

Trial to Assess Chelation Therapy Protocol Revision Change Table for Version 4.0 (May 5, 2006) Replaces Version 3.0 (February 17, 2004)

The following table lists proposed text modifications to the Trial to Assess Chelation Therapy protocol dated February 17, 2004 (version 3.0). In column one the table references the section, page and paragraph number; column two references the exact text in version 3.0 of the protocol; column three states the proposed text change and is indicated by italicized text or within quotes; lastly column four states the rationale for the change.

Version 3.0 Page # (section, paragraph #)	Version 3.0 Text	Proposed Text Change	Rationale for Change
11 (2.1, 1)	<p>“We will enroll 2372 patients 50 years of age or older with a prior myocardial infarction.”</p> <p>“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 –8 weeks apart”</p> <p>“Following the infusions, patients will be followed up to an additional 32 months.”</p>	<p>Delete: “2372 patients” Replace with: “1950 patients”</p> <p>We will enroll <i>1950 patients</i> 50 years of age or older with a prior myocardial infarction.</p> <p>Delete: “8” Replace with: “6”</p> <p>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 – <i>6</i> weeks apart</p> <p>Insert: continue high-dose vitamin supplements and be contacted quarterly until 60 months of participation or the end of the study.</p> <p>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.</p>	Update number of patients and clarify length of follow-up period.

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11 (2.1)	Flowchart	Updated flowchart with correct number of patients: All patients :1950 Chelation patients: 975 Placebo patients: 975 High-dose supplement patients: 487 High-dose supplement placebo patients: 488	Update number of patients.
13 (3.2)	Update organizational chart	*Split clinical units into 130 US sites and 20 non-US sites. *Removed name of vitamin and mineral supplier.	Update number of clinical sites, include non-US sites.
14 (3.3, 1)	Update Figure 3 to reflect correct Clinical Coordinating Structure. “In order to preserve the blinded nature of the trial, two physician Research Associates have been identified.”	Update hierarchy of Clinical Trial Manager. Remove Administrative Director, update Administrative Assistant to read Administrative Staff. Insert: “who are not directly involved with the day-to-day coordination and administration of the CCC.” In order to preserve the blinded nature of the trial, two physician Research Associates have been identified <i>who are not directly involved with the day-to-day coordination and administration of the CCC.</i> ”	Update flowchart to reflect present structure and clarify role of physician Research Associates within the CCC.
15 (3.4)	“DCC staff will prepare data reports at specified intervals for review by an independent DSMB and will collaborate with other study investigators in the preparation of study presentations and publications.” “The DCC is also responsible for quality assurance of the electronic data capture system	Insert: “NIH and” “DCC staff will prepare data reports at specified intervals for review by <i>NIH and</i> an independent DSMB and will collaborate with other study investigators in the preparation of study presentations and publications.” Insert: “TrialMaster®,” The DCC is also responsible for quality assurance of <i>TrialMaster®</i> , the electronic	Include NIH as reviewers. Identify EDC system for clarity

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	and the internet-based communications network between management and performance sites.”	data capture system and the internet-based communications network between management and performance sites.	
15 (3.5)	“3) assess detailed QOL data at 6 months, 1 year and 2 years after enrollment in a random subset of 1,000 patients;”	Delete: “1,000 patients” Replace with: “900 patients” 3) assess detailed QOL data at 6 months, 1 year and 2 years after enrollment in a random subset of 900 patients;”	Reduced number to achieve 85% power in new Recruitment Plan
15 (3.6)	<ul style="list-style-type: none"> • communicate on a real-time basis (internet-based) with sites, CCC, and DCC; • change dosing immediately based on safety labs and standing orders; • suspend shipment and notify the CCC when safety labs are not received, or have reached predefined alert values; • deliver blinded vitamins and supplements or their identical placebos; 	<p>Delete: “on a real-time basis (internet-based).” “communicate with sites, CCC, and DCC.”</p> <p>Delete: “change dosing immediately based on safety labs and standing orders” Replace with: “Adjust accordingly the EDTA dose as calculated by electronic data capture system or via verbal order by Clinical Trial Manager.”</p> <p>Delete: “suspend shipment and notify the CCC when safety labs are not received, or have reached predefined alert values” Replace with: “Identify patients who are not scheduled to receive weekly infusions and coordinate with Clinical Trial Manager if the patient’s shipment should be suspended due to entry into maintenance infusion phase, study safety lab delay, missed visit, or other event(s) as identified by Clinical Trial Manager.”</p> <p>Insert: “identify and coordinate with Clinical Trial Manager if patient’s vitamin shipments should be changed due to patient intolerance to vitamins or entry into follow-up phase of study.”</p>	Clarify role of Central Pharmacy.

