyspnea before and after every infusion.		✓	✓	✓			
Infusion Vitals (pre, during, and post infusion)		✓	✓	✓			
Adverse Event Assessment		✓	✓	✓ *collected through 30 days after final infusion			
Endpoint Assessment		✓	✓	✓	✓	✓	✓
Inflammatory Markers (collected for first 600 patients)		At visit #s: 1, 30,		✓			
Phlebotomy/Labs	✓	At visit #s: 1, 2, 5, 10, 15, 20, 25, & 30	At visit # 36	✓			

DATA COLLECTION POINTS	Screen-ing Visit	Infusion Visit (Visit #s 1-30; Weekly Visits)	Infusion Visit (Visit #s 31-39)	Final Infusion (Visit # 40)	Follow-up Clinic Visit (1 Visit per Year, from last infusion to closeout)	Follow-up Telephone Call (3 per year 3 months after last infusion)	Closeout Clinic Visit (5 years post randomization or by 7/31/09)
Concomitant Medications		At visit #s: 15, 30	At visit #36	✓			
EQOL Questionnaire	✓	Visit # 21 *DCRI to collect	Visit #s 32 and 38 (at 12 & 24 month marks, respectively) *DCRI to Collect at 12 and 24 months post randomization				

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. Assess patients for angina, heart failure, and dyspnea before and after every 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, calcium, LFTs, and urine dip sticks 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. Vitamins are dispensed as needed and unused vitamins supplies are collected at these visits.

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 Study Manual.

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 with the clinical sites at Investigators' Meetings and during training sessions.

6.2.10 Recommended Safety Materials

Clinical Sites should ensure the following safety materials are available during administration of infusions:

- Intravenous dextrose 50%
- Intravenous calcium gluconate or chloride
- Glucometer for measuring glucose levels in symptomatic diabetics (because diabetics on insulin have such devices, SIs and SCs should request their patients bring them to the infusion visits)
- Snacks or juice for empiric treatment of symptoms of hypoglycemia

6.2.11 Follow-up Assessments

Following the infusion phase, patients continue only the high-dose supplement (or placebo) arm. Patients will have contact with the clinical site 4 times yearly (i.e. quarterly) at 3-month intervals. Three of the contacts will be by telephone. During this follow-up phase, supplements are dispensed in a three-month supply to coincide with the quarterly telephone calls and annual visits. Any unused supplements are collected and disposed of by the site according to the site's drug destruction protocol. 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. All patients are followed for up to 32 months following the end of infusions (including patients prematurely discontinuing infusions and/or vitamins) with quarterly follow-up calls and annual clinic visits after the final infusion.

6.2.12 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. Sites should encourage patients to complete all study drug treatments, including infusions and vitamins and discuss any patients considering premature discontinuation with the CCC.

To assist with the issue of compliance, the DCC has regular telephone communication with the sites, reviews their data in the EDC system and conducts site-visits. The DCC carefully monitors the following recruitment, retention and compliance issues:

1) Enrollment rates, minority enrollment, projected vs. actual enrollment;
2) Drop-out rates from the infusion arm;
3) Drop-out rates from the oral supplement arm;
4) Study drug accountability as reported by sites for the infusions, low-dose and high-dose regimens;
5) Use of evidence based medications;
6) Adherence to patient safety requirements.

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 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, Principal Investigator 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. Draft minutes of all DSMB meetings will be prepared by DCC Staff, reviewed by NCCAM and NHLBI staff, and promptly distributed to the committee members by the Data Coordinating Center.

In TACT, patient safety is monitored by a combination of physical and laboratory examinations that result in delivery of email notifications to the site coordinator, site investigator, the Clinical Coordinating Center (CCC) and the DCC.

Monitoring of the appearance or worsening of heart failure/angina/rhythm disturbances/and hypertension, the following are required at each infusion visit: patient weight, blood pressure, heart rate, and limited cardiopulmonary exam. Additionally, an assessment of CCS (angina) and NYHA (heart failure) classes, and a check for dyspnea and or rales is performed pre and post every infusion. Heart failure is monitored by measuring patient's weight at baseline and at each infusion visit. Abnormal results generate an automated email notification with recommendations for medical management of the patient. Sites are instructed on the clinical action necessary if an abnormal result is found. For weight gain, specifically any 5 pound weight gain from baseline weight or three pound weight gain between infusion visits, automated email notifications are generated instructing the site to assess the patient for signs or symptoms of fluid overload so that a treatment and follow-up plan can be formulated.

Laboratory examinations are carried out on all patients during specific infusion visits, as detailed in the following table:

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

	Screen	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
Magnesium	X		X	X	X	X	X	X	X	X	X
Glucose	X		X	X	X	X	X	X	X	X	X
CBC/plt	X		X	X	X	X	X	X	X	X	X
LFT	X		X	X	X	X	X	X	X	X	X
Urine Dipstick	X			X		X		X			
Iron panel		X							X		
Lipids		X							X		
***hs-CRP**		X							X		X

*C-reactive protein is drawn for only the first 600 patients randomized into the trial.

Abnormal laboratory results generate either a: **Lab Alert** or **Lab Delay**. Lab delays result in a two types of email notifications is that lab delays result in a two-week delay for the upcoming infusion and a blood re-draw, while an alert typically results in an increase in infusion time and/or consultation with the CCC. Sites are instructed on the necessary steps they must follow after an abnormal lab result for the current infusion visit, next lab sample, future infusion visits, and follow-up.

Lab alerts help site coordinators monitor the patients' metabolic, hematologic, kidney, and liver functioning. Monitoring of patient's blood sugar levels is done by urine dipstick and blood serum glucose level. When urine dipstick results in glycosuria equal to 3 or 4, any proteinuria, or positive hematuria the site coordinator must consult the CCC.

Additional lab alerts evaluating hematocrit, magnesium, potassium, iron, and lipids are generated if an abnormal lab value is obtained.

Guidelines for Abnormal Lab Results-Lab Alerts

Lab delays help site coordinators monitor results that assess the functionality of kidneys, the liver, and several hematologic measurements (platelets, WBC's, neutrophils, and RBC's count).

In patients whose creatinine is greater than or equal to twice the value obtained at or reaches 2.5 mg/dl,[50] whichever is lower, the following will occur:

1) The next infusion will be withheld for two weeks if the patient is in the weekly infusion phase of the trial.
2) Labs will be re-drawn two weeks later. If the labs return to normal range, are less than double baseline value, or are less than 2.5 mg/dL the site will resume the infusion schedule.

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.

Guidelines for Abnormal Lab Results-Lab Delays

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, corrected calcium below 8.0 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.

TACT also monitors laboratory values for abnormal results that are considered to be clinically important and warrant the patient's primary care provider and/or referring clinician to be notified. When abnormal, clinically important lab values are entered, the electronic data capture system automatically generates an email alert instructing the Site to contact the patient's primary care provider and/or referring doctor.

6.5 Site Monitoring

6.5.1 Data Collection and Reporting

The 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 monitoring reports regularly 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. The DCC will continuously monitor the number of delinquent forms at each site and provide update reports to the CCC regularly. 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. Site visit reports are submitted to the CCC and NIH.

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 fulfill 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

A 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:

1. Associated – There is a reasonable possibility that the adverse event may have been caused by the study intervention

2. 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 defined as an adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure or the risk information 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 defined as an adverse drug experience, the specificity and severity of which is consistent with the current investigator brochure or the risk information 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 serious adverse events that occur from initiation of study drug through 30 days post final infusion are to be reported immediately (within 24 hours) using the electronic data capture system. Adverse events that are serious and drug (infusion) therapy related or result in death will be followed by 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 all SAE data including all deaths to:

1. ascertain the seriousness
2. ascertain drug (infusion) therapy relationship
3. verify that all data are complete, and
4. follow-up with the site for incomplete data and/or data clarification.

This will include, but will not be limited to ensuring that serious criteria have been met and the SAE data received are reviewed, entered and coded using the MedDRA coding dictionary. The DCRI Medical Monitor will review adverse events that are serious and drug (infusion) therapy related or result in death for medical clarity and unexpectedness.

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

The DCRI Safety Surveillance will provide DCRI Regulatory Services with the event specific forms necessary to report the expedited adverse event according to country specific regulatory law. This

will include all deaths assessed by the DCRI Medical Monitor as warranting expedited reporting to the regulatory authorities and all adverse events that are serious, unexpected and drug (infusion) therapy related (as assessed by the site investigator or the DCRI Medical Monitor). The DCRI Medical Monitor will provide Mt. Sinai an Investigator Notification letter by calendar day 13. Mt. Sinai will distribute the letters to the investigators using the electronic data capture system by calendar day 15 of DCRI's initial notification of the SAE. Investigator Notification letters will not disclose the treatment group. The Investigator will be responsible for notifying the local IRB in accordance with local requirements and notifying study patients of any additional risks. Questions regarding these notifications will be forwarded to DCRI Medical Monitor and/or DCRI Safety Surveillance.

SAE line listings, from the clinical database, will be provided to the DSMB chairman regularly for review. All SAE's are reported to the regulatory authorities in accordance to country specific regulatory law.

All reported SAEs will be followed until resolution, stabilization or until 60 days after the last patient enrolled in the trial completes the study drug (infusion) therapy. Unresolved SAEs may be closed (final outcome assigned as "unresolved") per the discretion of the DCRI Medical Monitor and/or the DCC PI.

All deaths assessed by the DCRI Medical Monitor as warranting expedited reporting and all drug-related serious adverse events must be reported to the site's local IRB/IEC in accordance to the site specific SOP, local IRB/IEC SOP and the local regulations regarding the reporting of adverse and serious adverse events.

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

DCRI Safety Surveillance will also report specific adverse and/or serious adverse events, not otherwise eligible for expedited SAE reporting as in Section 6.5.4.2, within 2 business days to the DSMB or its designee, and the NCCAM and NHLBI Program Officers. The adverse events for enhanced scrutiny include:

1) Heart failure hospitalization during the entire infusion phase of the patient's participation in the study, not otherwise subject to expedited SAE reporting.
2) Any disposition of the patient to the hospital or emergency room within 24 hours following study drug (infusion) therapy, not otherwise subject to expedited SAE reporting.

These events would not be eligible for expedited SAE reporting if the causality criterion were not met. Notification of these events will be made electronically.

6.5.4.3 Unmasking Requests from the DSMB and FDA

All 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.

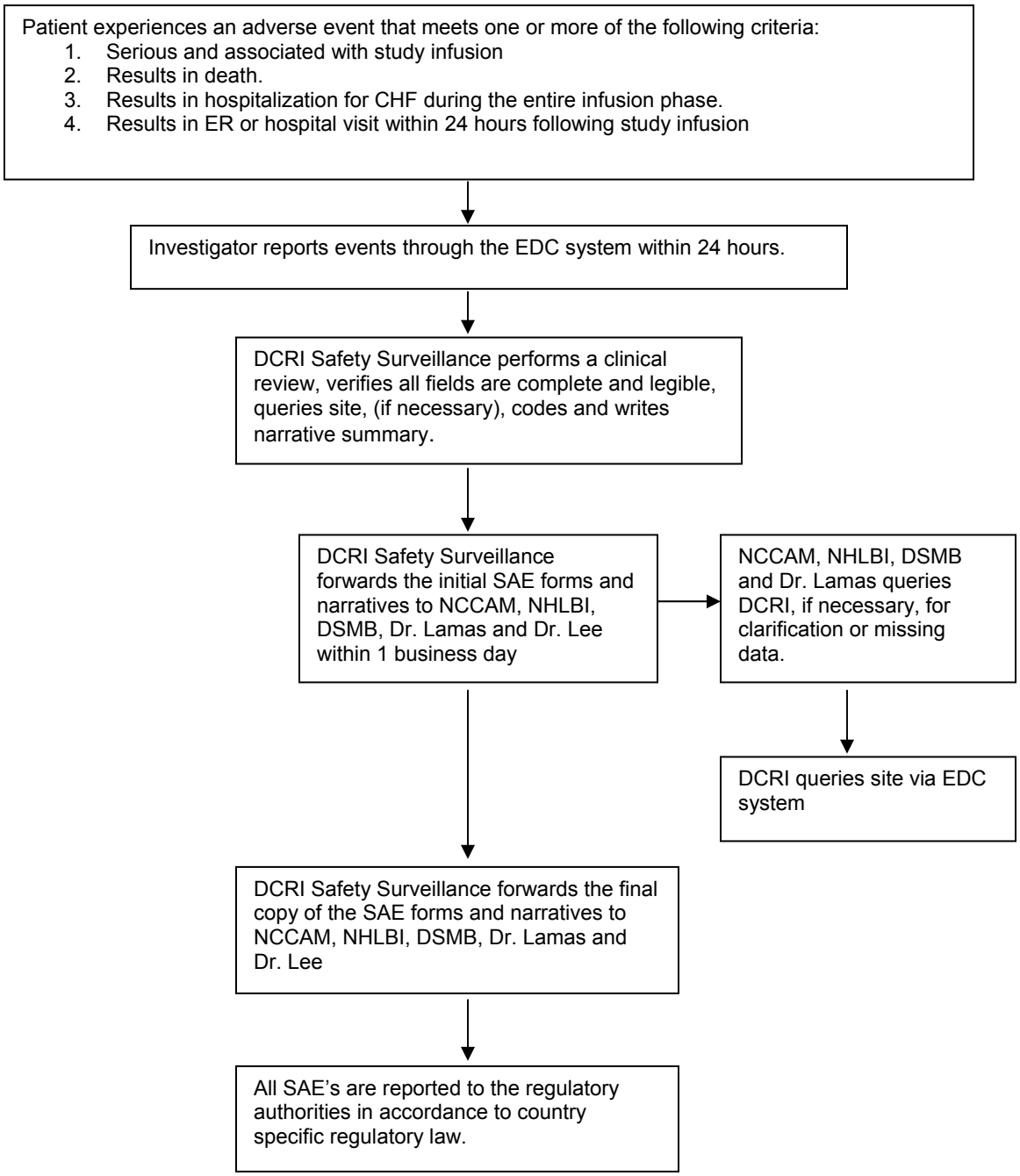
Dr. Lee will provide the FDA with unmasked drug assignments (by patient) once the clinical database is locked and data analysis is completed.

6.5.4.4 Unmasking Requests from the sites to DCRI

If the 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 other nephrotoxic, but clinically necessary drugs.

