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Appendix 1: Statistical Considerations

) Sample Size and Power Calculations

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

vent rates for the primary composite endpoint and other clinical outcomes were examined in a roup of 7,002 patients with a history of myocardial infarction enrolled in the Duke Cardiovascular)isease Database between 1986 and 2000. These patients all underwent cardiac catheterization, but therwise satisfied all the inclusion/exclusion criteria specified for TACT. Based on follow-up of these)atients starting one month after their angiography (to avoid counting early interventional)rocedures based on treatment decisions made at the time of catheterization), the three-year rate for he occurrence of either death, myocardial infarction, or rehospitalization for a revascularization)rocedure 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 ates 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

compliance with the chelation infusions, since the vitamins will be much more convenient and or patients to comply than undergoing a three-hour infusion each week. We do not expect "drop-ins" in this trial given the blinded nature of both the chelation and the vitamin es. Finally, we have made allowance for loss to follow-up of up to 3% of patients in the trial. on these various assumptions, 2,372 patients will provide the trial with >85% power to detect reduction in the primary endpoint *for each treatment factor in the 2x2 factorial design*. Thus el of power that this number of patients will provide for detecting clinically meaningful ent differences is excellent.

tatistical Analysis

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

his factorial design, the primary statistical assessments will involve a comparison of the EDTA ation therapy arm with the placebo infusion group, and a comparison of high-dose nin/mineral supplementation with low-dose supplementation. The log-rank test[1], which is a ial case of the more general Cox proportional hazards model[2], will be the primary analytic tool in two-group comparisons for assessing outcome differences with respect to the primary clinical point. This approach focuses on the time from trial entry until the first occurrence of any ponent of the composite primary endpoint, taking into account varying lengths of patient follow- and censored observations. Using this procedure, the analysis strategy will be to first perform -group comparisons for each treatment factor in the study design, adjusting only for the other ign factor. That is, we will compare the outcomes of patients randomized to EDTA chelation rapy vs. those of the patients randomized to placebo infusion, stratified (adjusted) for the vitamin plementation groups. Also, we will compare the outcomes of patients randomized to high-dose plements versus the outcomes of those assigned low-dose supplements, adjusting for whether patients were allocated to EDTA chelation therapy or placebo infusion. These standard two- up comparisons will constitute the primary analyses to assess treatment differences. The nificance level for each comparison with respect to the primary endpoint will be set at α=0.05. plan-Meier survival estimates[3] based on the primary endpoint will be calculated for each treatment oup to display the outcome results graphically. Using the Cox proportional hazards model, hazard tios with 95% confidence intervals will be calculated for each treatment factor (EDTA chelation vs. acebo, and high dose vs. low-dose vitamins) as a further descriptive summary of the treatment fects. Prior to the hazard ratio calculations, however, the appropriateness of the proportional azards assumption of the Cox model will be assessed by an examination of log(-log) of the survival urves versus time, by use of a time-dependent covariate of treatment x log time, or by other formal sts of proportional hazards as outlined in Harrell.[4] Of special interest in assessing the effects of

:helation therapy will be a comparison of the event rates for the patients randomized to EDTA :helation 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, Q-wave versus non Q-wave), 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 (≤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".

Interim analyses

erim analyses will be performed at prescribed intervals (approximately every six months) for sentation to the Data and Safety Monitoring Board. The primary objective of these analyses will to ensure the safety of the patients enrolled in the trial. In these analyses, the accumulating data be evaluated for an unacceptably high frequency of negative clinical outcomes in any of the atment arms. In addition, however, the interim monitoring reports will also involve a review of the ntrol arm event rates for each treatment factor, status of patient recruitment, compliance with the dy protocol and therapy guidelines, the frequency of protocol violations, timeliness and accuracy in e submission of data forms, and other factors which reflect the overall progress and integrity of the dy. Prior to each meeting of the DSMB, the Data Coordinating Center will conduct the desired tistical analyses in accordance with the approved charter and prepare a summary report that will carefully and confidentially reviewed by the DSMB. The extracted data files and analysis programs each DSMB report will be archived and maintained at the Data Coordinating Center for the life of e study.

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

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

he analytic approach that will be used at the interim analyses for assessing treatment differences vill be the time-to-event analysis methods described in the study protocol, except that interpretation f statistical significance associated with treatment comparisons of the key study endpoint will be uided using the group sequential stopping boundaries outlined above.[7,8,9] The appropriateness of

e log-rank test (or equivalently the Cox model) in the group sequential framework has ly been well established.[10,11,12,13] For each of these interim analyses, the critical value of the istic and the corresponding p-value required for significance in that particular analysis will be ed so that significance can be assessed precisely. If significantly large and important nt differences are observed at any of the interim analyses, the Data and Safety Monitoring ıay recommend that randomization of patients be stopped, or that the design and conduct of be appropriately modified. The interim analyses will also include a presentation of Kaplan- urvival estimates and hazard ratios with confidence intervals to descriptively summarize the The appropriateness of the proportional hazards assumption will be assessed as outlined in tistical analysis appendix to the study protocol. Of special interest in the interim analysis will comparison of patients randomized to EDTA chelation therapy vs. the placebo infusion group time when the infusion phase of the intervention is completed. This analysis will only be gful after an adequate number of patients (20% or more of the overall population) have been d through the infusion phase of the intervention.