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16 (3.7)	“analysis of all screening and safety laboratory tests, as specified in the protocol, excluding the specialized markers of oxidative stress and inflammatory processes.”	Delete: “excluding markers of oxidative stress and inflammatory processes.”	All study screening and safety labs are administered through one laboratory.
16 (3.8)	<p>“We estimate that up to 150 clinical sites will be sufficient to enroll 2372 eligible patients over 36 months.”</p> <p>All Site Investigators have will have experience in the treatment and management of CAD and, at least, experience in participation in clinical trials, or equivalent training provided by TACT.</p> <p>“Internet access on-site, so sites can comply with the electronic data capture system;”</p>	<p>Delete: “2372” Replace with: “1950” Delete: “36” Replace with: “54” Insert: “(4.5 years)” We estimate that up to 150 clinical sites will be sufficient to enroll 1950 eligible patients over 54 months (4.5 years).</p> <p>Delete: “have” 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.</p> <p>Insert: “High-speed” <i>High-speed</i> internet access on-site, so sites can comply with the electronic data capture system;</p>	<p>Update correct number of patients and follow-up period.</p> <p>Correct typo</p> <p>Clarify all sites must have high-speed internet to join study.</p>
16 (3.8)	Update table with correct number of patients, enrollment (months), active sites, pt/site/mo, pt/site	Revised table.	Reflect correct number of patients and monthly enrollment.
17 (4.0)	Add new sentence after section: “In order to maximize accuracy and speed of communications between the CCC, DCC, the Accu-Care Services Pharmacy, and the clinical sites, an	<p>Insert: “Services for this system, TrialMaster will be provided by Omnicomm Systems.”</p> <p>Insert: at end of section.</p>	Identify Omnicomm and their role in the study.

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	enhanced Internet-based data collection will be used in TACT.”	<p>“Omnicom Systems will:</p> <ul style="list-style-type: none"> • 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 <i>TrialMaster</i>®, the electronic data capture system and the internet-based communications network.” 	
18 (5.4)	“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, and the NHLBI Program Officer.”	<p>Delete: “,” and “and” Insert: “and other study team members as needed”.</p> <p>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, <i>and other study team members as needed.</i></p>	Identify other team members that will be included in Operations Committee.
19 (6.1.1)	“TACT will randomize 2372 patients...”	<p>Delete: “2372” Insert: “1950” TACT will randomize <i>1950</i> patients...</p>	Reflect correct number of patients.
20 (6.1.1.1)	Add items from recruitment plan: Tier 1	<p>Insert:</p> <ul style="list-style-type: none"> • 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. 	Add revised recruitment plan

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20 to 21 (6.1.1.1)	Add items from recruitment plan: Tier 2	Insert: <ul style="list-style-type: none"> • 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. 	Add revised recruitment plan
21 (6.1.2)	<p>“Men or women age 50 years and older (women must be postmenopausal).”</p> <p>“2. Documented myocardial infarction (MI) over 6 weeks prior to evaluation.”</p> <p>“Either of the following criteria</p>	<p>Delete: “(women must be postmenopausal).”</p> <p>Insert: Number 1</p> <p>Insert: “postmenopausal” and “at time of randomization”</p> <p>1. Men and <i>postmenopausal</i> women age 50 years and older <i>at time of randomization</i>.</p> <p>Delete: “evaluation”</p> <p>Insert: “randomization”</p> <p>2. Documented myocardial infarction (MI) over 6 weeks prior to <i>randomization</i>”.</p> <p>Insert: “Patients meeting either of the</p>	Clarify inclusion criteria and include new inclusion criterion.