6.5.4.5 SAE General Process Flow Chart

TACT General SAE Review Process



6.5.4.6 Screening for non-serious adverse events

Nonserious adverse events of interest will be collected 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 clinical site. Accordingly, relevant baseline economic and quality of life data, including eight scales from the Medical Outcomes Study Short Form (SF-36),[70] the Duke Activity Status Index (DASI),[71] and bed and disability day questions from the National Interview Survey,[72] job class and days lost from work developed for the Bypass Surgery and Revascularization Investigation EQOL Study,[73] and angina symptom status assessment from the Seattle Angina Questionnarie[74] will be collected via a structured interview conducted by the Site Coordinator, prior to randomization. Measurement of utilities by the EuroQol[75] also will be included during this baseline interview. All of these data will be repeated on a random subset of 900 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 8.

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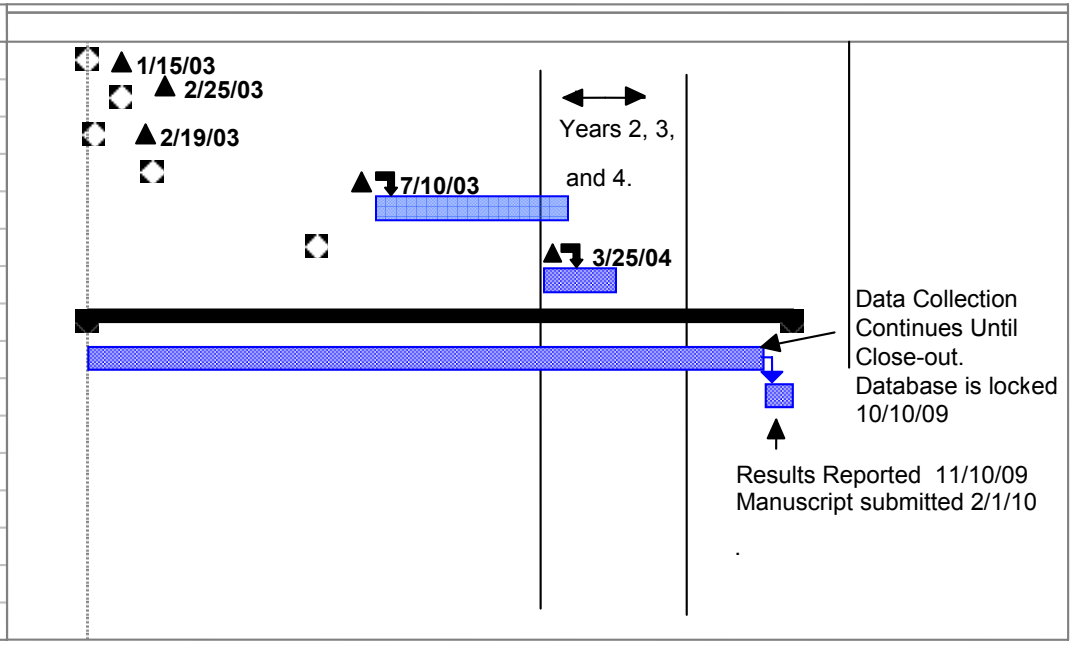
9.0 TIMELINE

ID	Task Name
1	**Complete Protocol**
2	**DSMB Meeting**
3	**Complete IND Application**
4	**Host First Investigators Meeting**
5	**Initiate First Set of Sites**
6	**Host Second Investigators Meeting**
7	**Initiate Second Set of Sites**
8	**Data and Reporting**
9	**Collect Data**
10	**Analyze Data and Produce Reports**



Appendix 1: Statistical Considerations

1.0 Sample Size and Power Calculations

Several design factors and research objectives were considered when developing sample size estimates for the trial. First, patient enrollment was determined so there would be a sufficient number of endpoints to provide a high degree of confidence (at least 85-90% power) for detecting clinically important differences in the primary endpoint. Second, important secondary endpoints, including measures of quality-of-life, also have been considered. Third, we considered it important for the overall sample to be large enough to permit exploration of treatment effects in selected subgroups of patients where chelation therapy might be particularly advantageous, or where the question of a treatment benefit from chelation therapy is particularly relevant. The pre-specified subgroups in the trial are described in Section 1.1 of this appendix. Fourth, because the treatment protocol is very intensive (requiring frequent clinic visits for intravenous therapy over an extended period of time), it is likely (despite our best efforts) that some patients will prematurely discontinue therapy (drop-out) and thus not realize the full benefits of the intervention. This likelihood has been reflected in the sample size calculations. Finally, the sample size has been determined to provide a robust level of confidence of detecting clinically important therapeutic effects even if our projections of event rates and treatment differences prove to be optimistic.

Event rates for the primary composite endpoint and other clinical outcomes were examined in a group of 7,002 patients with a history of myocardial infarction enrolled in the Duke Cardiovascular Disease Database between 1986 and 2000. These patients all underwent cardiac catheterization, but otherwise satisfied all the inclusion/exclusion criteria specified for TACT. Based on follow-up of these patients starting one month after their angiography (to avoid counting early interventional procedures based on treatment decisions made at the time of catheterization), the three-year rate for the occurrence of either death, myocardial infarction, or rehospitalization for a revascularization procedure was 28.4 %. When we also include stroke or hospitalization for angina as outcome events, the three-year rate increases to well over 30%. These data cover a 14-year span during which therapeutic innovations have improved patient outcomes. To address the concern that event rates have fallen in more recent times, we examined published data from the CARE trial (a study of cholesterol-lowering therapy in post-MI patients) and secured further reassuring data from WIZARD, a recent large-scale trial of relatively low-risk patients who survived a myocardial infarction and in whom any revascularization had taken place at least 6 months prior. In CARE, the event rate for the composite of *coronary* death, non-fatal myocardial infarction, or revascularization was approximately 20% at 2.5 years. In WIZARD, the event rate at 2.5 years for the combined endpoint of death, non-fatal myocardial infarction and hospitalizations for unstable angina or coronary

revascularizations, was 19.4%. It should be noted that strokes were not included in the WIZARD endpoint (nor in the endpoint reported above for CARE) but are included in the TACT endpoint. Based on a synthesis of these data, it is reasonable to assume that the 2.5 year primary event rate in TACT for the control arm associated with each treatment factor in the study design will be comparable to event rates observed for *treated* patients in the CARE and WIZARD trials, namely 20% or higher. The level of compliance with EDTA (or placebo) infusion therapy expected in TACT has been estimated based on a careful review of the previous literature in this area and estimates from the experience of contemporary chelation practitioners. We have assumed that 7.2% of patients per year (20% over 3 years) will discontinue therapy, and conservatively that no therapeutic benefit will occur in any of these patients. We have further assumed that adherence to the vitamin regimens will be at least as high as compliance with the chelation infusions, since the vitamins will be much more convenient and easier for patients to comply than undergoing a three-hour infusion each week. We do not expect therapy "drop-ins" in this trial given the blinded nature of both the chelation and the vitamin therapies. Finally, we have made allowance for loss to follow-up of up to 3% of patients in the trial. Based on these various assumptions, 1950 patients will provide the trial with >85% power to detect a 25% reduction in the primary endpoint *for each treatment factor in the 2x2 factorial design*. Thus the level of power that this number of patients will provide for detecting clinically meaningful treatment differences is excellent.

1.1 Statistical Analysis

Statistical analysis will be performed at the DCC at Duke University. Although the methodologic approaches and operational details of the data analysis will be coordinated by the study biostatisticians, the major analyses of the study data will be highly collaborative among the DCC, the CCC, and the Steering Committee, involving both statisticians and physicians to ensure appropriate interpretation of the data. All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "intention-to-treat;" that is, subjects will be analyzed (and endpoints attributed) according to the treatment arm to which patients were randomized, regardless of compliance to assigned regimen. Statistical comparisons will be performed using two-sided significance tests, supplemented with extensive use of confidence intervals and graphic displays.

In this factorial design, the primary statistical assessments will involve a comparison of the EDTA chelation therapy arm with the placebo infusion group, and a comparison of high-dose vitamin/mineral supplementation with low-dose supplementation. The log-rank test[1], which is a special case of the more general Cox proportional hazards model[2], will be the primary analytic tool in the two-group comparisons for assessing outcome differences with respect to the primary clinical endpoint. This approach focuses on the

time from trial entry until the first occurrence of any component of the composite primary endpoint, taking into account varying lengths of patient follow-up and censored observations. Using this procedure, the analysis strategy will be to first perform two-group comparisons for each treatment factor in the study design, adjusting only for the other design factor. That is, we will compare the outcomes of patients randomized to EDTA chelation therapy vs. those of the patients randomized to placebo infusion, stratified (adjusted) for the vitamin supplementation groups. Also, we will compare the outcomes of patients randomized to high-dose supplements versus the outcomes of those assigned low-dose supplements, adjusting for whether the patients were allocated to EDTA chelation therapy or placebo infusion. These standard two-group comparisons will constitute the primary analyses to assess treatment differences. The significance level for each comparison with respect to the primary endpoint will be set at α=0.05. Kaplan-Meier survival estimates[3] based on the primary endpoint will be calculated for each treatment group to display the outcome results graphically. Using the Cox proportional hazards model, hazard ratios with 95% confidence intervals will be calculated for each treatment factor (EDTA chelation vs. placebo, and high dose vs. low-dose vitamins) as a further descriptive summary of the treatment effects. Prior to the hazard ratio calculations, however, the appropriateness of the proportional hazards assumption of the Cox model will be assessed by an examination of log(-log) of the survival curves versus time, by use of a time-dependent covariate of treatment x log time, or by other formal tests of proportional hazards as outlined in Harrell.[4] Of special interest in assessing the effects of chelation therapy will be a comparison of the event rates for the patients randomized to EDTA chelation therapy versus the control infusion group at the time when the infusions are completed.

Although the primary analysis in this 2 x 2 factorial design will involve separate comparisons of the treatment arms defined by each treatment factor (i.e., EDTA chelation and vitamin supplements), we will also assess whether an interaction exists between the two treatment factors. The size and design of the study assume that any effects of the two treatment factors will be additive (i.e., that there is no interaction between them). This issue will be examined, however, in the analysis.

In a trial of this size, randomization is very likely to ensure an equal distribution of prognostic factors. Nonetheless, additional analyses involving covariate adjustment for prognostic factors will be performed with the Cox model. Such adjustment will be limited to a relatively small, prospectively defined set of patient characteristics that are known *a priori* to have a prognostic relationship with the clinical outcomes of interest. This adjustment will serve as a prelude to additional analyses examining differential treatment effects. The adjustment variables will include age, sex, race, infarct location (anterior versus non-anterior), time from index MI until study enrollment, history of diabetes, and previous revascularization.

If the data provide evidence of an overall difference in outcome between treatment groups, we will examine whether the therapeutic effect is similar for all patients, or whether it varies according to specific patient characteristics. In particular we will focus on whether the relative therapeutic benefit differs according to patient age, sex, race, infarct location, time from index MI to enrollment, and the presence/absence of diabetes. These issues will be addressed formally with the Cox model by testing for interactions between treatments and the specific baseline variables.

Secondary endpoint analyses will be performed for the individual components of the primary composite endpoint, and for other secondary clinical endpoints using the log-rank and Cox model methodology outlined above. The frequency of occurrence of adverse events in each patient group will be summarized graphically as well as with appropriate descriptive statistics. Quality of life and cost data will be analyzed by the TACT EQOL Coordinating Center in close collaboration with the Data Coordinating Center.

In addition to the assessment of treatment interactions indicated above, a limited number of pre-specified subgroup analyses of the primary outcome will be performed. Specifically, treatment comparisons will be performed within subgroups defined by age (elderly (>70) versus younger ($\leq$70) patients); subgroups defined by gender, with special emphasis on results in women; subgroups defined by race, with emphasis on results in minority patients; and subgroups defined by MI location, time from index MI to trial enrollment, and presence/absence of diabetes. Treatment effects for the primary endpoint as characterized by the hazard ratio (with 95% confidence intervals) will be calculated and displayed for the subgroups defined by the variables listed above. The appropriateness of the proportional hazards assumption of the Cox model for the calculation of hazard ratios in these subgroups will be assessed as described above for the primary analysis. The subgroup comparisons will be carefully interpreted in conjunction with the formal interaction tests described above. Indeed, many of these subgroup analyses fall within the NIH-permitted category of "plans to conduct valid analyses of the interventions in sex/gender and racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups".

1.2 Interim analyses

Interim analyses will be performed at prescribed intervals (approximately every six months) for presentation to the Data and Safety Monitoring Board. The primary objective of these analyses will be to ensure the safety of the patients enrolled in the trial. In these analyses, the accumulating data will be evaluated for an unacceptably high frequency of negative clinical outcomes in any of the treatment arms. In addition, however, the interim monitoring reports will also involve a review of the control arm

event rates for each treatment factor, status of patient recruitment, compliance with the study protocol and therapy guidelines, the frequency of protocol violations, timeliness and accuracy in the submission of data forms, and other factors which reflect the overall progress and integrity of the study. Prior to each meeting of the DSMB, the Data Coordinating Center will conduct the desired statistical analyses in accordance with the approved charter and prepare a summary report that will be carefully and confidentially reviewed by the DSMB. The extracted data files and analysis programs for each DSMB report will be archived and maintained at the Data Coordinating Center for the life of the study.

To address the statistical problems related to the multiplicity of statistical tests performed on an accumulating set of data,[5,6] a group sequential method similar to that proposed by O'Brien and Fleming[7] will be used as a guide in interpreting interim analyses. This approach requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final analysis is near the "nominal" critical value. The actual method for the interim monitoring that will be employed in TACT is the general approach to group sequential testing developed by Lan and DeMets[8] for which neither the number of looks nor the increments between looks must be pre-specified. Rather, the Lan-DeMets approach only requires specification of the rate at which the Type I error (which in this trial is α= 0.05) will be "spent". The method allows "spending" a little of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05. One such spending function generates boundaries that are nearly identical to the O'Brien-Fleming boundaries. It is this approach that will be used in TACT, namely two-sided O'Brien-Fleming[7] type boundaries generated using the flexible Lan-DeMets[8] approach to group sequential testing.

Assuming that the DSMB will conduct its first formal data review in the latter half of the first year of recruitment, and then continue those reviews approximately every 6 months thereafter through the patient recruitment period (3 years) and the follow-up phase (1 year), there will be approximately 7-8 reviews of the data. With 8 interim analyses approximately equally spaced in time, the Lan and DeMets "spending function" that approximates the O'Brien-Fleming stopping boundaries involves a very stringent alpha level (0.00001) for declaring significance at the first interim analysis. At the subsequent interim analyses, the required significance levels will be somewhat less stringent. The requirements for significance at each interim analysis, depending on exactly when the analysis occurs, can be computed with the Lan-DeMets methodology. The final analysis can be undertaken with a significance level of approximately 0.04, relatively close to the nominal 0.05 level.