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

ıpproach to interim monitoring outlined above will be carried out in parallel for the assessment th treatments in the 2 x 2 factorial design.

the primary endpoint is a composite of death and several non-fatal outcomes, it will also be rtant to monitor the mortality component of this endpoint as part of the safety monitoring of the Thus mortality rates and associated confidence intervals for each arm in the factorial study ın will also be monitored at the interim reviews to ensure that the safety of patients enrolled in rial is not compromised. A summary of the incidence of other serious adverse events will also be larly reviewed by the DSMB.

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

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Appendix 2: 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.

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x 3: 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 4: 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 4 (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

pp 72-74 withheld in entirety
"proprietary info"

Appendix 6: Concomitant Therapies/Routine Medical Care

e Coordinating Centers of the trial strongly recommend that TACT patients be treated in cordance with the prevailing guidelines regarding treatment for post-MI patients. These guidelines ll be reviewed on a yearly basis and any modifications applicable to TACT patients will be sseminated throughout the study. Compliance with evidence-based therapy of TACT patients will e 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 latest reported NRMI [http://www.nrmi.org/index.html] incidences 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

is goal should apply to both those with established CHD as well as those with CHD risk . Thus, all TACT patients should have a goal of LDL < 100mg/dl. This can be reached, h therapeutic lifestyle changes including diet and exercise. In addition, these persons can on medications including statins, nicotinic acids or fibrates.

noreceptor Blockers

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

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

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

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

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

nsin Converting Enzyme Inhibitors

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

ression of tissue ACE within the heart probably arises from vascular endothelium. In the of myocardial necrosis and fibrosis, relatively high concentrations of ACE can be found in the dium compared with normal ventricular myocardium. These observations, coupled with nce in both rat model of MI and large randomized clinical trials, have established that use of ibitors begun after a patient has recovered from acute MI improves long-term survival, d the infarct was large and anterior in location and results in significant impairment of LV tility. Specifically, in the Survival and Ventricular Enlargement (SAVE) trial,[7] patients received

t a mean 11 days after onset of infarction, resulting in approximately 20% reduction in
The Acute Infarction Ramipril Efficacy (AIRE) trial,[8] in which patients who had been in
art failure during the first day of their infarct and were then randomly assigned an average
after onset of infarction to either ramipril or placebo, resulted in an approximate risk
of 27% in all-cause mortality. Similarly, the Trandolapril Cardiac Evaluation (TRACE) trial,[9]
atients with LV dysfunction on echocardiogram were randomly assigned to receive either
il or placebo a median of 4 days after onset of infarction, demonstrated a 22% reduction in

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

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

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Appendix 7: EQOL Analyses

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

conomic Data

irect Medical Costs

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

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

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.

Cost Analyses

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,

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

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

Effectiveness Analyses

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

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

CE = cost effectiveness
LE = life expectancy

the time of analysis, costs will be adjusted to the most recent year for which the consumer price dex has been published. Both costs and life expectancy will be discounted to present value at a % annual discount rate (with rates from 0 to 7% examined in sensitivity analyses). It is clear that e majority of patients will remain alive at the conclusion of the trial. Thus, a method is required for ɔnverting observed trial experience into the corresponding lifetime survival and cost figures needed ɔr use in the incremental cost-effectiveness calculations. The need for lifetime cost-effectiveness ıtios derives from the lack of adequate benchmarks for other time frames. Although use of a ıorter time frame (e.g., 2 years) is attractive because it can reduce or eliminate the need for ifficult and uncertain extrapolations, cost-effectiveness ratios expressed in terms of the shorter time ames will typically be larger (more unfavorable) than the corresponding lifetime values. Clearly, herefore, 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 ifetime extrapolation of costs and survival benefits are necessary to provide study results comparable o 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.

e are two general methods that we have previously used to make the necessary lifetime ıpolations called for in cost-effectiveness analysis of an empirical dataset: use of secondary data ces on which to base the extrapolation and use of a Markov model. An important secondary data ce that we have available for use in this study is the extensive Duke Cardiovascular Disease ıbank. The Databank currently contains over 10,000 patients referred for coronary angiography '1-2000) who would meet the principal eligibility criteria for TACT and for whom we have up to ears of follow-up. Their survival data could be used to supplement and extend the empirical T survival data using a Cox regression model-based approach, similar to the one we used essfully in the GUSTO I and PURSUIT cost-effectiveness analyses.