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	(A or B)”	<p>following criteria (A, B, or C) will qualify:</p> <p>Insert after item B: “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:</p> <p>C. Past ischemic symptoms, electrocardiographic abnormalities consistent with myocardial infarction, and corresponding segmental wall motion abnormality or scar on an imaging study.”</p>	
22 (6.1.3)	<ul style="list-style-type: none"> • Coronary or carotid revascularization procedure within the last 6 months. • Hospitalization for heart failure within 6 months. • History of cigarette smoking within the last 3 months. • Any severe, non-coronary medical condition likely to affect patient survival within 4 years. 	<p>Insert: “prior to randomization”</p> <ul style="list-style-type: none"> • Coronary or carotid revascularization procedure within 6 months <i>prior to randomization</i>. • Hospitalization for heart failure within 6 months <i>prior to randomization</i>. • History of cigarette smoking within 3 months <i>prior to randomization</i>. <p>Insert: “after randomization (e.g. significant pulmonary disease or malignant cancer or valvular disease)” and “If uncertain contact Clinical Coordinating Center prior to randomizing patient.”</p> <ul style="list-style-type: none"> • Any severe, non-coronary medical condition likely to affect patient survival within 4 years <i>after randomization (e.g. significant pulmonary disease or malignant cancer or valvular disease). If</i> 	<p>Clarify time frame study exclusions apply.</p> <p>Clarifies severe non-coronary condition(s) that can affect patient survival within 4 years as an exclusion criteria.</p>

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		<i>uncertain contact Clinical Coordinating Center prior to randomizing patient.</i>	
22 (6.1.5)	Insert new sentence after the following sentence: “The Site Coordinator will call the patient to notify him or her of final eligibility for TACT, and if applicable, schedule the first infusion.”	Insert: “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.”	Clarifies screening labs expire within 30 days of assessment.
23 (6.2, 1)	“The chelation solution ⁵⁰ will be administered over 3 hours at an administration rate of 166 cc/hour and consist of 500ml of sterile water and the additives listed in the chart below.” Insert new sentence after previous sentence.	Delete: “over” Replace with: “for a minimum of”: The Chelation solution ⁵⁰ will be administered <i>for a minimum of</i> 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. Insert: “The high-dose vitamin pills are administered daily from the first infusion visit until end of patient follow-up.”	Clarifies infusion time cannot be less than three hours. Identifies high-dose vitamins are part of the study treatment regimen.
24 (6.2, 3)	Insert new sentences after EDTA lean body weight bullets.	Insert: “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	Clarify how EDTA dose is adjusted.

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		infusion.”	
25 (6.2)	New paragraph and formula at end of section.	<p>Insert: “Serum calcium is corrected by albumin level to generate a corrected calcium value that is an estimation of ionized calcium as follows:</p> <p>corrected calcium = serum calcium + (0.8 x [normal serum albumin - patient’s albumin])”</p>	Identify calculation of corrected calcium.
36 (6.2.2)	0.9N NaCl	<p>Delete: N Insert: “%” 0.9% NaCl</p>	Corrected units.
37	Text at end of Low-Dose Regimen Table and text at end of High-Dose Regimen Table	<p>Delete: “These supplements, produced by OleoMed S.A., Madrid, Spain, are administered in an olive oil based gel capsule.” “These vitamins are produced by PAL Laboratories, Inc., Miami, FL.”</p>	Remove vitamin supplier information.
38-39 (6.2.3)	“Compliance with the vitamin components of the study will be monitored by pill count.”	<p>Insert: “at the site.” Compliance with the vitamin components of the study will be monitored by pill count <i>at the site</i>.</p>	Clarifies that the monitor is not responsible for counting pills.
39 (6.2.5)	<p>Insert new sentence after: “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).”</p> <p>“TACT projects that the last patient will be randomized 1.5 years (78 weeks) before study close-out. In this case, the 10 maintenance infusions will be administered over 2 – 8 weeks apart.”</p>	<p>Insert: “The 30 weekly infusions should be scheduled weekly. Interruptions in the first 30 weekly infusion schedule should not be greater than 6 weeks.”</p> <p>Delete: “1.5 years (78 weeks)”, “2-8 weeks”. Replace with: “16 months (64 weeks)”, “2-6 weeks”. TACT projects that the last patient will be randomized <i>16 months (64 weeks)</i> before study close-out. In this case the</p>	<p>Clarifies acceptable interruption during weekly infusion phase.</p> <p>Adjusts new infusion schedule according to the revised timeline.</p>