The analytic approach that will be used at the interim analyses for assessing treatment

differences will be the time-to-event analysis methods described in the study protocol, except that interpretation of statistical significance associated with treatment comparisons of the key study endpoint will be guided using the group sequential stopping boundaries outlined above.[7,8,9] The appropriateness of using the log-rank test (or equivalently the Cox model) in the group sequential framework has previously been well established.[10,11,12,13] For each of these interim analyses, the critical value of the test statistic and the corresponding p-value required for significance in that particular analysis will be presented so that significance can be assessed precisely. If significantly large and important treatment differences are observed at any of the interim analyses, the Data and Safety Monitoring Board may recommend that randomization of patients be stopped, or that the design and conduct of the trial be appropriately modified. The interim analyses will also include a presentation of Kaplan-Meier survival estimates and hazard ratios with confidence intervals to descriptively summarize the results. The appropriateness of the proportional hazards assumption will be assessed as outlined in the statistical analysis appendix to the study protocol. Of special interest in the interim analysis will be the comparison of patients randomized to EDTA chelation therapy vs. the placebo infusion group at the time when the infusion phase of the intervention is completed. This analysis will only be meaningful after an adequate number of patients (20% or more of the overall population) have been followed through the infusion phase of the intervention.

Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the originally projected sample size. As an aid in this latter assessment, the Data Coordinating Center will supplement the group sequential analyses outlined above with calculations of conditional power based on the method of stochastic curtailment (also known as futility analysis).[14,15,16] This procedure evaluates the conditional probability that a particular statistical comparison will be significant (or not significant) at the end of the trial at the α level used in the design, given the hypothesized treatment difference and the data obtained to date. Conditional power for the primary composite clinical endpoint will be computed and provided to the DSMB as part of the interim study reports, and will include calculations based on the originally hypothesized treatment difference as well as the observed treatment difference up to that point in the trial.

The approach to interim monitoring outlined above will be carried out in parallel for the assessment of both treatments in the 2 x 2 factorial design.

Since the primary endpoint is a composite of death and several non-fatal outcomes, it will also be important to monitor the mortality component of this endpoint as part of the safety monitoring of the trial. Thus mortality rates and associated confidence intervals for each arm in the factorial study design will also be monitored at the interim

reviews to ensure that the safety of patients enrolled in the trial is not compromised. A summary of the incidence of other serious adverse events will also be regularly reviewed by the DSMB.

If protocol modifications are warranted at any point of the trial, there will be extensive discussion and close consultation among the Executive Committee, the DSMB, and NCCAM and NHLBI staff.

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Appendix 2: Prototype of INFORMED CONSENT FORM

HIPAA COMPLIANT VERSION FOR SITES IN UNITED STATES

Consent for Participation in a Clinical Research Study

Trial to Assess Chelation Therapy (TACT): Grant # 1 U01 AT001156-01
Study Sponsors: National Institutes of Health (NCCAM and NHLBI)

YOU ARE ASKED TO READ THE FOLLOWING FORM TO MAKE SURE THAT YOU COMPLETELY UNDERSTAND WHAT WILL HAPPEN IF YOU AGREE TO TAKE PART IN THIS RESEARCH STUDY. SIGNING THIS FORM MEANS THAT THE STUDY HAS BEEN EXPLAINED TO YOU AND THAT YOU GIVE YOUR PERMISSION TO TAKE PART. THE FEDERAL GOVERNMENT REQUIRES YOUR APPROVAL IN WRITING BEFORE YOU TAKE PART IN ANY RESEARCH STUDY. IT IS IMPORTANT THAT YOU KNOW WHAT WILL TAKE PLACE AND WHAT RISKS ARE INVOLVED BEFORE YOU DECIDE WHETHER OR NOT TO TAKE PART IN THIS STUDY.

Introduction

You are being asked to take part in a research study to test the effectiveness of chelation therapy for patients who have survived a heart attack. The study will involve 1950 patients like you at up to 150 clinical centers. Your participation in this 5-year study will include up to 28 months of intravenous infusions and oral treatments (pills), followed by up to 32 additional months of follow-up and additional pills.

Purpose of the Study

The purpose of this study is to determine the effectiveness of chelation therapy for patients who have survived a heart attack.

Background

Chelation therapy, as used in this study, consists of 40 treatments through a vein in your arm (infusion) of a solution of vitamins and dissolved materials that are thought to bind specific toxic elements circulating in your blood. These elements, known as heavy metals, include iron, copper, and calcium, and may contribute to the development of heart disease. The Food and Drug Administration has approved chelation therapy for treatment of lead poisoning, but not as a treatment for heart disease. Chelation therapy has been practiced in the community for many years. The present clinical practice of chelation therapy also involves the use of high-dose antioxidant vitamins, minerals, and nutritional supplements taken by mouth. However, like with chelation

therapy, there is no evidence that these supplements are beneficial for patients like you. The Trial to Assess Chelation Therapy (TACT) will test chelation solution versus a placebo (a substance with no active ingredient) salt-water solution, and high-dose vitamins and minerals taken by mouth versus placebo vitamins. All patients will also receive a low-dose vitamin.

Procedures

If you agree to take part in this study, you will be scheduled for a screening visit. During this visit, a complete medical history and a simple physical examination will be performed. We will also obtain samples of your blood (two tablespoonfuls) to check your blood cell counts as well as your kidney and liver function. You will be asked questions about how you rate your health, about your activities, how you are feeling emotionally and some questions about your working status, education, and income. We expect this screening visit to take about 90 minutes to carry out. Once the laboratory tests are complete, you will be contacted by the research staff and told whether you are eligible, and, if so, asked to schedule your first infusion visit.

Also, at the screening visit, you will be asked to fill out a Confidential Patient Information Form. This form will ask for specific information such as your name, address, phone number, social security number, and other identifiers that will be entered confidentially by the Study Coordinator. The information will be used by the research staff and the Economics and Quality of Life Coordinating Center at the Duke Clinical Research Institute to follow your care and check for changes in your health.

The research staff will call for a treatment assignment and you will be assigned randomly by a computer (by chance, like flipping a coin) to one of these four groups:

Chelation solution + High-dose supplements*	Chelation placebo + High-dose Supplements*	Chelation solution + High-dose Supplement placebos*	Chelation placebo + High-dose Supplement placebos*

*All patients take low-dose supplements during infusion period only.

All patients, including yourself, will receive a total of 40 infusions, beginning with one infusion per week for 30 weeks, followed by an additional 10 infusions given approximately once every 2 weeks to once every 2 months. It will take up to 28 months to complete all the required infusions. Each infusion consists of receiving the solution slowly through a needle in your vein. The needle will be inserted by trained medical personnel under sterile conditions and each infusion will last for a minimum of 3 hours. You will have blood drawn for laboratory tests during 10 of your visits. Each time, you

will have approximately 1 tablespoonful of blood drawn. During each visit, you will be asked how you feel, and whether you have had any complaints or other problems. In addition, the research staff will ask you whether you have had any new heart problems or hospitalizations, and will measure your blood pressure and perform a simple physical exam. Because of the time of the infusions, you should count on being at the clinic for at least 5 hours. If you live far away from your doctor's office, you may spend a lot of time traveling back and forth.

If you are assigned to the chelation group you will receive a standard intravenous mixture established by the American College for Advancement in Medicine.

The components are as follows. Please review the list of components carefully and notify us if you have an allergy to any of them:

Additive	Role of Additive
Up to 3 grams of EDTA	Chelating agent
2 grams of magnesium chloride	To reduce local discomfort and replace losses
100 mg of procaine HCL	To reduce local discomfort
2500 units of heparin	To reduce local inflammation of veins
7 grams of ascorbate (Vitamin C)	For anti-oxidant properties
2 mEq Potassium	To replace losses
840 mg sodium bicarbonate	To act as a buffer and reduce discomfort
250mg pantothenic acid	For anti-oxidant properties
100mg of thiamine	For anti-oxidant properties
100mg of pyridoxine	To replace chelation losses

Because chelation therapy may also remove important vitamins and other nutritional elements needed by the body, all patients, including yourself, will be required to take vitamins and nutritional supplements. These supplements will be taken on a daily basis. You will be assigned by chance to receive either high-dose vitamin supplements or high-dose vitamin supplement placebos. Neither you nor the research staff will know to which group you have been assigned. On the day of actual infusion, you will be asked to take these supplements 3-5 hours after the infusion to avoid the possibility of the supplements being removed by the chelation therapy. We will ask you to bring these supplements with you to every infusion visit, to ensure that you are taking them as required.

The high dose vitamin and mineral schedule consists of 3 pills to be taken twice daily. The pills contain the following components. Please review the list and notify us if you have an allergy to any of the components:

High Dose Regimen (Taken twice daily)	**Total amount you will take compared to the recommended Daily Value**
Vitamin A (as fish liver oil and beta-carotene)	5 times
Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)	20
Vitamin D_3 (as cholecalciferol)	¼
Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)	13 $^1/_3$
Vitamin K_1 (as phytonadione)	¾
Thiamin (vitamin B_1) (as thiamin mononitrate)	66 $^2/_3$
Niacin (as niacinamide and niacin)	10
Vitamin B_6 (as pyridoxine hydrochloride)	25
Folate (as folic acid)	2
Vitamin B_{12} (as cyanocobalamin)	16 $^2/_3$
Biotin	Same
Pantothenic acid (as d-calcium pantothenate)	40
Calcium (as calcium citrate and calcium ascorbate)	½
Iodine (from kelp)	Same
Magnesium (as magnesium aspartate, magnesium ascorbate and magnesium amino acid chelate)	1¼
Zinc (as zinc amino acid chelate)	1 $^1/_3$
Selenium (as selenium amino acid chelate)	2 $^8/_9$
Copper (as copper amino acid chelate)	Same
Manganese (as manganese amino acid chelate)	4
Chromium (as chromium polynicotinate)	1 $^2/_3$
Molybdenum (as molybdenum amino acid chelate)	2
Potassium (as potassium aspartate and potassium ascorbate)	Less than $^1/_8$
Choline (as choline bitartrate)	There is no Daily Value established for these supplements.
Inositol	
PABA (as para-amino benzoic acid)	
Boron (as boron aspartate and boron citrate)	

Vanadium (as vanadyl sulfate)	
Citrus Bioflavonoids	
These supplements are taken in up to 6 tablets or capsules daily.	

All patients will receive a low-dose set of vitamins, 1 pill to be taken once daily, during the infusion period. This low-dose schedule is presented in the table below. Please review the list for any allergies that you may have:

Low-Dose Regimen (Taken once daily)	**Amount**	**% Daily Value**
Vitamin B6 (as pyridoxine hydrochloride)	25mg	1250%
Zinc (as zinc gluconate)	25mg	167%
Copper (as copper gluconate)	2mg	100%
Manganese (as manganese gluconate)	15mg	750%
Chromium (as chromium picolinate)	50mcg	42%

These supplements, produced by OleoMed S.A., Madrid, Spain, are administered in an olive oil based gel capsule.

In order to make sure patients and their physicians are "blinded" to which group you have been assigned, all patients assigned to the high-dose vitamin supplement placebo group will be taking pills that are identical to those that the high-dose group is taking.

As part of this study you may be chosen at random to be interviewed by the research staff from the Economics and Quality of Life Center at the Duke Clinical Research Institute. These interviews, done over the phone, will be scheduled at 6 months, 1 year and 2 years after the initial enrollment to the study. The research staff will ask you questions regarding any changes in how you feel, in your ability to perform your daily activities, or in your working status. If you are chosen, the information will allow us to understand the possible effects of chelation and vitamins on the quality and economics of patients' lives. All of these data will be analyzed using coded information without your name or other identifiable information that could be made public. The calls will take about 15-25 minutes to complete.

After the 40 infusion visits have been completed, research staff from [INSERT YOUR INSTITUTION'S NAME HERE] will call you every 3 months until the end of the study to find out how you are doing and whether you have had any heart problems since the

last visit or call. During this time it will be important to continue to take your high-dose vitamins. You will also be asked about any hospitalizations or heart procedures you may have had between study visits. If you have been hospitalized during the follow-up period, it will be necessary for you to sign a release so that we can have access to any medical records related to that hospitalization. In addition, you will be asked to return for a visit each year and at the end of the study. At each visit, you will be asked questions about your medical condition and undergo a simple physical exam.

If you are a woman and are able to become pregnant, you are not eligible to participate in this study.

Your Responsibilities

As a participant in this study you are required to do the following:

- Allow at least 5 hours for each infusion visit.
- Bring your study vitamins in their original packaging (bottle and blister packs) to each infusion visit. You will receive a new set of vitamins every 2 months from your Site Coordinator.
- After your 40th infusion, continue to bring your vitamins every 3 months to your Site Coordinator. Your Site Coordinator will provide a new 3-month supply of vitamins during these visits.
- Take the 3 high-dose pills twice per day during the infusion and follow-up periods.
- Take the 1 low-dose capsule once per day, during the infusion period.
- On the day of your infusions, take your assigned vitamins 3-5 hours after your infusion.
- If someone on the research staff calls you on the telephone, please answer all their questions.
- Continue taking all other medications for your heart disease and other conditions as prescribed by your physician.

Risks and Side Effects

This treatment may cause the side effects listed below. However, there may be some side effects that we cannot predict.

EDTA, or ethylenediamine tetraacetate is in the chelation solution. It is approved for use by the FDA as a treatment for lead poisoning but not for coronary artery disease. It binds heavy metals like lead, copper, and iron, and allows them to be excreted in the urine. EDTA rarely may cause allergies, or kidney problems. EDTA also binds to calcium in blood. Symptoms of low blood calcium, such as tingling, muscle cramps, lightheadedness, severe muscular spasms, heart rhythm problems, and low blood

pressure may occur with a rapid infusion, and rarely, with a correctly-administered infusion. You will be monitored carefully for these side effects. The infusion will be monitored closely so it does not go in too quickly, and your blood pressure will be checked before, during, and after the infusion. If your kidney function is not good, you will not be allowed to participate in the study. If your kidney function gets worse during the infusions, then the dose of EDTA will be reduced, or the infusions will be stopped. As part of monitoring your kidney function, you will need to inform your study physician if you are unable to urinate for 12 hours. You may develop flu-like symptoms such as low-grade fevers, sneezing, muscle and joint aches, headaches and watery eyes. These symptoms usually occur 4 to 8 hours after receiving the infusion. These symptoms are usually seen when high doses of EDTA are given, or if the infusion rate is too rapid. Patients with diabetes have been reported to develop low blood sugar during the infusion. For this reason, if you are diabetic, we will ask you to snack before the infusion, and monitor you for symptoms of low blood sugar.

