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Mount Sinai
MEDICAL CENTER

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INFORMED CONSENT

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

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

1. **Why is this research being done?**

You are being asked to take part in a research study to test the effectiveness of chelation therapy for patients who have survived a heart attack. Chelation therapy, as used in this study, consists of up to 40 treatments through a vein in your arm (infusion) of a solution of vitamins and dissolved materials that are thought to bind specific toxic elements circulating in your blood. These elements, known as heavy metals, include iron, copper, and calcium, and may contribute to the development of heart disease. Although the Food and Drug Administration has not approved chelation therapy as an effective treatment for heart disease, chelation therapy has been practiced in the community for many years. The present clinical practice of chelation therapy also involves the use of high-dose antioxidant vitamins, minerals, and nutritional supplements taken by mouth. However, with chelation therapy, there is no evidence that these supplements are beneficial for patients like you. The Trial to Assess Chelation Therapy (TACT) will test chelation solution versus a placebo (a substance with no active ingredient) salt-water solution, and high-dose vitamins and minerals taken by mouth versus placebo vitamins. All patients will also receive a low-dose vitamin.

The research is being carried out because many people each year receive chelation therapy, and vitamin and mineral supplements, even though there is no reliable evidence of their effectiveness.

2. How many people will take part in the research study?

The study will involve 1950 patients like you at approximately 150 clinical centers.

3. How long will I be in the research study?

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

4. What will happen in the research study?

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

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

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

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

All patients, including yourself, will receive a total of 40 infusions, beginning with one infusion per week for 30 weeks, followed by an additional 10 infusions given approximately once every 2 weeks to once every 2 months. It will take up to 28 months to complete all the required treatments. Each treatment consists of

receiving the solution slowly through a needle in your vein. The needle will be inserted by trained medical personnel under sterile conditions and each infusion will last for a minimum of 3 hours. You will have blood drawn for laboratory tests during 10 of your visits. Each time, you will have approximately 1 tablespoonful of blood drawn. During each visit, you will be asked how you feel, and whether you have had any symptoms. In addition, the research staff will ask you whether you have had any new heart problems or hospitalizations, and will measure your blood pressure and perform a simple physical exam. Because of the time of the infusions, you should count on being at the clinic for at least 5 hours. If you live far away from your doctor's office, you may spend a lot of time traveling back and forth.

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

The components are:

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

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

The high dose vitamin and mineral schedule consists of 3 pills to be taken twice daily:

High Dose Regimen (Taken twice daily)	Total amount you will take in 6 pills compared to the recommended Daily Value
Vitamin A (as fish liver oil and beta-carotene)	5 times
Vitamin C (as calcium ascorbate, magnesium ascorbate and potassium ascorbate)	20
Vitamin D_3 (as cholecalciferol)	1/4
Vitamin E (as d-alpha tocopheryl succinate and d-alpha tocopheryl acetate)	13 1/3
Vitamin K_1 (as phytonadione)	3/4
Thiamin (vitamin B_1) (as thiamin mononitrate)	66 2/3
Niacin (as niacinamide and niacin)	10
Vitamin B_6 (as pyridoxine hydrochloride)	25
Folate (as folic acid)	2
Vitamin B_{12} (as cyanocobalamin)	16 2/3
Biotin	Same
Pantothenic acid (as d-calcium pantothenate)	40
Calcium (as calcium citrate and calcium ascorbate)	1/2
Iodine (from kelp)	Same
Magnesium (as magnesium aspartate, magnesium ascorbate and magnesium amino acid chelate)	1 1/4
Zinc (as zinc amino acid chelate)	1 1/3
Selenium (as selenium amino acid chelate)	2 8/9
Copper (as copper amino acid chelate)	Same
Manganese (as manganese amino acid chelate)	4
Chromium (as chromium polynicotinate)	1 2/3
Molybdenum (as molybdenum amino acid chelate)	2
Potassium (as potassium aspartate and potassium ascorbate)	Less than 1/8
Choline (as choline bitartrate)	There is no Daily Value established for these supplements.
Inositol	
PABA (as para-amino benzoic acid)	
Boron (as boron aspartate and boron citrate)	
Vanadium (as vanadyl sulfate)	
Citrus Bioflavonoids	

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

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

These supplements are produced by Douglas Laboratories, Pittsbrugh, PA.

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

After the initial enrollment visit, research staff from the Economics and Quality of Life Center at the Duke Clinical Research Institute may contact you by telephone at 6 months, 1 year and 2 years to ask how you are doing. They will ask if there are any changes in how you feel, in your ability to perform your daily activities, or in your working status. Not everyone in the study will answer these questions. This group of 900 patients will be chosen by chance. If you are chosen, the information will allow us to understand the effects of chelation and vitamins on the quality and economics of patients' lives. You will also be asked about any hospitalizations, heart procedures or doctor visits you may have had between study visits to better understand the costs of your illness. All of these data will be analyzed using coded information without your name or other identifiable information publicized. The calls will take about 15-25 minutes to complete.

After the 40 infusion visits have been completed, or if infusions have been stopped for other reasons, research staff from Mount Sinai Medical Center and/or the Duke Clinical Research Institute follow-up group will call you every 3 months until the end of the study to find out how you are doing and whether you have had any heart problems since the last visit or call. During this time it will be important to continue to take your high-dose vitamins. If you have been hospitalized during the follow-up period, it will be necessary for you to sign a release so that we can have access to your medical records. In addition, you will be asked to return for a visit each year and at the end of the study. At each visit, you will be asked questions about your medical condition and you will be asked to have an electrocardiogram (ECG) of your heart.