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		10 maintenance infusions will be administered 2-6 weeks apart.	
39 (6.2.6.2)	“4] Sites that fall below the latest reported NRMI [http://www.nrmi.org/index.html] incidences will be contacted by the CCC to determine reasons for non-compliance with evidence-based therapies.”	<p>Delete: “the latest reported NRMI [http://www.nrmi.org/index.html] incidences”</p> <p>Replace with: “10%” “the overall study median value”</p> <p>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.</p>	Updates to present methodology of Site Report Cards.
41 (6.2.7— chart)	<p>Add a new line to chart after the Limited Physical Exam row.</p> <p>“Infusion Vitals (one per hour; pre, during and post infusion)”</p> <p>Physical Exam at screening</p> <p>Inflammatory Markers</p> <p>Add a new line to chart.</p> <p>“*DCRI to Collect”</p>	<p>Insert: “Assess patients for angina, heart failure, and dyspnea before and after every infusion.”</p> <p>Place check marks in columns INF visit 1-30 and 31-39, and 40.</p> <p>Delete: “one per hour” Infusion Vitals (pre, during and post infusion)</p> <p>Delete: Row of Physical Exam. Add: check mark at screening for Limited Physical Exam.</p> <p>Insert: Parentheses indicating inflammatory markers are collected on first 600 patients. Delete: Visit 40 in first column and place check mark in visit 40 column.</p> <p>Add: Row Concomitant Medications with check marks at visits: 15, 30, 36, 40</p> <p>Last Row (EQOL) change column for Infusion Visits 1-30 to read: *DCRI to collect at 6 months post randomization.</p> <p>Revise: Infusion Visits 31-39 to read:</p>	<p>Additional safety measures added to protocol.</p> <p>Clarifies when site must administer infusion vitals, physical exam, and check for concomitant medications.</p>

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	<p>Correct header for “Follow-up Telephone calls 3 per year 28 months to closeout</p> <p>Correct header for Close out Visit</p>	<p>DCRI to collect at 12 and 24 months post randomization”</p> <p>Revise: Follow-up Telephone Calls (3 per year 3 months after last infusion)</p> <p>Final Close-out Visit (5 years post randomization or by 7/31/09)</p>	
42 (6.2.8)	<p>Insert new sentence after “Vital signs and a brief cardiopulmonary exam will be measured before, once during, and after the infusion.”</p> <p>“Safety labs, consisting of CBC, platelet count, creatinine, glucose, magnesium, and calcium will be drawn at baseline...”</p> <p>Add new sentence at end of paragraph.</p>	<p>Insert: “Assess patients for angina, heart failure, and dyspnea before and after every infusion.”</p> <p>Insert: “, LFTs, and urine dipsticks” Safety labs, consisting of CBC, platelet count, creatinine, glucose, magnesium, calcium, <i>LFTs, and urine dipsticks</i> will be drawn at baseline...”</p> <p>Insert: “Vitamins are dispensed as needed and unused vitamins supplies are collected at these visits.”</p>	<p>Add LFTs and urine dipsticks to specified safety labs.</p> <p>Add additional reminder when to check patient’s vitamin supply.</p>
43 (6.2.11)	<p>Header: Routine Visits</p> <p>“Following the infusion phase, patients will have contact with the clinical site 4 times yearly at 3-month intervals.”</p>	<p>Delete: “Routine Visits” Replace with: “Follow-up Assessments”</p> <p>Insert: “continue only the high-dose supplement (or placebo) arm as dispensed. Any unused supplements are collected.” and “(i.e. quarterly).”</p> <p>Following the infusion phase, patients <i>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</i></p>	<p>Routine visits does not adequately describe these visits.</p> <p>Reinforces that during follow-up phase patients only continue high-dose supplement regimen.</p>