During the infusions, you may experience a "burning-like" sensation at the site of the infusion, or through the vein. Certain medications (such as magnesium and a local anesthetic) are added to the solution to reduce this discomfort.

EDTA has the ability to remove certain vitamins and minerals that are needed by your body. You will be provided with supplements to be taken by mouth that will replace these elements. Although the risk of removal of these minerals is small, this can cause symptoms such as fatigue, dry skin, tingling sensation in your hands and feet, a skin rash, diarrhea, and constipation. EDTA also may reduce the effectiveness of some of the medications you are taking.

As described earlier, magnesium chloride and potassium chloride are included in the infusion solution. Magnesium and potassium are essential salts that are components of all cells in the body. Potassium can cause burning at the site where the intravenous line is placed. However, there are no other likely side effects expected from the doses to be infused.

Vitamins B1, B6, pantothenic acid, and vitamin C also are included in the infusion solution. These essential vitamins have no significant side effects. However, vitamin C is being used at a higher dose than usual.
Heparin, also included in the infusion solution, is a commonly used blood thinner that is used to prevent clotting of the vein used for the intravenous infusion. The principal side effect of heparin at the doses used in this study is an allergy that could lead to bleeding or blood clots. You will be closely monitored for this, and the heparin will be stopped if an allergy seems to occur.

Procaine, also included in the infusion solution, is a local anesthetic that will prevent stinging or discomfort during the intravenous infusions. The main side effect is the possibility of allergy. Sodium bicarbonate is a naturally occurring substance that increases the ability of the kidney to excrete impurities. It is included in the infusion solution.

If your heart is weak, you may be at risk of developing fluid in your lungs, swelling in your ankles, or rapid weight gain. This fluid accumulation is also known as heart failure, and is a result of the heart's inability to tolerate the amount of fluid that will be infused. Your weight will be monitored to make sure you are not accumulating fluid. If your doctor determines that your weight gain is related to the infusions, the infusions will be temporarily stopped. Additionally, your doctor may determine it is necessary to give you a diuretic (water pill) in order to prevent any further fluid from accumulating in your lungs that may lead to shortness of breath. People who already have a history of decreased heart function will be at greater risk. If you have had fluid in your lungs due to a weak heart within the last 6 months, you will not be permitted to participate in the study.

Since chelation therapy is given intravenously, you will have some discomfort at the needle puncture site. There is also a risk of bruising, swelling, and redness developing at the site of the intravenous infusion. Rarely, a serious blood infection may develop that would require antibiotic treatment. It is very important for you to report any pain, swelling, or redness at the site of the needle punctures, as well as any fever or chills, to your doctor or study investigator. You may also experience these discomforts when having your blood drawn.

The oral anti-oxidant vitamin, mineral, and nutrient supplements being provided are well tolerated and have low risks of serious side effects. Beta-carotene, however, one of the supplements used, has been associated with a higher rate of cancer in patients who smoke. Smokers are not eligible to participate in this study, and it is important that you not start smoking while you are participating.

You will be informed in a timely manner if new information becomes available that may affect your willingness to continue participation in this study.

Finally, there does remain the risk of serious unanticipated side effects that we cannot predict, because this type of study has never been carried out in so many patients.

If you experience one of these side effects, the sponsor (National Institutes of Health) and/or the Data Coordinating Center, (Duke Clinical Research Institute) may need to review your entire medical record.

If you have any questions about the risks or discomforts, contact [INSERT SITE INVESTIGATOR'S NAME AND PHONE NUMBER HERE].

Benefits

You may or may not receive any medical benefit from your participation in this study. In the future, other people with a similar condition may benefit from the knowledge obtained from this study.

Alternative Treatments

If you choose not to participate in this study, your other cardiac treatments as directed and recommended by your doctor will not be affected. You should continue to use proven standard medicines for heart attack patients whether or not you participate in this research study.

Right to Withdraw

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at [INSERT NAME OF INSTITUTION/HEALTH CARE PROVIDER HERE]. If you do decide to withdraw, we ask that you contact Dr. in writing and let know that you are withdrawing from the study. mailing address is [INSERT SITE INVESTIGATOR'S ADDRESS HERE].

Involuntary Withdraw

Your doctor may ask you to leave this study if he/she feels it is appropriate or necessary. Your doctor will notify you if this should occur. This in no way will affect your continued medical care and treatment by your physician. Should you decide to discontinue your study participation early, you are asked to contact [INSERT SITE INVESTIGATOR'S NAME HERE] to arrange for final study visit procedures. In addition, the investigator, the sponsor, or the FDA, without regard to your consent, may

terminate your participation in this study if either party believes it to be in your best interest. Such conditions may include, but are not limited to, a serious adverse reaction, a worsening of your condition, or lack of cooperation on your part.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the information from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.
Costs

You or your insurance company will not be charged for the study treatments or for tests required by the study. All the study medications are provided free of charge to participating research subjects.

Should you have a complication of chelation therapy that requires medication or hospitalization, the study and/or its researchers will be unable to pay for those costs, and you and/or your insurance company will be responsible for the costs resulting from the complication.

You will not be paid to participate in this study.

If you do not sign this consent form, you will continue to receive care from your regular physician, but not as a part of this study.

Confidentiality

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except as previously addressed in this consent, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of [INSERT SITE INSTITUTION NAME HERE]. For records disclosed outside of [INSERT SITE INSTITUTION NAME HERE], you will be assigned a unique code number. The key to the code will be kept in a locked file at the Duke Clinical Research Institute (DCRI).
As part of the study, Dr.[INSERT SITE INVESTIGATOR'S NAME HERE] and [CHOOSE HIS/HER] study team will report the results of your study-related laboratory tests to those named below. These test results will be reported to the TACT Clinical Coordinating Center, TACT Clinical Events Committee, Accu-Care Pharmacy Services, and OmniComm Systems.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include, for example, representatives from the Food and Drug Administration,

representatives of [INSERT NAME OF PI HERE], the Institutional Review Board, DCRI associates, NCCAM and NHLBI. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

The following parties may review your study and medical records without your permission, or the permission of your legal representative, as they deem necessary:

Department of Health and Human Services (DHHS),
United States Food and Drug Administration (FDA),
Duke Clinical Research Institute (DCRI),
Mount Sinai Clinical Coordinating Center,
Quantum Healthcare Consultants,
OmniComm Systems,
Accu-Care Services Pharmacy,
[INSERT YOUR INSTITUTION NAME HERE]
[INSERT YOUR INSTITUTIONAL REVIEW BOARD'S NAME HERE]

In addition, the pharmacy preparing the study infusions (Accu-Care Services Pharmacy) and the prescribing study physician will know who you are.

In addition to signing this informed consent form, you are required to sign a separate consent form that allows your research doctor or investigator to receive your study medications directly from Accu-Care Services Pharmacy.

Record Retention

Your study results will be retained in your research record for 3 years after the end of the study. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at the clinical site. Any research information in your medical record will be kept indefinitely.

Information that could identify you by name will not be used if the results of this study are published.

Injury

In case of injury, please contact [INSERT SITE INVESTIGATOR NAME AND CONTACT PHONE NUMBER (24-HR PHONE NUMBER)]. Immediate necessary care is available if you are injured as a result of taking part in this study. However, there is no provision for free medical care or for monetary compensation for such injury. Financial compensation for research-related injury or loss of wages is not available.

Patient's Rights

If you have any questions regarding your rights as a patient, please contact [INSERT APPROPRIATE NAME AND PHONE NUMBER].

Statement of Consent

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask the questions I have, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time without affecting my future medical care. I have been told that I will be given a signed copy of this consent form."

_____ _____
Name of Subject Date

_____
Signature of Subject

_____ _____
Name of Person Obtaining Consent Date

_____
Signature of Person Obtaining Consent

_____ _____
Name of Witness Date
(if applicable)

_____
Signature of Witness (if applicable)

Non-US SITES VERSION

Consent for Participation in a Clinical Research Study

Trial to Assess Chelation Therapy (TACT): Grant # 1 U01 AT001156-01
Study Sponsors: National Institutes of Health (NCCAM and NHLBI)

YOU ARE ASKED TO READ THE FOLLOWING FORM TO MAKE SURE THAT YOU COMPLETELY UNDERSTAND WHAT WILL HAPPEN IF YOU AGREE TO TAKE PART IN THIS RESEARCH STUDY. SIGNING THIS FORM MEANS THAT THE STUDY HAS BEEN EXPLAINED TO YOU AND THAT YOU GIVE YOUR PERMISSION TO TAKE PART. THE UNITED STATES FEDERAL GOVERNMENT AND HEALTH CANADA REQUIRES YOUR APPROVAL IN WRITING BEFORE YOU TAKE PART IN ANY RESEARCH STUDY. IT IS IMPORTANT THAT YOU KNOW WHAT WILL TAKE PLACE AND WHAT RISKS ARE INVOLVED BEFORE YOU DECIDE WHETHER OR NOT TO TAKE PART IN THIS STUDY.

Introduction

You are being asked to take part in a research study to test the effectiveness of chelation therapy for patients who have survived a heart attack. The study will involve 1950 patients like you at up to 150 clinical centers. Your participation in this 5-year study will include up to 28 months of intravenous infusions and oral treatments (pills), followed by up to 32 additional months of follow-up and additional pills.

Purpose of the Study

The purpose of this study is to determine the effectiveness of chelation therapy for patients who have survived a heart attack.

Background

Chelation therapy, as used in this study, consists of 40 treatments through a vein in your arm (infusion) of a solution of vitamins and dissolved materials that are thought to bind specific toxic elements circulating in your blood. These elements, known as heavy metals, include iron, copper, and calcium, and may contribute to the development of heart disease. The United States Food and Drug Administration has approved chelation therapy for treatment of lead poisoning, but not as a treatment for heart disease. Chelation therapy has been practiced in the community for many years. The present clinical practice of chelation therapy also involves the use of high-dose antioxidant vitamins, minerals, and nutritional supplements taken by mouth. However, like with

chelation therapy, there is no evidence that these supplements are beneficial for patients like you. The Trial to Assess Chelation Therapy (TACT) will test chelation solution versus a placebo (a substance with no active ingredient) salt-water solution, and high-dose vitamins and minerals taken by mouth versus placebo vitamins. All patients will also receive a low-dose vitamin.

Procedures

If you agree to take part in this study, you will be scheduled for a screening visit. During this visit, a complete medical history and a simple physical examination will be performed. We will also obtain samples of your blood (30 mL) to check your blood cell counts as well as your kidney and liver function. You will be asked questions about how you rate your health, about your activities, how you are feeling emotionally and some questions about your working status, education, and income. We expect this screening visit to take about 90 minutes to carry out. Once the laboratory tests are complete, you will be contacted by the research staff and told whether you are eligible, and, if so, asked to schedule your first infusion visit.

Also, at the screening visit, you will be asked to fill out a Confidential Patient Information Form. This form will ask for specific information such as your name, address, phone number, and other identifiers that will be entered confidentially by the Study Coordinator. The information will be used by the research staff and the Economics and Quality of Life Coordinating Center at the Duke Clinical Research Institute to follow your care and check for changes in your health.

The research staff will call for a treatment assignment and you will be assigned randomly by a computer (by chance, like flipping a coin) to one of these four groups:

Chelation solution + High-dose supplements*	Chelation placebo + High-dose Supplements*	Chelation solution + High-dose Supplement placebos*	Chelation placebo + High-dose Supplement placebos*

*All patients take low-dose supplements during infusion period only.

All patients, including yourself, will receive a total of 40 infusions, beginning with one infusion per week for 30 weeks, followed by an additional 10 infusions given approximately once every 2 weeks to once every 2 months. It will take up to 28 months to complete all the required infusions. Each infusion consists of receiving the solution slowly through a needle in your vein. The needle will be inserted by trained medical personnel under sterile conditions and each infusion will last for a minimum of 3 hours. You will have blood drawn for laboratory tests during 10 of your visits. Each time, you

will have approximately 1 tablespoonful of blood drawn. During each visit, you will be asked how you feel, and whether you have had any complaints or other problems. In addition, the research staff will ask you whether you have had any new heart problems or hospitalizations, and will measure your blood pressure and perform a simple physical exam. Because of the time of the infusions, you should count on being at the clinic for at least 5 hours. If you live far away from your doctor's office, you may spend a lot of time traveling back and forth.

If you are assigned to the chelation group you will receive a standard intravenous mixture established by the American College for Advancement in Medicine.

The components are as follows. Please review the list of components carefully and notify us if you have an allergy to any of them:

Additive	Role of Additive
Up to 3 grams of EDTA	Chelating agent
2 grams of magnesium chloride	To reduce local discomfort and replace losses
100 mg of procaine HCL	To reduce local discomfort
2500 units of heparin	To reduce local inflammation of veins
7 grams of ascorbate (Vitamin C)	For anti-oxidant properties
2 mEq Potassium	To replace losses
840 mg sodium bicarbonate	To act as a buffer and reduce discomfort
250mg pantothenic acid	For anti-oxidant properties
100mg of thiamine	For anti-oxidant properties
100mg of pyridoxine	To replace chelation losses

Because chelation therapy may also remove important vitamins and other nutritional elements needed by the body, all patients, including yourself, will be required to take vitamins and nutritional supplements. These supplements will be taken on a daily basis. You will be assigned by chance to receive either high-dose vitamin supplements or high-dose vitamin supplement placebos. Neither you nor the research staff will know to which group you have been assigned. On the day of actual infusion, you will be asked to take these supplements 3-5 hours after the infusion to avoid the possibility of the supplements being removed by the chelation therapy. We will ask you to bring these supplements with you to every infusion visit, to ensure that you are taking them as required.