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

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

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

The observed survival experience in the TACT trial will be modeled to ensure that estimated ferences in life expectancy are based solely on treatment-effect differences and not on covariate balances that may exist between the survivors in each treatment group. This survival model will atify on treatment group (if necessary to satisfy the proportional hazards assumption) and adjust other significant predictors of survival within the TACT follow-up period.

Finally, using the models described above, we will produce a covariate-specific lifetime survival ediction for each patient. The individual predicted survival estimates will be averaged over all tients for both treatment groups to produce a mean predicated survival estimate for each atment group. The estimated mean survival curves will then be integrated over a lifetime to obtain ean life expectancy for each treatment group. Differences between the area under each survival rve will be computed to obtain the incremental life expectancy due to the investigational treatment. l the major steps in this methodology have been successfully used in the recently published JRSUIT cost-effectiveness analysis.

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

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

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

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

/iewed recently by O'Brien and colleagues, there are two schools of thought about cost- iveness analyses. The traditional approach is to hold that the models are deterministic. This ach uses sensitivity analyses to assess the reasonableness and importance of starting neters. More recently, as cost-effectiveness analyses have been built on empirical large-scale mized trial data, it has been possible to view the inputs to cost-effectiveness ratios (i.e., costs, al outcomes) as stochastic, and therefore possessing a quantifiable level of uncertainty. The ods of quantifying the uncertainty around cost-effectiveness ratios constitute an area of active rch. Many, including our group, favor the use of a nonparametric bootstrap approach. In the ntly published Bypass Angioplasty Revascularization Investigation (BARI) cost-effectiveness /sis, we assessed the precision of the ratio of costs to the effectiveness of treatment using the strap method (1000 samples with replacement with a cost-effectiveness ratio calculated for each ple). We propose to use a similar methodology for the TACT cost-effectiveness analysis. In tion, we will perform comprehensive sensitivity analyses around major assumptions and apolations. For empirically derived parameters such as survival differences, costs, and utilities, confidence intervals will be used to define plausible variations from observed values. We will ermine threshold values for those variables that yield cost-effectiveness ratios of $50,000 and 0,000 per life year added.

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

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

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

uality of Life and Health Status Data

xpected Health-Related Quality of Life Effects

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

Ve 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 1,000 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

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

alyses

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

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

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

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

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

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

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

:her potential problem in the analysis of quality of life data is the occurrence of missing values. ɜe can arise because of missed follow-up, patient incapacity, or patient refusal to participate in or all of the interview. We will, in conjunction with Dr. Lee, be very carefully tracking study ɛnt follow-up to minimize unnecessary loss of data. Our group has extensive experience in wing large, geographically diverse cohorts in randomized trials (such as the 41,000 patient rnational GUSTO trial that had a 98% follow-up rate or the Duke Databank population of over)00 patients with a 97% successful follow-up rate). We have individuals in our group (including cy Clapp-Channing, the EQOL Study Coordinator) who have particular expertise in finding "lost" ents. Thus, our principal approach to missing data will be to minimize its occurrence. However, ent refusal and patient incapacity will create missing values even with 100% follow-up. We ect refusal rates to be quite low overall in this study. In a 2966 patient quality of life substudy in GUSTO trial, we had a 1% refusal rate at each of the three interviews. The rate of patient ıpacity in the trial is uncertain but should be similarly low. Thus, we expect to have analyzable ɜ on ≥ 95% of surviving patients at each follow-up interview.

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Appendix 8: 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 Study Chair, Co-Chair, Project Directors, the Project Coordinator, the Project Administrator, the Project Administrative Assistant, the Principal 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 Principal Investigator of each participating unit 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.

TRIAL TO ASSESS CHEATION THERAPY
INITIAL FINANCIAL DISCLOSURE STATEMENT

undersigned **agree to disclose** financial interests as outlined in Trial to Assess Chelation Therapy policy onflict of Interest and below during my participation in the TACT.

_____ No _____ (If not willing to disclose, you are ineligible for participation)

ncial disclosures:

, my spouse or dependent children own or will buy or trade stock or stock options in any of the companies providing medication, equipment or financial support in the trial.*

NE ____ or 1A <$10,000 or 1B $10,000-$100,000 or 1C >$100,000

A, 1B or 1C, describe below.

Retainer-type consultant position with one or more of the companies.*

NE ____ or 2A <$10,000 or 2B $10,000-$30,000 or 2C >$30,000

2A, 2B or 2C, describe below.

Ad hoc consultant relationships to companies providing drugs or financial support to the trial.

ONE ____ or ____ Yes (indicate below)

Participation of investigators in any educational activities sponsored by the companies.

ONE ____ or ____ Yes (indicate below)

Participation of investigators in other research projects supported by the companies.

ONE ____ or ____ Yes (indicate below)

osures

NAME of Company	Nature of Relationship Indicate #1-5 (For 1, 2 indicate A, B or C)

estigator (Type name) Signature Date

ompanies include: Pharmed, Omnicomm, Quantum, and Quest.

Literature Cited

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