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43 (6.2.12, 2)	<p>“To assist with the issue of compliance more directly, the DCC will conduct site-visits to the infusion sites as part of their larger, clinical site-visit process. To assist in the identification of sites for review, each clinical site will be required to specify both the clinical and infusion sites prior to receiving final approval to enroll patients. The role of the DCC in monitoring compliance includes:</p> <ol style="list-style-type: none"> 1) Carefully monitoring drop-out rate from the infusion arm throughout the course of the trial. 2) Carefully monitoring drop-out rate from the oral supplement arm throughout the course of the trial. 3) Carefully monitoring pill counts as reported by sites, both for the low-dose as well as the high-dose regimens.” 	<p>Delete: Entire paragraph Replace with: “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:</p> <ol style="list-style-type: none"> 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.” 	Clarifies role of DCC in helping sites with patient compliance and follow-up.
44 (6.3)	<p>“Whenever a clinical event occurs that is a component of the primary endpoint or of the secondary clinical endpoints, the clinical site is responsible for notifying the DCC within 24 hours of discovery via the electronic data capture system.”</p>	<p>Delete: “within 24 hours of discovery”</p> <p>“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.”</p>	Clarifies timeframe for reporting endpoints
44 (6.4, 2)	<p>“Minutes of all DSMB meetings will be prepared by the Data Coordinating Center and promptly distributed to the committee members.”</p>	<p>Insert: “Draft” and “DCC staff, reviewed by NCCAM and NHLBI staff.” Reorder: “by the Data Coordinating Center.” <i>Draft</i> minutes of all DSMB meetings will be prepared by <i>DCC staff, reviewed by NCCAM and NHLBI staff</i> and promptly distributed to the committee members by the Data Coordinating Center.”</p>	Clarifies role of DSMB and DCC when preparing DSMB minutes.

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44 (6.4)	New Paragraphs #3-5 after previous sentences above.	<p>Insert: “In TACT, patient safety is monitored by a combination of laboratory and physical examinations that result in delivery of email notifications to the site coordinator, site investigator, the Clinical Coordinating Center (CCC) and the DCC.</p> <p>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. 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.</p> <p>Laboratory examinations are carried out on all patients during specific infusion visits, as detailed in the following table:”</p> <p>Move: table entitled “Schedule of routine monitoring examinations...” here.</p> <p>Insert Note after table: “*C-reactive protein is drawn for only</p>	<p>Adds information on physical examinations and defines lab alerts and lab delays. Moves table for monitoring visits between text for clarity. Addresses C-reactive protein is only drawn on the subsample of patients.</p>

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		<p>the first 600 patients randomized into the trial.”</p> <p>Insert: “*” to hs-CRP notation in table</p> <p>Insert: “Abnormal laboratory results generate either a: Lab Alert or Lab Delay. 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.”</p>	
44 (6.4)	New paragraph #6	<p>Insert: “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.</p> <p>Additional lab alerts evaluating hematocrit, magnesium, potassium, iron, and lipids are generated if an abnormal lab value is obtained.</p>	Text to accompany lab alerts not previously mentioned in Version 3.0.
44 (6.4)	New Paragraph #7	<p>Insert: “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).”</p>	
44 (6.4, 3)	In patients whose creatinine	Delete: “doubles from baseline”	Clarifies