The high dose vitamin and mineral schedule consists of 3 pills to be taken twice daily. The pills contain the following components. Please review the list and notify us if you have an allergy to any of the components:

High Dose Regimen (Taken twice daily)	**Total amount you will take in 6 pills compared to the recommended Daily Value**	
Vitamin A (as fish liver oil and beta-carotene)	5 times	
Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)	20	
Vitamin D3 (as cholecalciferol)	¼	
Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)	13 1/3	
Vitamin K1 (as phytonadione)	¾	
Thiamin (vitamin B1) (as thiamin mononitrate)	66 2/3	
Niacin (as niacinamide and niacin)	10	
Vitamin B6 (as pyridoxine hydrochloride)	25	
Folate (as folic acid)	2	
Vitamin B12 (as cyanocobalamin)	16 2/3	
Biotin	Same	
Pantothenic acid (as d-calcium pantothenate)	40	
Calcium (as calcium citrate and calcium ascorbate)	½	
Iodine (from kelp)	Same	
Magnesium (as magnesium aspartate, magnesium ascorbate and magnesium amino acid chelate)	1¼	
Zinc (as zinc amino acid chelate)	1 1/3	
Selenium (as selenium amino acid chelate)	2 8/9	
Copper (as copper amino acid chelate)	Same	
Manganese (as manganese amino acid chelate)	4	
Chromium (as chromium polynicotinate)	1 2/3	
Molybdenum (as molybdenum amino acid chelate)	2	
Potassium (as potassium aspartate and potassium ascorbate)	Less than 1/8	
Choline (as choline bitartrate)	150 mg	*
Inositol	50 mg	*
PABA (as para-amino benzoic acid)	50 mg	*
Boron (as boron aspartate and boron citrate)	2 mg	*
Vanadium (as vanadyl sulfate)	39 mcg	*
Citrus Bioflavonoids	100 mg	*

*There is no Daily Value established for these supplements. The amount listed is the actual amount you will take every day.

All patients will receive a low-dose set of vitamins, 1 pill to be taken once daily, during the infusion period. This low-dose schedule is presented in the table below. Please review the list for any allergies that you may have:

Low-Dose Regimen (Taken once daily)	Amount	% Daily Value
Vitamin B6 (as pyridoxine hydrochloride)	25mg	1250%
Zinc (as zinc gluconate)	25mg	167%
Copper (as copper gluconate)	2mg	100%
Manganese (as manganese gluconate)	15mg	750%
Chromium (as chromium picolinate)	50mcg	42%

These supplements, produced by Douglas Laboratories®, Pittsburgh, PA, United States.

In order to make sure patients and their physicians are "blinded" to which group you have been assigned, all patients assigned to the high-dose vitamin supplement placebo group will be taking pills that are identical to those that the high-dose group is taking.

As part of this study you may be chosen at random to be interviewed by the research staff from the Economics and Quality of Life Center at the Duke Clinical Research Institute. These interviews, done over the phone, will be scheduled at 6 months, 1 year and 2 years after the initial enrollment to the study. The research staff will ask you questions regarding any changes in how you feel, in your ability to perform your daily activities, or in your working status. If you are chosen, the information will allow us to understand the possible effects of chelation and vitamins on the quality and economics of patients' lives. All of these data will be analyzed using coded information without your name or other identifiable information that could be made public. The calls will take about 15-25 minutes to complete.

After the 40 infusion visits have been completed, research staff from [INSERT YOUR INSTITUTION'S NAME HERE] will call you every 3 months until the end of the study to find out how you are doing and whether you have had any heart problems since the last visit or call. During this time it will be important to continue to take your high-dose vitamins. You will also be asked about any hospitalizations or heart procedures you may have had between study visits. If you have been hospitalized during the follow-up

period, it will be necessary for you to sign a release so that we can have access to any medical records related to that hospitalization. In addition, you will be asked to return for a visit each year and at the end of the study. At each visit, you will be asked questions about your medical condition and undergo a simple physical exam.

If you are a woman and are able to become pregnant, you are not eligible to participate in this study.

Your Responsibilities

As a participant in this study you are required to do the following:

- Allow at least 5 hours for each infusion visit.
- Bring your study vitamins in their original packaging (bottle and blister packs) to each infusion visit. You will receive a new set of vitamins every 2 months from your Site Coordinator.
- After your 40th infusion, continue to bring your vitamins every 3 months to your Site Coordinator. Your Site Coordinator will provide a new 3-month supply of vitamins during these visits.
- Take the 3 high-dose pills twice per day during the infusion and follow-up periods.
- Take the 1 low-dose capsule once per day, during the infusion period.
- On the day of your infusions, take your assigned vitamins 3-5 hours after your infusion.
- If someone on the research staff calls you on the telephone, please answer all their questions.
- Continue taking all other medications for your heart disease and other conditions as prescribed by your physician.

Risks and Side Effects

This treatment may cause the side effects listed below. However, there may be some side effects that we cannot predict.

EDTA, or ethylenediamine tetraacetate is in the chelation solution. It is approved for use by the FDA as a treatment for lead poisoning but not for coronary artery disease. It binds heavy metals like lead, copper, and iron, and allows them to be excreted in the urine. EDTA rarely may cause allergies, or kidney problems. EDTA also binds to calcium in blood. Symptoms of low blood calcium, such as tingling, muscle cramps, lightheadedness, severe muscular spasms, heart rhythm problems, and low blood pressure may occur with a rapid infusion, and rarely, with a correctly-administered infusion. You will be monitored carefully for these side effects. The infusion will be

monitored closely so it does not go in too quickly, and your blood pressure will be checked before, during, and after the infusion. If your kidney function is not good, you will not be allowed to participate in the study. If your kidney function gets worse during the infusions, then the dose of EDTA will be reduced, or the infusions will be stopped. As part of monitoring your kidney function, you will need to inform your study physician if you are unable to urinate for 12 hours. You may develop flu-like symptoms such as low-grade fevers, sneezing, muscle and joint aches, headaches and watery eyes. These symptoms usually occur 4 to 8 hours after receiving the infusion. These symptoms are usually seen when high doses of EDTA are given, or if the infusion rate is too rapid. Patients with diabetes have been reported to develop low blood sugar during the infusion. For this reason, if you are diabetic, we will ask you to snack before the infusion, and monitor you for symptoms of low blood sugar.

During the infusions, you may experience a "burning-like" sensation at the site of the infusion, or through the vein. Certain medications (such as magnesium and a local anesthetic) are added to the solution to reduce this discomfort.

EDTA has the ability to remove certain vitamins and minerals that are needed by your body. You will be provided with supplements to be taken by mouth that will replace these elements. Although the risk of removal of these minerals is small, this can cause symptoms such as fatigue, dry skin, tingling sensation in your hands and feet, a skin rash, diarrhea, and constipation. EDTA also may reduce the effectiveness of some of the medications you are taking.

As described earlier, magnesium chloride and potassium chloride are included in the infusion solution. Magnesium and potassium are essential salts that are components of all cells in the body. Potassium can cause burning at the site where the intravenous line is placed. However, there are no other likely side effects expected from the doses to be infused.

Your weight will be monitored to make sure you are not accumulating fluid. If your doctor determines that your weight gain is related to the infusions, the infusions will be temporarily stopped. Additionally, your doctor may determine it is necessary to give you a diuretic (water pill) in order to prevent any further fluid from accumulating in your lungs that may lead to shortness of breath.

Vitamins B1, B6, pantothenic acid, and vitamin C also are included in the infusion solution. These essential vitamins have no significant side effects. However, vitamin C is being used at a higher dose than usual.

Heparin, also included in the infusion solution, is a commonly used blood thinner that is used to prevent clotting of the vein used for the intravenous infusion. The principal

side effect of heparin at the doses used in this study is an allergy that could lead to bleeding or blood clots. You will be closely monitored for this, and the heparin will be stopped if an allergy seems to occur.

Procaine, also included in the infusion solution, is a local anesthetic that will prevent stinging or discomfort during the intravenous infusions. The main side effect is the possibility of allergy. Sodium bicarbonate is a naturally occurring substance that increases the ability of the kidney to excrete impurities. It is included in the infusion solution.

If your heart is weak, you may be at risk of developing fluid in your lungs, swelling in your ankles, or rapid weight gain. This fluid accumulation is also known as heart failure, and is a result of the heart's inability to tolerate the amount of fluid that will be infused. Your weight will be monitored to make sure you are not accumulating fluid. If your doctor determines that your weight gain is related to the infusions, the infusions will be temporarily stopped. Additionally, your doctor may determine it is necessary to give you a diuretic (water pill) in order to prevent any further fluid from accumulating in your lungs that may lead to shortness of breath. People who already have a history of decreased heart function will be at greater risk. If you have had fluid in your lungs due to a weak heart within the last 6 months, you will not be permitted to participate in the study.

Since chelation therapy is given intravenously, you will have some discomfort at the needle puncture site. There is also a risk of bruising, swelling, and redness developing at the site of the intravenous infusion. Rarely, a serious blood infection may develop that would require antibiotic treatment. It is very important for you to report any pain, swelling, or redness at the site of the needle punctures, as well as any fever or chills, to your doctor or study investigator. You may also experience these discomforts when having your blood drawn.

The oral anti-oxidant vitamin, mineral, and nutrient supplements being provided are well tolerated and have low risks of serious side effects. Beta-carotene, however, one of the supplements used, has been associated with a higher rate of cancer in patients who smoke. Smokers are not eligible to participate in this study, and it is important that you not start smoking while you are participating.

You will be informed in a timely manner if new information becomes available that may affect your willingness to continue participation in this study.

Finally, there does remain the risk of serious unanticipated side effects that we cannot predict, because this type of study has never been carried out in so many patients.

If you have any questions about the risks or discomforts, contact [INSERT SITE INVESTIGATOR'S NAME AND PHONE NUMBER HERE].

Benefits

You may or may not receive any medical benefit from your participation in this study. In the future, other people with a similar condition may benefit from the knowledge obtained from this study.

Alternative Treatments

If you choose not to participate in this study, your other cardiac treatments as directed and recommended by your doctor will not be affected. You should continue to use proven standard medicines for heart attack patients whether or not you participate in this research study.

Right to Withdraw

You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at [INSERT NAME OF INSTITUTION/HEALTH CARE PROVIDER HERE].

Involuntary Withdraw

Your doctor may ask you to leave this study if he/she feels it is appropriate or necessary. Your doctor will notify you if this should occur. This in no way will affect your continued medical care and treatment by your physician. Should you decide to discontinue your study participation early, you are asked to contact [INSERT SITE INVESTIGATOR'S NAME HERE] to arrange for final study visit procedures. In addition, the investigator, the sponsor, or the FDA, without regard to your consent, may terminate your participation in this study if either party believes it to be in your best interest. Such conditions may include, but are not limited to, a serious adverse reaction, a worsening of your condition, or lack of cooperation on your part.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the information from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Costs

You will not be charged for the study treatments or for tests required by the study. All the study medications are provided free of charge to participating research subjects.

Should you have a complication of chelation therapy that requires medication or hospitalization, the study and/or its researchers will be unable to pay for those costs, and you will be responsible for the costs resulting from the complication.

You will not be paid to participate in this study.

If you do not sign this consent form, you will continue to receive care from your regular physician, but not as a part of this study.

Confidentiality

Study records that identify you will be kept confidential as required by law.

Your records may be reviewed in order to meet regulations. Reviewers may include, for example, representatives from the United States Food and Drug Administration, your country's government health agencies (federal, state, and/or local), representatives of [INSERT NAME OF PI HERE], the Research Ethics Board, DCRI associates, NCCAM and NHLBI. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

In addition, the pharmacy preparing the study infusions (Accu-Care Services Pharmacy) and the prescribing study physician will know who you are.

In addition to signing this informed consent form, you are required to sign a separate consent form that allows your research doctor or investigator to receive your study medications directly from Accu-Care Services Pharmacy.

Information that could identify you by name will not be used if the results of this study are published.

By signing this consent you are authorizing such access.

Injury

In case of injury, please contact [INSERT SITE INVESTIGATOR NAME AND CONTACT PHONE NUMBER (24-HR PHONE NUMBER)]. Immediate necessary care is available if you are injured as a result of taking part in this study. However, there is no provision for free medical care or for monetary compensation for such injury. Financial compensation for research-related injury or loss of wages is not available.

Patient's Rights

If you have any questions regarding your rights as a patient, please contact [INSERT APPROPRIATE NAME AND PHONE NUMBER].

Statement of Consent

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask the questions I have, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time without affecting my future medical care. I have been told that I will be given a signed copy of this consent form."

_____ _____
Name of Subject Date

_____
Signature of Subject

_____ _____
Name of Person Obtaining Consent Date

_____
Signature of Person Obtaining Consent

_____ _____
Name of Witness Date
(if applicable)

_____
Signature of Witness (if applicable)

Appendix 3: Definition of Congestive Heart Failure

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema.[1]

In TACT, patients who, in the opinion of the treating physician, have symptoms and signs of fluid overload are ineligible. Such patients may be treated and when stable, enrolled.

Literature Cited

1Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm. Accessed February 25, 2003.

Appendix 4: Summary of Dosing Regimens and Renal Adjustments for Chelation Therapy for Various Indications

	Lead Toxicity	Hypercalcemia	TACT
Disodium EDTA	***Not reported***	Dosage: 50mg/kg/day Max: 3gm/day 5 consecutive days Adjustment: No adjustment for renal function. May be repeated.	Dosage: 50mg/kg/day Max: 3gm/day Once weekly Adjustment: Adjusted for renal clearance
Calcium Disodium EDTA	Dosage: 50mg/kg/day 5 consecutive days Adjustment: Adjustment for renal function.	***Not reported***	***Not reported***

Appendix 5: Peer Reviewed Literature: Case Series & Case Reports of Chelation for CVD

Author (citation)	Sample Size	Entry Criteria	Adverse Events												
			Local pain - burning	Nausea	Vomiting	GI symptoms	Dermatitis	Renal Insufficiency	hypoglycemia	hypocalcemia	parasthesias	Visual / hearing impairment	Death	Hypotension	Other
Case Series															
Casdorph (1981)	18	atherosclerotic heart disease		X	X						X				
Clarke (Am J Med Sci, 1955;229:142-149)	22	various, including angina	most patients reported	several patients reported		2	5								
Clarke (Am J Med Sci. Dec 1956;654-666)	20	CHD											1		
Hancke (J Adv Med 1993;6:161-171)	470	claudication and or angina						8				2			4 vertigo
Lamar (Angiology 1964;15:379-395)	15	diabetics with vascular disease	X					X	X	X					
Meltzer (1961) Amer J of Med Sc; 51-57.	81	Coronary artery disease	30 initially	15 mild; 1 moderate; 2 severe	15 mild; 1 moderate; 2 severe	2 abdominal cramps				20 mild	20 mild - associated with hypocalcemia			8 mild; 23 moderate; 2 severe	
Robinson (1982)	248	symptoms, ECG													

X=event occurred, but number not reported
Blank=not reported

No adverse events reported:
McGillen (New Eng J Med 1988;318:1618-1619)
Wirebaugh (Ann Pharmaco 1990;24:22-25)
Boyle (Circ and Scl Dis 1961;243-252)
Clarke (Am J Med Sci 1960;239:732-744)
Kitchell (Am Journ Card 1963;11:501-506)
Kitchell (1961)
Lamar (J Amer Geri Soc 1966;14:272-294)
Meltzer (Metal-Binding in Medicine, Philadelphia, Pa.: JB Lippencott,1960)
Olszewer (Med Hypothyses 1988;27:41-49)
Ruldolf (Journ Adv Med 1991;4:157-166)