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

5. Are there any risks or discomforts?

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

EDTA, or Edetate Disodium is in the chelation solution. It binds heavy metals like lead, copper, and iron, and allows them to be excreted in the urine. Death is a rare complication of EDTA infusions. EDTA rarely may cause allergies, or kidney problems. EDTA also binds to calcium in blood. Symptoms of low blood calcium, such as tingling, muscle cramps, lightheadedness, severe muscular spasms, heart rhythm problems, and low blood pressure may occur with a rapid infusion, and rarely, with a correctly-administered infusion. You will be monitored carefully for these side effects. The infusion will be monitored closely so it does not go in too quickly, and your blood pressure will be checked before, during, and after the infusion. If your kidney function is not good, you will not be allowed to participate in the study. If your kidney function gets worse during the infusions, then the dose of EDTA will be reduced, or the infusions will be stopped. As part of monitoring your kidney function, you will need to inform your study physician if you do not urinate for 12 hours. You may develop flu-like symptoms such as low-grade fevers, sneezing, muscle and joint aches, headaches and watery eyes. These symptoms usually occur 4 to 8 hours after receiving the infusion. These symptoms are usually seen when high doses of EDTA are given, or if the infusion rate is too rapid. Patients with diabetes have been reported to develop low blood sugar during the infusion. For this reason, if you are diabetic, we will ask you to snack before the infusion, and monitor you for symptoms of low blood sugar.

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

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

As described earlier, magnesium chloride and potassium chloride are included in the infusion solution. Magnesium and potassium are essential salts that are

components of all cells in the body. Potassium can cause burning at the site where the intravenous line is placed. However, there are no other likely side effects expected from the doses to be infused.

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

Heparin, also included in the infusion solution, is a commonly used blood thinner that is used to prevent clotting of the vein used for the intravenous infusion. The principal side effect of heparin at the doses used in this study is an allergy that could lead to bleeding or blood clots. You will be closely monitored for this, and the heparin will be stopped if an allergy seems to occur.

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

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

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

The anti-oxidant vitamin, mineral, and nutrient supplements taken by mouth are generally well tolerated, taken by millions of people, and have low risks of serious side effects. Beta-carotene, however, one of the supplements used, has

been associated with a higher rate of cancer in patients who smoke. Smokers are not eligible to participate in this study, and it is important that you not start smoking while you are participating.

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

If you have any questions about the risks or discomforts, contact Gervasio A. Lamas, MD at 305-243-7170 or 305-778-8689, which is a 24-hour phone number.

6. What are my responsibilities?

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

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

7. Are there benefits to taking part in this research study?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other patients with coronary artery disease in the future.

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8. What other choices do I have if I don't take part in this research study?

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

9. Will I need to pay for the tests and procedures?

You or your insurance company will not be billed for the study-related procedures. They will be provided to you without cost. Should you have a complication of chelation therapy that requires medication or hospitalization, the study and/or its researchers will be unable to pay for those costs, and you and/or your insurance company will be responsible for the costs resulting from the complication.

10. Will I receive payment for taking part in this study?

You will not be paid to participate in this study.

11. What about confidentiality?

Your role in this research study and any information collected about you in this study, including your medical records (known as Protected Health Information, or "PHI") will be protected as required by state and federal laws (including HIPAA) that govern the confidentiality and privacy of medical, personal and genetic information. If your PHI is being used in this research study, you will either be asked to sign a specific permission form called an "Authorization" which explains who can see this information and how it can be used, or we will obtain approval for a waiver of Authorization from our Institutional Review Board. Without your Authorization, we may also use or disclose information related to your medical, personal or genetic condition if any information that could identify you has first been removed. Whether your PHI is being collected, or not, the following parties may review PHI without Authorizations:

(A) a person or company subject to the jurisdiction of the Food and Drug Administration ("FDA")
(B) a researcher as necessary to prepare a research protocol or for similar purposes; or
(C) any other person set forth in MSMC's Notice of Privacy Practices if permitted or required by law.

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The results of this study will be published; however, you will not be identified in these publications. The Pharmacy preparing the study infusions (Accu-Care Services Pharmacy) and the prescribing study physician will know who you are.

12. Is there compensation for research related injury?

Financial compensation for research-related injury or loss of wages is not available.

13. Who can answer my questions?

If you do not understand anything related to this study or have an illness or problem related to your taking part in this study, please contact:

Gervasio A. Lamas, MD
Site Investigator
Mount Sinai Medical Center/Division of Cardiology
305-674-2162

For questions about your rights as a research participant, contact the Coordinator of the Mount Sinai Medical Center Institutional Review Board (a group of people who review the research to protect your rights) at 305-674-2790.

14. What are my rights if I take part in this research study?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. This will not affect your continued medical care and treatment by your doctor. If you decide to withdraw from the study, please notify Dr. Lamas in writing. His mailing address is 4300 Alton Road, Butler Building; Miami Beach, FL 33140.

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

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

The results of this study may be published; however you will not be identified in the publications.

15. I HAVE READ THIS INFORMED CONSENT FORM AND HAVE BEEN GIVEN THE OPPORUNITY TO DISCUSS AND ASK QUESTIONS ABOUT THIS RESEARCH STUDY. I WILL ALSO RECEIVE A SIGNED COPY OF THIS INFORMED CONSENT FORM AND AGREE TO PARTICIPATE.

Printed Name, Address & Telephone No. of Participant:

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Signature of Participant Date

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Printed Name of Witness Date Signature of Witness Date

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Signature of Principal Investigator or Designated Representative Date

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