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	<p>doubles from baseline or reaches 2.5 mg/dl,⁵⁰ whichever is lower, the following will occur:</p> <ol style="list-style-type: none"> 1) The next infusion will be withheld if the patient is in the weekly infusion phase of the trial. 2) Labs will be re-measured prior to scheduling the next infusion 2 weeks later. 	<p>Replace with: “is greater than or equal to twice the value obtained at”</p> <p>In patients whose creatinine <i>is greater than or equal to twice the value obtained at</i> baseline or reaches 2.5 mg/dl,⁵⁰ whichever is lower, the following will occur:</p> <p>Insert: “for two weeks”</p> <ol style="list-style-type: none"> 1) The next infusion will be withheld <i>for two weeks</i> if the patient is in the weekly infusion phase of the trial. <p>Delete: “re-measured prior to scheduling the next infusion 2 weeks later”</p> <p>Insert: “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.”</p> <ol style="list-style-type: none"> 2) Labs will be <i>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.</i> 	<p>creatinine clearance lab delay.</p>
45 (6.4, 4)	<p>“As regards to metabolic functions, serum calcium below 9 mg/dL or glucose below 50 mg/dL shall be deemed a relative contraindication to EDTA.”</p>	<p>Delete: “9” Replace with: “8.0”</p> <p>Delete: “serum”</p> <p>Insert: “corrected</p> <p>“As regards to metabolic functions, <i>corrected</i> calcium below 8.0 mg/dL or glucose below 50 mg/dL shall be deemed a relative contraindication to EDTA.”</p>	<p>Update with new value</p>
45 (6.4)	<p>Last paragraph</p>	<p>Insert: “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</p>	<p>Explains purpose of lab sensitive values for PCP notification.</p>

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		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.”	
46 (6.5.3)	“In addition to these multiple levels of data checks, the CEC will conduct an independent and blinded review of the key outcome events.”	Replace with: “Site visit reports are submitted to the CCC and NIH.”	Clarify site visit reports
49 (6.5.4.2, 1)	“DCRI Safety Surveillance will review the SAE data to verify that all data are complete and follow-up with the site for incomplete data and/or data clarification.”	Replace with: “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.”	Clarify DCRI Safety Surveillance role when reviewing SAE data.
	“This will include, but will not be limited to ensuring that serious criteria have been met, the SAE data received is reviewed, data based and coded using MedDRA coding dictionary.”	Insert: “and”, “are”, and “entered” This will include, but will not be limited to ensuring that serious criteria have been met <i>and</i> the SAE data received <i>are</i> reviewed, <i>entered</i> and coded using MedDRA coding dictionary.	Clarify role of DCRI Safety Surveillance.
49 (6.5.4.2, 1)	“The DCRI Medical Monitor will review adverse events that are serious and drug (infusion) therapy related or result in death for medical clarity and regulatory reportability.”	Delete: “regulatory reportability” Insert: “unexpectedness”. The DCRI Medical Monitor will review adverse events that are serious and drug (infusion) therapy related or result in death for medical clarity and	Clarify role of DCRI medical monitor.

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		<i>unexpectedness.</i>	
49 (6.5.4.2, 2)	“DCRI Safety Surveillance will notify the NIH, Dr. Lamas, and the Data and Safety Monitoring Board (DSMB) chairman 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.”	Delete: “chairman” “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.”	Adverse Events are reported to all DSMB members.
49 (6.5.4.2, 3)	“The DCRI Safety Surveillance will generate a MedWatch form for all adverse events that are serious, drug (infusion) therapy related and unexpected by calendar day 5 for review. DCRI Regulatory Services will notify the FDA by written report for all adverse events that are serious, drug (infusion) therapy related and unexpected within 15 calendar days from receipt of the initial notification of the SAE. For adverse events that are serious, drug (infusion) therapy related and unexpected and result in death or are life-threatening DCRI Regulatory Services will notify the FDA by phone or fax within 7 calendar days.”	Replace with: “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).”	Added new requirement for DCRI Medical Monitor to determine if non drug related deaths warrant expedited reporting to regulatory authorities
49 (6.5.4.2, 5)	Insert new sentence after: “SAE line listings, from the clinical database, will be provided to the DSMB chairman regularly for review.”	Insert: “All SAE’s are reported to the regulatory authorities in accordance to country specific regulatory law.”	Added new time line for submission of SAE line listings for the DSMB. Added submission of unmasked and