Appendix 5 (continued): Peer-Reviewed Literature: Chelation for Lead Poisoning

Author (citation)	Sample Size	Entry Criteria	Adverse Events										
			Adverse Events not reported	Worsening angina	Vascular event	Fatigue/ faintness	GI symp-toms	Dermatitis	Renal Insufficiency	Phlebitis at infusion site	hypocalcemia	Pain	Other
Case Series													
Besunder J., et al. (J PEDIATR) 1997; 130:966-071	45	Lead poisoning in children					Vomiting during therapy was observed more frequently in the BAL+ EDTA group		No pts. were observed to have an increase in BUN or Cr levels				The ALT increased significantly after 5 days in the BAL+EDTA group only.
Meol D., Kumar K.; (Pediatrics) 1982; 70:259-262	130	Lead poisoning in children											
Waters R., et al (Biol Trace Element Res) 2001 (83) ; 207-221	16	Urinary metal excretion before and after IV infusion if EDTA											

X=numbers not reported

Adverse events not reported in the articles listed below:
Batuman V., et al. (Environ Res) 1989; 48:70-75
Bessman, S.P., Ried, H., & Rubin, M. (Med Ann Dist Columbia); 1952; 31(); 321-14.
Brangstrup Hansen, JP., Dossing, M., and Paulev, PE. (J Ocuup Med); 1981; 23(1); 39-43.
Hryhorczuk, D., et. Al. (Am J Ind Med); 1985;8(); 33-42.
Kety, S.S. and Letonoff, T.V. (Proc Soc Exp Biol Med); 1941; 46(): 476-7.
Markowitz, M., et al (J PEDIATR) 1984; 104();337-341
Lin J.,Tan, D., Hsuk., Yu, C. (Arch Intern Med) 2001; 161(); 264-271

Appendix 6: TACT vs. ACAM Published Supplement Regimen

Multi-Vitamin/Mineral/Trace Element	Total Daily Amount		
	TACT Low Dose Regimen (1 Pill)	TACT High Dose Regimen (6 Pills)	ACAM Published Regimen[1]
Vitamin A (as fish liver oil and beta-carotene)		25,000IU	5,000 - 10,000 IU listed for Vitamin A 10,000 - 20,000 IU listed for beta carotene
Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)		1,200mg	1,000 - 2,000 mg
Vitamin D_3 (as cholecalciferol)		100IU	50 - 400 IU
Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)		400IU	200 - 800 IU
Vitamin K_1 (as phytonadione)		60mcg	Not listed
Thiamin (vitamin B_1) (as thiamin mononitrate)		100mg	50 -150 mg
Niacin (as niacinamide and niacin)		200mg	25 - 100 mg
Vitamin B_6 (as pyridoxine hydrochloride)	25 mg	50mg	15 -25 mg
Folate (as folic acid)		800mg	400 - 800 mcg
Vitamin B_{12} (as cyanocobalamin)		100mcg	50 -200 mcg
Biotin		300mcg	200 - 300 mcg
Pantothenic acid (as d-calcium pantothenate)		400mg	250 -500 mg
Calcium (as calcium citrate and calcium ascorbate)		500mg	500 - 1000 mg
Iodine (from kelp)		150mcg	100 - 200 mcg
Magnesium (as magnesium aspartate, magnesium ascorbate and magnesium amino acid chelate)		500mg	400 - 600 mg

Multi-Vitamin/Mineral/Trace Element	Total Daily Amount		
	TACT Low Dose Regimen (1 Pill)	TACT High Dose Regimen (6 Pills)	ACAM Published Regimen[1]
Zinc (as zinc amino acid chelate)	25 mcg (as zinc gluconate)	20mg	15 -25 mg
Selenium (as selenium amino acid chelate)		200mcg	150 - 200 mcg
Copper (as copper amino acid chelate)	2 mg (as copper gluconate)	2mg	2 - 3 mg
Manganese (as manganese amino acid chelate)	15 mg (as manganese gluconate)	20mg	15 - 25 mg
Chromium (as chromium polynicotinate)	50 mg (as chromium picolinate)	200mcg	150 - 200 mcg
Molybdenum (as molybdenum amino acid chelate)		150mcg	50 - 100 mcg
Potassium (as potassium aspartate and potassium ascorbate)		99mg	50 -99 mg
Choline (as choline bitartrate)		150mg	50 - 100 mg
Inositol		50mg	50 -100 mg
PABA (as para-amino benzoic acid)		50mg	50 - 100 mg
Boron (as boron aspartate and boron citrate)		2mg	0.5 -1 mg
Vanadium (as vanadyl sulfate)		39mcg	15 - 30 mcg
Citrus Bioflavonoids		100mg	50 - 150 mg

See text for details of the process used to develop the actual formula for the TACT supplements.

Literature Cited

[1]Rozema TC. Special Issue: Protocols for chelation therapy. J Adv Med 1997;10(1):74.

Appendix 7: Concomitant Therapies/Routine Medical Care

The Coordinating Centers of the trial strongly recommend that TACT patients be treated in accordance with the prevailing guidelines regarding treatment for post-MI patients. These guidelines will be reviewed on a yearly basis and any modifications applicable to TACT patients will be disseminated throughout the study. Compliance with evidence-based therapy of TACT patients will be encouraged and enforced in the following ways:

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, below.
3. Sites will receive a quarterly "Report Card" of their use of indicated therapies.
4. Sites that fall below the 10% of the overall study median value will be contacted by the CCC to determine reason for non-compliance with evidence-based therapies.
5. Sites with continued non-compliance and no valid reasons for such may be suspended from future patient accrual.

Secondary Prevention

TACT patients all have had a prior MI. As such, guidelines for patients with established coronary disease apply.

Long-Term Use of Aspirin

The long-term use of aspirin in the post-infarct patient results in a significant reduction in subsequent mortality.[2] In six randomized, placebo-controlled trials in which patients were randomly selected between 1 week and 7 years after the initial infarct, meta-analysis reveals a reduction in vascular mortality of 13% among those randomly assigned to aspirin with a reduction in nonfatal reinfarction of 31% and nonfatal stroke of 42%. Although all of these trials involved the use of aspirin in doses ranging from 300 to 1500 mg/d, a recent trial of patients with chronic stable angina pectoris in which aspirin 75 mg/d was used demonstrated a significant reduction of 34% in the primary endpoint of nonfatal MI and sudden death. This suggests long-term use of aspirin in the postinfarction patient in a dose as low as 75 mg/d can be effective, with the likelihood that side effects can be reduced. Clopidigrel may be used as an alternative in aspirin allergic patients. Ticlopidine, an antiplatelet agent that has been effectively used in unstable angina and cerebrovascular disease, has not been studied in major clinical trials involving patients with acute MI. Other antiplatelet agents such as sulfinpyrazone and dipyridamole have been used in the post-infarct patient, but there is no evidence from these clinical trials that they were any more efficacious than aspirin alone.

Management of Lipids

Recent clinical trials[3] suggest that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures and strokes in persons with established CHD. An LDL cholesterol of <100 mg/dl is the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints as well as by prospective epidemiologic studies. This goal should apply to both those with established CHD as well as those with CHD risk

equivalents. Thus, all TACT patients should have a goal of LDL < 100mg/dl. This can be reached, first, through therapeutic lifestyle changes including diet and exercise. In addition, these persons can be started on medications including statins, nicotinic acids or fibrates.

Beta-Adrenoreceptor Blockers

Several studies involving tens of thousands of patients, have demonstrated the benefits of β-blockers in post-MI population. This benefit is seen with a reduction in mortality due to sudden cardiac death, as well as non-sudden cardiac death.

Of the currently available agents, only timolol,[4] propanolol[5] and metoprolol[6] have been shown to have a reduction in mortality. The benefits observed in their respective studies, range fro 27% to 36%. The benefit of long-term use of β-blockers is magnified even more, in high-risk individuals. These are currently defined as individuals with: prior infarction, anterior wall infarction, advanced age, complex ventricular ectopy and hemodynamic evidence of LV systolic dysfunction.

It is still debatable if low-risk individuals (those not fitting the above criteria) benefit from long-term use of these agents. The benefit-risk analysis, accounting for the potential adverse effects of long-term use of these agents, favors its use in this population.

There are no studies showing that the long-term administration of β-blocking agents in post-MI patients who underwent revascularization, is beneficial. However, it is believed that the effects on this population should not be any different than in those individuals that did not get any form of revascularization.

The collective totality of the evidence shows a reduction in mortality, a reduction in re-infarction and an increase in the probability of long-term survival by almost 40% in post-MI patients. The benefits outweigh the potential and minimal risks associated with special populations such as in patients with diabetes, asthma, obstructive pulmonary disease and peripheral vascular disease. For this reason, β-blockers are recommended for the long-term use in post-MI patients, even in the populations described above.

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are also of value in selected patients who have recovered from an acute infarction through their ability to interfere with ventricular remodeling and thus attenuating ventricular dilation over time. The clinical result is a lessened likelihood for development for CHF and death. In addition, the likelihood of a recurrent MI may also be reduced.

The expression of tissue ACE within the heart probably arises from vascular endothelium. In the setting of myocardial necrosis and fibrosis, relatively high concentrations of ACE can be found in the myocardium compared with normal ventricular myocardium. These observations, coupled with experience in both rat model of MI and large randomized clinical trials, have established that use of ACE inhibitors begun after a patient has recovered from acute MI improves long-term survival, provided the infarct was large and anterior in location and results in significant impairment of LV contractility. Specifically, in the Survival and Ventricular Enlargement (SAVE) trial,[7] patients received captopril at a mean 11 days after onset of infarction, resulting in approximately 20% reduction in

mortality. The Acute Infarction Ramipril Efficacy (AIRE) trial,[8] in which patients who had been in clinical heart failure during the first day of their infarct and were then randomly assigned an average of 5 days after onset of infarction to either ramipril or placebo, resulted in an approximate risk reduction of 27% in all-cause mortality. Similarly, the Trandolapril Cardiac Evaluation (TRACE) trial,[9] in which patients with LV dysfunction on echocardiogram were randomly assigned to receive either trandolapril or placebo a median of 4 days after onset of infarction, demonstrated a 22% reduction in mortality.

The Studies of Left Ventricular Dysfunction (SOLVD) trial[10] evaluated the ACE inhibitor enalapril in 4228 asymptomatic patients with LV ejection fraction less than 0.35, 80% of whom had experienced a prior MI. However, randomization was carried out considerably later on the average than in the SAVE and AIRE trials. The prevention arm of the SOLVD trial revealed a trend toward improved mortality but not a statistically significant difference. On the other hand, SOLVD did demonstrate a significant risk reduction of 20% for the combined endpoints of death or development of CHF requiring hospitalization.

In secondary analyses of the ACE inhibitor trials[7], the benefit of treatment appears to be primarily in patients with anterior infarctions of LV ejection fraction below 40%. Some rationale exists for the use of these drugs in all patients after MI, based on the observation in the SAVE trial that the likelihood of recurrent MI was reduced by approximately 25% in treated patients. However, this finding is based on post hoc analysis and is currently being studied in prospective trials. Therefore, all TACT patients whose ejection fraction is below 45% should be administered ACE inhibitors; as well as all diabetics with normal ejection fraction.

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[9]Kober L, Torp-Pedersen C, Clarsen JE, et al. A clinical trial of the ACE inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670-1676.

[10]The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685-691.

Appendix 8: EQOL Analyses

This appendix provides additional details on the economic analyses, cost-effectiveness analyses, and the quality of life data collection and analyses.

Economic Data

Direct Medical Costs

We expect patients in this study to be ambulatory and stable at the time of enrollment. Thus, the major medical resources of interest to the study are those involved in the administration of the chelation strategy and the high-dose supplement strategy and those required to treat the patient's CAD from study enrollment through 24 months (the minimum follow-up for all patients). Follow-up care will include both hospitalizations and outpatient visits and tests. Some of this care will be required for the patient's CAD and some may be provided for unrelated co morbidity.

In this trial, we will measure and compare all-cause medical resource use, rather than CAD-specific care.

The cost of the chelation therapy strategy includes not only the cost of the infusion bag, but also the personnel to assess the patient and administer the infusion plus any routine laboratory testing considered a part of the chelation strategy. We will work with Dr. Martin Dayton, the chelation consultant to the TACT CCC, and the chelation practitioner co-investigators at the TACT clinical sites to define the major resource inputs and associated costs of the chelation therapy strategy.

For each study patient, major follow-up resource use will be recorded on the clinical case report form. Interval resource use data will be collected at each follow-up clinical contact on hospitalizations (including length of stay and reason for admission), major diagnostic tests, and medication use. Any custodial care or nursing home stays will also be recorded. Hospital and physician costs will be calculated from these data as described below.

Indirect Costs Due to Lost Productivity

Medical problems and their treatment regimens can affect a variety of economic measures other than direct medical costs. Whether these factors should routinely be incorporated into an economic analysis using the societal viewpoint remains quite controversial For this study, at baseline we will collect a brief information set about the patient's employment status and type of work (for those who have worked within the previous six months). We will also collect the patient's total annual employment income. Additional demographic/socioeconomic measures to be collected at baseline include years of education, marital status, and number of persons in the household. Follow-up data collection will include an assessment of follow-up work status and interval changes including time lost from work. These data will be used for descriptive purposes and to estimate indirect costs of illness that can be used in a cost-effectiveness sensitivity analysis to determine whether differential changes in productivity between the two treatment arms in each of the two randomized comparisons (should such changes be observed) affect the economic attractiveness of the investigational therapy arm.

Estimation of Costs

We will estimate the major components of true direct medical care costs using a societal perspective. Hospital costs will be assigned using hospital billing data from prior DCRI economic trials in similar cohorts. We will use the resource use variables in TACT to develop a resource-based regression model that will partition the costs of hospitalization among these variables. With these derived cost weights and the resource data from TACT we can estimate the costs of hospitalization in this trial. Physician visit costs will be estimated using the Medicare Fee Schedule along with counts of major procedures and days in the hospital. The costs of the chelation therapy will be developed as described above.

An alternative to the use of hospital billing data for the estimation of hospital costs is the use of Medicare Diagnosis-Related Group (DRG) reimbursement rates. These have the advantage of representing a national cost estimate for hospital care, but have the strong disadvantage of being insensitive to shifts in resource use that do not affect the DRG assignment. We will use these data in secondary analyses from the CMS perspective.