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			masked line listings and additional recipients.
49 (6.5.4.2, 7)	“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.”	<p>Insert: “All deaths assessed by the DCRI Medical Monitor as warranting expedited reporting and”</p> <p><i>All deaths assessed by the DCRI Medical Monitor as warranting expedited reporting and</i> 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.</p>	Added new requirement for DCRI Medical Monitor to determine if non-drug related deaths warrant expedited reporting to regulatory authorities.
50 (6.5.4.2.1)	<p>“1) Heart failure hospitalization during the weekly infusion phase of the study protocol, not otherwise subject to expedited SAE reporting.</p> <p>2) Any disposition of the patient to the hospital or emergency room within 12 hours following study drug (infusion) therapy, not otherwise subject to expedited SAE reporting.”</p>	<p>Delete: “weekly” and “study protocol”</p> <p>Insert: “entire” and “patient’s participation in the study”</p> <p>“1) Heart failure hospitalization during the <i>entire</i> infusion phase of the <i>patient’s participation in the study</i>, not otherwise subject to expedited SAE reporting.”</p> <p>Delete: “12”</p> <p>Replace with: “24”</p> <p>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.</p>	Updated new reporting of heart failure during the entire infusion period of the study. Revised reporting criteria to include reporting of adverse events 24 hours after infusion therapy.
50 (6.5.4.4)	“If the clinical site wishes to unmask for an adverse event, the clinical site will contact Dr. Lamas via the DCRI helpline to	Delete: “via the DCRI helpline”	The DCRI helpline has been disabled. Sites can

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	discuss the clinical details of the case.”		contact Dr. Lamas directly.
51 (6.5.4.5)	SAE General Process Flow Chart	Replace with: “TACT General Expedited SAE Process Flow Diagram”	Inserted updated flow diagrams.
52 (6.5.4.6)	“Nonserious adverse events of interest will be collected on a screening checklist that specifies symptoms by different organ systems, such as gastrointestinal, cardiorespiratory, skin, etc. This data will be collected at multiple points throughout the trial.”	Delete: “on a screening checklist that specifics symptoms”	A screening checklist is not used to collect adverse events of interest.
54 (8.0)	“All of these data will be repeated on a random subset of 1,000 patients by telephone interviewer staff from the EQOL Coordinating Center.”	Delete: “1,000 patients” Replace: “900 patients” All of these data will be repeated on a random subset of <i>900 patients</i> by telephone interviewer staff from the EQOL Coordinating Center.	Reduced number to achieve 85% power in new Recruitment Plan
60 (9.0 Timeline)	Update with revised timeline from recruitment plan	Change dates for: Database lock and first results presentation. Deleted study year when study is expected to end.	Update with dates for approved study extension.
62 (Appendix 1, 1.0, 1)	“Based on these various assumptions, 2,372 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.”	Delete: “2,372” Replace with: “1,950”	Corrected number of patients.