Professional fees will be indexed to the major cardiac procedures and other physician services performed on each patient as identified on the TACT case report forms. Since the Medicare Fee Schedule is keyed to the current procedural terminology (CPT) codes, a map will be created between case report form and other study form procedures and CPT codes so these fees can be assigned. We have used this approach successfully in a number of recent trials. Because there is no Medicare Fee or CPT code for chelation, we will work with the chelation experts in TACT to estimate an appropriate cost. Specific reference will be made to other outpatient-based infusion therapies that do have established Medicare Fees.

Total costs will be estimated by summing hospital, outpatient, professional, and medication costs.

<u>Cost Analyses</u>

Costs for the two therapeutic arms in each of the two primary comparisons will be compared in three stages: short-term costs (30 weeks), intermediate-term costs (1 year), and long-term costs (2 years). The short-term cost picture will cover the intensive phase of therapy, defined as the total medical costs incurred during the first 30 weeks after enrollment in the trial. For the chelation therapy arm, these will include the cost of treatment for the first 30 infusions plus adjunctive medical therapy and any early complications that occur. For the placebo infusion arm this will include the cost of the initial medical regimen along with the cost of any early complications that occur. The cumulative one year cost comparison will include the costs of therapy plus any subsequent induced costs (or cost savings) over an arbitrarily defined intermediate follow-up period. The cumulative comparison of total study costs out to 2 years will provide a longer-term perspective on cost differences and will also provide the basis for lifetime extrapolations required for cost-effectiveness analysis.

In order to provide a second perspective on cost differences for each strategy in TACT, we will also directly measure resource consumption levels for each treatment arm. In particular, we will tally major healthcare resource items used, including hospital days (intensive care, step-down units,

wards), cardiac procedures (e.g., cardiac catheterization, coronary angioplasty, coronary stenting, coronary bypass surgery), and adjunctive therapies.

Primary statistical comparisons will be performed between the two treatment arms by intention-to-treat. For statistical testing of cost data, our current approach is to use a nonparametric test, such as the Wilcox on rank sum test, but we can use a standard t-test after log transformation of the data. If log transformation does not establish an approximately normal distribution, we will explore the class of Box-Cox transformations to find the best symmetrizing transformation. Confidence limits around the observed cost differences can be created using several different approaches. In recent work, we have used bootstrap methods for this.

Cost-Effectiveness Analyses

To estimate the cost-effectiveness of the experimental arms, we will calculate a set of base case cost-effectiveness ratios that define the incremental cost required to add an extra life year with the investigational chelation therapy arm relative to control medical therapy, and corresponding analyses for the two supplement arms. A second series of analyses will calculate the corresponding cost-utility ratio. These analyses will use the societal perspective and will be based, to the extent possible, on the empirical data from the TACT trial. Where extrapolations from empirical data and other assumptions are required, extensive sensitivity analyses will be performed. The cost-effectiveness ratio will take the general form:

$$CE_{Incremental} = \frac{Cost_{Investigational} - Cost_{Control}}{LE_{Investigational} - LE_{Control}}$$

CE = cost effectiveness
LE = life expectancy

At the time of analysis, costs will be adjusted to the most recent year for which the consumer price index has been published. Both costs and life expectancy will be discounted to present value at a 3% annual discount rate (with rates from 0 to 7% examined in sensitivity analyses). It is clear that the majority of patients will remain alive at the conclusion of the trial. Thus, a method is required for converting observed trial experience into the corresponding lifetime survival and cost figures needed for use in the incremental cost-effectiveness calculations. The need for lifetime cost-effectiveness ratios derives from the lack of adequate benchmarks for other time frames. Although use of a shorter time frame (e.g., 2 years) is attractive because it can reduce or eliminate the need for difficult and uncertain extrapolations, cost-effectiveness ratios expressed in terms of the shorter time frames will typically be larger (more unfavorable) than the corresponding lifetime values. Clearly, therefore, the time frame of a cost-effectiveness ratio can substantially affect its interpretation. Thus, as recommended by the US Public Health Service Guidelines on cost effectiveness, we feel that lifetime extrapolation of costs and survival benefits are necessary to provide study results comparable to those of most prior medical cost-effectiveness analyses. However, we will also present cost-effectiveness ratios based on the within-trial, 2-year follow-up that is expected for all patients. These will represent secondary analyses.

There are two general methods that we have previously used to make the necessary lifetime extrapolations called for in cost-effectiveness analysis of an empirical dataset: use of secondary data sources on which to base the extrapolation and use of a Markov model. An important secondary data source that we have available for use in this study is the extensive Duke Cardiovascular Disease Databank. The Databank currently contains over 10,000 patients referred for coronary angiography (1971-2000) who would meet the principal eligibility criteria for TACT and for whom we have up to 20 years of follow-up. Their survival data could be used to supplement and extend the empirical TACT survival data using a Cox regression model-based approach, similar to the one we used successfully in the GUSTO I and PURSUIT cost-effectiveness analyses.

For TACT-eligible patients identified in the Duke Database who have survived $\geq$ 2 years following their index MI, we will use their follow-up data to estimate TACT patient-specific life expectancy in 4 major steps:

1) Using Cox Proportional Hazards regression methodology for left-truncated and right-censored data, model the hazard of death as a function of age, adjusting for additional prognostic factors through covariates. This model "adjusts for" age as the metric over which the hazard is computed and treats additional prognostic factors as covariables. By estimating the hazard over the age metric (rather than over the time metric, as is traditionally done), we can produce data-based survival predictions through a much longer time period due to the broad representation of ages in our database. The hazard relationship, which under proportional hazards is well estimated through the age range represented in our data, will be used for prediction on a patient by patient basis. Thus, the need for parametric extrapolation of the data used in our GUSTO I analysis is eliminated.

2) Again using a Cox Proportional Hazards regression model together with the extensive post-MI survival experience available in the Duke Database, we will estimate the long-term survival impact of a non-fatal endpoint MI occurring within the 3 year average follow-up period for TACT. This model will provide a measure of the increased relative risk attributable to an MI for later incorporation in the individual patient predictions.

3) The observed survival experience in the TACT trial will be modeled to ensure that estimated differences in life expectancy are based solely on treatment-effect differences and not on covariate imbalances that may exist between the survivors in each treatment group. This survival model will stratify on treatment group (if necessary to satisfy the proportional hazards assumption) and adjust for other significant predictors of survival within the TACT follow-up period.
4) Finally, using the models described above, we will produce a covariate-specific lifetime survival prediction for each patient. The individual predicted survival estimates will be averaged over all patients for both treatment groups to produce a mean predicated survival estimate for each treatment group. The estimated mean survival curves will then be integrated over a lifetime to obtain mean life expectancy for each treatment group. Differences between the area under each survival curve will be computed to obtain the incremental life expectancy due to the investigational treatment. All the major steps in this methodology have been successfully used in the recently published PURSUIT cost-effectiveness analysis.

Utilities will be assessed at baseline and at 3 points in follow-up using the EuroQoL method In order to convert these data to quality-adjusted life expectancies (QALE), assumptions must be made about the distribution of utilities in the study population after the 2-year follow-up. Most prior studies have

applied a constant utility value to survival data to generate QALE estimates. While this approach has the advantage of computational simplicity, we will examine a data-driven alternative. Specifically, we will perform a regression analysis of patient utilities using the empirical TACT data collected to identify major baseline determinants (including treatment assignment). We will also test to see whether there are any important treatment-by-covariate interactions that need to be included in the model. Finally, we will examine the stability over time of utilities and the temporal relationship with major determinants. The resulting model can then be used to assign (predict) utility values to each year of survival after the second year for each TACT patient.

We will use a similar approach for estimating post-2-year cost differences between treatment groups. A regression model will be constructed to define the major baseline determinants of medical costs in TACT (including treatment group). We will test for important treatment-by-covariate interactions and will examine whether determinants of short-term costs (i.e., 6 months) differ from those of intermediate (i.e., 12 months) or long-term (i.e., 2 years) costs.

Thus, we will have a rich empirical data set involving 2 years of cost and utility data and up to 4 years of survival data. We will also create estimates for each TACT patient of life expectancy, quality-adjusted life expectancy, and lifetime medical costs. These data will be used to calculate the lifetime and within-trial cost effectiveness and cost-utility ratios. The lifetime incremental cost-effectiveness ratio will be the principal measure (reference or base case) reported from these analyses with the cost-utility ratio and within trial ratios being secondary. Although the US Public Health Service Panel on Cost Effectiveness in Health and Medicine has recommended that the reference case employ quality-adjusted life expectancy (QALYs), QALYs remain very controversial in medicine. Thus, we prefer to use life expectancy in the reference case with QALYs used in a sensitivity analysis. The cost-effectiveness analyses will use a 3% discount rate in the reference case for both costs and life expectancy.

As reviewed recently by O'Brien and colleagues, there are two schools of thought about cost-effectiveness analyses. The traditional approach is to hold that the models are deterministic. This approach uses sensitivity analyses to assess the reasonableness and importance of starting parameters. More recently, as cost-effectiveness analyses have been built on empirical large-scale randomized trial data, it has been possible to view the inputs to cost-effectiveness ratios (i.e., costs, clinical outcomes) as stochastic, and therefore possessing a quantifiable level of uncertainty. The methods of quantifying the uncertainty around cost-effectiveness ratios constitute an area of active research. Many, including our group, favor the use of a nonparametric bootstrap approach. In the recently published Bypass Angioplasty Revascularization Investigation (BARI) cost-effectiveness analysis, we assessed the precision of the ratio of costs to the effectiveness of treatment using the bootstrap method (1000 samples with replacement with a cost-effectiveness ratio calculated for each sample). We propose to use a similar methodology for the TACT cost-effectiveness analysis. In addition, we will perform comprehensive sensitivity analyses around major assumptions and extrapolations. For empirically derived parameters such as survival differences, costs, and utilities, 95% confidence intervals will be used to define plausible variations from observed values. We will determine threshold values for those variables that yield cost-effectiveness ratios of $50,000 and $100,000 per life year added.

Major sensitivity analyses to be performed will consider 1) variations in relative efficacy from that observed in the trial; 2) variations in the persistence of benefits observed during the TACT Trial (i.e.,

survival curves converge or diverge after 4 years); 3) variations in the initial treatment-related costs of the chelation therapy and placebo infusion arms; 4) variation in the follow-up costs for these two arms; 5) variations in the utility value of the survivors; and 6) variations in the discount rate applied (0-7%). If significant indirect cost differences are observed between treatments these will be added to the total medical costs in a sensitivity analysis. Appropriate two-way and higher-order sensitivity analyses will be defined at the time of analysis based on the results of the above one-way sensitivity analyses.

It must be emphasized that although the general plan of our cost-effectiveness analyses can be specified, there is clearly an iterative quality to building successful cost-effectiveness models.

Quality of Life and Health Status Data

Expected Health-Related Quality of Life Effects

Because chelation therapy and high-dose supplements are being used in TACT in a stable post-MI population in anticipation of future events more than as a treatment for ongoing cardiac symptoms, their likely effects on quality of life over the duration of the study are difficult to anticipate. However, it is reasonable to assume that any beneficial effects of chelation on coronary atherosclerosis might be accompanied by less angina, improved functional status, and possibly less heart failure symptoms.

We have no prior trial data involving the use of chelation therapy for CAD that would allow us to anticipate the specific quality of life benefits of the chelation strategy being tested in TACT. Thus, we feel that a comprehensive but efficient quality of life assessment that is able to detect both positive and negative effects of the investigational arm is a critical portion of the overall TACT project.

Content of Health-related Quality of Life Battery

Because there is no consensus or ideal quality of life measure that is clearly suited for use in TACT, we propose to use a battery of validated instruments that build on a generic core supplemented by more detailed and/or disease-specific measures where necessary to provide a comprehensive assessment of health-related quality of life. The major quality of life effects of the chelation therapy arm are likely to manifest themselves as changes in what the patient can do (or feels capable of doing) physically, the level of somatic symptoms, and the level of psychological well-being. These domains will be assessed in detail. Other quality of life effects, such as altered role functioning and social functioning, would be expected to occur as a consequence of changes in the physical or psychological status. These domains will be assessed briefly. Because of the paramount importance of maintaining an efficient overall study operation without excessive burden of data collection, the desire for comprehensiveness in quality of life assessment must be carefully balanced against the efficiency and cost of data collection.

The generic core instrument we propose to build on is the Medical Outcomes Study Short Form (SF-36).[46,47] This profile has the advantage of being comprehensive in scope and widely used, with a large normative database available. However, its brevity and generic focus necessarily limit its sensitivity as a stand-alone instrument. The SF-36 is composed of 9 scales, which can be used separately or as a set: physical function, role function-physical, role function-emotion, general

health, bodily pain, social function, psychological well-being/mental health, vitality, and health transitions. Each scale is scored separately and is customarily transposed to a 0 to 100 scale.

Recent work has suggested that the SF-36 physical function scale is not as sensitive to clinically important changes over time in coronary disease patients as is a disease-specific measure. Thus, we will supplement the SF-36 with the 12-item Duke Activity Status Index (DASI), which has been validated in cardiac patients against maximal oxygen uptake measured at exercise (VO_2 max). Unlike most other physical function scales (such as the one in the SF-36), which are constructed using psychometric principles, the DASI was constructed specifically to be a questionnaire-based analog of the maximal exercise stress test used for cardiac patients. We have used this scale extensively in prior clinical trials. DASI will be one of three pre-specified major quality of life endpoints for TACT. We will also obtain three brief supplemental measures of functional status, the Bed Days and Disability Days questions from the National Health Interview Survey, and a four-level ordinal global assessment of the effect of the patient's health on his or her ability to do activities.

The presence of anginal symptoms will be assessed with the symptom scales from the Seattle Angina Questionnaire. They will be supplemented with the Canadian Cardiovascular Society Class for angina, which will be collected at baseline and at 3 points during follow up as part of the Quality of Life questionnaire.

General psychological well-being/mental health will be assessed using a five-item mental health scale from the SF-36. This measure has been shown to correlate well with clinically diagnosed anxiety and depression. This scale will be the second of three pre-specified major quality of life endpoints for TACT. General health perceptions will be assessed using the five-item scale from the SF-36 that includes a five level ordinal ranking of the patient's overall health (excellent to poor). Scales from the SF-36 will be used to assess role functioning (both physical and emotional related limitations), bodily pain, social functioning, and vitality. Employment details will be obtained using an abbreviated series of questions adapted from the NHLBI Bypass, Angioplasty, Revascularization Investigation (BARI) Substudy in Economics and Quality of Life (SEQOL).

Measurement of Utilities

Patient-specific utilities will be assessed by patient interview using the EuroQoL. The EuroQoL-5D consists of two parts: a 5 dimension assessment of "your own health state today," which allows for definition of 243 discrete health states that can be mapped to previously derived population utility weights, and a self-rating (0-100) "thermometer" of current health-related quality of life.

Types of Assessments

EQOL data will be collected on all randomized patients at baseline by the Site Coordinator. During follow-up, EQOL personnel at the DCRI will conduct the QOL interviews, using a structured interview format, with 900 patients randomly selected from the total sample of patients enrolled in TACT. The baseline quality of life questionnaire will supply comprehensive information on pre-randomization status including utilities that can be used to check that randomization did achieve balance between the treatment groups and can be used to put follow-up outcomes in perspective. The follow-up assessments will be used to assess differential treatment-related changes over time. Two types of questionnaires will be employed during study follow-up: full and proxy. Full questionnaires will

repeat all the measures from the baseline interview and will be administered at six months, one year, and two years. During other scheduled clinical contacts, patients will be asked about interval medical care resource use; these data will be recorded on the case report forms. Proxy questionnaires will be used when a patient has died or become incapacitated in the follow-up interval. Items on the proxy form will be those that can be reliably obtained from a relative or caretaker, such as details of interval medical care.

Analyses

For each of the quality of life measures examined in this study, data analysis will proceed in two stages. First, we will provide simple descriptive and comparative analyses by intention-to-treat. Second, we will examine changes over time from baseline and identify the major determinants of those changes using regression analysis. To deal with the multiple comparisons problem arising from testing each individual scale separately, we propose two complementary approaches. First, we will pre-specify functional status (from the Duke Activity Status Index), psychological well-being (from the SF-36), and patient utilities (from the EuroQoL) as the primary quality of life comparisons of interest and assign all other comparisons to a secondary (exploratory) status. Second, we will employ a type of Bonferroni correction that controls the Type 1 error rate for families of comparisons (e.g., different functional status measures).

Using data collected at the baseline interview, we will summarize quality of life in each domain for both treatment groups defined according to intention-to-treat. This preliminary comparison will ensure that the randomization process assigned essentially identical groups of patients to the two treatment arms. With 1000 randomized patients in the QOL substudy, the groups should be balanced on major quality of life parameters.

Comparison of follow-up outcomes will consider three phases of trial follow-up: early (i.e., the six-month interview), intermediate (i.e., the 1-year interview), and late (i.e., the 2-year interview). We have chosen not to collect follow-up quality of life data past the point where all patients in the trial will be followed (i.e., 2 years) in part because of the difficulty in accounting for censoring in differential length of follow-up and analyses of these types of data, but primarily because the proportion of the population receiving these longer follow-ups will be significantly smaller than the total cohort and consequently statistical power will be much lower for such comparisons.

There are two important methodologic challenges in the analysis of these data that must be considered: the effect of differential mortality in the treatment arms and the effect of missing data (from death, incapacity, or loss to follow-up). If the primary study hypothesis is confirmed, analysis of quality of life data may be complicated by the fact that the chelation therapy is more successful at keeping patients alive. While the mortality difference in this trial is not expected to be large, even a relatively small difference may create a paradox in the quality of life data such that the more effective therapy is associated with worse quality of life (since the patients with the worst quality of life may have died in the medical arm but have been saved in the chelation arm.) There are three potential analytical solutions to this problem that we have used: ordinal endpoints, compound endpoints, and Korn's "area under the quality of life" curve. The ordinal endpoint approach involves insertion of death into the quality of life scale (e.g., DASI) as the worst possible outcome. This has the advantage of explicitly accounting for death in the analysis of these endpoints. However, potential problems are also created since the worst scale value may be a legal value that is already

assigned to some living patients. In this case, assigning the dead patients to this state is equivalent to assuming equality between the worst health state reflected on this scale and death. This often does not reflect the views of the patients in these lowest health states. A related option, therefore, is to reconstruct the scale as an ordinal measure with death by itself at the lowest level. As long as ordinal analysis methods are used, no assumption is required about how much worse death is than the lowest (living) health state on the scale. This solution may be adequate for scales that already exist on an ordinal scale but may be problematic for interval data scales that have both a rank ordering and a specification of the distance between items on the scale (e.g., DASI).

An alternative approach we have used for this problem is to model a compound endpoint that explicitly incorporates both survival and quality of life data. For example, we could use regression models to compare treatments according to the probability of being alive at a specified follow-up point (e.g., 2 years) and in a health state $\geq$ some specified level.

Another alternative we will examine is based on Korn's recently published work involving methodology developed for analyzing quality of life data collected at periodic intervals in a clinical trial where there is a need to account for missing data due to patient death, missed follow-up visits, or to unequal follow-up with resulting censoring. This method involves estimating the distribution function of an area under the quality of life score for each treatment group. Each individual patient assessment (baseline, 6 months, 1 year, and 2 years) is scored separately and an interpolated area under the curve (AUC) will be calculated for each patient (quality of life score versus follow-up time). Korn's method of applying survival analysis to quality of life data provides a method of dealing with non-random censoring of the quality of life curve due to death.[57]

Another potential problem in the analysis of quality of life data is the occurrence of missing values. These can arise because of missed follow-up, patient incapacity, or patient refusal to participate in part or all of the interview. We will, in conjunction with Dr. Lee, be very carefully tracking study patient follow-up to minimize unnecessary loss of data. Our group has extensive experience in following large, geographically diverse cohorts in randomized trials (such as the 41,000 patient international GUSTO trial that had a 98% follow-up rate or the Duke Databank population of over 20,000 patients with a 97% successful follow-up rate). We have individuals in our group (including Nancy Clapp-Channing, the EQOL Study Coordinator) who have particular expertise in finding "lost" patients. Thus, our principal approach to missing data will be to minimize its occurrence. However, patient refusal and patient incapacity will create missing values even with 100% follow-up. We expect refusal rates to be quite low overall in this study. In a 2966 patient quality of life substudy in the GUSTO trial, we had a 1% refusal rate at each of the three interviews. The rate of patient incapacity in the trial is uncertain but should be similarly low. Thus, we expect to have analyzable data on $\geq$ 95% of surviving patients at each follow-up interview.

Literature Cited

[1]Hlatky MA, Boineau RE, Higginbotham MB et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Amer J Cardiol 1989;64:651-4.

[2]Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: Manual & Interpretation Guide. Boston: Nimrod Press, 1993.

[3]EuroQol Group. A new facility for the measurement of health related quality of life. Hlth Policy 1990;16:199-208.

Appendix 9: Conflict of Interest

Introduction

The Trial to Assess Chelation Therapy (TACT) is a multicenter study designed to test the effects of chelation therapy and antioxidant and mineral supplements in reducing further clinical cardiovascular events in patients with coronary heart disease. Because the findings of this investigation may have implications for future clinical practice, potential conflicts of interest will be addressed.

The TACT Investigators recognize that bias is a concern for any clinical trial, and the study design has incorporated a number of safeguards against the introduction of bias. These include randomization into one of the four treatment groups, the management and analysis of data by a DCC, the use of an independent Clinical Events Committee for determination of clinical end points, and an independent Data and Safety Monitoring Board to monitor the study and evaluate the safety and efficacy of the treatments. This randomized, double-blind, placebo-controlled, 2x2 factorial trial will compare chelation therapy and high and low-dose antioxidant and mineral supplements.

Nevertheless and despite these safeguards the TACT Investigators realize that concerns about real or potential conflicts of interest may arise. In a broad study comparing strategies of treatment using common medications and therapies, it may be impossible to entirely eliminate any possible appearance of conflict of interest, as this would essentially require the investigators to give up many routine professional activities. Where potential conflicts exist, the TACT Investigators have endorsed the rational management of these potential conflicts according to pre-agreed guidelines and principles. The TACT Investigators have agreed to a policy on conflict of interest, which has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The TACT Investigators also endorsed the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine[1] dealing with these issues, and have agreed to make the TACT policy consistent with the record of that conference.

To address actual or perceived conflicts of interest, the participating TACT Investigators voluntarily agree to abide by the guidelines described in this policy statement.

Individuals to be Governed by These Guidelines

Members of the TACT Research Group who will be governed by these guidelines include the TACT Principal Investigator, the Project Director, the Project Administrator, the Project Administrative Assistant, the Site Investigator at each Clinical Site, professional staff in the CCC, DCC, and EQOL CC. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for TACT at clinical sites, affiliated hospitals or Core Laboratory will also be governed by these guidelines.

The Site Investigator of each participating site will review the guidelines with all appropriate staff prior to the start of patient recruitment and will review the guidelines at least annually thereafter.

Time Period of the Policy

The guidelines set forth in this policy commence at the start of patient recruitment and will terminate at the time of initial public presentation or publication of the principal results. Investigators not privy to end point data who discontinue participation in the trial during recruitment will be subject to these guidelines until their departure from the study.

Financial Guidelines

Activities not explicitly prohibited, but to be reported annually to the Study Chair and maintained by the CCC include:

- Stock or stock option in any of the pharmaceutical companies or medical equipment companies who have provided financial support for the study.
- Retainer-type consultant positions with these companies for the time period defined above.
- An ad hoc consultant relationship to companies providing drug devices or financial support to the trial.
- Participation of investigators in any educational activities sponsored by the companies.
- Participation of investigators in other research projects supported by the companies.
- Financial interests in these companies, over which the investigator has no control, such as mutual funds or blind trusts do not need to be reported.

CCC will maintain conflict of interest statements updated annually from each site principal investigator.

Reporting of Financial Disclosures and Other Activities

The TACT Investigators agree to update their financial disclosures and related activities as described above on an annual basis and submit these data to the CCC for storage. The CCC will maintain the confidentiality of these records and present them to a review committee, to be constituted by the Study Chair. In the case of actual or perceived conflict of interest, the Study Chair will bring it to the attention of the NHLBI Program Office and the Data and Safety Monitoring Board to discuss whether an individual should be eligible for certain study activities such as membership on policy making committees or writing teams for study manuscripts.

Review of Policy Statement

The TACT Investigators agree to review these guidelines on an annual basis and take any additional steps to insure the scientific integrity of the trial.

Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest may vary between participating institutions, in addition to the above policy, it is expected that investigators will comply with the policies on conflict of interest, which exist within their individual participating institutions (i.e., medical schools and hospitals). This is the responsibility of each individual investigator.

Prototype Investigator and Sub-Investigator Conflict of Interest Form

Investigator:	**Sponsor Name:** MSMC-MHI, NIH

Name of Investigator/Sub-Investigator completing this form (print or type):

_____

Your mailing address:

_____

_____

Information Reported: ☐ Initial ☐ Update ☐ One-Year Follow-Up

Do any of the financial interests or arrangements described below apply to you, or any member of your immediate family (spouse and/or dependent children) during the time you will be conducting the Clinical Trial and for one year after completion:

YES	NO	
☐	☐	A significant equity interest in the Sponsor, companies involved in TACT, * or companies producing the type of products used in the trial, that when aggregated for the investigator and the investigator's spouse and dependent children exceeds $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does represent more than a 5 % ownership interest in any single entity. If YES, please describe: _____ _____
☐	☐	Salaries, royalties or other payments that when aggregated for the investigator and the investigator's spouse and dependent children over the next twelve months, are reasonably expected to exceed $10,000. If YES, please describe: _____ _____

I declare that the information provided on this form is, to the best of my knowledge and belief, accurate and complete. This form is to be updated annually OR if within one year, new reportable significant financial interests are obtained. If my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of one year from the date of this form, I agree to notify Mt. Sinai Medical Center promptly.

Your Signature:_____**Date Signed:** _____

*The Pharmed Group, Omnicomm, Quantum Healthcare Consultants, Accu-Care, Quest Diagnostics, DCRI
Please retain a copy of each completed form for the Investigator's Regulatory Binder.

Designated Official Review
I have reviewed this Conflict of Interest Form and believe that:

- ☐ **no potential for conflict of interest/commitment exists**
- ☐ **potential for conflict exists, and steps have been taken to resolve the potential conflict, as outlined in the attached letter**
- ☐ **a potential conflict of interest/commitment exists that requires review**

Printed Name: _____ **Date: _____**

Signature: _____

Prototype Investigator and Sub-Investigator Financial Disclosure

Investigator:	**Sponsor Name:** MSMC-MHI, NIH

Name of Investigator/Sub-Investigator completing this form (print or type):

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_____

_____

Your mailing address:

_____

_____

Information Reported: ☐ Initial ☐ Update

Do any of the financial interests or arrangements described below apply to you, or any member of your immediate family (spouse and/or dependent children) during the time you will be conducting the Clinical Trial and for one year after completion:

YES	NO	
☐	☐	A significant equity interest in the Sponsor, companies involved in TACT, * or companies producing the type of products used in the trial, that exceeds US$50,000 or that has a value that cannot be easily determined through reference to public prices. For example, any ownership interest, stock options, or other financial interest (including patent, trademark, copyright, licensing agreement and/or royalty arrangement). If YES, please describe: _____
☐	☐	Significant payments of other sorts from the Sponsor, companies involved in TACT, * or companies producing the type of products used in the trial, the total of which exceeds US$25,000, excluding the costs of conducting the trial or other clinical trials. For example, payments made to the investigator or the institution to support activities (including a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If YES, please describe: _____
☐	☐	A proprietary interest in the test product such as a patent, trademark, copyright, licensing or royalty agreement. If YES, please describe: _____
☐	☐	Financial agreement with Sponsor, companies involved in TACT, companies involved in TACT, * or companies producing the type of products used in the trial, whereby the value of compensation could be influenced by the outcome of the trial. For example, compensation that is explicitly greater for a favorable outcome, an equity interest in the Sponsor company (such as stock and/or stock options), or compensation tied to future sales of the product, such as a royalty interest. If YES, please describe: _____

I certify that the above information, to the best of my knowledge and belief, is complete and accurate. Furthermore, I agree to promptly notify the trial Principal Investigator if my financial interests, or those of my spouse or dependent children, change during the course of the trial or within one year after trial completion.

Your Signature:_____**Date Signed:** _____

*The Pharmed Group, Omnicomm, Quantum Healthcare Consultants, Accu-Care, Quest Diagnostics, DCRI
Please retain a copy of each completed form for the Investigator's Regulatory Binder.

Literature Cited

[1]Parmley WW. 21st Bethesda Conference: ethics in cardiovascular medicine, October 5-6. J Amer Coll Cardiol 1990;16:1-36.