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68 (Appendix 2)	Appendix 2: Prototype of HIPAA COMPLIANT INFORMED CONSENT FORM	<p>Delete: “HIPAA Compliant” Appendix 2: Prototype of INFORMED CONSENT FORM</p> <p>Insert: new line prior to ICF: “HIPAA COMPLIANT VERSION FOR SITES IN UNITED STATES”</p> <p>Two versions of ICF: the international version does not include HIPAA compliant language and inclusion of Health Canada in confidentiality sections.</p>	Incorporate international sites ICF.
68 (Appendix 2, 2)	“The study will involve 2372 patients like you...”	<p>Delete: “2372 patients” Replace with: “1950 patients”</p> <p>The study will involve <i>1950</i> patients like you...</p>	Update new patient recruitment number.
68 (Appendix 2, 4)	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 a low-dose vitamin.	<p>Insert: “placebo vitamins. All patients will also receive”</p> <p>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.</p>	Clarifies that high-dose vitamins versus placebo and that all patients receive a low-dose vitamin.
69 (Appendix 2, 4)	“The needle will be inserted by trained medical personnel under sterile conditions and each infusion will last for 3 hours.”	<p>Insert: “a minimum of”</p> <p>The needle will be inserted by trained medical personnel under sterile conditions and each infusion will last for <i>a minimum of 3</i> hours.</p>	Clarifies minimum time for each infusion visit.

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72 (Appendix 2, 4)	<p>“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 call.”</p> <p>Insert new sentence after previous sentence.</p>	<p>Insert: “visit or”</p> <p>After the 40 infusion visits have been completed, research staff from [INSERT YOUR INSTITUTION 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 <i>visit or</i> call.</p> <p>Insert: “During this time it will be important to continue to take your high-dose vitamins.”</p>	<p>Clarifies 3-month follow-up can be either visit or call.</p> <p>Clarifies to patient must continue vitamins after infusions are completed</p>
73 (Appendix 2, bullets)	<p>“-Take the 3 high-dose pills twice per day”</p>	<p>Insert: “during the infusion and follow-up periods”</p> <p>-Take the 3 high-dose pills twice per day <i>during the infusion and follow-up periods.</i></p>	<p>See above</p>
73 (Appendix 2, 2)	<p>Risk and Side Effects: “EDTA rarely may cause allergies, kidney problems, or if given too quickly may cause low calcium, muscular spasms, heart rhythm problems, and low blood pressure that might be serious.”</p>	<p>Delete: “or if given too quickly may cause low calcium, muscular spasms, heart rhythm problems, and low blood pressure that might be serious.”</p> <p>Insert: “or”</p> <p>Insert: “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.”</p> <p>“EDTA rarely may cause allergies, or</p>	<p>Describe symptoms of hypocalcaemia to patients.</p>

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		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.”	
74 (Appendix 2, 5)	“If your heart is weak, you may be at risk of developing fluid in your lungs as a result of the heart’s inability to tolerate the amount of fluid that will be infused.”	<p>Delete: “as a”</p> <p>Insert: “, swelling in your ankles, or rapid weight gain. This fluid accumulation is also known as heart failure, and is a”</p> <p>“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.</p>	Explain heart failure and fluid accumulation.
74 (Appendix 2, 5)	Risks and Side Effects: Insert new sentences after section above.	Insert: 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 which may lead to shortness of breathe.	Inform patient potential risks of fluid retention and association with heart failure.

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74 (Appendix 2, 8)	“You or your legally authorized representative will be informed in a timely manner if new information becomes available that may affect your willingness to continue participation in this study.”	Delete: “or your legally authorized representative”	All study patients are capable of providing consent and do not require a legal representative for consent.
78	Legally Authorized Representative in signature lines	Delete: “Legally Authorized Representative”	See above
87 (Appendix 7, bullets)	“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.”	Delete: “the latest reported NRMI [http://www.nrmi.org/index.html] incidences” Replace with: “the overall study median value” 4. Sites that fall below <i>the overall study median value</i> will be contacted by the CCC to determine reason for non-compliance with evidence-based therapies.”	See above.
97 (Appendix 8, 6)	“EQOL personnel at the DCRI will conduct the QOL interviews using a structured interview format, with 1000 patients randomly selected from the total sample of patients enrolled in TACT.”	Delete: “1,000 patients” Replace: “900 patients” “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.”	Reduced number to achieve 85% power in new Recruitment Plan